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ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

ACTA MED PORT. ISSN:0870-399X e-ISSN:1646-0758

1 | 24

Número 1
Série II
Lisboa

Volume 37
Janeiro 2024
Publicação Mensal

FICHA TÉCNICA

AMP ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

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Sede do Editor / Redação: Av. Almirante Gago Coutinho, 151. 1749-084 Lisboa, Portugal. Tel: +351 21 151 71 00 E-mail: secretariado@actamedicaportuguesa.com

ISSN:0870-399X | e-ISSN: 1646-0758

Assinaturas: Nacional: 300 Euros; Internacional: 350 Euros

AMP37(1) - Janeiro de 2024

Registo: Inscrito na Entidade Reguladora para a Comunicação Social com o Nº 106 369

Depósito legal: 20 957/88

Estatuto Editorial: http://www.actamedicaportuguesa.com/estatuto-editorial

Conselho Científico

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Intelligent Plagiarism as a Misconduct in Academic Integrity

O Plágio Inteligente como Má Conduta na Integridade Académica

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Acta Med Port 2024 Jan;37(1):1-2 ▪ https://doi.org/10.20344/amp.20233

Keywords: Artificial Intelligence; Plagiarism; Scientific Integrity Review
Palavras-chave: Integridade Científica; Inteligência Artificial; Plágio

Scientific research is based on the assumption of academic integrity and respect for ethical principles. However, plagiarism and other forms of misconduct have become problems that undermine the credibility of the scientific community. This has led to increasing awareness and attention to these topics nowadays.

Plagiarism is a grave breach of academic and scientific ethics, involving the misappropriation, whether intentional or not, of another's idea or work without proper citation of the original source.[1] It manifests in various forms and degrees of severity: from replicating small excerpts without citation, to the practice of 'salami publishing' – where a substantial work is dissected into smaller pieces for publication in different journals as distinct articles or outcomes. Incorrect bibliographic references, publication biases, and even publishing entire articles resulting from self-plagiarism or outright duplication are other forms.[2] It is essential to note that non-literal plagiarism, or the practice of rephrasing ideas in an indirect manner without attribution, is also considered unethical.

Scientific journals play a vital role in the detection and sanction of plagiarism[3]: editorial offices have traditionally essentially relied upon chance detection by reviewers or editors to discover that submitted work had been previously published. Now, due to efficient search engines, online publishing, and software algorithms, journals increasingly use software that can efficiently scan thousands of manuscripts in seconds and match the submitted text to already published text.

However, the emergence of advanced plagiarism masking techniques such as the use of automatic translators, the replacement of words and sentences, the use of manipulated or falsified images and diagrams, and even the purchase and sale of scientific publications through commercial services (paper mills) has become a worrying future trend. Technological advances and easy access to information have increased the opportunities for plagiarism through even more sophisticated and subtle methods. These include the use of pre-trained intelligent generative transformers or writing tools that enable automatic 'completion' of documents.[4]

On the one hand, we find Natural Language Processing (NLP) models that, among other things (virtual assistants, automated translation, analysis of feelings, grammar correction, automatic summarisation, semantic search...) create texts with Artificial Intelligence (AI). These models are focused on processing and understanding human language with the help of technologies that use algorithms to analyse, understand and produce texts. Regarding the latter[5] it is unlikely that traditional plagiarism checkers can be used to detect this form of cheating, as the NLP model generates a unique AI-generated response instead of copying an existing one.

On the other hand, artificial intelligence (AI) covers a broader field than just language processing and understanding, because it is developed through systems and machines that can perform tasks that require human intelligence, which has been an unprecedented development in recent months, particularly since the launch of AI chatbots in November 2022 and of ChatGPT (GPT - Generative Pretrained Transformer) in 2018. These programs were developed by the company OpenAI, which made a tool that is easy to understand and use available to society. Consequently, numerous authors are currently focused on providing their insights regarding its applications:

- AI can be a useful tool in academic writing, helping to organize material, edit and/or revise, solve problems, make decisions, and learn independently.[6]
- These types of technologies are leading to a post-plagiarism era where people and technology co-author texts, resulting in a human-technology hybrid.[7]
- In this sense, such applications cannot be included in the authorship when writing publications, but their use could be explained in the introduction, merits, or acknowledgments, as being responsible for the scientific results. In this sense, AI chatbots are not human and, therefore, in the current legal system, a text automatically generated by an AI chatbot cannot be a copyrightable work.[8] Journals such as Nature and Science have expressed the view that these

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Recebido/*Received*: 27/09/2023 - **Aceite/*Accepted*:** 11/10/2023 - **Publicado *Online*/*Published Online*:** 30/11/2023 - **Publicado/*Published*:** 03/01/2024

tools cannot be given authorship credits. However, there are already publications where GPT is listed as an author.[9]

We could be talking in this case about intelligent plagiarism, understood, in the words of the undersigned authors as the act of using AI and big data to generate texts automatically, but without using the appropriate data sources. In other words, using AI text generation capabilities to create content that appears to be original, but is actually based on copying and adapting existing material without acknowledging proper sources. Intelligent plagiarism involves the fraudulent use of technology and can be considered the misuse of knowledge or ideas. Artificial intelligence can train itself by sourcing large amounts of data and learning to produce coherent texts, but that does not justify the unethical use of technology to plagiarize or credit other people's intellectual work.

In principle, the use of AI tools should not, *a priori*, be considered any kind of academic dishonesty or abuse, but what it can cause depends more on how the tool is used. An example is using AI tools to automatically generate parts or even an entire scientific article without properly identifying the original authorship. This may include the creation of separate sections such as introduction, methods, results, and conclusions without actual authorship input, which would undermine academic integrity and violate ethical principles of research and dishonest behavior in the publication of scientific articles.[10]

There is currently an open debate surrounding the need and implications of adopting this type of technology in research and in society in general. The discussion revolves around whether researchers should avoid using this technology or exercise caution in its use, particularly in the context of training future research personnel. In this regard, the Committee on Learning and Teaching of the European University Association recently published a document with key points on the impact of AI tools in higher education and responsible use, where it is pointed out that any attempt to ban AI would be futile and that the higher education sector must adapt its approaches in such a way that AI is used effectively and appropriately. While there are several shortcomings associated with the use of AI such as lack of references to information sources, biases in data and algorithms, intellectual property and copyright, or issues related to privacy, data security, and fairness, there are also numerous potential benefits for academic work, including greater efficiency, personalized learning, and new ways of working.

The application of these systems based on chatbots has challenges and limitations related to ethics, whereby awareness, sustainability, and continuous adaptation to the development of these systems will become an emergency situation.[11] It is important to note that the dishonest use of AI in the development of a research paper goes against the basic ethical principles of research such as honesty, transparency, and due attribution. Such practices can damage the credibility of science and undermine faith in scientific progress.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research was financed by the Departament of Culture, Education, Vocational Training and Universities, General Secretariat of Universities, Xunta de Galicia, Spain.

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Patient-Centered Medicine and Self-Care of Patients with Type 2 Diabetes: A Cross-Sectional Study

A Medicina Centrada no Paciente e os Autocuidados dos Doentes com Diabetes Tipo 2: Um Estudo Transversal

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Acta Med Port 2024 Jan;37(1):3-9 ▪ https://doi.org/10.20344/amp.18584

ABSTRACT

Introduction: Even though the prevalence rate of diabetes in Portugal is one of the highest in Europe, no studies on the association between patient centered medicine, diabetes self-care, and glycemic control have been published. Assuming that patient centered medicine increases adherence to treatment through the improvement of the doctor-patient relationship, the aim of this study was to assess the influence of patient-centered medicine on the self-care of patients with type 2 diabetes patients' (T2DM) in two Family Health Units in Central Portugal, according to gender and age.

Methods: A cross-sectional study was conducted in two Family Health Units in Central Portugal between the 25th November 2021 and the 15th January 2022. Patients with type 2 diabetes were invited to fill in the Patient-Centered Medicine questionnaire, for patients (PCM-p) (where higher values represent worse results) and the Summary of Diabetes Self-Care Activities Measure (SDSCAM), (where higher values represent better results), while healthcare professionals filled in the epidemiologic variables on pre-defined days.

Results: A sample of 298 patients with type 2 diabetes was studied. Linear regressions for the association between SDSCAM scale factors and PCM-p showed significant associations for general diet (β = -0.07, $p < 0.001$), specific diet (β = -0.10, $p < 0.001$), exercise (β = -0.03, $p = 0.008$), foot care (β = -0.11, $p < 0.001$) and medication adherence in general (β = -0.06, $p = 0.001$). Multiple linear regression including the association between glycated hemoglobin (HbA1c) and the SDSCAM scale dimensions showed that specific diet was associated with lower HbA1c levels (β = -0.01, $p = 0.007$) and blood sugar testing (β = 0.01, $p < 0.001$) and that a higher score in PCMp was associated with higher HbA1c levels (β = 0.06, $p < 0.001$). Male patients (β = -6.93, $p = 0.007$) and older patients (β = -0.42, $p = 0.001$) were associated with lower scores in the specific diet. The male gender was associated with higher scores in exercise (β = 7.62, $p = 0.029$), lower scores in foot care (β = -6.06, $p = 0.029$) and lower scores in medication adherence to injectable medicines/6.2 (β = -0.73, $p = 0.018$). Age was associated with a lower score in medication (β = -0.03, $p = 0.045$) and a higher PCMp total score (β = 0.07, $p = 0.030$).

Conclusion: Patient-centered medicine in type 2 diabetics is associated with better self-care behaviors in patients with type 2 diabetes. Gender and age differences were observed in self-care behaviors and age differences were observed in Patient Centered Medicine.

Keywords: Blood Glucose Self-Monitoring; Diabetes Mellitus, Type 2; Family Practice; Patient-Centered Care; Portugal; Self Care

RESUMO

Introdução: Apesar de Portugal ser um dos países com maior prevalência de diabetes, não existem estudos que relacionem a medicina centrada no paciente com autocuidados e controlo glicémico. Partindo do pressuposto de que a medicina centrada no doente aumenta a adesão terapêutica em resultado da melhoria da relação médico-doente, pretendeu-se verificar com este estudo a influência deste modelo de Medicina nos autocuidados da diabetes tipo 2, em duas unidades de Saúde Familiar do Centro de Portugal, segundo o sexo e a idade.

Métodos: Estudo transversal em duas unidades de Saúde Familiar da região Centro, entre 25 de novembro de 2021 e 15 de janeiro de 2022. Os doentes com diabetes tipo 2 preencheram os questionários *Summary of Diabetes Self-care Activities* e *Patient Perception of Patient Centeredness*, e a equipa de saúde preencheu as variáveis epidemiológicas em dias pré-definidos.

Resultados: Reuniu-se uma amostra de 298 diabéticos tipo 2. As regressões lineares para a associação entre as dimensões da escala *Summary of Diabetes Self-care Activities* e as da *Patient Perception of Patient Centeredness* mostraram associações significativas relativamente à dieta geral (β = -0,07, $p < 0,001$), à dieta específica (β = -0,10, $p < 0,001$), ao exercício, (β = -0,03, $p = 0,008$), aos cuidados dos pés (β = -0,11, $p < 0,001$) e à adesão à medicação em geral (β = -0,06, $p = 0,001$). A regressão linear múltipla para a hemoglobina glicada com as dimensões significativas da *Summary of Diabetes Self-care Activities* mostrou uma associação entre a dieta específica e menor valor de hemoglobina glicada (β = -0,01, $p = 0,007$), e que valores superiores de glicémia capilar (β = 0,01, $p < 0,001$) e maior pontuação na *Patient Perception of Patient Centeredness* estavam associados a uma maior hemoglobina glicada (β = 0,06, $p < 0,001$). O sexo masculino (β = -6,93, $p = 0,007$) e idosos (β = -0,42, $p = 0,001$) foi associado a menor pontuação na dieta específica. O sexo masculino foi associado a maiores níveis de exercício (β = 7,62, $p = 0,029$), menores cuidados dos pés (β = -6,06, $p = 0,029$) e menor pontuação na adesão a medicação injetável (β = -0,73, $p = 0,018$). A idade avançada foi associada a menor pontuação na medicação 6.2 (β = -0,03, $p = 0,045$) e maior pontuação no *Patient Perception of Patient Centeredness* (β = 0,07, $p = 0,030$).

Conclusão: A medicina centrada associou-se a melhores comportamentos de autocuidado em doentes com diabetes tipo 2. Foram observadas diferenças nos autocuidados relativamente ao género e à idade e na medicina centrada no doente relativamente à idade.

Palavras-chave: Autocuidado; Automonitorização da Glicemia; Diabetes Mellitus Tipo 2; Medicina Centrada no Paciente; Medicina Familiar; Portugal

INTRODUCTION

Diabetes is a major cause of death and disability globally. It is one of the most common noncommunicable diseases and its prevalence rate continues to grow, affecting 463 million adults (in 2019).[1-3]

In 2020, diabetes affected 14.2% of the Portuguese population aged 20 to 79 years, making Portugal one of the

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Recebido/*Received*: 18/05/2022 - **Aceite/*Accepted*:** 12/12/2022 - **Publicado *Online*/*Published Online*:** 31/03/2023 - **Publicado/*Published*:** 03/01/2024

European countries with highest prevalence rate of diabetes, according to the International Diabetes Federation (IDF).[3,4]

Diabetes self-care activities contribute to successful self-management. These self-care behaviors have a positive correlation with glycemic control, better quality of life and reduction of diabetic complications, and can be evaluated by the Summary of Diabetes Self-Care Activities (SDSCA).[4]

Multiple demographic, socio-economic and social factors can positively influence self-care activities of patients with diabetes. However, the clinician's role in promoting self-care remains vital.[5]

According to the American Diabetes Association and the IDF, patient-doctor communication should be advocated in the management of diabetes[3] as it improves disease knowledge, quality of life self-care and better glycemic control. However, poor communication is a very common patient complaint and it causes[6] patients to avoid discussing self-care problems with doctors.[7]

Patient-centered medicine (PCM) is a clinical method with evidence of promoting a better relationship between doctor and patient, enabling and empowering the patient, and thus facilitating adherence to treatment.[8,9]

According to Stewart *et al*, it is based on four components: (1) exploring health, illness, and illness experience; (2) understanding the patient as a whole; (3) seeking understanding; and (4) improving the doctor-patient relationship. These components are measured considering the patients' perspective.[9]

An improved doctor-patient relationship as well as an increased patient education and knowledge about diabetes are likely to increase the awareness and adherence to self-care.[9,10]

A review article advocates that PCM allows a 1% reduction in blood glucose and in HbA1C levels.[11] It also increases therapeutic adherence, knowledge about the disease and the commitment in decision-making.[11] This study was motivated given the absence of published Portuguese studies on both topics simultaneously.

The aim of this study was to ascertain if the practice of PCM, in the patient's perspective, the PCMp, influenced self-care behaviors in T2DM patients from two Primary Care practices, the Family Health Units (FHUs) Mondego and Manuel da Cunha. Furthermore, this study also determined the association between PCMp and self-care activities in glycemic control by HbA1c value, considering gender and age.

We hypothesized that PCMp practice was associated with better self-care activities and improved glycemic control.

METHODS

Ethical considerations

The Ethics Committee of the Central Portugal Regional Health Administration approved this study. Written agreements from the authors of the scales, authorization from the technical council of the FHUs, as well as patient informed consent were obtained.

Design and population

A cross-sectional study was conducted in the 1321 adult patients of both the Mondego and Manuel Cunha FHU´s T2DM patient population. Sample size was calculated using an online calculator, available on the website *praticaclinica.com.br,* for a confidence interval of 95% and error margin of 5%. Using the *praticaclinica.com.br* website, the following formula was applied: $n = N.Z^2.p.(1-p) / Z^2.p.(1-p) + e^2.N-1$, where N = population size, Z = critical value of the normal distribution at the required confidence level, *p* = sample proportion, e = margin of error. Participants were allocated based on the pre-defined days of study performance, decided by the authors. As exclusion criteria, patients with cognitive impairment due to dementia or severe diabetic retinopathy or with reading and comprehension difficulties were not included.

All T2DM patients with a diabetes consultation during the study period were invited by the administrative staff of the FHUs.

Procedures

After invitation, the patients completed the informed consent form which included a precedent explanation about all aspects of the study that was written in an accessible away for patients. The invitation was followed by filling in the SDCA Summary of Diabetes Self-Care Activities scale (SDSCA), while waiting for the medical appointment, and the PCMp scale was completed at the end of the medical appointment. Both scales are adapted and validated for European Portuguese.

After the medical appointment the latest hemoglobin A1C value and the sociodemographic data, such as age and gender of patient were registered by a doctor or nurse. Diabetes was considered controlled if HBA1c was < 7%.[12] Subsequently, the questionnaires and the informed consent form were filed in order to ensure anonymity. The clinicians were not aware of the scheduled days of the study.

Instruments

Self-care variables

Diabetes self-care behaviors were assessed using the 7-item scale version of the Summary of Diabetes Self-Care Activities (SDSCA), culturally adapted and validated for European Portuguese by Bastos *et al*.[13]

Each item (from 1 to 6) contained a score from 0 to 7 corresponding to the weekdays, and the aim of the scale was to assess the frequency of self-care activities. Self-care included general diet (healthy diet, vegetable and fruit consumption), specific diet (weekly consumption of red meat, carbohydrates, alcoholic beverages and sugar), physical exercise, blood glucose monitoring, foot care and medication adherence. Item 6 included medication adherence, with item 6.1 being related to adherence in general, 6.2 to adherence to injectable medicines and item 6.3 to oral medication.

Dimensions of SDSCA were rated from 0 to 100, with better results corresponding to higher scores. Higher scores in a specific diet dimension corresponded to a worse self-care activity. For this study, these scores were inverted in order to standardize answers. Patients chose to respond to item 6.1 or 6.2 and 6.3. Therefore, we used total number of days for item 6.1 and mean number of days if both 6.2 and 6.3 and statistics were performed separately, according to the original scale validation article.[14]

Item 7 included smoking habits in a "yes" or "no" question, followed by the questions "how many cigarettes per day" and "when did you smoke your last cigarette" if the answers were positive. Better scores on general diet, physical exercise, blood glucose monitoring, foot care and medication items revealed better self-care. Lower scores on specific food items, smoking habits and a higher number of cigarettes per day were associated with worse self-care.[1,10,14]

Patient-centered medicine

The quality of medical practice was assessed using the Patient Centered Medicine, patient version (PCMp) scale, culturally adapted and validated for European Portuguese.[15] This 9 item scale created by Moira Stewart includes the following questions: (1) Were your reasons for today's appointment discussed?, (2) Were you satisfied with the conversation about your problem(s)?, (3) Did the doctor listen to what you had to say?, (4) Did the doctor explain your problem?, (5) Did you talk about what each one should do to improve?, (6) Did the doctor explain the treatment?, (7) Did the doctor talk to you about the ease of this treatment for you?, (8) Do you feel that your doctor understands you? and (9) Has the doctor talked to you about personal or family issues that may affect your health?. The answer options were "Completely", "Partially", "A little" and "None". The options were converted in the SPPS statistical program to "0", "1", "2" and "3", with lower scores being associated with a more patient-centered medical practice.[15]

Statistical analyses

Statistical analysis was performed with SPSS, version 26. Descriptive statistics were presented as means (M) and standard deviations (SD) for quantitative variables with symmetrical distributions and frequencies (n) and percentages (%) for categorical variables. Symmetry was considered when the skewness coefficient was [-1, 1]. Linear regressions were implemented to assess linear associations with continuous outcomes, after screening for Pearson correlations. Unstandardized coefficients (β) were used to measure the effect size of the independent variables in the outcome. Residual's normality was assessed with the Shapiro Wilk test and by observing histograms. Variance's homoscedasticity was assessed by observing no trend in the plot of standardized residuals *versus* standardized predicted values. No outliers were found outside the interval [-3; 3]. Logistic regression was used to assess associations with binary outcomes. Adjusted odds ratios (aOR) were calculated to measure the effect size of the independent variables in the outcome. Multivariate regression models were implemented including significant ($p < 0.05$) and marginally significant ($p < 0.10$) independent variables for both linear and logistic regression models.

Table 1 – Descriptive statistics and matrix correlations of the measures in this study

	Range	M (SD)	Correlations									
SDSCA			**1**	**2**	**3**	**4**	**5**	**6.1**	**6.2**	**6.3**	**7**	**8**
1. General diet	[0 - 100]	64.08 (21.93)	1	0.055	0.307**	0.273**	0.264**	0.227**	0.104	0.200**	**-0.264****	-0.061
2. Specific diet	[0 - 100]	58.48 (22.52)		1	0.113	0.104	0.204**	0.097	0.195**	0.059	**-0.408****	**-0.216****
3. Exercise	[0 - 100]	32.17 (30.06)			1	0.184**	0.235**	0.169**	0.033	0.172**	**-0.136***	0.106
4. BS testing	[0 - 100]	33.92 (32.31)				1	0.145*	0.161**	0.390**	0.125*	0.070	**0.327****
5. Foot care	[0 - 100]	83.00 (23.85)					1	0.349**	-0.054	0.196**	**-0.450****	-0.041
6.1 Medication	[0 - 7]	6.41 (1.76)						1	0.134*	0.713**	**-0.180****	**0.126***
6.2 Medication	[0 - 7]	1.22 (2.66)							1	0.098	0.023	**0.206****
6.3 Medication	[0 - 7]	5.98 (2.28)								1	-0.084	**0.157****
7. PPCMP total score	[0 - 27]	4.29 (5.50)									1	**0.366****
8. HbA1C	[4.4 - 10.6]	6.97 (1.04)										1

PPCMP: patient perception of patient-centeredness; BS testing: blood sugar testing
*: $p < 0.05$
**: $p < 0.01$

RESULTS

Sample characterization

A total sample of 298 was calculated and 298 patients with type 2 diabetes were included in the analysis. The sample, composed of 136 (45,6%) female participants, was aged between 29 and 93 years old, mean 67.40 ± 10.19. The mean value of HbA1C was 6.97 ± 1.04%, ranging from 4.4% to 10.6%. The prevalence rate of HbA1c ≥ 7% was n = 35.2% (n = 105).

SDSCA-Scale and PCMp-Questionnaire

After observing the distribution of SDSCA and PPCMP, the corresponding scores were calculated. For SDSCA the recommendations of transforming scores in [0 - 100] were followed, by using the formula: [(sum of items/max range) x 100]. The PCMp total score was calculated as the sum of all its items. Table 1 shows descriptive results for SDSCA dimensions, PCMp total score and HbA1C and Pearson correlations for all these variables. Considering the goal of studying the associations of SDSCA dimensions with PCMp, Pearson correlation was used to measure the strength between SDSCA dimensions and PCMp. Negative correlations between general diet (r = -0.264, $p < 0.01$), specific diet (r = -0.408, $p < 0.01$), exercise (r = -0.136, $p < 0.05$), foot care (r = -450, $p < 0.01$), 6.1 general medication (r = -0.180, $p < 0.01$) and PPCMP were found.

To assess the correlation between HbA1c and SDSCA dimensions, these results were also included in the correlation matrix. Pearson correlations between SDSCA dimensions and HbA1c detected a negative correlation between HbA1c and specific diet (r = -0.216, $p < 0.01$) and a positive correlation between HbA1c and blood sugar testing (r = 0.327, $p < 0.01$), medication in general 6.1 (r = 0.126, $p < 0.05$), injectable medicines 6.2 (r = 0.206, $p < 0.01$), oral medication 6.3 (r = 0.157, $p < 0.01$) and PCMp total score (r = 0.366, $p < 0.01$).

T-tests showed that smoking at least once in the past seven days was significantly associated with higher PCMp total score ($p = 0.048$).

After observing correlations and *T*-test results, linear regressions were performed. After Pearson correlations between SDSCA dimensions and PCMp to measure the strength of correlation were performed, we selected the associations that were statistically significant associations. Table 2 shows linear regressions for associations between SDSCA factors (DV) and PPCMP (IV) adjusted for sex and age. Significant associations were found for general diet, decreasing, on average, -0.07 for each unit of PCMp score (β = -0.07, $p < 0.001$), for specific diet, decreasing, on average, -0.10 for each unit of PCMp score (β = -0.10, $p < 0.001$), for exercise, decreasing, on average, -0.03 for each unit of PCMp score (β = -0.03, $p = 0.008$), for foot care, decreasing, on average, -0.11 for each unit of PCMp score (β = -0.11, $p < 0.001$) and for general medication 6.1, decreasing, on average, -0.06 for each unit of PPCMP score (β = -0.06, $p = 0.001$). The model with the highest quality was model 2, for specific diet, with 17.1% of specific diet variance, explained by PCMp, sex and age.

Logistic regression results for the association of smoking in the last seven days with PCMp, adjusted for sex and age showed that the chance of smoking in the last seven days increased 9% for each unit increase in PCMp score {aOR = 1.09, 95% CI= [1.03, 1.16], $p = 0.002$}.

Pearson correlations between SDSCA dimensions and HbA1c retrieved significant associations between them. Table 3 shows a multiple linear regression HbA1C (DV)

Table 2 – Linear regressions for SDSCA factors association with PPCMP

DV	β	SE	*p*-value	R^2
Model 1: General diet	-0.07	0.01	$p < 0.001$	0.083
Model 2: Specific diet	-0.10	0.01	$p < 0.001$	0.171
Model 3: Exercise	-0.03	0.01	$p = 0.008$	0.030
Model 4: Foot care	-0.11	0.01	$p < 0.001$	0.214

Regressions adjusted for sex and age

Table 3 – Linear regressions for HbA1C association with SDSCA dimensions and PPCMP

IV	B	SE	*p*-value	R^2
Specific diet	-0.01	≈0.00	$p = 0.007$	0.258
BS testing	0.01	≈0.00	$p < 0.001$	
Medication 6.1	-0.01	0.04	$p = 0.427$	
Medication 6.2	0.05	0.02	$p = 0.051$	
Medication 6.3	0.06	0.03	$p = 0.138$	
PPCMP	0.06	0.01	$p < 0.001$	

Regressions adjusted for sex and age; BS testing: blood sugar testing

association with the significant SDSCA dimensions (IVs), detected in the correlation matrix, adjusted for sex and age. Specific diet was associated with less HbA1c (β = -0.01, *p* = 0.007), blood sugar testing (β =0.01, *p* < 0.001) and higher score in PCMp. Worse results were associated with higher HbA1C (β = 0.06, *p* < 0.001). Results as high as 25.8% of HbA1c were explained by specific diet, blood sugar testing, medication, PPCMP, sex, and age.

In this context, a logistic regression was also implemented, considering HbA1C > 7%. A significant association for blood sugar testing was found {aOR = 1.02, 95% CI= [1.01, 1.02], *p* < 0.001}, with 2% more chance of HbA1c > 7% for each unit increase in blood sugar testing and for PCMp {aOR = 1.16, 95% CI= [1.10, 1.22], *p* < 0.001}, with 15% more chance of HbA1c > 7% for each unit in PCMp.

Regressions between age and gender, with each SDSCA dimension, PCMp total score and HbA1c, to find an association between these variables, were performed. Table 4 presents associations of age and gender with each SDSCA dimension, PPCMP total score and HbA1c. Males (β = -6.93, *p* = 0.007) and older patients (β = -0.42, *p* = 0.001) were associated with a lower score for a specific diet. Males were associated with a higher score in exercise (β = 7.62, *p* = 0.029), a lower score in foot care (β = -6.06, *p* = 0.029). Male patients presented lower scores in injectable medicines 6.2 (β = -0.73, *p* = 0.018), as well as older patients (β = -0.03, *p* = 0.045). Older age was associated with higher PCMp total score (β = 0.07, *p* = 0.030).

Logistic regression results for the association of smoking in the previous seven days with sex and age showed that male patients were 2.91 times more likely to have smoked compared to women {aOR = 2.91, 95% CI= [1.27, 6.71], *p* = 0.012}, and that odds decreased 3% for each year of age {aOR = 0.97, 95% CI= [0.94, 1.00[, *p* = 0.041}.

DISCUSSION

To our knowledge, the current study is the first one to investigate the association of self-care activities and PCM practice and its influence on disease control in Portuguese patients with T2DM.

Self-care activities, involving medication adherence, blood sugar testing, foot care and diet are necessary for successful management of diabetes.[10]

Patient-centered medicine is linked to alliance, communication, health promotion and self-care care entailing better results and health outcomes.[10,16]

This convenience sample was mostly male (n = 162, 53,7%), as expected, according to Portuguese National Health Service data.[17]

The prevalence rate of HbA1c ≥ 7%, patients with uncontrolled T2DM, was 35.2% (n = 105).

After Pearson correlations between SDSCA dimensions and PCMp, significant associations were found for general diet, specific diet, exercise and foot care to PCMp, adjusted for sex and age. Therefore, a better patient-centred medical practice, is likely to increase exercise levels and promote a better general and specific diet, foot care and medication adherence.

According to Williams *et al*, patients with T2DM consider PCM as an important factor for self-management, and that is significantly associated with better self-care behaviors.[10] Additionally, to Devoe *et al,* effective doctor-patient communication favors interactions and has a significant impact on patient behaviors and health outcomes.[18]

A significant association of smoking in the last seven days with PCMp, adjusted for sex and age showed that higher values on the PCMp scale were associated with a greater probability of smoking.

PCMp elements may be applied to patient-centered tobacco management. Therefore, according to Gould *et*

Table 4 – Linear regressions for age and gender association with SDSCA dimensions, PPCMP total score and HbA1C

	Independent variables β (SE) ***p*-value**		
DV	**Sex** (male)	**Age**	**R^2**
Model 1: General diet	-2.39 (2.55) *p* = 0.349	0.18 (0.13) *p* = 0.147	≈0.00
Model 2: Specific diet	**-6.93 (2.56) *p* = 0.007**	**-0.42 (0.13) *p* = 0.001**	0.049
Model 3: Exercise	**7.62 (3.47) *p* = 0.029**	0.32 (0.17) *p* = 0.063	0.019
Model 4: BS testing	-3.91 (3.77) *p* = 0.301	-0.02 (0.19) *p* = 0.920	≈0.00
Model 5: Foot care	**-6.06 (2.77) *p* = 0.029**	0.03 (0.14) *p* = 0.854	0.010
Model 6.1: Medication	-0.16 (0.21) *p* = 0.433	0.14 (0.01) *p* = 0.159	≈0.00
Model 6.2: Medication	**-0.73 (0.31) *p* = 0.018**	**-0.03 (0.02) *p* = 0.045**	0.023
Model 6.3: Medication	0.12 (0.27) *p* = 0.654	0.01 (0.01) *p* = 0.420	≈0.00
Model 7: PPCMP total score	0.22 (0.64) *p* = 0.734	**0.07 (0.03) *p* = 0.030**	0.010
Model 8: HbA1C	-0.09 (0.12) *p* = 0.455	0.01 (0.01) *p* = 0.120	≈0.00

PPCMP: patient perception of patient-centeredness; BS testing: blood sugar testing

al,[19] maintaining a long-standing doctor-patient relationship enables the adoption of solutions and goals that favor an eventual smoking cessation.

Specific dietary scores were rated from 0 - 100, with the remaining dimensions of SDSCA. Therefore, better scores corresponded to higher scores, closer to 100. Regarding medication adherence, one of the topics was "On how many of the last seven days did you take your recommended diabetes medication?"; related to item 6.1, another topic was "On how many of the last seven days did you take your recommended insulin injections?" and item 6.3 asked "On how many of the last SEVEN DAYS did you take your recommended number of diabetes pills?". Patients chose to respond to item 6.1, or 6.2 and 6.3. Therefore, we used total number of days for item 6.1 and used mean number of days if both 6.2 and 6.3. Statistics were performed separately, according to the original scale validation article.[14]

After Pearson correlations between SDSCA dimensions and HbA1c were performed to measure the strength of correlation, an association was found between HbA1c (DV) and the significant SDSCA dimensions (IVs), adjusted for sex and age, showing that better levels of HbA1c were associated with a better specific diet.

Better diabetes self-care behaviors were related with a better glycemic control, which concurs with the findings of Amer *et al.*[20] To Silva-Tinoco *et al*, self-care activities mediate the influence of diabetes knowledge on glycemic control.[1]

Lower scores in blood sugar testing were associated with lower HbA1c. Self-monitoring in type 2 diabetes is currently not recommended, as the scale is outdated.[20] Therefore, these results are not suitable for analysis. We can also assume that the patients who follow the recommendations are more likely to have a controlled disease.

Worse scores in PCMp and not having had a PCM consultation were associated with higher HbA1C. Studies have shown an improvement in glycemic control of type 2 diabetes by PCM,[10,21] but other studies could not find such results after adjusting for appropriate confounders.[10]

Slingerland *et al* suggested that PCM is not effective for patients with a baseline HbA1c < 7% but provides value for patients with type 2 diabetes with a baseline HbA1C > 8.5%, which may justify its implementation.[22]

Regressions between age and gender with each SDSCA dimensions, PCMp total score and HbA1c revealed that male and older patients presented worse specific dietary scores. A review article showed that men were less likely to attend medical appointments, to perform preventive care and were more likely to be overweight when compared to women.[23] Women tended to have more health care responsibilities than men.[24]

In this study, males were shown to exercise more receive foot care less often. However, previous research demonstrated that women reported having significantly better exercise habits than men.[25]

Males and elderly patients showed worse adherence to injected medication (item 6.2), and older patients presented worse PCMp total scores. The explanation for age-related differences in health care communication is ambiguous. Prior studies suggested that the communication of health-care providers with older patients is less effective. Health-care providers may be more tolerant with the inadequacies of older people, and it has been found that the satisfaction levels of elderly patients rise between 65 to 80 years and then decrease.[26]

In this study, male patients had a higher prevalence rate of smoking habits and older patients presented a lower prevalence rate, which is in line with previous results.[23]

This study has some limitations. The present results have limited geographic coverage, even though it was representative of the studied population; and its quality of an observational cross-sectional study.

Moreover, the SDSCA scale was outdated in the item referring to glucose self-measurement, since it is no longer recommended, and the self-reported data may bias the present results. Social desirability response and memory are biases to be considered. The exclusion criteria – severe diabetic retinopathy – may have resulted in a selection bias to the study, excluding patients with severe disease.

Larger studies covering other regions and districts of Portugal will allow a better picture and probably better health out-comes. Future studies should investigate what parameters influence diabetes evolution and control.

CONCLUSION

The Summary of Diabetes Self-Care Activities scale showed that the practice of patient-centered medicine was associated with better self-care behaviors in T2DM2 patients, particularly for general diet, specific diet, exercise and foot care.

Patient-centered medicine and self-care activities, especially specific diet, can lead to a better glycemic control.

There were differences in self-care behaviors between gender and age in PCMp scores, with male and older patients having worse ratings. No significant gender and age differences in HA1c levels were found.

The importance of the family physician's role in self-care of type 2 diabetes patients must be further investigated.

AUTHOR CONTRIBUTIONS

SS, LMS: Conception of the work, data collection and analysis, writing and approval of the manuscript.

AMP: Conception of the work, writing and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Implementation of a Pilot Study to Analyze Circulating Tumor DNA in Early-Stage Lung Cancer

Implementação de um Estudo Piloto para Análise de ADN Tumoral Circulante no Cancro do Pulmão em Estádio Inicial

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Acta Med Port 2024 Jan;37(1):10-19 ▪ https://doi.org/10.20344/amp.19487

ABSTRACT

Introduction: Liquid biopsies based on plasma circulating tumour deoxyribonucleic acid (ctDNA) have shown promise in monitoring lung cancer evolution. The expression of ctDNA across time, its relationship with clinicopathological parameters and its association with lung cancer progression through imaging allow us to weigh how useful ctDNA could be in monitoring surgically resectable lung cancer. The aim of this study was to assess the impact of ctDNA analysis implementation in early-stage lung cancer.

Methods: A cohort of 47 patients was sequentially recruited. Only 34 patients with early-stage lung cancer were included. All patients had a tissue specimen and five blood samples drawn: at the preoperative stage, from the pulmonary vein, at surgical discharge, at the first follow-up and at the last follow-up. All blood samples were evaluated for ctDNA expression.

Results: On average, the maximum yield of ctDNA was obtained in liquid biopsies at the surgical discharge of patients when compared with PO, PV, and F1 ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$ respectively). No statistically significant differences were found when comparing the last follow-up to surgical discharge ctDNA expression ($p = 0.851$). The correlation between ctDNA concentration according to five-time points and the four clinicopathological characteristics showed that patients younger than 70 years had a statistically significant reduction of the concentration of ctDNA at the preoperative and surgical discharge time point [β = -16 734 (-27 707; - 5760); $p = 0.003$; β = -21 785 (-38 447; -5123); $p = 0.010$], as opposed to an increase of the concentration of ctDNA at the pulmonary vein and last follow-up time points [β = 8369 (0.359; 16 378); $p = 0.041$; β = 34 402 (12 549; 56 254); $p = 0.002$] all with a confidence level of 95%. In the cases where actionable mutations were identified in tissue biopsies, the expected mutation was found in five out of six patients plasma samples at the pre-operatory time point and in two out of six patients plasma samples at the pulmonary vein time point. Two out of six patients with actionable mutations had disease progression.

Conclusion: The results of this pilot study suggest that the maximum yield of ctDNA is obtained at the surgical discharge of the patients and that the pre-operatory timepoint is the one offering the highest sensitivity for the detection of actionable mutations in ctDNA in early-stage lung cancer.

Keywords: Circulating Tumor DNA; Early Detection of Cancer/methods; High-Throughput Nucleotide Sequencing; Lung Neoplasms; Mutation; Neoplasm Staging

RESUMO

Introdução: As biópsias líquidas baseadas no ácido desoxirribonucleico tumoral circulante (ctADN) no plasma têm-se mostrado promissoras na monitorização da evolução do cancro do pulmão. A expressão do ctADN ao longo do tempo, sua relação com parâmetros clínico-patológicos e sua associação com a progressão do cancro de pulmão através da imagem, permitem-nos avaliar o quanto útil o ctADN pode ser na monitorização do cancro do pulmão ressecável cirurgicamente. O objetivo deste estudo foi avaliar o impacto da implementação da análise de ctADN no cancro do pulmão em estádio inicial.

Métodos: Uma coorte de 47 pacientes com cancro de pulmão em estádio inicial foi recrutada sequencialmente. Apenas 34 pacientes foram incluídos. Todos os pacientes colheram uma amostra de tecido e cinco amostras de sangue: no pré-operatório, da veia pulmonar, na alta cirúrgica, no primeiro seguimento e no último seguimento. Todas as amostras de sangue foram avaliadas quanto à expressão de ctADN.

Resultados: Em média, o rendimento máximo de ctADN foi obtido em biópsias líquidas obtidas na alta cirúrgica dos pacientes quando comparado com as colheitas nos momento pré-operatório, da veia pulmonar, e no primeiro seguimento ($p < 0,0001$, $p < 0,0001$, $p < 0,0001$, respetivamente). Não houve significado estatístico ao comparar as biópsias líquidas obtidas no último seguimento com a expressão do ctADN na alta cirúrgica ($p = 0,851$). A correlação entre a concentração de ctADN nos cinco momentos de colheita e as quatro características clínico-patológicas mostrou que pacientes com menos de 70 anos tiveram redução significativa da concentração de ctADN no momento pré-operatório e na alta cirúrgica [β = -16 734 (-27 707; -5760); $p = 0,003$; β = -21 785 (-38 447; -5123); $p = 0,010$] em oposição a um aumento da concentração de ctDNA na veia pulmonar e no último seguimento [β = 8369 (0,359; 16 378); $p = 0,041$; β = 34 402 (12 549; 56 254); $p = 0,002$] todos com nível de confiança de 95%. Nos casos em que foram identificadas mutações acionáveis em biópsias de tecido, a mutação esperada foi encontrada em cinco de seis amostras de plasma de pacientes no momento pré-operatório e em duas de seis amostras de plasma de pacientes no momento da veia pulmonar. Dois dos seis pacientes com mutações acionáveis apresentaram progressão da doença.

Conclusão: Os resultados deste estudo piloto sugerem que o rendimento máximo do ctDNA é obtido na alta cirúrgica dos pacientes e que o momento pré-operatório é o que oferece a maior sensibilidade para a deteção de mutações acionáveis no ctDNA no cancro do pulmão em estádio inicial.

Palavras-chave: Detecção Precoce de Cancro/métodos; DNA Tumoral Circulante; Estadiamento de Neoplasias; Mutação; Neoplasias do Pulmão; Sequenciamento de Nucleotídeos em Larga Escala

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Recebido/*Received*: 16/12/2022 - **Aceite/*Accepted*:** 04/05/2023 - **Publicado *Online*/*Published Online*:** 25/07/2023 - **Publicado/*Published*:** 03/01/2024

INTRODUCTION

Lung cancer (LC) is the deadliest tumor worldwide, with nearly 1.8 million deaths in 2020.[1-3] The best subgroup of patients with a chance of surgery with curative intent are those at an early stage (I - IIIA) corresponding to 20% to 25% of the cases of non-small cell lung cancer (NSCLC) diagnosed each year even though radical resection has curative intent and is the cornerstone for patients with early-stage LC, tumor relapse occurs in about 30% to 70% of patients. Adjuvant chemotherapy can reduce the risk of disease recurrence by 16% and increase five-year overall survival by 5.4% when compared with placebo.[4-7]

Early detection of recurrence is associated with better outcomes. Screening with low-dose computed tomography (CT) has been shown to reduce LC mortality in high-risk population, but its implementation is low due to socio-economical limitations.[8] Until now, no biomarkers with high specificity and sensitivity could identify patients at high-risk of recurrence, and TNM staging and performance status are the only tools that clinicians can rely on.

In 1948, circulating cell-free tumor deoxyribonucleic acid (cfDNA) was first identified in human blood by Mandel *et al*.[9] The discovery of cfDNA in blood samples is what has been defined as a form of 'liquid biopsy'. The cfDNA released from cancer patients is referred to as circulating tumor DNA (ctDNA) and is only a portion of all cfDNA. The percentage of ctDNA in overall cfDNA of patients with cancer can range from 0.1% to over 10%. An extremely sensitive technique must be used to detect mutations or other changes present in ctDNA at low variant allele frequencies (AF) of 0.003% or lower.[10]

A cancer biomarker is a molecular component that can give us advantages in facing cancer. It should provide prognostic and predictive information, detecting the disease while measurable, within a high-risk population, while it is not yet clinically apparent.[11] Despite all this potential and many published studies showing the usefulness of molecular genetic techniques as auxiliary diagnostic tools, the latter are not being used in routine clinical practice in Portugal for early-stage lung cancer.[12] This study is part of our plan to establish and implement protocols for transposing molecular genetic knowledge and techniques from the bench to clinical practice in the medium-term.

The primary aim of this study was to integrate the routine use of ctDNA in lung cancer surgical patients, and to evaluate the quantitative evolution of ctDNA across time and its correlation with clinicopathological variables at five specific data collection time points.

Even though liquid biopsies are a useful strategy to screen for actionable mutations that are routinely used in advanced lung cancer both at the diagnostic and post-progression stages, their usefulness in surgically resectable lung cancer has not yet been addressed. Our second aim was to assess whether cancer cells remaining in the body after surgery will be important in predicting tumor recurrence by assessing the importance of genotyping tumor and plasma samples for actionable mutations where ctDNA is most expressed. Finally, we aimed to assess if ctDNA is a critical tool in the postsurgical management of lung cancer patients with actionable mutations, as well as its usefulness as a guide to detect residual postsurgical ctDNA and disease progression.

METHODS

Study cohort

A prospective, single-center, observational study was conducted by the Centro Hospitalar Universitário de São João (CHUSJ), EPE. The study protocol was approved by the Ethics Committee of Centro Hospital Universitário de São João, EPE on May 11, 2017 (approval number: CES01). The methods were conducted under the precepts of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

All patients had to sign an informed consent form to be included in the study. Eligible patients were either women or men, aged over 18 years old, and had pathological confirmation of early-stage non-small cell lung cancer (as per the criteria of the American Joint Committee on Cancer, 8th edition, criteria). Forty-seven patients were initially recruited from our center between the May 29, 2017 and January 28, 2019. Thirteen patients were excluded as they either did not meet the inclusion criteria or because data for subsequent analysis was not available. This study cohort included 34 patients. The study design was distributed between the Cardiothoracic and the Pulmonology departments. Patients were referred to the Cardiothoracic Department after full diagnosis and staging procedures and accepted for surgical treatment in multidisciplinary thoracic diseases oncologic group meetings. Thirty-four patients with NSCLC underwent radical surgery at the Department of Cardiothoracic Surgery. Information related to clinical and radiological evolution, as well as information related to treatments they had undergone during the disease, and their response, was collected throughout time (Fig. 1).

Sample collection

Tumor samples (TS) were collected during surgical resection. Five blood samples were taken from each of the patients: at the preoperative peripheral stage (PO), from the pulmonary vein (PV), at surgical discharge (SD), at first follow-up (F1), and last follow-up (LF). Additional samples drawn during follow-up at other intermediate points were also accepted, according to the flowchart (Fig. 1). A total of

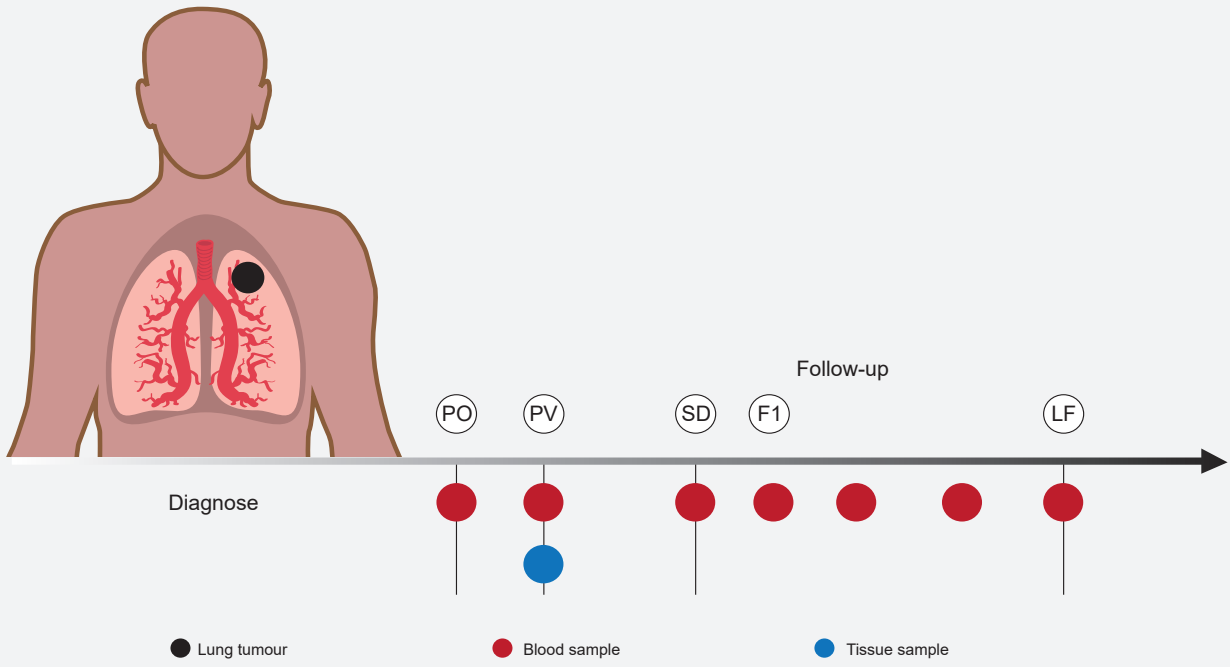

Figure 1 – Flowchart
PO: pre-operative; PV: pulmonary vein; SD: surgical discharge; F1: first follow-up; LF: last follow-up

34 samples of tumor tissue and 34 peripheral blood samples were collected at the preoperative time point, 34 blood samples were collected during the intraoperative act from the corresponding pulmonary vein, and 34 peripheral blood samples were obtained at surgical discharge. During the surgical period, 102 blood samples were collected, and during follow-up, a total of 108 samples were withdrawn. This total 34 tissue samples and 210 viable blood samples that were sent for processing to the I3S Institute. Another 210 blood samples were stored in the tumor bank of the Hospital of São João in the Department of Pathology, for later use, if necessary for further evaluations. The final number of samples analyzed was 210 (Fig. 2).

Laboratory procedures

The tumor sample was collected immediately after surgical resection. Histological specimens were fixed with formalin (formalin-fixed paraffin-embedded tissue, FFPE). After pathological and immunohistochemical evaluation, samples were used for DNA extraction using the QIAamp DNA Mini Kit. DNA was quantified with NanoDrop Lite Spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) or Qubit® 2.0 Fluorometer (Invitrogen, Waltham, MA, USA).

Blood samples collected into EDTA tubes were processed within one to four hours after withdrawal, were centrifuged at 1600 g/min for 10 minutes, and peripheral blood lymphocytes were separated and stored at -80°C until use. The plasma was collected by centrifuging the supernatant from the blood samples again at 18 000 g/min for five minutes and was stored at -80°C until further use.[13-17] Ion Ampliseq Colon and Lung panelTM were used for tissue biopsies and Oncomine lung circulating free tumor DNA assay for circulating free tumor DNA (cfDNA) samples. All amplified products will be used to prepare libraries and sequenced using the ion PGMTM or S5TM system. The QuantStudio 3D Digital PCR system TM will be used to confirm selected results.

Statistical analysis

The sample size was limited by the availability of specimens for subsequent analysis following a sequential standard molecular diagnostic approach. Most of the analysis was descriptive. Categorical data were described as absolute (n) and relative frequencies. Medians, interquartile ranges (IQR), and minimum and maximum values were determined for continuous variables. Non-parametric Wilcoxon-matched pairs signed-rank tests were used to infer the difference in the quantity of ctDNA (ng/mL) present in the blood of lung cancer patients at different and between different data collection time points (PO, PV, SD, F1 and LF). Significance values were adjusted using the Bonferroni correction for several tests. A Kruskall–Walli's test, a non-parametric version of the one-way ANOVA model, was performed between all-time points. Linear regression

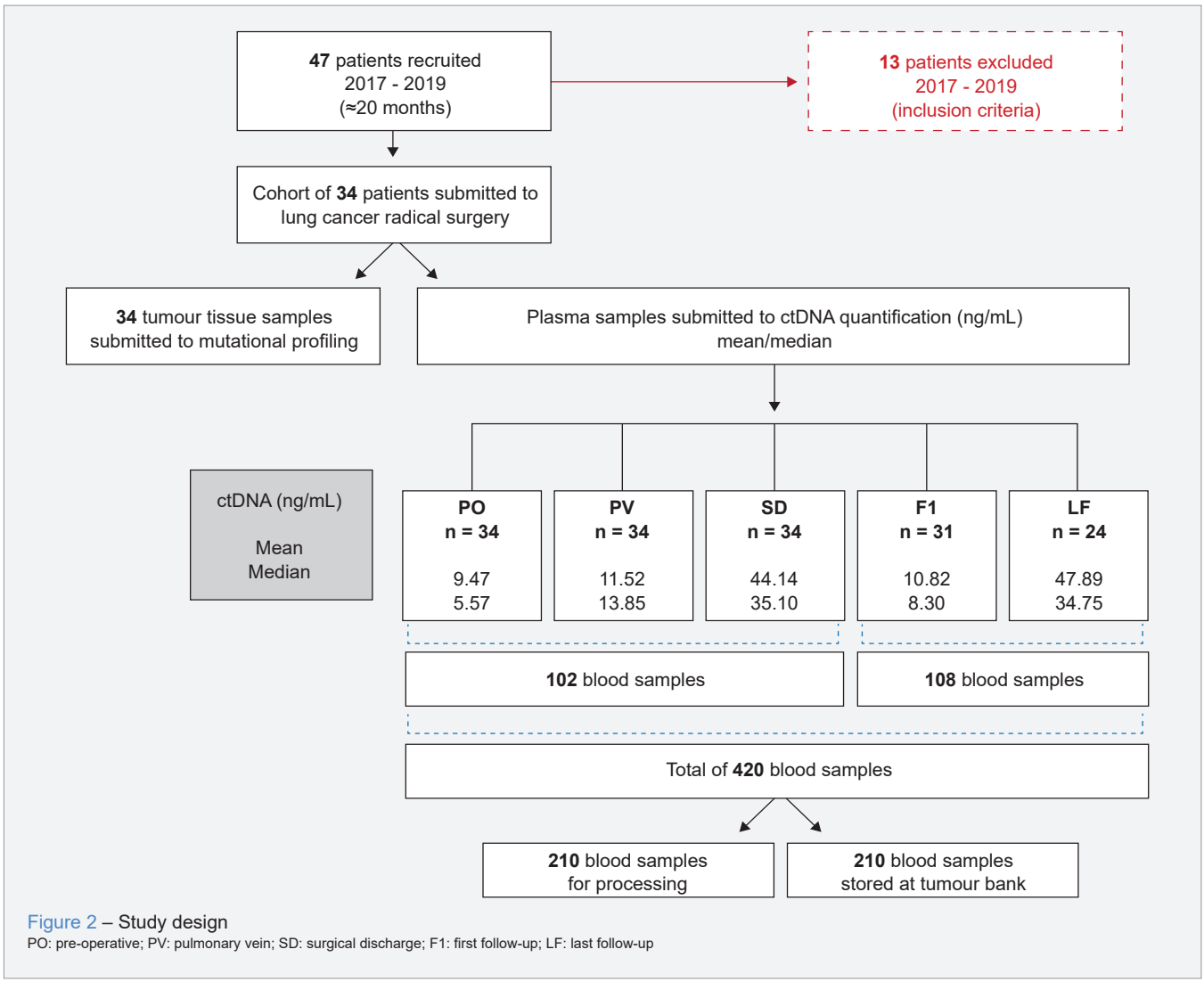

Figure 2 – Study design
PO: pre-operative; PV: pulmonary vein; SD: surgical discharge; F1: first follow-up; LF: last follow-up

models were developed to estimate the effect of the four categorical variables (age, sex, smoking status, tumor size) in ctDNA concentration during each specific data collection time point. Additionally, we created a linear regression model with the same equation and repeated measurements to consider all time points in the same analysis. In order to account for the potential effect of outliers in all models, we used a robust estimator of the effects instead of a model-based estimator.

Molecular relapse ctDNA progression was defined as the quantity of ctDNA (ng/mL) present in the plasma samples at the last follow-up greater than at surgical discharge. Imaging features of relapse were defined according to the comparative assessment of the last CT evaluation and the CT performed after surgery.

RESULTS

Clinicopathological characteristics

Over 20 months, 47 patients were assessed for eligibility in this study, starting on May 29, 2017 until January 28, 2019. Thirteen patients were excluded according to inclusion criteria (Fig. 2). This cohort of patients included 34 patients, 15 of the female sex (44.12%) and 19 of the male sex (55.88%), with a median age at diagnosis of 64.5 years, with an interval between 50 and 79 years of age. The mean follow-up time was 699.88 days, and the median follow-up time was 809.50 days (range: 3 to 1337 days).

Concerning smoking habits, 13 were non-smokers (38.23%), and 21 were former and active smokers (61.77%). According to the clinical stage of the tumor in question, we observed that cT1N0M0 was the predominant stage with twenty-one patients included (55.2%), from a cohort of 34 patients. Surgically, one patient

underwent left pneumectomy, three bilobectomy, and thirty patients with lobectomy and mediastinal lymph node emptying in all cases. According to the pathological stage of the 32 naive patients, 20 patients presented with stage I (62.5%), 11 patients with stage II patients (34.37%), and one patient with stage III (3.13%). Two patients underwent neoadjuvant therapy followed by surgery, one staged as ypT3N0M0R1 and the second one as ypT0N2M0R0. Twenty-seven patients had a diagnosis of adenocarcinoma (79.41%), six had a diagnosis of squamous cell carcinoma (17.65%), and one patient was diagnosed with large cell neuroendocrine carcinoma and adenocarcinoma (mixed pattern) (2.94 %). Concerning the prognostic factors, the following were considered: venous (V), lymphatic (L), perineural invasion (PN), invasion of the visceral pleura (VP) and residual tumor resection margin (R). The 34 patients presented the following results: ten patients with no prognostic factors (29.41%), five patients with one factor (14.71%), nine patients with two factors (26.47%), and ten patients with three prognostic factors (29.41%).

Table 1 – Patients' clinical features

Variable	n = 34 (%)
Sex	
Female	15 (44.12)
Male	19 (55.88)
Age (years)	
Median	64.5
Range	50 to 79
Smoking status	
Non-smoker	13 (38.23)
Former & active smoker	21 (61.77)
Type of Surgery & mediastinal lymph node emptying	
Pneumectomy	1 (2.94)
Bilobectomy	3 (8.82)
Lobectomy	30 (88.24)
Histology	
Adenocarcinoma	27 (79.41)
Squamous carcinoma	6 (17.65)
Large cell neuroendocrine carcinoma & adenocarcinoma	1 (2.94)
Disease Stage (n = 32)	
I	20 (62.50)
II	11 (33.37)
III	1 (3.13)
ypTNM (n = 2)	
ypT3N0M0R1	1
ypT0N2M0R0	1
Number of Prognostic Factors	
0	10 (29.41)
1	5 (14.71)
2	9 (26.47)
3	10 (29.41)
Type of prognostic factors	
V1	16 (47.05)
L1	16(47.05)
PN1	3 (8.82)
PV1	16(47.05)
R1 (microscopic margins)	2 (5.88)
Post-surgical outcome	
Surveillance	10 (29.41)
Adjuvant chemotherapy	17 (50.00)
Lost in follow-up	7 (20.59)
Outcome	
Alive	30 (88.24)
Died	4 (11.76)
Follow-up (days)	
Mean time	699.88 (3 - 1337)
Median time	809.50 (3 - 1337)

Of the 34 patients included in the study, ten patients stayed under surveillance (29.41%), seventeen patients underwent adjuvant chemotherapy (50.00%) and seven patients were lost in the follow-up (20.59%). Until the last evaluation, four patients died (11.76%) and the remaining are alive. Only one of the patients that died was lost during follow-up. All clinical features can be analyzed in Table 1.

Quantification of ctDNA plasma samples over time

Quantitative differences in ctDNA concentrations obtained from plasma were noted between the preoperative stage (PO), extracted from the pulmonary vein (PV), at surgical discharge (SD), at first follow-up (F1), and last follow-up (LF). The average volume of plasma obtained at surgical discharge was 3.85 mL. The absolute values of ctDNA of the 34 patients obtained overtime and CT last evaluation too [Appendix 1 Table A.1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19487/15190)]. The mean and median molecular follow-up time were 413.8 and 417.0 days (range: 94 to 678 days) respectively. The mean and median imaging follow-up was 764.48 and 834.0 days (range: 150 to 1337 days) respectively.

More ctDNA was shed directly from the tumor bed into the vein that drains blood directly from the tumor when compared to peripheral blood samples obtained before surgery (PV > PO; $p = 0.002$) and a greater increase was observed at surgical discharge when compared to the first two withdrawals (SD > PV and SD > PO; $p = < 0.001$).

At the first follow-up (F1) or baseline assessment, lower ctDNA concentrations were identified when compared to surgical discharge. At surgical discharge (SD), ctDNA concentration when compared with PO, PV, and F1 and the differences were statistically significant ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$ respectively).

At the last follow-up (LF) or during longitudinal monitoring, ctDNA expression increased when compared with PO, PV, and F1 ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$ respectively) (Fig. 3: green lines). No statistically significant differences were observed when comparing the last follow-up to surgical discharge ctDNA expression ($p = 0.851$) and also between the first follow-up and PV or PO (Fig. 3: red lines). Significance values were adjusted using the Bonferroni correction for several tests performed with similar results [Appendix 1 Table A.2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19487/15190)]. The Kruskall–Walli's test results were inferior to 0.001.

The correlation between ctDNA concentration according to five-time points (dependent variables) and the four clinicopathological characteristics (categorical variables): sex, age, smoking status, and tumor size was analyzed. The number of patients included at each collection point and the mean time of blood withdrawal was 34 patients at PO, PV and SD, 31 at F1 and 24 at LF. The mean time of blood withdrawal was 0.0, 0.0, 5.5, 33.65, and 413.8 days respectively.

Patients younger than 70 years had a significant reduction of the concentration of ctDNA at the preoperative and surgical discharge time point [β= -16 734 (-27 707; -5 760); $p = 0.003$; β = -21 785 (-38 447; -5123); $p = 0.010$] with a confidence level of 95%. As opposed to an increase of the concentration of ctDNA at the pulmonary vein and last follow-up time points [β = 8369 (0.359; 16 378); $p = 0.041$; β = 34 402 (12 549; 56 254); $p = 0.002$, with a confidence level of 95%]. The joint model value is β = -9235 (-15 352; -3118); $p = 0.004$ with a confidence level of 95%. The evaluation of ctDNA according to sex, smoking status, and tumor size at all time points was not statistically significant across all collection points as shown in Table 2.

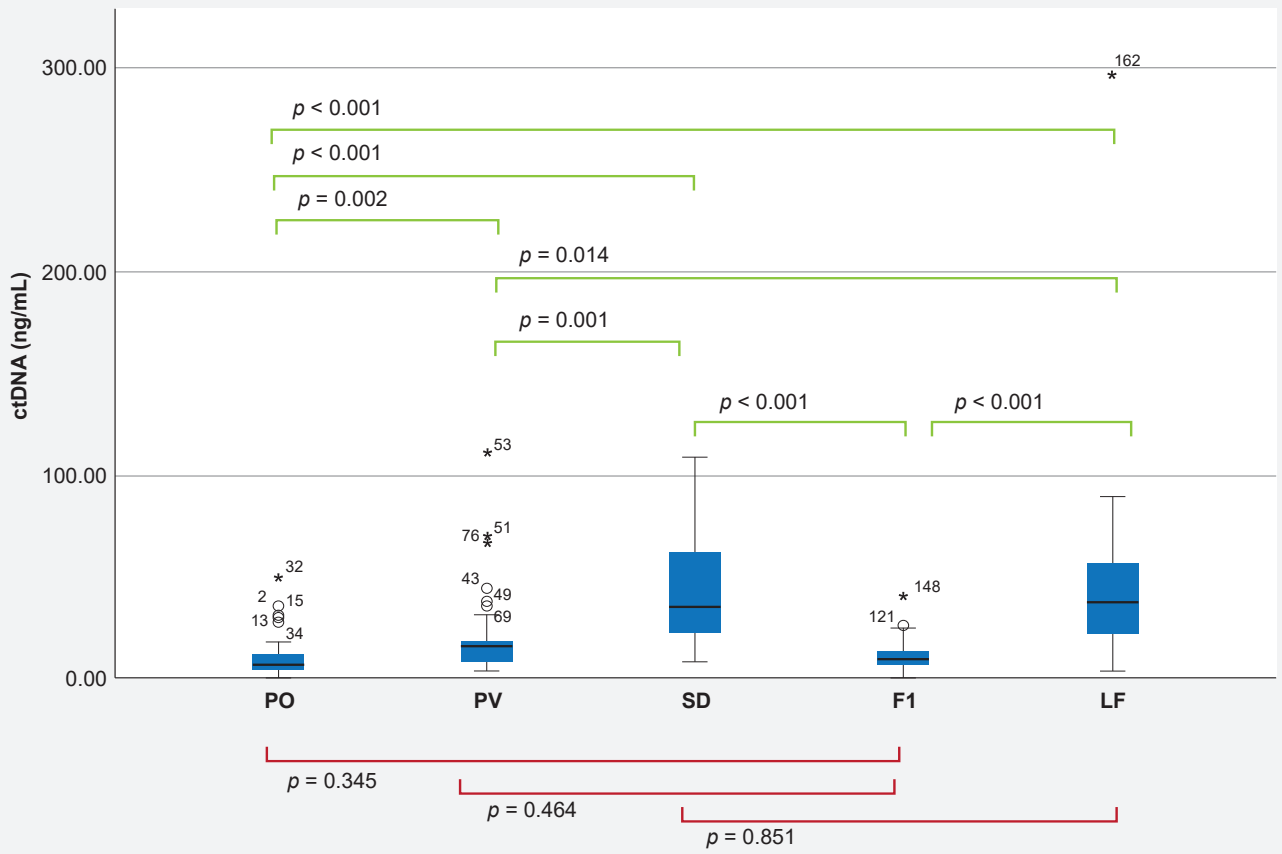

Figure 3 – ctDNA concentration at five time points (p adjusted value)
PO: pre-operative; PV: pulmonary vein; SD: surgical discharge; F1: first follow-up; LF: last follow-up
Green lines: statistical significance. Red lines: not statistically significant.

Table 2 – Statistical analysis of ctDNA evolution according to five time points and clinicopathological features

		PO	PV	SD	F1	LF	Joint model
Age	**< 70 years vs > 70 years**	**β -16.734 IC: -27.707; -5.760 *p* = 0.003**	**β 8.369 IC: 0.359; 6.378 *p* = 0.041**	**β -21.785 IC: -38.447; -5.123 *p* = 0.010**	β -4.920 IC: -12.404; 2.564 *p* = 0.198	**β 34.402 IC: 12.549; 56.254 *p* = 0.002**	**β -9.235 IC: -15.352; -3.118 *p* = 0.004**
Sex	**Female vs Male**	β 1.323 IC: -7.087; 9.732 *p* = 0.758	β -7.579 IC: -17.839 2.681 *p* = 0.148	β 2.485 IC: -22.065; 27.035 *p* = 0.843	β 0.212 IC: -3.951; 4.376 *p* = 0.920	β -15.852 IC: -46.416; 14.712 *p* = 0.309	β 1.316 IC: -3.827; 6.458 *p* = 0.609
Smoking status	**Non-smoker vs Active & former smoker**	β -5.228 IC: -13.771; 3.314 *p* = 0.230	β 8.468 IC: -3.043; 19.978 *p* = 0.149	β 17.137 IC: -7.049; 41.322 *p* = 0.165	β -3.320 IC: -6.968; 0.329 *p* = 0.075	β -7.628 IC: -26.455; 11.200 *p* = 0.427	β -4.480 IC: -9.767; 0.807 *p* = 0.095
Tumour size	**T1 ≤ 3cm vs T2 > 3cm**	β -0.388 IC: -7.174; 6.399 *p* = 0.911	β 7.443 IC: -1.007; 15.893 *p* = 0.084	β -18.505 IC: -42.897; 5.887 *p* = 0.137	β 1.520 IC: -3.739; 6.779 *p* = 0.571	β -5.313 IC: -52.750; 42.124 *p* = 0.826	β 0.738 IC: -4.760; 6.236 *p* = 0.788

PO: pre-operative; PV: pulmonary vein; SD: surgical discharge; F1: first follow-up; LF: last follow-up

Tumor mutational profile

Of the 34 patients, only 29 patients had appropriate tumor samples for mutational profiling through the NGS technique. Several mutations and different associations were identified. The allelic frequency was evaluated. Five samples were not processed for technical issues [Appendix Table A.3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19487/15190)].

Within each tumor, the mutational profile in each tumor sample was determined by the allele frequency. The most predominant mutations were *TP53* and *KRAS* with 30.8% and 34.6%, followed by *EGFR* with 19.2% mutations. Other mutations such as *MET*, *BRAF*, *PIK3CA* and *MPL* were also identified. Three tumor samples showed translocations (EML4-ALK.E13A20).

Correlation of mutational profile of ctDNA from blood samples with tumor samples

Of the 34 patients, only 26 had appropriate ctDNA from blood samples at surgical discharge, where quantitative ctDNA expression was greatest, for mutational profiling. By NGS, no somatic mutations were identified at surgical discharge from the 26 patients.

Because of these results, only blood samples where actionable mutations were detected in tumor tissue were subjected to sequencing analysis at the pre-operative stage, from the pulmonary vein, at surgical discharge and last follow-up. These were cross-checked with the tumor mutational profile. The allelic frequency was evaluated for each one.

We performed NGS of liquid biopsies in cases where actionable mutations in *EGFR* and *BRAF* were identified in tissue biopsies. We found the expected mutation in five out of six patients at the pre-operative time point and in two out of six at the pulmonary vein time point. The mutation allele fraction detected was always very low in the range of 0.1% to 0.2%. During surveillance, two out of six patients showed imaging progression on days 828 and 724 as shown in Table 3.

DISCUSSION

The initial findings of this study led us to understand the differences in expression of ctDNA concentration over time, at specific time points, which is particularly relevant during the first week post-surgery.

According to the literature, the volume of plasma extracted is important so that a successful amount of ctDNA can be extracted. According to Crowley *et al*, the most frequently used protocols to obtain ctDNA required approximately 1 mL of plasma (3 mL of blood).[18] In the studies by Veldore and and Messaoudi a mean average of approximately 10 mL of plasma volume was required to increase analytical sensitivity.[17,19] However, no standard collection volume has been established. At surgical discharge, our samples had a mean of 3.85 mL of plasma like in the study by Gale *et al*.[20]

Regarding ctDNA concentration at surgical discharge, higher concentrations of ctDNA were observed due to surgery where more ctDNA was shed resulting from post-surgical trauma as observed in the study by Abbosh.[21] The mean time for blood withdrawal was 5.5 days (range: 4 - 12 days) in our study when compared to the study by Abbosh where plasma samples were collected two to five days after surgery.

At the first follow-up (F1) or a landmark time point, a lower concentration

Table 3 – Tumor and ctDNA samples with actionable mutation (n = 6)

Patient #	Tumour sample AF (%) Mutated gene AA change	NGS PO AF (%) ctDNA (ng/mL) days	NGS PV AF (%) ctDNA (ng/mL) days	NGS SD AF (%) ctDNA (ng/mL) days	NGS LF AF (%) ctDNA (ng/mL) days	Imageology progression CT scan days
#6	27.0 *EGFR* p.Asp770delinsGlyTyr	0.1 9.8 0	Negative 44.0 0	Negative 48.9 5	Negative 57.1 499	**Positive** **828**
#14	55.8 *EGFR* p.Leu747_Pro753delinsSer	**0.2** 2.3 0	**0.1** 7.0 0	Negative 16.6 7	Negative 17.8 447	**Positive** **724**
#21	20.0 *BRAF* p.Val600Glu	Negative 6.4 0	Negative 10.8 0	Negative 31.1 5	Negative 5.6 29	Negative
#28	9.7 *EGFR* p.Leu858Arg	**0.1** 4.2 0	Negative 4.2 0	Negative 12.2 4	Negative 62.13 312	Negative
#29	8.1 *EGFR* p.Leu747_Ala750delinsPro	**0.1** 3.6 0	**0.1** 10.2 0	Negative 14.9 5	Negative 10.9 22	Negative
#34	30.6 *EGFR* p.Leu747_Ala750delinsPro	**0.1** 49.2 0	Negative 16.3 0	Negative 108.0 8	Negative 11.9 109	Negative

PO: pre-operative; PV: pulmonary vein; SD: surgical discharge; ctDNA: circulating tumour DNA; AA: amino acid; AF: allele frequency; CT: computed tomography

of ctDNA was detected when compared to SD and LF (Fig. 3), at a mean of 33.65 days (range: 17 to 109 days). At this point, however, the results could not be affected by surgical trauma. This was also observed in the study by Chaudhuri[22] where blood was collected within four months of treatment completion, and one month after surgery according to the studies by Zang and Li.[23,24] At F1, a smaller interquartile amplitude was observed as well as at the PO and PV data collection points as confirmed in Fig. 3. The first follow-up is probably the best time to consider ctDNA post-surgery samples, as a prognostic biomarker of early-stage lung cancer.

Nevertheless, the patients that showed an increase of ctDNA at the last follow-up or during longitudinal monitoring at a mean of 413.8 days (range: 94 to 678 days) [Appendix 1, Table A.1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19487/15190)], were those that eventually corresponded to the concept of molecular progression, or as a negative predictive biomarker of response to curative surgery. These results reflect those observed in the study by Chaudhuri, where samples were collected every 60 to 180 days after curative-intent treatment.[22] During the last follow-up, these patients did not suffer surgical trauma or other traumatic interventions which could induce the release of ctDNA into circulation. The best probable timing to consider withdrawing blood samples for ctDNA quantification post-surgery is during intermediate time points until the last follow-up, where seven patients showed molecular relapse and CT progression [Appendix 1, Table A.1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19487/15190)]. The ctDNA concentration at LF may be considered a predictive biomarker of tumor recurrence after curative surgical treatment. When comparing F1 with PV and PO, no statistically significant differences were found, neither between LF and SD; probably due to the expression of ctDNA, at each time point (Fig. 3; red lines). In between these, statistically significant differences were found as shown in Fig. 3 (green lines).

Considering the different time points, a greater tendency of expressing ctDNA with statistical significance was found in patients older than 70 years, as expected due to biological factors such as DNA damage over time and shortening telomeres, or in other words, physiological aging.[25,26]

As described in the literature, approximately 53% of lung cancer cases occur in individuals between 55 to 74 years old and 37% occur in individuals over 75 years old, with the median age at diagnosis being 70 years old.[26] This justifies the age cut-off considered in this study. Our cohort of patients had a median age at diagnosis of 64.5 years, with an interval between 50 and 79 years of age. The increase of ctDNA concentration favoring patients younger than 70 years from the pulmonary vein time-point can be physiologically justified considering the tumoral drainage area. Although the median age of these patients at pulmonary vein time-point (n = 34) and at the last follow-up

(n = 24) was, respectively, 64.5 years and 62.5 years, this could eventually support the increase of ctDNA concentration favoring patients younger than 70 years.

Moreover, the mutational profile analysis was performed through the NGS technique in tissue and plasma samples at surgical discharge where quantitative expression of ctDNA was greatest. Mutated allelic frequency (MAF) is the best way to evaluate ctDNA over time. MAF is important when facing two oncogenic driver mutations, mutations that are responsible for initiation of cancer, helping to define the predominant one, namely which one is leading to progression. Regarding the study by Veldoure *et al*, a concordance with an accuracy of 96.97% was observed between the mutational profile of tissue and plasma samples through allele-specific real-time PCR and NGS techniques.[4]

Although surgery offers the best chance of cure from early-stage non-small cell lung cancer, which corresponds to approximately 16% of all lung cancer patients[4], many patients still suffer from recurrent disease which is thought to be due to the presence of minimal or molecular residual disease. Today's standard of care as postoperative adjuvant treatment for completely resected stage I-III NSCLC is platinum doublet chemotherapy which results in a 5% increase in 5-year survival.[27] On the other hand, 95% of patients are either those whose disease cannot be cured by the adjuvant treatment or those who are cured by surgery alone and thus do not require adjuvant therapy. Considering resected epidermal growth factor receptor (EGFR) mutated NSCLC patients', a recent meta-analysis has shown improved disease-free survival and a nonsignificant improvement in overall survival, in patients who received adjuvant EGFR inhibitors after curative surgery compared to those who received chemotherapy or no further treatment.[28] As well as other recent studies, it was demonstrated that after chemoradiotherapy, patients with detectable ctDNA had better outcomes when treated with immune checkpoint inhibitors than those with undetectable ctDNA following chemoradiotherapy regardless of further immunotherapy.[29] The importance of these observations highlights the importance of clinicians escalating or de-escalating therapy according to ctDNA expression after curative treatment.

In our pilot study, mutational profile concordance was not observed at the SD time point and was only observed at the PO and PV time points (with the PO time-point being the one offering the highest sensitivity). This may be justified by the extremely low mutated allelic frequency detected and by its proximity to the sensitivity threshold detection level of NGS.

Despite the limited number of cases, the results observed showed that, even in situations of early-stage lung cancer there is ctDNA identifiable by NGS from the liquid biopsy. The clinical relevance of this observation is still unclear. However, these results should strongly encourage research using non-invasive methods to identify the risk of recurrent tumors after surgery with curative intent, select the optimal adjuvant treatment for each lung cancer patient, minimize toxicity, and improve quality of life and survival. Our study supports the idea that MP concordance may predict the risk of recurrence in resected tumors as later confirmed in CT scan progression in two out of the six patients, and as also shown in recent studies. ctDNA longitudinal analysis appears to be a pioneering model to dynamically predict recurrence in a setting characterized by economic and tissue availability constraints.[21,22,27]

Several limitations of our study should be acknowledged, namely that a cohort of 34 patients with early-stage LC underwent curative surgical treatment and no control arm was contemplated. A validation study will be necessary to confirm these preliminary results. The viability of the analysis was compromised due to the sample size (210 plasma samples and 24 out of 34 patients with plasma samples at LF), which may justify the low amount of statistically significant results obtained over time. The need for rapid processing creates logistic challenges and the potential for preanalytical variability caused by fluctuations in ctDNA concentration and purity due to differences in processing times. Consequently, samples were excluded from a rigid teamwork scheme under high observation. This study is part of our plan to establish and implement protocols for transposing molecular genetic knowledge and techniques from bench to clinical practice in the medium-term.

CONCLUSION

Our results suggest that the quantitative expression of ctDNA is greatest at surgical discharge and at last the follow-up time point; its' decline at the first follow-up time point is likely due to the elimination of ctDNA post-surgical injury, and this is probably the best timing to consider the value of ctDNA as a prognostic biomarker of early-stage LC.

ACKNOWLEDGEMENTS

We acknowledge the work of the members of the department of Cardiothoracic Surgery and Pulmonology, especially all doctors, nurses and technicians involved, as well as all the collaboration of the patients and their relatives. We would like to thank the Portuguese Foundation for Science and Technology (FCT-Portugal) for the Strategic project "Institute for Research and Innovation in Health Sciences" (POCI-01-0145-FEDER-007274).

AUTHOR CONTRIBUTIONS

JEM: Study design, data collection and analysis, writing of the manuscript.

TTG, JCM, VH: Supervision and critical review.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Parental Perception of Their Child's Weight Status in Portugal: An Observational Study

Perceção do Peso dos Filhos em Portugal: Um Estudo Observacional

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Acta Med Port 2024 Jan;37(1):20-26 ▪ https://doi.org/10.20344/amp.19510

ABSTRACT

Introduction: Parental perceptions of a child's weight status may influence family readiness to foster healthy behaviors. Our aim was to observe parental perceptions of their child's weight status in two time periods and in multiple population subgroups.

Methods: Data were collected in two national projects, 2009 - 2010 (n = 6577) and 2016 - 2017 (n = 7594), in public and private kindergartens and primary schools in Portugal (children aged three to 10 years old). Parents filled out a questionnaire regarding their perception of their child's weight status, namely: 1) too thin, 2) thin, 3) normal weight, 4) with some excess weight, or 5) with a lot of excess weight. Children's height and weight were objectively collected, and the International Obesity Task Force cut-offs were used to classify overweight and obesity. Accurate and misclassification levels were calculated for children according to their sex, age, as well as child and parental weight status, while considering differences within and between the two time periods.

Results: Overall, accuracy in parental perception of their child's weight was higher in 2016 - 2017 than in 2009 - 2010, regardless of children's sex, age, parental weight status, and education (65.7% and 60.5%, respectively). However, the ability of parents to detect obesity was ~ 50% lower in 2016 - 2017 compared with 2009 - 2010.

Conclusion: Even though parental perception of their child's weight was better in 2016 - 2017 than in 2009 - 2010 , the inverse result was found among children with obesity. Strategies are needed to encourage parents to improve their perception of the appropriate weight for their child.

Keywords: Child; Overweight; Parents; Pediatric Obesity

RESUMO

Introdução: A perceção que os pais têm do peso dos filhos pode influenciar a adoção de comportamentos saudáveis. O objetivo deste trabalho foi observar a perceção que os pais têm do peso dos filhos em dois períodos (2009 - 2010 e 2016 - 2017) e em vários subgrupos da população.

Métodos: Os dados foram recolhidos no âmbito de dois projetos nacionais (2009 - 2010: n = 6577; 2016 - 2017: n = 7594), em infantários e escolas primárias, públicas e privadas, em Portugal continental (crianças entre os três e os 10 anos). Através de um questionário, os pais descreveram os filhos em relação ao peso atual: 1) muito magro, 2) magro, 3) normal, 4) com algum peso a mais, ou 5) com muito peso em excesso. A altura e o peso das crianças foram recolhidos objetivamente e os pontos de corte da *International Obesity Task Force* foram usados para classificar o estado nutricional da criança. A acuidade da perceção parental foi calculada de acordo com o sexo, a idade, e o peso da criança, assim como com o peso dos pais; as diferenças entre os dois períodos foram registadas.

Resultados: No geral, a acuidade da perceção que os pais têm do peso dos filhos foi maior em 2016 - 2017 do que em 2009 - 2010, independentemente do sexo e idade da criança, e do estado nutricional e nível educacional dos pais (65,7% e 60,5%, respetivamente). No entanto, a perceção de obesidade nas crianças foi cerca de 50% mais baixa em 2016 - 2017 do que em 2009 - 2010.

Conclusão: Este estudo mostrou uma acuidade da perceção do peso maior em 2016 - 2017 do que em 2009 - 2010, contudo, o contrário verificou-se em crianças com obesidade. São necessárias estratégias para ajudar os pais a melhorarem a perceção do peso adequado para os seus filhos.

Palavras-chave: Criança; Excesso de Peso; Obesidade Pediátrica; Pais

INTRODUCTION

Childhood obesity remains a global public health issue, including in Portugal, where one in three children is overweight or obese.[1] A declining trend has been found, but it is not consistent in all the population [e.g., individuals with lower socioeconomic status (SES)].[2] Although identified as a global health priority, tremendous challenges remain in connecting the dots between when and where to intervene.[3] This is of concern since childhood obesity is associated with multiple poor physical and psychological outcomes.[4]

The causes of childhood obesity are complex and include the interplay of individual, social, and environmental factors. Effective strategies to tackle child obesity have been on the public agenda in many countries throughout the last few decades, including the promotion of a healthy lifestyle. However, while raising awareness among parents regarding childhood obesity, those public health strategies do not appear to have had an impact on the identification of excess weight by parents in their own children.[5] High rates of

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Recebido/*Received*: 20/12/2022 - **Aceite/*Accepted*:** 10/05/2023 - **Publicado *Online*/*Published Online*:** 26/06/2023 - **Publicado/*Published*:** 03/01/2024

parental underestimation of children's weight have been reported in many international studies.[6,7] This underestimation is somewhat consistent in children with excess weight, but varying results have been found to be associated with children's sex, age, and family socioeconomic status.[5,8]

Parental perception of their children's weight plays an important role in obesity prevention and treatment since the family needs to be willing, able, and ready to make the necessary lifestyle changes (e.g., healthy eating habits, higher physical activity levels) and ultimately seek treatment for obesity.[9] The aim of this study was to observe and compare the accuracy of parental perceptions of their child's weight status in 2009 and 2016 and to identify possible shifts in parental misperception in different subpopulation groups.

METHODS

Study design and sampling

Repeated cross-sectional studies were conducted in 2009 - 2010 and in 2016 - 2017, using a nationally representative sample of Portuguese children. More details are available elsewhere.[2] Briefly, in 2009 - 2010 the sampling was based on a stratified random design that accounted for the number of children by age (three to 10 years) and sex. Schools were randomly selected in the Porto, Coimbra and Lisbon districts, and all the students were invited to participate. In 2016 - 2017, three to 10-year-old children from the 118 schools participating in the 2009 - 2010 study were included. The participation rate was 57.4% and 61.4% in 2009 - 2010 and 2016 - 2017, respectively.

Ethics approval

The 2009 - 2010 study protocol was approved by the Portuguese Committee for Data Protection, which requires anonymity and non-transmissibility of data, as corroborated by the Direção-Geral de Inovação e Desenvolvimento Curricular (DGIDC). In 2016 - 2017, the study was approved by Direcção Geral do Ensino (Portuguese Ministry of Education) and Comissão Nacional de Proteção de Dados (CNPD, the Portuguese Data Protection Authority; authorization number 745/2017). All procedures were in accordance with the guidelines laid down in the Declaration of Helsinki of 1975, revised in Hong Kong 1989. Prior to data collection, written informed consent was obtained from the children's parents.

Inclusion criteria

Children between the ages of 3.0 and 10.9 years from the three aforementioned Portuguese districts, with complete information on height, weight, and parental perception of their child's weight.

Measures

Paternal education, with the scoring based on the Portuguese Education system and categorized as low (nine or less years of completed schooling), medium (10 - 12 years), and high (university degree), was used as a proxy measure of SES. Parental self-reported weight and height were used to calculate body mass index (BMI); the WHO definitions were used to classify parental weight categories.

Parents were also asked about their child's weight status ("Do you consider (the child) now to be too thin, thin, normal weight, with some excess weight, or with a lot of excess weight?"). Staff trained in standard anthropometric methods measured children's height and weight at school using calibrated equipment. BMI was calculated and categorized according to the International Obesity Task Force (IOTF).[10] The perceived classification of children's weight status was classified as accurate if: underweight children were classified as 'too thin' or 'thin'; normal weight children were classified as 'normal weight'; overweight children were classified as 'with some excess weight'; and children with obesity were classified as 'with a lot of excess weight'.

Parental underestimation of their child's weight status was observed in the following cases: children with normal weight were perceived as 'too thin' or 'thin'; overweight children were perceived as 'too thin', 'thin' or 'normal weight'; and children with obesity were perceived as 'too thin', 'thin', 'normal weight' or 'with some excess weight'. Parental overestimation of their child's weight status was considered if: children with underweight were perceived as 'normal weight', 'with some excess weight' or 'with a lot of excess weight'; children with normal weight were perceived as 'with some excess weight' or 'with a lot of excess weight'; and overweight children were perceived as 'with a lot of excess weight'.

Statistical analysis

Children's weight status and parental perceived weight status were estimated for each time period. The agreement between the parental perception and the real weight of the child was assessed by the Cohen kappa coefficient. Accurate and misclassification levels were calculated according to children's sex, age, and weight status, as well as parental weight status, and family SES. The Chi-squared (χ^2) distribution was used to determine differences within and between the time periods. Analyses were performed in SPSS Statistics® for Windows®, v.27.

RESULTS

The final sample was made up of 14 171 children (7043, 49.7% boys); 6577 in 2009 - 2010 and 7594 children in 2016 - 2017 (Table 1). Children's weight status differed significantly between periods, with a lower prevalence rate of

overweight and obesity in 2016 - 2017 than in 2009 - 2010, while more underweight children were observed in 2016 - 2017 than in 2009 - 2010 ($p < 0.001$).

There were statistically significant differences between children's weight status (IOTF classification) and parental perception. In 2009 - 2010, there was a slight agreement between the two measures, $K = 0.19$ (95% CI: 0.17 to 0.21), $p < 0.001$; in 2016 - 2017, the agreement between the two categorizations was fair, with $K = 0.24$ (95% CI: 0.22 to 0.26), $p < 0.001$. In both periods, the lowest agreement was found in children with obesity, followed by overweight children (Table 1 and Fig. 1).

There were no statistically significant differences in parental weight perception according to the children's sex. However, in 2016 - 2017, underestimation was significantly more prevalent in older children than in younger children. Underestimation was also significantly more common in children of lower SES and among children of overweight or obese parents. Moreover, parental underestimation of their child's weight was more common if the child was overweight or obese (Table 1).

Most parents (75.8% in 2009 - 2010; 78.9% in 2016 - 2017) were able to accurately assess their child's weight if the child fell in the normal weight category; however, that number decreased to 26.9% (2009 - 2010) and 28.6% (2016 - 2017) in children with overweight, and to 8.5% (2009 - 2010) and 4.3% (2016 - 2017) in children with obesity. Parental report of their children having 'a lot of excess weight' (i.e., obesity) was more prevalent in children with the most severe form of obesity (i.e., IOTF BMI ≥ 35) compared with children with obesity but whose BMI was between 30 and 35, both in 2009 - 2010 (20.4% *vs* 3.8%) and in 2016 - 2017 (9.8% *vs* 2.5%) (Fig. 1).

The overall accuracy to estimate children's weight status was higher in 2016 – 2017, particularly among mothers with obesity (+ 11.4%) followed by fathers with obesity (+ 7.8%). However, the inverse result was found considering parental ability to accurately perceive obesity among their children (Table 1).

DISCUSSION

This study highlights two different results, namely: 1) while the incidence of childhood obesity declined between the samples, the inability of parents to detect obesity declined, and 2) although the accuracy in the parental perception of their child's weight was better in 2016 - 2017 than in 2009 - 2010, this was not true for children with obesity. This is worrying since underestimating obesity is more detrimental than underestimating normal weight or overweight, theoretically and practically.

The results point to a plateau in overweight and obesity prevalence, similar to what has been reported before in Portugal[2] and other developed countries.[1] Our findings also show that the majority of parents considered their child to be of average weight (71.2%), and few parents rated their child as having overweight or obesity (10.6%), even though almost one in four children were classified as having overweight or obesity for their age and sex. Underestimation was particularly high in children with obesity (95.7%). These findings support previous research which found that many parents are incapable of recognizing their child's weight status.[6,8,11] A study considering 22 European countries found parental underestimation levels of 82.3% and 93.8% in the overweight and obesity categories, respectively.[7] In Portugal, previous data shows that one in three parents misperceive their child's weight, of which 93% underestimate it.[12]

This is perhaps not surprising given that many adults are unable to recognize overweight in themselves,[13] but the reasons for the lack of recognition of childhood overweight and obesity remain unclear. It may be difficult for parents to understand what obesity is because children are continuously experiencing changes in body composition and size. Moreover, the definition of overweight and obesity may be confusing to parents because it has shifted over time and is different among various healthcare professional organizations.[14] Parents may also be reluctant to admit that their child had 'a lot of excess weight' because of social pressure to maintain a lower weight and/or the stigma often attached to obesity. Furthermore, parents who live with their children daily normally do not notice or have the perception of real body changes as they are used to seeing them every day. The social comparison hypothesis or societal forces might also help explain our findings: 1) parents will compare their child to peers or friends of their child; hence, with childhood obesity becoming increasingly common, some excess weight may go unnoticed by many parents, or the socially accepted ideal body weight may also be shifting accordingly; 2) parents will experience external pressures such as the ones conveyed by the media, which may be focusing on the severely obese only and consequently may distort the parents' understanding of what qualifies as 'obesity'.

We found that children with obesity were less likely to be correctly identified in the recent survey compared with peers of similar weight who were surveyed six to seven years earlier. Similar results were reported for children in the USA for data collected in 1988 - 1994 and 2005 - 2010.[15,16] Inversely, another study carried out among North American children observed that parental perceptions of children with overweight and obesity remained stable between 2005 and 2014.[14] In the Netherlands, 3.7% of parents improved (without statistical significance) their perception of their overweight child between 2009 and 2013.[17] Cultural models and standards of beauty that can vary among different cultures, or gender differences such as social expectations of boys'

Table 1 – Parental perceptions of the weight status of their child, according to sex, age, SES and weight status (defined by the International Obesity Task Force criteria) in 2009 - 2010 and 2016 - 2017

		2009 - 2010 – Parental Perception				2016 - 2017 – Parental Perception				χ^2, *p*-value[a]
		n (%)	Accurate	Overestimate	Underestimate	n (%)	Accurate	Overestimate	Underestimate	
Sex	Boys	3217 (48.9)	59.8	2.0	38.2	3826 (50.4)	66.6	2.5	31.0	40.62 (2), $p < 0.001$
	Girls	3360 (51.1)	61.1	2.3	36.6	3768 (49.6)	64.9	2.8	32.3	15.46 (2), $p < 0.001$
	χ^2, *p*-value[b]			2.27 (2), $p = 0.32$				2.95 (2), $p = 0.23$		
Age	3 - 5 years	2060 (31.3)	62.0	2.2	35.7	2177 (28.7)	69.3	3.0	27.7	32.93 (2), $p < 0.001$
	6 - 10 years	4517 (68.7)	59.8	2.1	38.1	5417 (71.3)	64.3	2.5	33.2	26.06 (2), $p < 0.001$
	χ^2, *p*-value[b]			3.42 (2), $p = 0.18$				22.97 (2), $p < 0.001$		
SES	Low	1734 (26.6)	55.6	2.2	42.2	905 (12.0)	62.2	2.8	35.0	13.04 (2), $p = 0.00$
	Medium	1878 (28.8)	60.8	2.1	37.2	2564 (34.0)	63.8	2.9	33.3	9.17 (2), $p = 0.01$
	High	2898 (44.5)	63.5	2.2	34.3	4066 (54.0)	67.7	2.5	29.8	16.36 (2), $p = 0.00$
	χ^2, *p*-value[b]			29.34 (4), $p < 0.001$				16.44 (4), $p = 0.00$		
Child Weight Status	Underweight	211 (3.2)	62.1	37.9	NA	415 (5.5)	64.6	35.4	NA	0.38 (1), $p = 0.54$
	Normal weight	4547 (69.1)	75.8	1.3	22.9	5510 (72.6)	78.9	0.9	20.2	14.89 (2), $p = 0.00$
	Overweight	1336 (20.3)	26.9	0.3	72.8	1246 (16.4)	28.6	0.3	71.1	0.87 (2), $p = 0.65$
	Obesity	483 (7.3)	8.5	NA	91.5	423 (5.6)	4.3	NA	95.7	6.64 (1), $p = 0.01$
	χ^2, *p*-value[b]			3107.68 (6), $p < 0.001$				3959.00 (6), $p < 0.001$		
Father Weight Status	Normal weight	2345 (42.9)	64.0	2.8	33.2	2553 (40.6)	69.5	2.6	27.8	17.14 (2), $p < 0.001$
	Overweight	2486 (45.5)	59.8	1.9	38.3	2899 (46.1)	64.4	2.8	32.7	20.85 (2), $p < 0.001$
	Obesity	637 (11.6)	54.5	1.3	44.3	843 (13.4)	62.3	1.5	36.2	9.45 (2), p = 0.01
	χ^2, *p*-value[b]			35.37 (4), $p < 0.001$				29.90 (4), $p < 0.001$		
Mother Weight Status	Normal weight	4202 (69.5)	63.9	2.2	33.9	4559 (65.6)	68.8	2.9	28.4	33.58 (2), $p < 0.001$
	Overweight	1342 (22.2)	55.8	2.2	42.0	1716 (24.7)	62.8	2.5	34.7	17.04 (2), $p < 0.001$
	Obesity	500 (8.3)	44.8	2.2	53.0	678 (9.8)	56.2	1.3	42.5	15.35 (2), $p < 0.001$
	χ^2, *p*-value[b]			86.87 (4), $p < 0.001$				69.45 (4), $p < 0.001$		
Total		6577 (100.0)	60.5	2.1	37.4	7594 (100.0)	65.7	2.6	31.6	52.61 (2), $p < 0.001$

[a]: Differences between 2009 - 2010 and 2016 - 2017; [b]: Differences between subgroup categories within each period; SES: socioeconomic status defined by parental education level; Child weight status calculated by the IOTF cut-off points

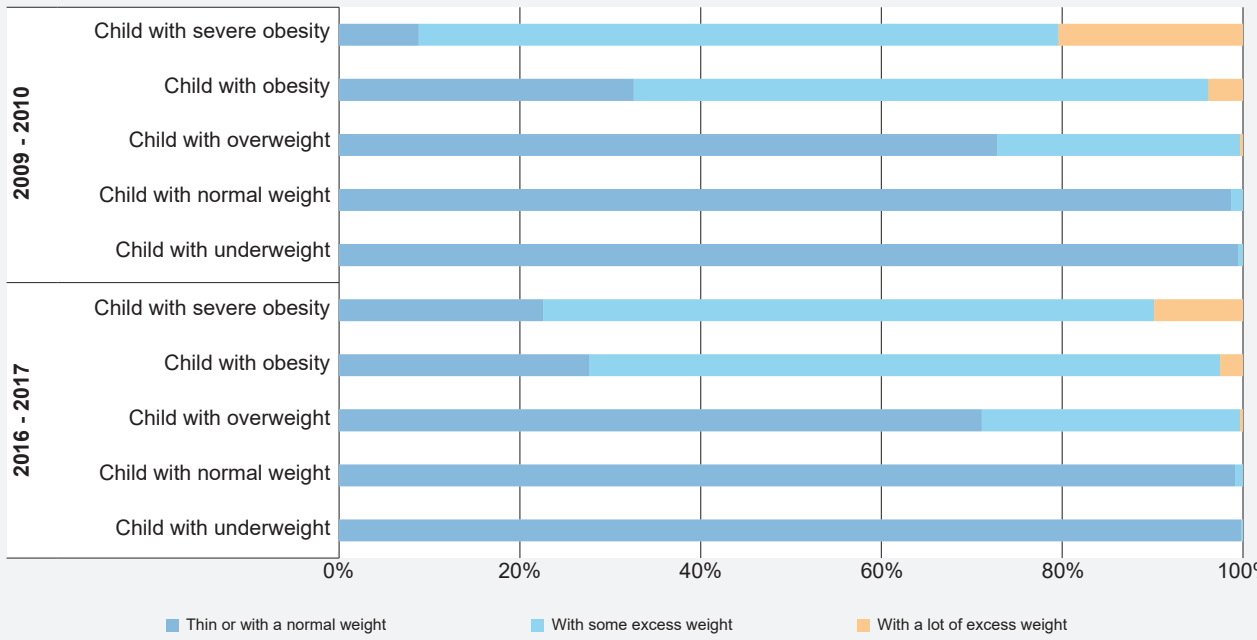

Figure 1 – Cross-prevalence of parental perception of their child's weight and children's weight status (IOTF cut-offs) by period (2009 - 2010 *vs* 2016 - 2017).

and girls' body size and shape, may also explain the different results across studies. Samples may also vary in age. Moreover, the use of different cut-off values can lead to different obesity classifications and may cause confusion.[7]

Although growing global awareness of childhood obesity and a larger focus on weight in general, many parents are still unable to identify when their own child is overweight or obese.[5] Preventive strategies to avoid excess weight gain are more likely if parents are concerned their child will be overweight as an adolescent or as an adult, and are not related to parental concern about the current weight of their child.[18] This suggests that many parents may not see overweight during childhood as particularly harmful or may see the excess weight as something that children will 'grow out of'.

Curiously, in the 2016 - 2017 sample, parental perception of their child's weight was significantly more accurate in younger than in older children, which is the inverse of what has been previously reported, including in Portugal.[17,19] This finding is important since overweight and obesity can be prevented and treated more easily in younger children. Conversely, our results followed the same tendency in other characteristics commonly associated with underestimation of the overweight status, namely: parental weight status (higher BMI)[12,20] and parental education levels (lower).[21,22] Qualitative work by McPherson *et al*[23] suggests that parents with a high BMI have been subjected to social stigma and, therefore, are more likely than underweight and healthy weight parents to avoid labels associated with overweight status. Other qualitative studies suggest that low-income mothers often equate being plump (i.e., slightly fat) with being healthy.[24] Interestingly, the child's sex was not associated with underestimating excess weight in our study. A similar result was found in Spain for children aged two to 14 years,[25] while other studies reported an association.[17,19]

Methods to help parents accurately perceive their child's weight and associated health risks are needed. However, many parents tend to classify their child as overweight only when the child is already within the obesity range, when it is more difficult to implement effective weight-related actions. Parental underestimation was found to be a major determinant of childhood obesity in Portugal,[12] which highlights the importance of this study. Schools and healthcare professionals are in an ideal position to take steps to remedy the self- and parental misperceptions concerning children's weight status, to educate and support parents and children about the complexity of obesity, and to address the modifiable risk factors, such as dietary habits and physical activity. But these actions should be implemented early to avoid children becoming overweight.

Several factors limit our analysis. First, the repeated cross-sectional study design was observational and therefore did not allow causal direction assessment. While observations from different survey years are instructive for

overall trends, more than two assessments may be necessary to evaluate generational shifting. Second, the wording of the question and variables on the questionnaire (e.g., 'with some excess weight'; 'with a lot of excess weight') may have led some parents to misperceive their child's weight status due to subjective interpretations and internalized weight bias. Moreover, the interpretation of 'normal weight' may be influenced by parents' weight status, peers' weight status, and media exposure. Third, a single question about perceived child weight was used rather than a silhouette rating scale, which may increase misperception rates. Studies using pictorial assessment methods for parents to visualize result in a slightly less underestimation of overweight/obesity.[19] However, the question allowed parents to classify children as being only mildly different from normal weight, thus increasing the likelihood of correct classification. Fourth, the study may have limited generalizability because of the sampling method used. Our findings cannot represent children and families from outside those three districts or living in rural areas. And last, we did not specify the relationship between proxies and children. Mothers may have a stronger influence on a child's lifestyle. However, a recent study showed no differences between fathers and mothers' perceptions of their child's body weight status.[8] Significant strengths include the large sample size (including preschool and school-aged children) and the spectrum of participants (including different socioeconomic levels), which gave us the ability to examine the issue among a diverse range of children. The assessment of transitions in perceptions in different population subgroups consists of interesting findings with important implications. Also, the data on children's height and weight were objectively collected by trained professionals following a standardized protocol. Besides, while child BMI is not the most accurate measure of adiposity, it is highly correlated with more direct measures of adiposity.

CONCLUSION

Overall, parental accuracy in the perception of their children's weight was higher in 2016 - 2017 than in 2009 - 2010; however, weight underestimation remains high (~ 30%) and the ability of parents to detect obesity declined. Strategies should be developed to target parental recognition of their child's weight status, particularly among those with obesity. Given their personal interaction with parents and children, schools and frontline clinical care providers can play a crucial role in promoting and encouraging parental healthy weight perceptions.

ACKNOWLEDGMENTS

We are grateful to all the schools, teachers, parents, and children who participated in the study.

AUTHOR CONTRIBUTIONS

DR: Data analysis and interpretation, writing, review, and approval of the manuscript.

AMMR, AG, HN, MRGS: Data collection, manuscript review and approval.

CP: Obtention of funding, data collection, manuscript review and approval.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

DR was funded by a FCT CEEC grant, REF 2020.03966.CEECIND.

This research was supported by grants FCOMP-01-0124-FEDER-007483 and PTDC/DTP-SAP/1520/2014 from the Portuguese Foundation for Science and Technology (FCT). The funder had no role in this study.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Hábitos Alimentares das Pessoas com Diabetes Mellitus Tipo 2 em Portugal: Um Estudo Transversal

Eating Habits of People with Type 2 Diabetes Mellitus in Portugal: A Cross-Sectional Study

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Acta Med Port 2024 Jan;37(1):27-35 ▪ https://doi.org/10.20344/amp.19738

RESUMO

Introdução: A nutrição é uma área de intervenção na prevenção e gestão da diabetes *mellitus*; por isso, é fulcral promover a capacitação da população para a adoção de hábitos alimentares saudáveis. Ainda que existam alguns estudos nesta área, não se conhecem os principais erros nos hábitos alimentares das pessoas com diabetes em Portugal. Os objetivos deste estudo foram identificar os principais erros nos hábitos alimentares das pessoas com diabetes *mellitus* tipo 2 em Portugal e avaliar a sua relação com variáveis sociodemográficas.

Métodos: Estudo transversal multicêntrico, em amostra de conveniência de pessoas com diabetes *mellitus* tipo 2 seguidas em Unidades de Cuidados de Saúde Primários. Aplicação do *UK Diabetes and Diet Questionnaire* (UKDDQ) – traduzido e adaptado, de julho a outubro de 2022. Análise estatística descritiva e inferencial.

Resultados: Amostra de 550 participantes, 52,2% do sexo feminino, 68,3% com 65 anos ou mais, 55,8% com nível de escolaridade igual ou inferior ao 1.º ciclo do ensino básico, 24,7% com insuficiência económica e tempo desde o diagnóstico médio de 10,60 ± 8,13 anos. Apenas 36,2% da amostra obteve um *score* UKDDQ considerado saudável. Menos de 50% obteve *scores* saudáveis para os itens "arroz ou massa ricos em fibras", "pão integral", "manteiga, margarina e óleos vegetais" e "vegetais e leguminosas". Somente 8,9% da amostra obteve *score* saudável para o consumo de fibras. Cerca de 70,4% obteve *score* saudável para o consumo de açúcares livres e 54,7% para o consumo de ácidos gordos saturados. Verificou-se a existência de uma correlação com significado estatístico positiva fraca entre o *score* UKDDQ e a idade ($\rho = 0,201$, $p < 0,001$), com escolha mais frequente de alimentos saudáveis com o aumentar da idade. As pessoas do sexo feminino reportaram hábitos alimentares mais saudáveis, particularmente no consumo de fibras e ácidos gordos saturados.

Conclusão: A maior parte da nossa amostra não usufruiu do potencial efeito positivo de uma alimentação saudável. Individualizam-se grupos de alimentos cujos consumos devem ser enfatizados ou desencorajados, particularmente, a necessidade de incentivar o consumo de alimentos ricos em fibra. Ações educacionais dirigidas devem ter especial foco em pessoas mais jovens e/ou do sexo masculino.

Palavras-chave: Comportamento Alimentar; Diabetes Mellitus Tipo 2; Ingestão de Alimentos

ABSTRACT

Introduction: Nutrition is a cornerstone of diabetes mellitus prevention and management; therefore, it is essential to enable patients to adopt healthy eating habits. Previous studies have not yet documented the main errors in the eating habits of Portuguese people with type 2 diabetes mellitus. This study aims to identify the main errors in the eating habits of people living with type 2 diabetes mellitus in Portugal and to evaluate its associations with sociodemographic variables.

Methods: Cross-sectional multicentric study in a convenience sample of people with type 2 diabetes mellitus in Primary Health Care Units. The UK Diabetes and Diet Questionnaire (UKDDQ) – translated and adapted, was applied from July to October 2022. Descriptive and inferential statistical analyses were conducted.

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Recebido/*Received*: 17/02/2023 - **Aceite/*Accepted*:** 28/08/2023 - **Publicado/*Published*:** 03/01/2024

Results: Of the 550 participants, 52.2% were female, 68.3% were 65 years or over, 55.8 % had an education level up to the fourth grade, 24.7% had economic deprivation, and the mean time since diagnosis was 10.60 ± 8.13 years. Only 36.2% of the sample had a healthy UKDDQ score. Less than 50% of the sample had healthy scores for the items "high-fiber rice or pasta", "high-fiber bread", "butter, margarine and vegetable oils" and "vegetables and pulses". Only 8.9% of the sample had a healthy consumption of fiber. About 70.4% reported healthy scores for the consumption of "high-added-sugar foods" and 54.7% for "high-saturated fat". A statistically significant weak positive correlation was found between the UKDDQ score and age ($\rho = 0.201$, $p < 0.001$) with a more frequent choice of healthy foods with increasing age. Female respondents reported healthier habits, particularly in the consumption of "high-saturated fat" and "high-fiber foods".
Conclusion: The majority of our sample did not take advantage of the potential benefits of healthy eating habits. The main food groups whose consumption should be emphasized or discouraged were individualized, particularly the need to encourage the consumption of high-fiber foods. Targeted educational actions must focus especially on younger and/or male patients.
Keywords: Diabetes Mellitus, Type 2; Eating; Feeding Behavior

INTRODUÇÃO

A diabetes *mellitus* (DM) constitui um problema mundial de saúde pública com incidência crescente. Globalmente, no ano de 2021, estimou-se afetar 537 milhões de pessoas e, em 2030, poderá afetar 643 milhões.[1] Em Portugal, no ano de 2018, mais de um milhão de pessoas viviam com esta patologia, estimando-se uma prevalência de 13,6%.[2]

Caraterizada por hiperglicemia persistente, a DM pode resultar em complicações macrovasculares e microvasculares, bem como descompensações agudas, nomeadamente cetoacidose, síndrome hiperglicémico hiperosmolar e hipoglicémia severa.[3,4] Em 2018, o Sistema Nacional de Saúde (SNS) registou 32 292 internamentos por descompensação/complicações da DM, tendo sido considerada a causa de morte em 3,8% dos óbitos em Portugal.[2]

Para a DM tipo 2, o tipo mais prevalente,[3] em associação com o tratamento farmacológico, considera-se fulcral a adoção de hábitos alimentares saudáveis, a atividade física regular, a cessação tabágica, a manutenção de peso corporal adequado e o cuidado psicossocial. Estas modificações do estilo de vida permitem reduzir os valores de hemoglobina glicada e prevenir, adiar e tratar comorbilidades relacionadas, como hipertensão arterial, dislipidemia ou obesidade. Reforça-se ainda a importância da capacitação da pessoa para que esta possa ter um envolvimento ativo na decisão terapêutica e autogestão da sua doença.[3–5]

Em relação à alimentação, recomenda-se a adoção de padrões alimentares que promovam simultaneamente o privilégio de alimentos saudáveis e a minimização do consumo de alimentos não saudáveis. As preferências individuais devem ser sempre tidas em conta, de forma a criar hábitos alimentares saudáveis e sustentáveis.[4,5] Consideramos alimentos não saudáveis todos aqueles com elevada densidade energética e baixo valor nutricional, que possuam simultaneamente alto teor de açúcares livres, ácidos gordos saturados ou trans e/ou sal, desnecessários para satisfazer as necessidades nutricionais para a manutenção da saúde.[6] Em situações em que é necessária a redução de peso, pode estar recomendado um défice no aporte calórico.[4,5]

A eficácia da terapêutica nutricional na redução significativa da hemoglobina glicada já foi demonstrada em Portugal para pessoas com DM tipo 1 e 2,[7] com resultados concordantes com estudos de outros países.[8,9]

Em Portugal, a alimentação inadequada, o excesso de peso, a obesidade e a desnutrição são, conjuntamente, o principal fator de risco para a carga de doença. Em 2019, os hábitos alimentares inadequados encontravam-se entre os fatores de risco das doenças crónicas não transmissíveis que mais conduziam à perda de anos de vida saudável e mortalidade, totalizando 7,3% dos *disability-adjusted life years* (DALY) e 11,4% da mortalidade. Em 2030, do total de óbitos projetados, estima-se que 13,84% seja atribuível a erros alimentares.[6,10]

Existem relatórios referentes aos hábitos alimentares da população portuguesa[6,11,12] e ainda um estudo, realizado em 2007, que caracterizou alguns conhecimentos e hábitos alimentares de pessoas com DM tipo 2.[13] No entanto, não se conhecem especificamente quais os principais erros nos hábitos alimentares das pessoas com DM tipo 2 em Portugal.

Pretende-se, com este estudo, identificar os principais erros nos hábitos alimentares das pessoas com DM tipo 2 em Portugal e, secundariamente, avaliar a sua relação com variáveis sociodemográficas. Os conhecimentos obtidos poderão ser utilizados na personalização do aconselhamento nutricional da população portuguesa com DM tipo 2, contribuindo para a sua capacitação e para uma melhor autogestão da sua doença.

MÉTODOS

Desenho do estudo

Realizou-se um estudo transversal através da aplicação da versão 3 do *UK Diabetes and Diet Questionnaire* (UKDDQ) e colheita de dados sociodemográficos.

População e amostra

A nossa população alvo foram as pessoas com DM tipo 2, vigiadas em unidades dos Cuidados de Saúde Primários (CSP) em Portugal.

Considerando a existência de 862 197 pessoas com DM na rede de CSP do SNS de Portugal Continental, em 2018,[2] para um nível de confiança de 95% e margem de

erro de 5%, estimou-se o tamanho amostral mínimo de 384 pessoas através da *Sample size calculator by* Raosoft®.[14]

Constituiu-se uma amostra de conveniência, de pessoas seguidas em unidades de CSP, para a qual se definiram como critérios de inclusão a codificação do diagnóstico de DM tipo 2 e idade igual ou superior a 18 anos. A existência de uma gravidez em curso foi considerada um critério de exclusão.

Recolha de dados

O parecer favorável da Comissão de Ética da Administração Regional de Saúde (ARS) do Centro foi obtido a 24 de fevereiro de 2022. As autorizações dos coordenadores das Unidades de Cuidados de Saúde Personalizados (UCSP) e das Unidades de Saúde Familiar (USF) colaboradoras foram obtidas antes de se iniciar a colheita de dados.

O questionário foi aplicado por profissionais de saúde, em papel, aos utentes que recorreram a consulta médica ou de enfermagem de diabetes planeada e que aceitassem participar no estudo, de julho a outubro de 2022. Foi atribuído um código a cada questionário que permitiu alocar as respostas ao local onde foi preenchido.

Antes da resposta ao questionário foram fornecidas informações acerca do estudo e, após a sua compreensão, foi assinado um consentimento informado pelo utente, ou no caso dos utentes analfabetos ou incapazes de assinar, pelo representante legal ou duas testemunhas imparciais. A participação foi voluntária, anónima e confidencial.

Instrumentos

O UKDDQ visa caracterizar os hábitos alimentares de adultos com DM tipo 2 ou com risco de a desenvolver, e foi validado através da comparação com diários alimentares de quatro dias. Foram facultadas opções de resposta para cada pergunta que contribui para o *score* e que caracterizam a frequência do consumo retrospetivo de um item alimentar, de A (escolha mais saudável) a E (escolha menos saudável).[15] Cada resposta foi posteriormente codificada num valor numérico – A = 5, B = 4, C = 3, D = 2, E = 1, F = 0 – variando o *score* médio entre 0 e 5. O questionário foi alvo de tradução e remoção da informação sobre o processo de codificação das respostas; o número de perguntas foi ajustado aos objetivos do estudo (excluíram-se três questões sobre a preocupação da pessoa com o seu peso, sobre a sua motivação para mudar os hábitos alimentares e a confiança nessa mudança), com autorização da equipa que o desenvolveu. Na sua versão final apresentava 24 perguntas, das quais 21 contribuíram para o cálculo do *score* geral médio do doente. Os dados sociodemográficos recolhidos foram os seguintes: idade, sexo, nível de escolaridade, tempo desde o diagnóstico de DM tipo 2 e o registo (ou não) de insuficiência económica no processo do utente.

Análise de dados

Para o tratamento e análise estatística dos dados recorreu-se ao programa IBM® SPSS® *Statistics* (versão 28.0.1.0).

Calcularam-se *scores* para cada item do questionário e para cada participante de acordo com o seu desempenho no geral (*score* UKDDQ) e nos conjuntos de perguntas específicas, avaliando o consumo de ácidos gordos saturados (manteiga e óleos vegetais, queijo com alto teor de gordura, carne processada, pastelaria com alto teor de gordura e leite), fibras (legumes, fruta e pão, cereais, arroz ou massa ricos em fibra) e açúcares livres (bolos e biscoitos, doces e chocolates, bebidas açucaradas e sobremesas doces). Quanto mais elevado o valor do *score*, maior o número de escolhas saudáveis feitas pelo participante no último mês. *Score* 'saudável' foi definido como *score* ≥ 4.

Realizou-se uma análise estatística descritiva das variáveis sociodemográficas da amostra e dos *scores* de cada item e de cada participante. Uma vez que a evidência estatística da amostra não aponta para a normalidade (teste de Kolmogorov-Smirnov), para efeitos de inferência estatística, recorreu-se a um teste não paramétrico (teste u de Mann-Whitney) e ao coeficiente de correlação de Spearman.

Considerando o valor absoluto das estimativas para o coeficiente de correlação de Spearman (ρ), a correlação foi classificada como fraca (ρ < 0,30), moderada (ρ ≥ 0,30 e < 0,60) ou forte (ρ ≥ 0,60).[16] O valor $p < 0,05$ foi estabelecido para se concluir sobre a significância estatística da estimativa ou do teste. Procedeu-se a uma análise multivariada por regressão linear com as variáveis que apresentaram associação significativa com o *score* total.

RESULTADOS

Caracterização da amostra

Foi estudada uma amostra composta por 550 participantes, sendo que 500 (90,9%) eram utentes em 16 unidades colaboradoras pertencentes à ARS Centro. Os restantes 50 participantes, eram utentes de unidades pertencentes à ARS Lisboa e Vale do Tejo e ARS Alentejo.

Quanto à caracterização da amostra, 52,5% dos participantes eram do sexo feminino e 68,3% tinham 65 anos ou mais de idade. No que diz respeito ao nível de escolaridade, a maioria dos participantes tinha um nível de escolaridade igual ou inferior ao 1.º ciclo de ensino básico (55,8%). O tempo desde o diagnóstico registado foi em média de 10,60 ± 8,13 anos. Cerca de 24,7% dos participantes tinham insuficiência económica registada no seu processo de utente.

Respostas ao questionário

Os itens do questionário para os quais mais de 50% dos

Tabela 1 – Caracterização sociodemográfica da amostra (n = 550)

Variável		n	%
Sexo	Masculino	263	47,8
	Feminino	287	52,2
Idade (anos)	Média ± DP	69,19 ± 10,40	
	Mínima	37	
	Máxima	92	
Nível de escolaridade Média ± DP: 6,65 ± 4,21 anos	Não sabe ler nem escrever	20	3,6
	Só sabe ler e escrever	21	3,8
	1.º ciclo do Ensino Básico	266	48,4
	2.º ciclo do Ensino Básico	68	12,4
	3.º ciclo do Ensino Básico	60	10,9
	Ensino Secundário	66	12,0
	Ensino Superior	49	8,9
Tempo desde o diagnóstico (anos)	Média ± Desvio Padrão	10,60 ± 8,14	
	Mínimo	0	
	Máximo	50	
Insuficiência económica (registada no processo do utente)	Não	414	75,3
	Sim	136	24,7

DP: desvio-padrão

participantes não atingiu *score* saudável foram: "arroz ou massa integrais", "pão rico em fibra", "manteigas, margarinas e óleos vegetais" e "vegetais e leguminosas", sendo estes os erros nos hábitos alimentares mais frequentes. Da análise individual destes itens, destaca-se o facto de que 80,4% da amostra nunca privilegiou o consumo de "arroz ou massa integrais" face a outras versões destes alimentos; 38,7% nunca optou por "pão rico em fibra"; 28,7% fez consumo diário de "manteiga, margarina e óleos vegetais"; apenas 7,8% consumiu "vegetais e leguminosas" uma vez ou menos por semana e 3,5% nunca ou raramente.

Cerca de 78,2% da amostra fez consumo diário de "pão" e 33,1% de "arroz ou massa". O consumo de "cereais de pequeno-almoço, aveia ou muesli" foi reduzido, com cerca de 76,4% da amostra a escolher a opção "nunca ou muito raramente".

Apenas 36,2% da amostra obteve *score* UKDDQ saudável. A limitação do consumo de açúcares livres foi relativamente cumprida, com cerca de 70,4% da amostra a atingir um *score* saudável, contrariamente ao consumo de fibras que pareceu ter pouca adesão, com apenas 8,9% a atingir um *score* saudável.

Correlações das respostas ao questionário com variáveis sociodemográficas

Com significância estatística, verificou-se a existência de correlação positiva fraca entre o *score* UKDDQ e a idade ($\rho = 0,201$; $p < 0,001$), revelando que, tendencialmente, quanto maior a idade, mais frequente a escolha de alimentos saudáveis. Com a idade, foram também encontradas correlações estatisticamente significativas positivas fracas com os *scores* do consumo de ácidos gordos saturados ($\rho = 0,169$; $p < 0,001$), de açúcares livres ($\rho = 0,181$; $p < 0,001$) e de vegetais e leguminosas ($\rho = 0,156$; $p < 0,001$).

Com o nível de escolaridade verificaram-se correlações estatisticamente significativas negativas fracas com o *score* UKDDQ ($\rho = -0,121$; $p = 0,005$) e os *scores* do consumo de ácidos gordos saturados ($\rho = -0,113$; $p = 0,008$), de açúcares livres ($\rho = -0,143$; $p < 0,001$) e de vegetais e leguminosas ($\rho = -0,092$; $p = 0,030$), bem como correlações estatisticamente significativas positivas fracas com os *scores* do consumo de pão rico em fibra ($\rho = 0,140$; $p = 0,001$) e de arroz e massa integrais ($\rho = 0,085$; $p = 0,046$). Foram também encontradas correlações negativas fracas, com significância estatística, entre o nível de escolaridade e as frequências de consumo de pão ($\rho = -0,090$; $p = 0,036$) e de arroz e massa ($\rho = -0,092$; $p = 0,031$).

O tempo desde o diagnóstico teve uma correlação estatisticamente significativa positiva fraca com os *scores* UKDDQ ($\rho = 0,137$; $p = 0,001$) e com o consumo de açúcares livres ($\rho = 0,152$; $p < 0,001$), sugerindo que, tendencialmente, quanto maior o tempo desde o diagnóstico, maior o cuidado da pessoa com a sua alimentação, em particular no consumo de açúcares livres.

Não foram encontradas correlações estatisticamente significativas com o consumo de fibras.

Tabela 2 – Erros mais frequentes nos hábitos alimentares dos participantes

Item do Questionário§	*Score* médio ± DP	IC 95%	*Score* mediano (AIQ)	*Score*(s) categórico(s) equivalente(s)	N.º (%) a atingir *score* saudável*	
Arroz ou massa integrais	1,57 ± 1,26	1,46 a 1,67	1 (0)	Nunca	73	(13,3)¶
Pão rico em fibra	2,67 ± 1,60	2,54 a 2,81	2 (3)	Menos de metade das vezes	214	(38,9)¶
Manteiga, margarina e óleos vegetais	2,96 ± 1,56	2,83 a 3,09	3 (4)	2 - 4 vezes por semana	219	(39,8)
Vegetais e leguminosas	3,02 ± 1,22	2,92 a 3,12	3 (2)	5 - 6 vezes por semana	271	(49,3)
Peixes gordos	2,80 ± 1,92	2,64 a 2,96	4 (4)	Uma vez por semana	298	(54,2)
Queijo gordo	3,77 ± 1,31	3,66 a 3,88	4 (2)	Uma vez ou menos por semana	341	(62,0)
Carnes processadas	3,82 ± 1,25	3,71 a 3,92	4 (2)	Uma vez ou menos por semana	342	(62,2)
Álcool	3,71 ± 1,78	3,56 a 3,86	5 (4)	Nunca ou muito raramente // uma vez ou menos por semana	379	(68,9)
Bebidas açucaradas	3,89 ± 1,55	3,76 a 4,02	5 (2)	Nunca ou muito raramente	391	(71,1)
Pequeno-almoço	3,82 ± 2,02	3,65 a 3,99	5 (2)	Todos os dias	405	(73,6)
Cereais de pequeno-almoço ricos em fibra	3,97 ± 1,63	3,83 a 4,11	5 (2)	Sempre // não consumi cereais	409	(74,4)¶

DP: desvio-padrão; IC: intervalo de confiança; AIQ: amplitude interquartil
*: *Score* saudável definido como *score* ≥ 4.
¶: O consumo da opção rica em fibra destes alimentos e o não consumo de qualquer opção destes foram ambos considerados saudáveis.
§: Desta tabela constam os itens aos quais < 75% da amostra obteve *scores* saudáveis, dados referentes a todos os itens do questionário podem ser consultados no Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19738/15279).

Tabela 3 – Número de respostas (%) a itens do questionário não integrados nos *scores*

Item do Questionário	Nunca ou muito raramente	1 vez por semana ou menos	2 - 6 vezes por semana	1 - 2 vezes por dia	3 - 4 vezes por dia	> 4 vezes por dia
Pão	20 (3,6%)	23 (4,2%)	77 (14,0%)	364 (66,2%)	58 (10,5%)	8 (1,5%)
Cereais de pequeno-almoço, aveia ou muesli	420 (76,4%)	48 (8,7%)	52 (9,5%)	30 (5,5%)	0	0
Arroz ou massa	19 (3,5%)	84 (15,3%)	265 (48,2%)	168 (30,5%)	14 (2,4%)	1 (0,2%)

O sexo feminino teve uma mediana no *score* UKDDQ que revela melhores hábitos alimentares (p < 0,001) em relação ao sexo masculino, de forma estatisticamente significativa (teste U de Mann-Whitney, Tabela 6). Foram encontradas diferenças com significância estatística no que diz respeito ao consumo de ácidos gordos saturados (p = 0,003) e de fibras (p = 0,0005), nos quais o sexo feminino teve melhor desempenho. Esta tendência manteve-se no consumo de açúcares livres, embora sem significância estatística.

Não se encontraram diferenças estatisticamente significativas nas medianas de qualquer um dos *scores* e ter ou não insuficiência económica (teste U de Mann-Whitney). No entanto, quanto aos erros nos hábitos alimentares mais frequentes, verificou-se, com significância estatística, maior mediana de consumo de manteiga, margarina e óleos vegetais (p = 0,042) nas pessoas que tinham insuficiência económica registada no seu processo de utente, mas maior mediana no *score* de consumo de vegetais e leguminosas (p = 0,031).

Após análise multivariada, apenas mantiveram relação independente e estatisticamente significativa com o *score* UKDDQ as variáveis 'idade' (B = 0,004 - 0,011; p < 0,001) e 'sexo' (B = 0,115 - 0,248; p < 0,001), com um R2 ajustado de 0,089.

DISCUSSÃO

Principais achados e comparação com a literatura existente

Apenas 36,2% da nossa amostra obteve um *score*

Tabela 4 – *Scores* UKDDQ, do consumo de ácidos gordos saturados, de fibras e de açúcares livres

Score	*Score* médio ± DP	IC 95%	*Score* Mediano (AIQ)	N.º (%) de participantes a atingir *score* saudável*	
UKDDQ	3,81 ± 0,41	3,78 a 3,84	3,86 (0,53)	199	(36,2)
Consumo de ácidos gordos saturados	3,93 ± 0,62	3,88 a 3,98	4 (0,8)	301	(54,7)
Consumo de fibras	3,05 ± 0,69	2,99 a 3,11	3 (1,0)	49	(8,9)
Consumo de açúcares livres	4,17 ± 0,69	4,12 a 4,23	4,25 (1,0)	387	(70,4)

DP: desvio-padrão; IC: intervalo de confiança; AIQ: amplitude interquartil
*: *Score* saudável definido como *score* de ≥ 4.

UKDDQ saudável. Em 2007, num estudo português com objetivos idênticos, dirigido à população com DM tipo 2, 31,2% da amostra tinha hábitos saudáveis pelo que parece haver concordância entre estes, ainda que o método de aferição dos hábitos alimentares tenha sido diferente.[13]

Os nossos dados revelam elevada representatividade de "arroz ou massa" e "pão" nos hábitos alimentares, e predileção por versões destes alimentos pouco ricos em fibra. Contrariamente, os "cereais de pequeno-almoço, aveia ou muesli" são pouco consumidos. No Inquérito Alimentar Nacional e de Atividade Física (IAN-AF), que caracterizou os hábitos alimentares de toda a população portuguesa, descreveram-se consumos elevados de pão e tostas, principalmente nos idosos, e consumo de cereais de pequeno-almoço pouco frequente nos idosos e adultos.[12]

Com o baixo consumo de "vegetais e leguminosas" descrito na amostra, era expectável que poucos participantes atingissem um *score* saudável para o consumo de fibras, tendo sido cerca de 8,9%. Já em 2017, um estudo que abordou o conhecimento da população portuguesa acerca de fibras alimentares concluiu que os conhecimentos sobre os seus benefícios para a DM estão, tal como o seu consumo, abaixo do desejado.[17] Reforça-se assim a necessidade de intervenções educacionais a este nível.

O IAN-AF descreveu consumo inferior ao desejado para hortícolas, fruta e leguminosas.[6,12] A maioria dos nossos participantes, descreveu um consumo de "vegetais e leguminosas" considerado não saudável, mas um consumo de "fruta" adequado. Esta discordância pode ser explicada pelo facto de, segundo os resultados do IAN-AF, haver maior consumo de fruta fresca pelos idosos,[12] grupo etário mais prevalente na nossa amostra.

O consumo de ácidos gordos saturados foi adequado para 54,7% dos participantes. Contudo, é importante denotar que o consumo de "manteiga, margarina e óleos vegetais" foi inadequado por parte de 60,2% dos participantes. Este comportamento é ligeiramente divergente do da população portuguesa que apresenta um consumo adequado de gorduras e óleos no geral.[6,12]

Dados do IAN-AF mostraram que o consumo de carnes processadas se encontra geralmente desadequado nos portugueses.[6,12] Cerca de 62,2% dos nossos participantes fez um consumo saudável destas, com frequências variáveis desde nunca até uma vez ou menos por semana. Estes resultados podem dever-se em parte à faixa etária predominante, uma vez que na população portuguesa são os idosos que fazem, menos frequentemente, um consumo desadequado destas.[12]

A frequência recomendada de consumo de açúcares livres foi adequada em 70,4% dos participantes. Num estudo português de 2007, com objetivos e população alvo idênticos, 32,1% da amostra consumia estes alimentos todas as semanas.[13] Parece haver concordância entre os dados de ambos os estudos, mantendo-se a limitação de os instrumentos usados terem sido diferentes. Dado a DM tipo 2 ser frequentemente descrita como cursando com "excesso de açúcar no sangue", devemos ter em consideração que, se por um lado as respostas aos itens que compõem este *score* podem estar altamente sujeitas ao viés da desejabilidade social, por outro, pode haver efetivamente um menor consumo deste tipo de alimentos pelo doente, que estabelece relação entre estes e o "açúcar no sangue". Cerca de 24,4% da população portuguesa apresenta um consumo de açúcares livres superior ao recomendado,[6,12] valor que é

Tabela 5 – Correlação de Spearman entre variáveis demográficas e *scores*

	Score UKDDQ	*Score* do consumo de ácidos gordos saturados	*Score* do consumo de fibras	*Score* do consumo de açúcares livres
Idade	**0,201** (p < 0,001)	**0,169** (p < 0,001)	0,072 (p = 0,091)	**0,181** (p < 0,001)
Nível de escolaridade	**- 0,121** (p = 0,005)	**- 0,113** (p = 0,008)	0,083 (p = 0,053)	**- 0,143** (p < 0,001)
Tempo desde o diagnóstico	**0,137** (p = 0,001)	0,082 (p = 0,055)	- 0,011 (p = 0,792)	**0,152** (p < 0,001)

DP: desvio-padrão; p = significância estatística

percentualmente inferior ao da nossa amostra.

Ainda que 29% do consumo alimentar total em peso dos portugueses inclua alimentos não presentes na roda dos alimentos como bolos, doces, bolachas, *snacks,* salgados, *pizzas*, refrigerantes, néctares e bebidas alcoólicas,[12] a maioria dos nossos participantes atingiu *scores* saudáveis para estes itens, com exceção do item "bebidas açucaradas" – sendo este o único item que compõe o *score* do consumo de açúcares livres com menos de 75% da amostra a obter *score* saudável – e do item "álcool". Contudo, os resultados da análise da frequência do consumo de álcool devem ser interpretados com precaução dado este ter sido considerado saudável pelo UKDDQ apenas quando o consumo ocorresse uma vez ou menos por semana.

Com o aumento da idade dos participantes, existe maior frequência de escolha de alimentos saudáveis, com redução do consumo de ácidos gordos saturados e açúcares livres e aumento do consumo de vegetais e leguminosas. Sem significância estatística, verificou-se também uma tendência para o aumento do consumo de fibras. Os comportamentos da nossa amostra, relacionados com a idade, são consistentes com os da população portuguesa.[12] No entanto, apesar do melhor desempenho em questionários como o UKDDQ, a limitação excessiva da variedade da dieta nos idosos aumenta o risco de desnutrição, algo que não deve ser esquecido.[18,19]

O comportamento dos participantes do sexo feminino – maior limitação de consumo de ácidos gordos saturados e privilégio de alimentos ricos em fibra – em relação a participantes do sexo masculino é consistente com os achados da aplicação do *International Health and Behaviour Survey* em Portugal. Contudo, este estudo abrangeu uma faixa etária muito limitada, entre os 17 e os 30 anos.[20] Estes achados são, no entanto, inconsistentes com os do IAN-AF, em que a ingestão inadequada de ácidos gordos saturados foi mais prevalente no sexo feminino e a ingestão diária de fibra foi superior no sexo masculino.[12] Na nossa amostra, o sexo feminino, embora sem significância estatística, pareceu também limitar mais o consumo de açúcares livres, contrariamente ao descrito no IAN-AF.[12]

Na população portuguesa, parece haver maior ingestão de fibras em pessoas com níveis mais elevados de escolaridade,[12] tendência que, embora sem significado estatístico, se verificou no nosso estudo. É importante referir que esta tendência se deveu essencialmente ao privilégio de opções ricas em fibra de pão, arroz e massa – ainda que a frequência de consumo destes alimentos (opções ricas ou pobres em fibra) seja menor em relação a pessoas com níveis de escolaridade inferiores. O consumo de vegetais e leguminosas não contribuiu para esta tendência uma vez que, na nossa amostra, parece reduzir com o aumento do nível de escolaridade.

No nosso estudo, em níveis mais elevados de escolaridade, verificou-se um maior consumo de ácidos gordos saturados e açúcares livres. No IAN-AF, a níveis mais elevados de escolaridade associou-se um consumo total inferior de ácidos gordos saturados e de açúcares livres,[12] apesar de, simultaneamente, também se verificar um maior consumo de alimentos como doces, bolos, bolachas, *snacks*, salgados e *pizzas*.[6,12] Note-se que o UKDDQ avalia frequências de consumo e não a contribuição para a ingestão alimentar total de cada item; por esta razão, a maior diversificação alimentar associada ao aumento da escolaridade pode refletir-se em piores *scores*. O facto de a escolaridade poder ser um mau preditor da adesão terapêutica deve ser mantido em mente,[21] tal como o uso de métodos de aferição diferentes entre os estudos comparados.

Pontos fortes e limitações

O UKDDQ não foi validado formalmente para a população portuguesa e podem existir vieses relacionados com a aplicação do questionário, nomeadamente o viés de

Tabela 6 – Relação entre a variável 'sexo' e *scores* – teste U de Mann-Whitney

Sexo	Masculino	Feminino
***Score* UKDDQ** (média ± DP)	3,71 ± 0,44	3,90 ± 0,36
p	**< 0,001**	
***Score* do consumo de ácidos gordos saturados** (média ± DP)	3,84 ± 0,66	4,02 ±0,58
p	**0,003**	
***Score* do consumo de fibras** (média ± DP)	2,97 ± 0,71	3,13 ± 0,66
p	**0,005**	
***Score* do consumo de açúcares livres** (média ± DP)	4,15 ± 0,70	4,19 ± 0,68
p	0,54	

DP: desvio-padrão; *p* = significância estatística

memória e o viés da desejabilidade social. Como qualquer instrumento de medida, o UKDDQ tem as suas limitações e pontos fortes inerentes, nomeadamente o uso de frequências para vários itens em vez de porções.[15] Para além disso, foi utilizada uma amostra com dispersão limitada pelo país (viés de seleção).

Por outro lado, o tamanho da amostra é representativo da população alvo e a coordenação com os colaboradores do estudo garantiu que o mesmo participante não pudesse ter respondido mais do que uma vez ao questionário. Foi removida a informação sobre o processo de codificação do questionário entregue aos participantes (que estava incluído no próprio questionário na versão original) numa tentativa de contradizer a tendência dos participantes em subestimar os consumos altos e sobrestimar os baixos consumos, na tentativa de demonstrar hábitos alimentares mais saudáveis.

Dado termos analisado uma amostra de conveniência, a demografia desta não reflete a prevalência da DM em Portugal no que diz respeito ao sexo dos participantes,[2] mas sim o facto de as utentes do sexo feminino serem quem mais frequenta os CSP.[22]

A idade média desta população reflete a faixa etária de maior prevalência da doença (60 – 79 anos)[2] e a escolaridade, e, por conseguinte, a formação académica expectável para esta faixa etária.[23] O facto de se ter analisado uma amostra variada em termos de idades e tempo desde o diagnóstico é um ponto forte deste estudo. Não é possível estimar a representatividade da amostra no que diz respeito ao contexto económico do doente. No entanto, a inclusão desta variável é também um ponto forte deste estudo, dada a sua influência na qualidade da alimentação[24,25] e consequente relação com a DM.[6,26]

Implicações

Apesar das limitações supramencionadas, os achados deste estudo, ao serem divulgados e integrados no aconselhamento nutricional em contexto de CSP, podem permitir uma abordagem mais personalizada às pessoas com DM tipo 2 em Portugal, potenciando o aumento do número de pessoas que usufrui do benefício de uma dieta saudável.

Investigação futura

Sugerimos que se proceda à validação formal deste instrumento e que, em adaptações subsequentes, se incluam itens como o consumo de batatas e outros tubérculos para melhor comparação com estudos portugueses.

Ainda que as limitações intrínsecas ao UKDDQ se mantenham,[15] seria pertinente repetir este estudo englobando mais regiões do país, para que seja possível perceber de que modo a geografia altera os hábitos alimentares das pessoas com DM tipo 2, visto que se documentaram diferenças na população geral com outros instrumentos de avaliação.[12]

Uma vez que o UKDDQ demonstra ser sensível a mudanças,[23] a sua aplicação seriada a pessoas com DM tipo 2 poderia descrever a evolução temporal dos hábitos alimentares[27] e identificar momentos preferenciais para ações educacionais dirigidas. A eficácia destas ações poderia ser também avaliada pela aplicação subsequente do UKDDQ.

Por outro lado, a avaliação simultânea de outros parâmetros que possam ser preditores dos hábitos alimentares – como a presença de outras comorbilidades, índice de massa corporal, medicação habitual, agregado familiar doméstico, número de refeições com/sem companhia, prática de exercício físico e fonte/confeção das principais refeições – poderia determinar subgrupos de risco que beneficiariam de um tipo de orientação mais específica, como a extensão do aconselhamento nutricional a familiares ou o planeamento de refeições semanais.

CONCLUSÃO

Através da caracterização dos hábitos alimentares, conclui-se que o potencial efeito positivo de uma alimentação saudável na gestão desta doença não é usufruído pela maioria dos doentes estudados.

Foi possível individualizar os principais grupos de alimentos cujos consumos devem ser enfatizados – "arroz ou massa ricos em fibras", "pão integral", "vegetais e leguminosas" – ou desencorajados – "manteiga, margarina e óleos vegetais", sendo que o baixo consumo de alimentos ricos em fibra é particularmente preocupante.

Futuras ações educacionais, integrando estes novos conhecimentos, devem ter em especial foco doentes mais jovens e/ou do sexo masculino, pelo que seria essencial investigar qual a melhor abordagem para conseguir modificar os hábitos nesta subpopulação de pessoas com diabetes.

APRESENTAÇÕES PRÉVIAS

O trabalho foi apresentado sob a forma de poster no IN4MED (estudantes), no AIMS Meeting (estudantes), no XXVIII Curso Pós-Graduado de Endocrinologia, Diabetes e Metabolismo, no 9.º Congresso Português de Diabetes e no 40.º Encontro Nacional de MGF.

AGRADECIMENTOS

Os autores agradecem a todas as unidades de saúde e médicos de família que colaboraram na recolha de dados: Luísa Baía, Liliana Constantino, Ana Luísa Serra, Ana Ernesto, Ana Ramalho e Carolina Santos.

CONTRIBUTO DOS AUTORES

BCR: Conceção e delineamento do estudo, recolha, análise e interpretação de dados, redação, revisão e

aprovação da versão final do manuscrito.

IR: Conceção e delineamento do estudo, análise e interpretação de dados, revisão crítica e aprovação da versão final do manuscrito.

TISC: Interpretação de dados, revisão crítica e aprovação da versão final do manuscrito.

PDM, GSR, AFF, ASCM, TB, FGF, AFC, CL, IMF, JAG, IVO, TDCG, ARP, ASAG, CFM, SPS, AC, PVC, BAR: Colheita de dados, revisão crítica e aprovação da versão final do manuscrito.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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A Revista Científica da Ordem dos Médicos

Validation and Cultural Adaptation of the Problem Areas in Diabetes-5 (PAID-5) Scale to European Portuguese

Validação e Adaptação Cultural da Escala "Problem Areas In Diabetes-5" (PAID-5) para Português Europeu

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Acta Med Port 2024 Jan;37(1):36-41 ▪ https://doi.org/10.20344/amp.18995

ABSTRACT

Introduction: Diabetes distress syndrome (DDS) can lead to poor outcomes and should be assessed with adapted and validated tools. One of these tools is the Problem Areas in Diabetes (PAID) scale, which assesses diabetes distress in people suffering from diabetes (PsD). A short five-item form, PAID-5, is an easier and quicker alternative to be used in clinical and research practices, than the previous one with 20-items and has been validated by the original authors. This study intended to perform the cultural adaptation and validation of the PAID-5 scale in European Portuguese.

Methods: To create the Portuguese version of PAID-5, translation-back translation, a clinical review, and a cognitive debriefing panel were performed. A convenience sample of 90 PsD was studied in three primary healthcare units for reliability and validity tests. Reliability was studied by the internal consistency (Cronbach's alpha) and the interval coefficient correlation (ICC) under a test-retest design. Structural validity was studied by principal component analysis. The construct validity was tested by the sensitivity of the PAID-5 total score with age, most recent HbA1c test, and socioeconomic class by the Socio-Economic Deprivation Index (SEDI). Criterion validity was tested by correlating the PAID-5 total score with the psychological distress questions of the Diabetes Health Profile 18 Questions (DHP-PDQ).

Results: A Cronbach's alpha coefficient value of 0.905 and an ICC of 0.905 were computed. In a sample of n = 90 PsD, 55.6% were males, 63.3% aged 65 years or more, SEDI was 5.2 ± 0.8 [3 to 6], 44.4% studied for less than 4 years, and 18.9% were living alone. The Spearman correlation between PAID-5 and DHP-PDQ total scores was ρ = 0.382, $p < 0.001$, between PAID-5 total score and age was ρ = -0.207, $p = 0.050$ and between PAID-5 total score and most recent HbA1c knowledge was ρ = 0.275, $p = 0.040$. There was no significant relationship between PAID-5 total score and SEDI ρ = 0.080, $p = 0.452$.

Conclusion: DDS can now be assessed in the Portuguese context, accounting for better intervention by primary care teams. PAID-5 has good psychometric properties and is a reliable scale to identify diabetes-specific distress in the Portuguese diabetic population.

Keywords: Diabetes Mellitus/psychology; Emotions; Portugal; Psychometrics; Surveys and Questionnaires

RESUMO

Introdução: A síndrome 'Sofrimento pela Diabetes' (SpD) deve ser detetada por instrumentos adaptados e validados um deles sendo a escala *Problem Areas in Diabetes* (PAID), uma formulação com cinco frases em vez das 20 da versão original de PAID, que é mais fácil e rápida de aplicar para fins clínicos e de investigação, tendo já sido validada pelos autores originais. Este estudo teve como objetivo realizar a adaptação cultural e validação da escala PAID-5 para o Português Europeu.

Métodos: Para criar a versão portuguesa de PAID-5 realizou-se tradução, retrotradução, revisão clínica e painel de *debriefing*. Numa amostra de conveniência de n = 90 pessoas com diabetes provenientes de três Unidades de Cuidados de Saúde Primários estudou-se a consistência interna e a fiabilidade. Realizou-se uma validação de constructo pelo alfa de Cronbach e pelo coeficiente de correlação intraclasse (ICC) em teste e reteste. Para validação estrutural utilizou-se a análise dos componentes principais e para validade de constructo usou-se a sensibilidade do somatório de PAID-5 com o mais recente valor de Hemoglobina A1c (HbA1c) e classe socioeconómica (SEDI). A validade de critério foi estudada correlacionando o somatório de PAID-5 com as questões de perfil psicológico de *Diabetes Health Profile – 18* (DHP-PDQ).

Resultados: A consistência interna, alfa de Cronbach, foi de 0,905 e o ICC de 0,905, numa amostra de 90 pessoas, sendo 55,6% homens e 63,3% tendo idade ≥ a 65 anos. O valor de SEDI foi de 5,2 ± 0,8 [3 a 6], 44,4% tinha formação académica inferior ao quarto ano e 18,9% viviam sós. A correlação de Spearman entre as pontuações totais de PAID-5 e de DHP-PDQ foi de ρ = 0,382, $p < 0,001$, com o valor mais recente da HbA1c de ρ = 0,275, $p = 0,040$ e entre as pontuações totais de PAID-5 e SEDI de ρ = 0,080, $p = 0,452$.

Conclusão: A síndrome SpD pode agora ser detetada no contexto português para melhor intervenção das equipas em Cuidados de Saúde Primários. A escala PAID-5 tem boas propriedades psicométricas e é fiável para a identificação da síndrome SpD na população diabética portuguesa.

Palavras-chave: Diabetes Mellitus/psicologia; Emoções; Inquéritos e Questionários; Portugal; Psicometria

INTRODUCTION

Diabetes is a highly prevalent chronic disease. In 2021, 10.5% of adults aged between 20 and 79 lived with diabetes, with an expected rise to 12.2% by 2045. The International Diabetes Federation (IDF) confirms that diabetes is one of the 21st century's fastest-growing global health emergencies. Approximately 6.7 million adult deaths occurred because of diabetes or its complications in 2021, corresponding to 12.2% of global deaths from all causes. According to the IDF, 13% of adults in Portugal were living with diabetes in 2021, making Portugal the fourth European country with the highest prevalence rate of diabetes.[1]

People suffering from diabetes (PsD) have a significant

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Recebido/*Received*: 20/01/2023 - **Aceite/*Accepted*:** 26/05/2023 - **Publicado *Online*/*Published Online*:** 27/07/2023 - **Publicado/*Published*:** 03/01/2024

and active role in controlling the disease, as they need specific diet, exercise, and adequate dosing of cutting-edge medication.[2] Self-management and worry about long-term complications such as ischemic heart disease or myocardial infarction, stroke, retinopathy, nephropathy, and neuropathy can be sources of stress. This can lead to a negative emotional impact called 'diabetes distress syndrome' (DDS), linked to non-adherence to lifestyle modifications, worse glycemic control, and poor health status.[3,4] DDS is part of this patient's daily life and has a prevalence rate of 36.0% in patients with type 2 diabetes.[5] Such a situation must be addressed in clinical practice at periodic intervals, like when a change in disease treatment or specific life circumstances occurs or when distress is suspected.[6] Therefore, to evaluate DDS, specific, validated tools are needed.

As a specific instrument to assess DDS, the Problem Areas in Diabetes (PAID) scale meets this need.[7,8] It has shown good psychometric properties and has already been translated and validated into several languages.[9-17] The PAID scale has 20 questions scored from 0 (not a problem) to 4 (serious problem) and allows the assessment of the negative emotional impact on PsD, with higher scores meaning more suffering. Lower levels of DDS can help improve the metabolic profile.[3] A short version of PAID, PAID-5,[18] includes five questions: (i) feeling scared when you think about living with diabetes; (ii) feeling depressed when you think about living with diabetes; (iii) worrying about the future and the possibility of serious complications; (iv) feeling that diabetes is taking up too much of your mental and physical energy every day; and (v) coping with complications of diabetes, to be answered on a Likert scale from not having a problem (0) to having a serious problem (4) with intermediates of minor problems, moderate problems and somewhat serious problems. This short version has been developed and validated, making it easier to apply in clinical and research practices for type 1 and type 2 diabetes. The PAID-5 has satisfactory sensitivity (94%) and specificity (89%) for recognition of diabetes-related emotional distress, correlated with the PAID-20 total score ($\rho = 0.92$, $p < 0.001$) and also with the WHO-5 score ($\rho = -0.47$, $p < 0.001$).[18]

This study intended to adapt PAID-5 to the European Portuguese language and validate it for the Portuguese culture.

METHODS

For linguistic equivalence, after obtaining permission from the author, Brian McGuire, to translate and use PAID-5, our aim was to create a Portuguese version of PAID-5, equivalent to the original version. Therefore, following scientific recommendations,[19] we asked two Portuguese translators to perform a first translation from the original PAID-5. Then, these two translated versions were merged into a consensual version by a panel of experts, and the outcome was sent to an English professional translator to perform a back translation. These researchers analyzed this back translation and compared it to the original one to verify if there were semantic differences. This last version was compared to the original, and the first version of the Portuguese PAID-5 was created.

Still in this cross-cultural adaptation phase, we applied this version to a sample of 25 PsD in order to evaluate the comprehension and the burden of questions to be answered.

Between August and October 2022, data were gathered from PsD in three primary healthcare units in central Portugal. One of the investigators, on randomly selected days, invited PsD to participate in this study before or after their clinical appointment on site.

As inclusion criteria, this study accepted PsD patients with type 1 or type 2 diabetes who attended their family physician appointments with European Portuguese as their native language and agreed to participate.

Besides the Portuguese version of PAID-5, the diabetes distress questions of the Diabetes Health Profile (DHP-18) were included in the (DHP-PDQ).[20] The DHP-PDQ is a measurement instrument of psychological and behavioral outcomes resulting from living with diabetes that has already been culturally adapted and validated for the Portuguese population.[21]

Context characterization questions for age, sex, number of co-inhabitants, average monthly financial income, level of formal education, and diabetes-related questions such as diabetes monitoring, knowledge of, and level of the most recent hemoglobin A1c (HbA1c), were also included.

This study aimed to test whether a higher score on the PAID-5 scale was associated with aging, knowledge about the most recent HbA1c test, and a lower socioeconomic index class.

An adapted formula for readability was performed (https://readable.com/features/readability-formulas/) to test for perceptibility, and we used descriptive statistical methods to characterize the sample and the Kolmogorov-Smirnov test for the distribution of the variables.

Reliability was first tested by the internal consistency of Cronbach's alpha for the first 25 patients, for credibility in the development of the process, and by the total sample. We also checked Cronbach's alpha to see if each item on the scale was excluded. The reproducibility test-retest was analyzed through the intraclass correlation coefficient (ICC).

To test the construct validity of the Portuguese version of PAID-5, we tested the structural validity and the known-group validity. The former test was accomplished by an exploratory factor analysis, previously confirmed by the

Kaiser-Meyer-Olkin (KMO) measure of sample adequacy and by the Bartlett sphericity test. The known-group validity was tested by correlating the total scores obtained by PAID-5 in different subsamples according to the patient's age, Socioeconomic Deprivation Index (SEDI) class,[22] and most recent knowledge of the HbA1c test.

SEDI, as defined by Lamnisos *et al*,[22,23] is a multidimensional concept measuring the relative disadvantage experienced by an individual or social group. It is a composite index formed by income, education, employment, housing, household, transportation, and demographics. For income, a definition of €500 was made due to the expected age, retirement, and relative level of income.

For criterion validity, we computed the Spearman correlation coefficient to assess the linear relationship between PAID-5 and the total score of the domain "psychological distress" from DHP-18. Participation was voluntary and confidential, and all participants gave previous written informed consent.

This study was approved by the Central Regional Health Authority's Ethics Committee and the coordinators of all primary care units. A p value of < 0.05 was defined for significant difference.

RESULTS

To confirm the content validity, there was no evidence of any difficulty in how the Portuguese version of PAID-5 was understood, and participants reported no doubts. Therefore, we made no changes between the first and second phases of the study.

The adapted ease-readability formula result was 61.02, meaning that it had a standard perceptibility. A response rate of 100% was obtained. The mean time to complete PAID-5 questions was 1.26 minutes, with values ranging from 0.37 seconds to 2.46 minutes.

According to Table 1, in a sample of 90 participants, 55.6% were males, 63.3% were aged 65 years or more, 52.2% had more than four years of formal education, 57.8% were receiving more than €500 per month, and 81.1% lived with at least one person (81.1%). Regarding the average monthly income question, 26 out of 90 patients did not answer that question, and so a calculated SEDI of 5.2 ± 0.8 in a maximum of 6 was obtained. For diabetes-related questions, 50.0% did not do any capillary glycemic control, 62.2% knew their most recent HbA1c, and 38.9% had the most recent HbA1c value over 6.5%.

As shown in Table 2, our study population generally experienced low levels of DDS.

The PAID-5 scores obtained in this study are presented in Table 2.

As for data normality, the one-sample Kolmogorov-Smirnov test indicated PAID-5 and DHP-PDQ scores, SEDI, and HbA1c had a non-normal distribution with a Lilliefors significance correction of < 0.001. The Spearman correlation between PAID-5 and DHP-PDQ total scores was significant and showed a weak positive correlation between the two scales

Table 1 – Total sample characterization (n = 90)

Variable	Value	n	%
Sex	Male	50	55.6%
	Female	40	44.4%
Age (years)	≥ 65	57	
	< 65	33	63.3%
	Min. – Max.	21 – 92	36.7%
	Mean ± standard deviation	64.5 ± 12.4	
Education (years)	≤ 4	40	44.4%
	> 4	47	52.2%
	Missing	3	3.3%
Monthly income (€)	≤ 500	12	13.3%
	> 500	52	57.8%
	Missing	26	28.9%
Living alone	Yes	17	18.9%
	No	73	81.1%
SEDI	Mean ± standard deviation	5.2 ± 0.8	
Performing diabetes control	Yes	45	50.0%
	No	45	50.0%
Knowledge of the most recent HbA1c	Yes	56	62.2%
	No	34	37.8%
Most recent HbA1c score	≤ 6.5%	21	23.3%
	> 6.5%	35	38.9%
	Do not know	34	37.8%

HbA1c: hemoglobin A1c

Table 2 – Descriptive of PAID-5 scores about diabetes stress (n = 90)

PAID-5 question	Mean	Median	Standard deviation
Being afraid of living with diabetes	1.5	1.5	1.2
Feeling depressed of living with diabetes	1.2	1.0	1.3
Feeling worried about the future and complications	2.3	2.0	1.2
Feeling that diabetes requires physical and mental energy	1.5	2.0	1.3
Dealing with complication associated with diabetes	1.8	2.0	1.3

(r = 0.382, $p < 0.001$).

For reliability, a total Cronbach's alpha coefficient value of 0.915 and, if an item was deleted, an alpha ranging from 0.884 to 0.911 was obtained. Regarding reproducibility, the test-retest ICC was 0.915 with a 95% confidence interval of 0.837 to 0.950.

To test the structural validity, factor analysis confirmed a one-factor solution accounting for 72.79% of the explained variance. KMO was 0.788, showing this was an adequate sample size for carrying out the factor analysis. In addition, the Bartlett sphericity test was significant ($\chi^2 = 88.411$, $p < 0.001$), indicating that the correlations between items were sufficiently substantial for carrying out the factor analysis.

Table 3 reveals that age and SEDI class showed a non-significant correlation with the PAID-5 total score, while knowledge of the most recent HbA1c test was significantly correlated with the PAID-5 total score, with PAID increasing while HbA1c decreased.

Still, regarding the PAID total score, Mann-Whitney U non-significant differences were found for sex, $p = 0.987$, diabetes control, $p = 0.052$, knowledge of the most recent HbA1c test, $p = 0.419$, SEDI level under or above the median, p = 0.334, monthly income (under or above €500), $p = 0.318$ and living alone or not, $p = 0.668$. For education (under or above four years) PAID-5 total score was significantly higher in those with more than four years (8.7 ± 5.2 *vs* 4.7 ± 4.7, $p = 0.034$).

DISCUSSION

The goal of this study was to adapt and validate the European Portuguese version of a simple and complete scale on diabetes distress, whose long and short version were already validated in other languages with good psychometric properties.[7-18]

The Portuguese PAID-5 scale showed good comprehensibility with a short time to answer.

Cronbach's alpha coefficient value showed excellent internal consistency of the PAID-5 scale,[19] confirming the scale's validity for the Portuguese culture. McGuire *et al*[18] obtained a Cronbach's alpha coefficient value of 0.83. This value is also in line with a Norwegian study.[14,24] In addition, the average measure ICC was excellent (0.915). This value is also in line with the Norwegian version of the PAID-5 ICC measure.[24]

The unidimensional structure of the Portuguese version of PAID-5 was verified. A statistically significant correlation with DHP-PDQ reinforced the validity of the PAID-5 scale. This correlation was weak, meaning that these two scales do not measure the same causes of diabetes distress. These scales are not the same but are complementary, and physicians can now use both to have a complete assessment. A significant strength of PAID-5 is that it takes less than a minute to complete, making it easier to use during patient appointments.

The PAID-5 total score correlated negatively with age, with younger patients scoring higher, and suffering more from diabetes distress. Other studies also showed a weak negative association between these two variables.[7,8,12,15] This result can be related to younger patients projecting diabetes as an obstacle in their future lives and needing to develop coping mechanisms.

Knowledge of the most recent HbA1c test had a weak positive correlation with the total score of the PAID-5 scale, showing that PsD who knew their most recent HbA1c value obtained higher scores on the scale. There is doubt regarding this analysis since it is impossible to know if patients are regularly aware of the most recent HbA1c value or if they knew this value because of recently acquired information during a medical appointment. Patients can suffer by knowing a result whose interpretation can be doubtful for them. This is an important research question since this study was on validation of a questionnaire on PsD and not just on diabetes as a disease.

Table 3 – Correlations between PAID-5 total score and age, most recent HbA1c knowledge, and SEDI class

Variable	n	Spearman correlation	*p*-value
Age	90	-0.032	0.763
Most recent HbA1c knowledge	56	-0,275	0.040
SEDI class	90	0.080	0.452

SEDI: socio-economic deprivation index; HbA1c: hemoglobin A1c

Regarding the SEDI class, the lack of a statistically significant correlation with PAID-5 means that diabetes distress is a social cross-sectional problem.

As reported in previous studies with PAID-20,[7-11,13,15,17] our study also revealed the most severe emotional problem was 'worrying about the future and the possibility of serious complications'. This means that PsD patients seem afraid of developing complications which can be long-time stressors. The study's sample generally experienced low levels of diabetes distress, as all the questions had a mean score between 1.2 and 2.3. Future research on this low level of distress, namely on how doctor's empathy can lead to patient empowerment and Patient-Centered Medicine practice, is justified.[25,26]

This study has some limitations. We obtained a convenience sample, predominantly composed of patients with type 2 diabetes, even though it was obtained on randomly selected days. Another limitation consists of missing data due to some patients' incomplete answers. Although the sample was relatively heterogeneous, with patients aged between 21 and 92 years old from both urban and rural contexts, another limitation of the study is just covering the central region of Portugal. To continue the validation process, we suggest using the European Portuguese version of the PAID-5 scale on larger and more heterogeneous samples from different parts of Portugal.

Despite these limitations, the results suggest that the European Portuguese version of the PAID-5 scale is an understandable and easy-to-apply instrument, presenting good psychometric values of reliability and validity; therefore, it can be considered adequate to measure diabetes distress in persons suffering from diabetes in Portugal. It allows the assessment of this problem in order to improve medical care, resulting in better health status and quality of life for patients with diabetes.

In the presence of diabetes distress, verifying the PAID-5 scale's responsiveness to change is now pertinent. Further studies can also ascertain if this scale is a valuable tool to evaluate caregivers' perceptions of the person's diabetes distress once their knowledge of perceptions can contribute to the early identification of this problem.

CONCLUSION

The results of this study suggest the adequacy of the validation process of PAID-5 to measure diabetes distress in Portugal. The PAID-5 European Portuguese version is a simple, easy-to-apply, and reliable measure of diabetes distress. This scale is as an easy tool to identify diabetes distress that can be used in further research and in clinical practice.

AUTHOR CONTRIBUTIONS

CP: Conception of the study, methods, software, data collection and management, resources for the study, manuscript writing and critical review, supervision.

LMS: Conception of the study, methods, software, data management, analysis and validation, resources for the study, manuscript writing and critical review.

IR: Conception of the study, methods, resources for the study, critical review of the manuscript and supervision.

PF: Software, data analysis and validation, critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

LMS has received payments from Departamento de Formação Médica do Serviço de Saúde da Região Autónoma da Madeira and from Administração Regional de Saúde do Alentejo.

IR has received consulting fees from Novo Nordisk; payment or honoraria from Boehringer Ingelheim, Astra Zeneca and MSD for lectures, presentations, speakers' bureaus, manuscript writing or educational events; support for attending meetings and/or travel from MSD, Ferrer Portugal and Novo Nordisk.

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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A Case Report of Radial Artery Pseudoaneurysm After Repeated Radial Puncture for Arterial Blood Gas

Um Caso Clínico de Pseudoaneurisma da Artéria Radial Após Punção Radial Repetida para Realização de Gasometria

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Acta Med Port 2024 Jan;37(1):42-45 ▪ https://doi.org/10.20344/amp.19697

ABSTRACT

Arterial blood gas, with subsequent radial arterial puncture as a simple access point, comprises a ubiquitous medical procedure in the diagnostic workup of patients admitted to the emergency department with dyspnea. Despite being a relatively safe and technically straightforward procedure, due to its considerable use, it is of vital importance to be able to promptly recognize its potential complications. We present the case of a 96-year-old female patient admitted to the emergency department with dyspnea and cough who underwent left radial arterial puncture for arterial blood gas. A total of three puncture attempts were performed until arterial blood was collected. Roughly two weeks upon observation, the patient was readmitted to the emergency department after the insidious appearance of a painful swelling in the left wrist, with progressive worsening since hospital discharge. On physical examination, a painful erythematous pulsatile swelling in the left wrist's volar aspect was observed, and further point-of-care ultrasound evaluation documented a cystic-like collection, communicating with the radial artery's lumen, and suggesting the probable diagnosis of iatrogenic radial pseudoaneurysm. The patient was hospitalized and underwent surgical resection of radial pseudoaneurysm, with subsequent arterial repair. Although severe complications from arterial blood gas have a low incidence rate, prompt diagnosis and management are required. Therefore, point-of-care ultrasound, as an additional diagnostic tool, may play a role in minimizing the risk of procedural complications.

Keywords: Aneurysm, False/diagnostic imaging; Blood Gas Analysis/adverse effects; Emergency Service, Hospital; Point-of-Care Systems; Radial Artery/diagnostic imaging; Ultrasonography

RESUMO

A gasometria arterial, com consequente punção arterial radial enquanto forma simplificada de acesso, constitui um procedimento médico ubíquo na abordagem diagnóstica dos doentes que recorrem ao serviço de urgência por dispneia. Apesar de se tratar de um procedimento relativamente seguro e tecnicamente simples, dada a sua elevada utilização, é especialmente importante ter a capacidade de reconhecer precocemente as potenciais complicações que dele poderão advir. Apresentamos, em seguida, o caso clínico de uma doente do sexo feminino com 96 anos de idade, que foi admitida no serviço de urgência por dispneia e tosse, tendo sido submetida a punção arterial radial esquerda para realização de gasometria arterial nesse contexto. Um total de três tentativas de punção foram efetuadas até colheita de sangue arterial com sucesso. Aproximadamente duas semanas após este episódio de urgência, a doente foi readmitida no serviço de urgência por aparecimento insidioso de tumefação dolorosa ao nível do punho esquerdo, em agravamento progressivo desde a data de alta hospitalar prévia. No exame físico foi documentada uma tumefação dolorosa, eritematosa e pulsátil na região volar do punho esquerdo, com subsequente avaliação por ecografia clínica à cabeceira-do-doente, documentando uma coleção com aparência cística, comunicando com o lúmen da artéria radial esquerda, enquadrável num diagnóstico provável de pseudoaneurisma radial de etiologia iatrogénica. A doente ficou internada e foi submetida a resseção cirúrgica do pseudoaneurisma radial, com subsequente reparação arterial cirúrgica. Embora as complicações severas da gasometria arterial apresentem baixa incidência, o seu diagnóstico deve ser precoce e a sua abordagem célere. Por conseguinte, o uso da ecografia clínica à cabeceira-do-doente, enquanto complemento diagnóstico prontamente disponível, poderá contribuir para minimizar o risco de complicações.

Palavras-chave: Artéria Radial/diagnóstico por imagem; Falso Aneurisma/diagnóstico por imagem; Gasometria/efeitos adversos; Serviço de Urgência Hospitalar; Sistemas Automatizados de Assistência Junto ao Leito; Ultrassonografia

INTRODUCTION

Arterial blood gas (ABG), with subsequent radial arterial puncture as a simple access point, constitutes a ubiquitous medical procedure in the diagnostic workup of patients admitted to the emergency department (ED) with dyspnea.[1]

Due to its ease of access, simple hemostasis and reduced risk of bleeding, the radial artery has been increasingly selected for performing percutaneous procedures with other diagnostic and therapeutic purposes, as it yields comparable results to other vascular access sites, but with fewer procedure-related complications.[2-5]

Despite being a relatively safe and technically straightforward procedure, it is of vital importance being able to promptly recognize its potential complications. Even though pain and regional hematoma are frequently observed, other possible iatrogenic complications include arterial occlusion/perforation, vasospasm, non-occlusive injury, arteriovenous fistulization, nerve damage or arterial pseudoaneurysm (PSA) formation.[1,4,6]

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Recebido/*Received*: 30/01/2023 - **Aceite/*Accepted*:** 28/04/2023 - **Publicado *Online*/*Published Online*:** 20/11/2023 - **Publicado/*Published*:** 03/01/2024

CASE REPORT

We present the case of a 96-year-old female patient, with prior relevant history of asthma, initially admitted to the ED with dyspnea and cough for two weeks. On physical examination, low peripheral oxygen saturation was detected (86%), as well as globally reduced vesicular murmur in pulmonary auscultation. For this reason, ABG was obtained using a 23-gauge needle with heparinized syringe after a total of three punctures in the left radial artery, with posterior haemostatic compression, displaying slight hypoxemia and hypocapnia. Blood work revealed elevated inflammatory markers with borderline value for high-sensitivity cardiac troponin (reference range < 40 pg/mL), so the patient underwent thoracic computed tomography (CT) scan with pulmonary angiography that depicted bilateral segmental pulmonary embolism. Treatment with low-molecular weight heparin was promptly initiated, and after recovery, the patient was discharged with oral anticoagulation using an anti-Xa factor inhibitor.

Roughly two weeks upon observation, the patient was readmitted to the ED after insidious appearance of painful swelling in the left wrist, with progressive worsening since hospital discharge. On physical examination, a painful erythematous pulsatile swelling in the left wrist's volar aspect was observed, without local signs of skin necrosis nor digital ischemia or neurological deficit (Fig. 1). Further point-of-care ultrasound (POCUS) evaluation documented a cystic-like collection, measuring about 16 mm (height) x 24 mm (width) x 32 mm (length), communicating with the radial artery's lumen, with a visible swirling pattern flow (Figs. 2 and 3). The lesion was easily compressible but refilled rapidly upon decompression, and there was no evidence of thrombus inside. The diagnosis of probable iatrogenic radial PSA due to repeated radial puncture was assumed. The patient was admitted and underwent surgical resection of radial PSA, with subsequent arterial repair. In the operating room, the presence of a vascular lesion of approximately 0.6 cm was confirmed. The patient went on to full recovery with discharge within four days.

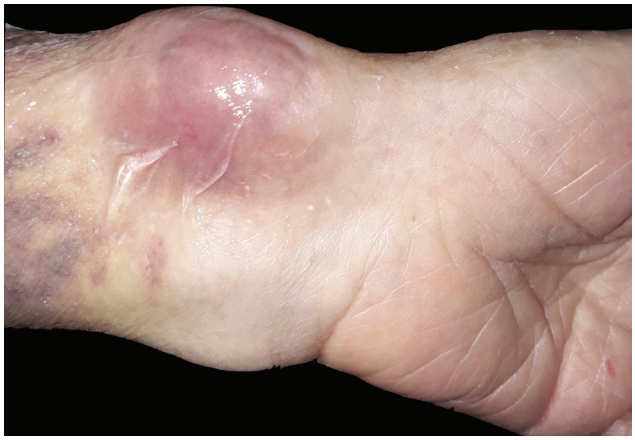

Figure 1 – Patient's left wrist with visible erythematous swelling

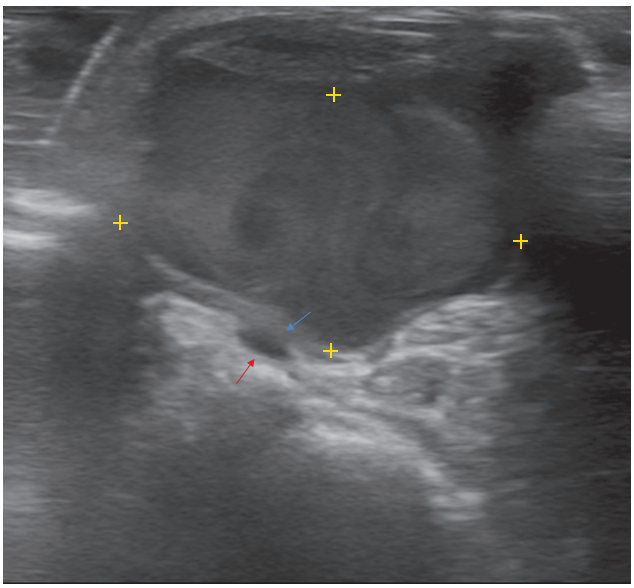

Figure 2 – Short-axis (transversal) view over left wrist swelling. The red arrow indicates the radial artery. The blue arrow pinpoints the vessel wall injury site, communicating with the pseudoaneurysmatic sac. The yellow markers limit the pseudoaneurysm's walls (width: 24 mm, height: 16 mm). A turbulent flow inside the pseudoaneurysm, forming a "yin-yang" sign, is visible.

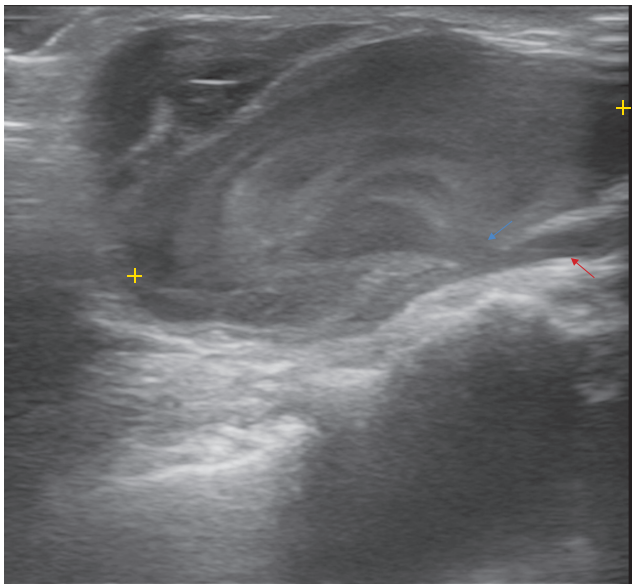

Figure 3 – Long-axis (longitudinal) view over left wrist swelling. The red arrow indicates the radial artery. The blue arrow pinpoints the vessel wall injury site, communicating with the pseudoaneurysmatic sac. The yellow markers limit the pseudoaneurysm's length (32 mm).

DISCUSSION

Iatrogenic radial PSA forms when an incomplete hemostatic plug, at the radial puncture site, leads to extravasation of blood outside the arterial wall, that is contained by a false aneurysmatic sac.[7]

It is a very uncommon complication of radial artery access, with a reported incidence rate of less than 0.1%, when considering cardiac catheterization.[8] However, a higher risk has been linked with multiple arterial punctures, delayed bleeding due to anticoagulation, larger needle/sheath sizes and inadequate post-procedural compression.[4] Furthermore, we believe that vascular ageing and progressive arterial stiffness in elderly patients may also play a role in increasing the possibility of arterial puncture complications, not only by often requiring multiple punctures, but also due to increased vascular frailty, which is particularly enhanced in patients under anticoagulation.

Pseudoaneurysm typically presents as an asymptomatic pulsatile swelling, that develops many days or weeks after arterial puncture. However, more severe presentations with distal ischemia and pain may occur, especially when ulnar collateral circulation is insufficient, which is most frequently seen in the elderly.[4,7,9] Easy compression of the blood-filled sac with subsequent fast refill, as well as, an audible bruit over the swelling are also suggestive of PSA.[7] Prompt POCUS assessment can easily confirm the diagnosis by displaying a pulsatile cystic-like collection with turbulent flow. A 'yin-yang' sign (similar to the traditional Chinese philosophical symbol), and a neck region that bridges communication between the true vessel lumen and the PSA sac are frequently observed on ultrasound. Spectral Doppler with a 'to-and-from' waveform at the neck region of the PSA is also highly suggestive of the diagnosis.[4,7,10]

The natural history of small asymptomatic PSA is spontaneous thrombosis and resolution within a few weeks. Therefore, conservative (serial observation, compression bandages and ultrasound-guided compression) or minimally invasive (ultrasound-guided thrombin injection) management is typically adequate. Symptomatic and larger PSA, with distal ischemia, frequently require surgical correction.[4,7,11,12] Despite PSA being a rare occurrence, controlling the risk factors predisposing to this complication may limit potentially severe consequences. Ultrasound-guided arterial puncture may play a role, particularly in populations like the elderly, with increased vascular frailty, anticoagulation therapy or complex vascular access.

POCUS is revolutionizing the clinical approach to critically ill patients, particularly in emergency scenarios, although its usefulness encompasses every moment of clinical contact. As a whole, it combines traditional clinical skills, that obviously retain their fundamental value, with newer and sophisticated means, allowing better diagnostic and therapeutic results within a shorter timeframe, that is essential in time-sensitive critical conditions, such as hemoperitoneum, cardiac tamponade, massive pneumothorax, among other scenarios. The portability of bedside ultrasound machines also allows us to incorporate this instrument in the clinical workup right at the patient's bedside, performing an evaluation based on clinical problems (we could even call it problem-based ultrasound) instead of the more traditional organ-oriented approach.

The usefulness of POCUS came to light during the SARS-CoV-2 pandemic, in which bedside lung ultrasound enabled resource optimization, and making a swifter diagnosis, while reducing the risk of staff infection.[13,14] Moreover, the value of ultrasound as an adjuvant tool for many invasive maneuvers is well established, leading to improved outcomes and reduced risks.

CONCLUSION

Since ABG, with radial artery puncture, is one of the most frequent procedures in clinical practice, healthcare professionals should be aware of possible complications, including those that are uncommon like PSA, in order to appropriately diagnose and manage them. Point-of-care ultrasound presents itself as a valuable tool to quickly confirm diagnosis and guide management, especially in patients at higher risk of developing complications, while offering the possibility of minimizing risks and improving efficacy, as already seen with other types of ultrasound-guided accesses.

AUTHOR CONTRIBUTIONS

NC, CC: Literature review, draft of the manuscript.
MB: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

NC has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from the School of Medicine of University of Minho and POCUS X – Point-of-care Ultrasound Training

Company; is a member of secretariat of Núcleo de Estudos de Ecografia – Sociedade Portuguesa de Medicina Interna (Ultrasound Study Group of the Internal Medicine Portuguese Society).

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Actinomycetoma by *Cellulosimicrobium cellulans* in a Young Man from Guinea-Bissau: Short Literature Review Regarding a Case Report

Actinomicetoma por *Cellulosimicrobium cellulans* num Jovem Guineense: Breve Revisão de Literatura a Propósito de um Caso Clínico

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Acta Med Port 2024 Jan;37(1):46-50 ▪ https://doi.org/10.20344/amp.17356

ABSTRACT

Mycetoma is caused by the subcutaneous inoculation of filamentous fungi or aerobic filamentous bacteria. *Cellulosimicrobium cellulans* is a gram-positive bacterium from the order *Actinomycetales* that rarely causes human disease. The diagnosis is based on the clinical presentation and identification of the causative microorganism. We present a short literature review regarding the case report of a young man diagnosed with actinomycetoma due to *Cellulosimicrobium cellulans* and treated with an association of amikacin and sulfamethoxazole/ trimethoprim (Welsh regimen).
Keywords: Actinomycetales; Mycetoma/diagnosis; Mycetoma/therapy

RESUMO

O micetoma é causado pela inoculação subcutânea de fungos filamentosos ou bactérias filamentosas aeróbias. *Cellulosimicrobium cellulans* é uma bactéria Gram positivo da ordem *Actinomycetales*, que raramente causa doença em humanos. O diagnóstico é baseado na apresentação clínica e na identificação do microrganismo. Apresentamos uma breve revisão de literatura, a propósito do caso clínico de um jovem com diagnóstico de actinomicetoma por *Cellulosimicrobium cellulans* tratado com uma associação de amicacina e sulfametoxazol/trimetoprim (esquema de Welsh).
Palavras-chave: Actinomycetales; Micetoma/diagnóstico; Micetoma/tratamento

INTRODUCTION

Mycetoma is a chronic, localized and slowly progressive disease of the skin and soft tissue, caused by ubiquitous bacteria (actinomycetoma) and fungi (eumycetoma).[1] It is endemic in tropical and subtropical areas. The treatment depends on the etiology and other factors, and the cure rate is variable.[2–4] *Cellulosimicrobium cellulans* (*C. cellulans*) is a Gram-positive bacteria that rarely causes human disease.[5,6]

We present the case of a young man from Guinea-Bissau diagnosed with actinomycetoma due to *C. cellulans*. The indolent clinical course and complications, related to the delayed diagnosis and multiple therapeutic regimens, underline the importance of its recognition in non-endemic countries.

CLINICAL REPORT

In 2017, a 17-year-old male from Guinea-Bissau was transferred under an agreement between the governments of Portugal and Guinea-Bissau to a Paediatric Infectious Diseases department in Portugal, for the investigation of intermittent fever and nodular exudative lesions of the left foot that had been evolving for six years. With no history of trauma, he initially had a painless nodule on the plantar aspect of the foot that gradually developed purulent discharge and a firm swelling.

On physical examination, he had multiple infiltrative nodules and sinuses, with purulent and haemorrhagic drainage, and oedema reaching the ankle and leading to important functional limitations (Fig. 1). The Laboratory tests revealed a normal blood cell count, elevation of C-reactive protein (52.7 mg/L) and erythrocyte sedimentation rate (44 mm/h). The interferon-gamma release assay (IGRA) was negative and the chest X-ray was unremarkable. A magnetic resonance imaging (MRI) of the left foot revealed a granulomatous mass with extensive local involvement of the subcutaneous tissue, muscles, and bones, with multiple nodular lesions showing the 'dot-in-circle' sign and several foci of avascular necrosis of the bone (Fig. 2).

The histologic examination of a tissue biopsy identified spore aggregates with periodic acid-reactive Schiff (PAS) stain. Admitting the diagnosis of eumycetoma, he was started on itraconazole.

Due to lack of clinical improvement, a second biopsy was performed. The histological examination showed a "granulomatous inflammatory infiltrate and basophilic filamentous microorganisms suggestive of *Actinomyces*" and the pan-bacterial polymerase chain reaction (PCR) identified *C. cellulans*, thus supporting the diagnosis of actinomycetoma.

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Recebido/*Received*: 21/10/2021 - **Aceite/*Accepted*:** 09/11/2022 - **Publicado *Online*/*Published Online*:** 15/03/2023 - **Publicado/*Published*:** 03/01/2024

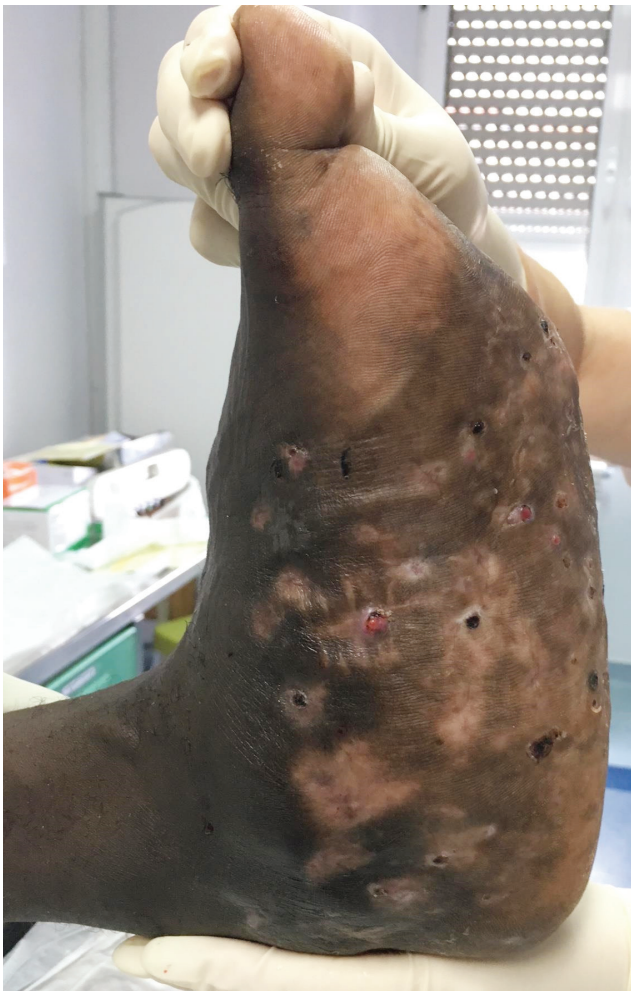

Figure 1 – Actinomycetoma of the left foot: multiple nodular lesions with sinuses and severe deformity

In the following months, the patient received sequential treatment with β-lactams, aminoglycosides and sulfamethoxazole/trimethoprim (STX/TMP) in monotherapy and underwent several surgical debridements, without improvement of the nodules and oedema.

In 2018, he received treatment with continuous oral STX/TMP in association with a four-week course of meropenem every two weeks, complemented by debridements and hyperbaric oxygen treatments.

In April 2019, the patient was transferred to the adult ID Department, with nine cycles of this regimen completed, showing regression of the oedema, but still with recurrence of the subcutaneous nodular lesions between meropenem courses. He was reassessed with an MRI, which, despite showing some improvement, identified multiple bone and subcutaneous lesions.

After a review of the literature, he was started on four courses of amikacin 15 mg/kg/day for three weeks and continuous oral STX/TMP 35 mg/kg/day, with two-week amikacin free periods.

The patient completed treatment, without relapse of the lesions after the second course of amikacin, and with full functional recovery. No otologic or renal toxicity occurred.

For the next 15 months, he was evaluated every three months, without recurrence of lesions on physical examination. In January 2021, the magnetic resonance imaging (MRI) showed significant decrease in the number of lesions, no new nodules and stable bone involvement (Fig. 3).

DISCUSSION

The first case of mycetoma was described by Dr John Gill, in the Indian town of Madura, in 1842, referring to the disease as Madura foot.[7,8] Since 2016, it is among the neglected tropical diseases according to the World Health Organization.[9]

Most cases occur in the 'Mycetoma Belt', which includes tropical and subtropical areas of Africa, Central and South America and Asia, particularly the Indian subcontinent. The true incidence and prevalence are unknown.[2,9–11] Some studies demonstrate a higher prevalence in men, while others show no difference between sexes.[1,10,12,13]

It is a chronic, localized and slowly progressive disease and most frequently affects feet and hands. It is characterized by painless subcutaneous granulomas, with sinuses draining pus, blood and grains, which results in destruction of structures and deformity.[2,4,7,14–16] Bone involvement may occur.[4,12,13,16,17]

Mycetoma is caused by ubiquitous fungi (eumycetoma) or filamentous bacteria (actinomycetoma), found in soil and plants of endemic countries, with more than 50 species identified.[2,3,12,14,15] It is most frequently caused by *Nocardia*, *Streptomyces,* and *Actinomadura*.[2,4,11,17] The disease evolves within weeks to years after skin trauma.[15–17]

The diagnosis is based on physical findings, biopsy or fine needle aspiration, and imaging. The identification of microorganisms can be made by histopathologic examination, culture and molecular techniques, and involvement of structures can be evaluated using radiography, ultrasonography, computed tomography scan, and MRI, with the last being more sensitive.[2,18] The 'dot-in-circle' sign, in ultrasound or MRI, is considered pathognomonic of musculoskeletal mycetoma.[18,19]

The differential diagnosis includes sporotrichosis, tuberculosis, osteomyelitis, coccidiomycosis, botryomycosis, other fungal infections, and neoplasms of the bone and soft tissues.[4,11]

The treatment choice depends on the causative agent, disease extension, and host factors. The combination of STX/TMP and amikacin, with or without rifampicin (Welsh regimen and modified Welsh regimen) showed good

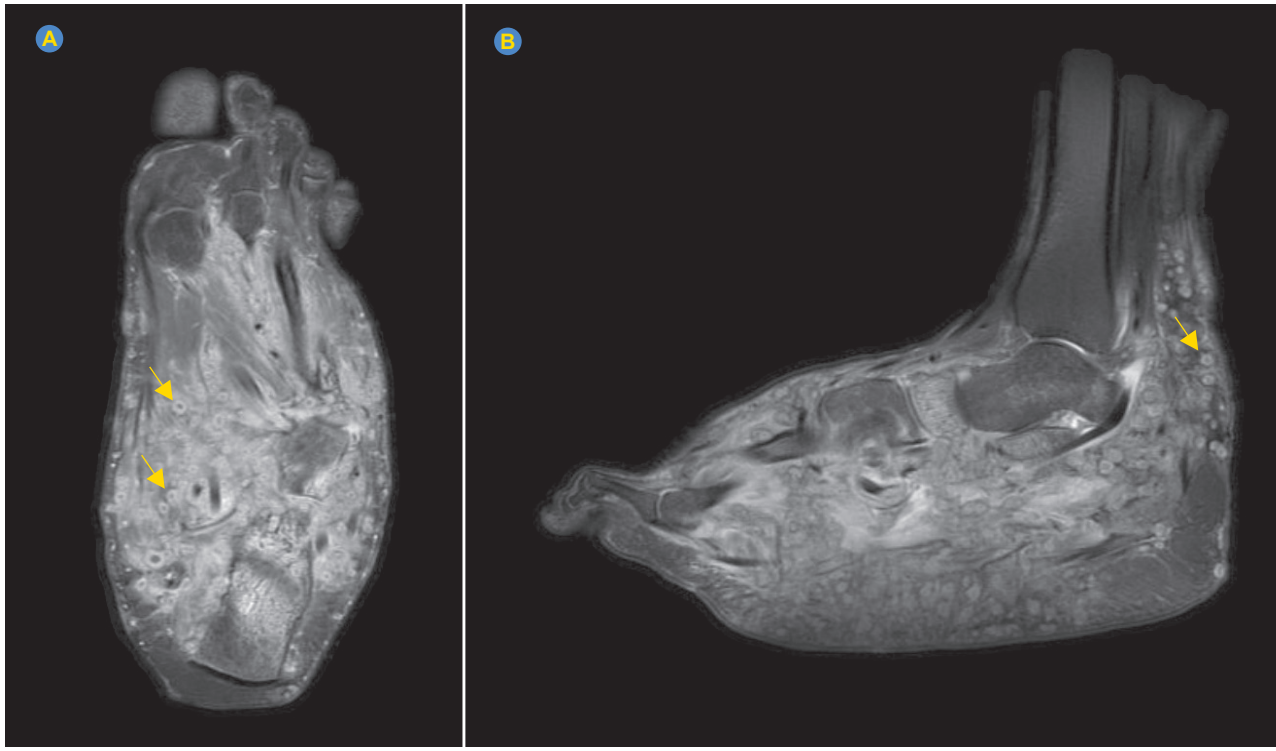

Figure 2 – MRI revealing nodular lesions, with 'dot-in-circle' sign (arrows), involving bone, muscles and subcutaneous tissue of the left foot

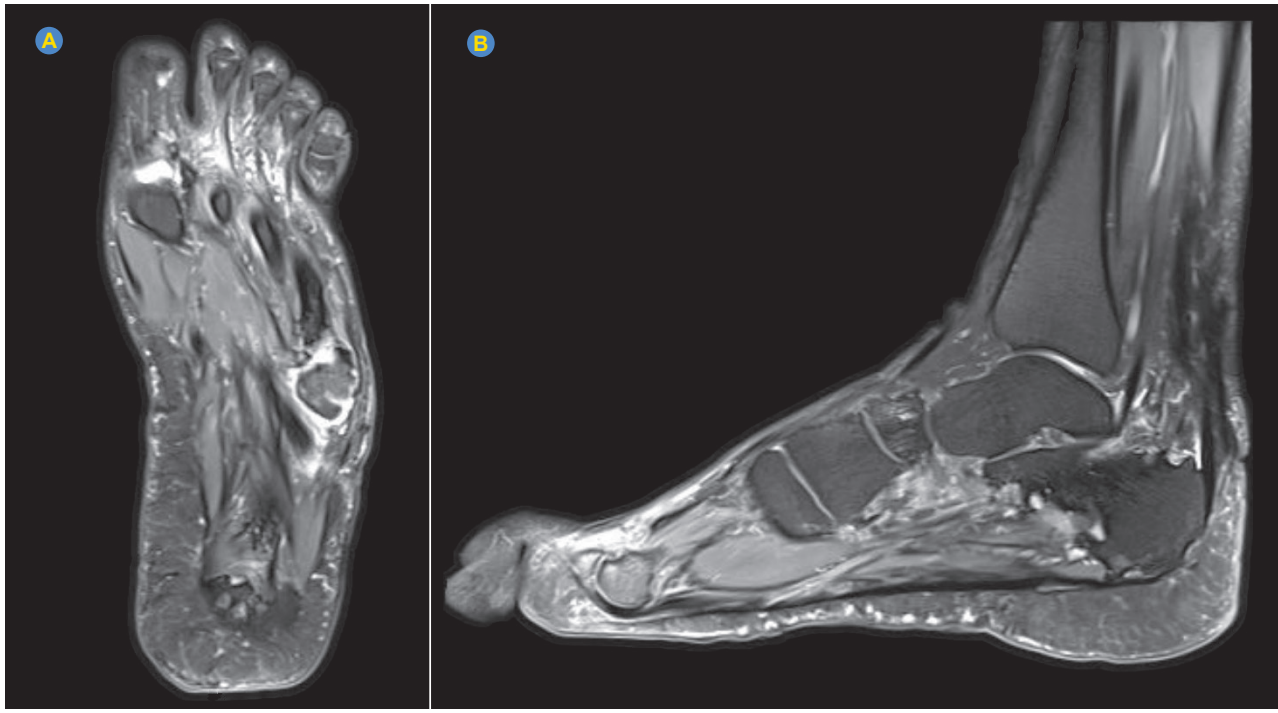

Figure 3 – Post-treatment MRI of the left foot showing regression of the lesions and tissue edema, with bone sequelae

outcomes.[11,13,16] The alternatives are STX/TMP and dapsone or rifampicin; amoxicillin/clavulanate and netilmicin, for STX/TMP and amikacin allergy, respectively; amikacin and meropenem or imipenem can be used in refractory cases; other combinations can be used as well.[4,12,13,15–17] The guidelines from the Mycetoma Research Centre of Khartoum recommend streptomycin and dapsone as first-line drugs.[20] Monotherapy is not recommended.[2,13,15,16]

Surgical treatment is indicated for localized lesions and for large lesions, in combination with antibiotics, to reduce the organism load.[17]

C. cellulans, formerly known as *Oerskovia xanthineolytica* and *Nocardia cellulans*, is a gram-positive bacillus from the order *Actinomycetales*, and is distributed widely in the environment. It is a rare human pathogen.[5,6]

In a literature review published in 2019, the main risk factors for *C. cellulans* infection were underlying chronic disease affecting the immune system and the presence of foreign bodies. Only one case of abscess formation related with intramuscular injections has been described. The isolates were susceptible to vancomycin, STX/TMP, imipenem and amikacin.[6]

The literature provides a good, albeit fragmented, overview of the presentation and etiology of mycetoma. However, there are no randomized controlled trials on the best therapeutic approach, leading clinicians to make decisions based on case reports, small retrospective studies, and scarce systematic reviews.

This case report describes a delayed and complex diagnosis of actinomycetoma, which happen often outside reference centres. Therefore, it emphasizes the importance of early recognition of the disease and identification of the causative microorganism.

Several factors may have contributed to the ineffectiveness of the previous therapeutic regimens, such as lesion extension, difficult identification of the microorganism and no antibiotic susceptibility testing, monotherapy regimen, and short courses of treatment.

The decision on the best therapeutic approach was also challenging due to lack of guidelines for the treatment of mycetoma in our setting and no information on the susceptibility profile of *C. cellulans.*

AUTHORS CONTRIBUTION

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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Penile Cellulitis Related to Mpox Genital Lesions

Celulite Peniana Relacionada com Lesões Genitais de Mpox

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Acta Med Port 2024 Jan;37(1):51-52 ▪ https://doi.org/10.20344/amp.19832

Keywords: Penile Diseases; Monkeypox virus; Monkeypox
Palavras-chave: Doenças do Pénis; Varíola dos Macacos; Vírus da Varíola dos Macacos

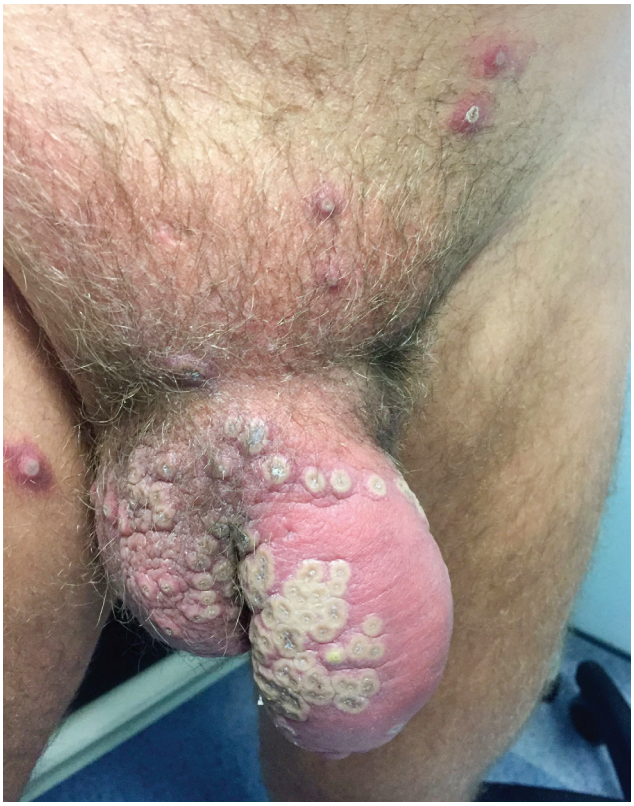

Figure 1 – Penile edema related to papules with central umbilication and pustules in the genital area

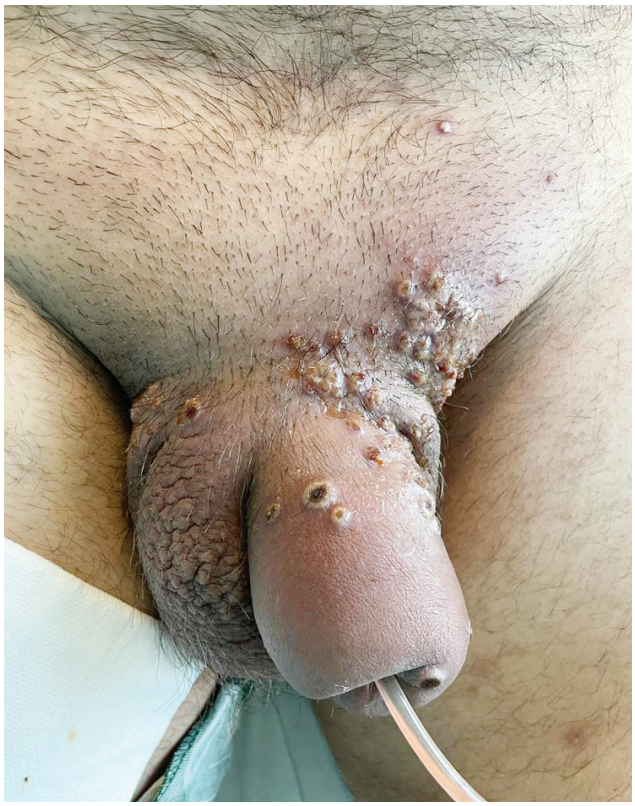

Figure 2 – Monkeypox lesions and penile edema leading to phimosis that required catheterization

A 40-year-old man presented to the emergency department with a five-day history of a genital papular rash. He had had unprotected sex with multiple male partners in the previous four weeks. A probable diagnosis of herpes simplex virus infection was assumed, and he was discharged with valacyclovir 1 g twice daily for seven days. However, four days later, he returned with an aggravation of his condition. The physical examination showed several lesions in the patient's genital area, upper and lower limbs at different stages of evolution, namely papules with central umbilication, pustules and edema of the penis (Fig. 1) with associated local pain. No fever was detected. Nucleic acid amplification tests for mpox virus were positive. In our institution, some cases of penile cellulitis related to mpox virus infection have been observed (Fig. 2), all with favorable evolution under antibiotic therapy, as the majority of the reported cases.[1] In a scenario of penile cellulitis of unexplained cause, particularly in men that have sex with men, testing for mpox virus infection is recommended.[2]

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Recebido/*Received*: 27/02/2023 - **Aceite/*Accepted*:** 03/05/2023 - **Publicado *Online*/*Published Online*:** 05/06/2023 - **Publicado/*Published*:** 03/01/2024

AUTHOR CONTRIBUTIONS

FOS: Data acquisition, analysis and interpretation. Writing of the manuscript.

AJC, JN: Critical review and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Utilização de Gadolínio nas Ressonâncias Magnéticas de Controlo em Doentes com Esclerose Múltipla: Recomendações Atuais

Use of Gadolinium in Follow-Up MRI of Multiple Sclerosis Patients: Current Recommendations

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Acta Med Port 2024 Jan;37(1):53-63 ▪ https://doi.org/10.20344/amp.20467

RESUMO

A esclerose múltipla é a doença desmielinizante do sistema nervoso central mais frequente, caracterizando-se pelo início precoce e incapacidade progressiva. A ressonância magnética, pela elevada sensibilidade e especificidade na deteção de lesões desmielinizantes, é o exame complementar mais útil nesta patologia, sendo a administração de meios de contraste com gadolínio um importante contributo na interpretação imagiológica. Embora o contraste seja imprescindível no âmbito do diagnóstico, a sua utilização por rotina na monitorização da atividade de doença, resposta ao tratamento e respetivas complicações é controversa. O objetivo deste artigo é reunir as recomendações atuais relativas à utilização do gadolínio no seguimento imagiológico da esclerose múltipla e definir um protocolo clínico efetivo e seguro. A revisão da literatura foi conduzida na PubMed, recorrendo aos termos 'esclerose múltipla', 'ressonância magnética' e 'gadolínio' ou 'meio de contraste'. Foram selecionados artigos publicados entre janeiro de 2013 e de 2023 relativos à segurança do gadolínio e à sua utilização na ressonância magnética de controlo dos doentes adultos com diagnóstico de esclerose múltipla. Apesar de nenhuma consequência biológica ou clínica ter sido inequivocamente atribuída à retenção cerebral do gadolínio, que foi reportada maioritariamente com agentes lineares, as autoridades de saúde têm vindo a recomendar a restrição do contraste a circunstâncias clínicas essenciais. Na esclerose múltipla, a deteção de lesões subclínicas com captação de gadolínio sem tradução em lesões novas/aumentadas nas sequências ponderadas em T2 ocorre raramente e com impacto na decisão terapêutica questionável. Por outro lado, o gadolínio assume uma sensibilidade superior no diagnóstico diferencial de surtos clínicos, na deteção de atividade inflamatória recente, antes e após o início de uma terapêutica e nos doentes com elevada carga lesional ou lesões difusas/confluentes nas sequências ponderadas em T2. Contrariamente ao rastreio da leucoencefalopatia multifocal progressiva, a monitorização da síndrome inflamatória de reconstituição imunológica beneficia também da inclusão do gadolínio. É exequível e segura a exclusão do gadolínio no seguimento imagiológico de rotina da esclerose múltipla, apesar do seu contributo adicional em circunstâncias clínicas específicas que devem ser do conhecimento articulado do neurologista e neurorradiologista.
Palavras-chave: Esclerose Múltipla/diagnóstico por imagem; Gadolínio; Meios de Contraste; Ressonância Magnética

ABSTRACT

Multiple sclerosis is the most frequent demyelinating disease of the central nervous system and is characterized by early onset and progressive disability. Magnetic resonance imaging, due to its high sensitivity and specificity in the detection of demyelinating lesions, is the most useful diagnostic test for this disease, with the administration of gadolinium-based contrast agents being an important contribution to imaging interpretation. Although contrast is essential for diagnostic purposes, its routine use in monitoring disease activity, response to treatment, and related complications is controversial. This article aims to collate current recommendations regarding the use of gadolinium in the imaging follow-up of multiple sclerosis and establish effective and safe guidelines for clinical practice. The literature review was conducted in PubMed, using the terms 'multiple sclerosis', 'magnetic resonance imaging' and 'gadolinium', or 'contrast media'. Articles published between January 2013 and January 2023 concerning the safety of gadolinium and the use of these contrast agents in follow-up scans of adult patients diagnosed with multiple sclerosis were selected. Although no biological or clinical consequences have been unequivocally attributed to the retention of gadolinium in the brain, which were mostly reported with linear agents, health authorities have been recommending the restriction of contrast to essential clinical circumstances. In multiple sclerosis, the detection of subclinical contrast-enhancing lesions with no corresponding new/ enlarging T2-WI lesions is rare and has a questionable impact on therapeutic decisions. On the other hand, gadolinium has a higher sensitivity in the differential diagnosis of relapses, in the detection of recent disease activity, before and after treatment initiation, and in patients with a large lesion burden or diffuse/confluent T2-WI lesions. Contrary to progressive multifocal leukoencephalopathy screening, monitoring of immune restitution inflammatory syndrome also benefits from the administration of gadolinium. It is feasible and safe to exclude gadolinium-based contrast agents from routine follow-up scans of multiple sclerosis, despite their additional contribution in specific clinical circumstances that should be acknowledged by the neurologist and neuroradiologist.
Keywords: Contrast Media; Gadolinium; Magnetic Resonance Imaging; Multiple Sclerosis/diagnostic imaging

INTRODUÇÃO

A esclerose múltipla (EM) é uma doença crónica imunomediada caraterizada por inflamação, desmielinização e neurodegenerescência do sistema nervoso central (SNC). Afeta cerca de 2,8 milhões de pessoas em todo o mundo[1] com uma prevalência estimada de 64,4 doentes/ 100 000 habitantes em Portugal.[2] É a doença desmielinizante do SNC mais frequente e carateriza-se por uma evolução variável, pautada por surtos clínicos e incapacidade progressiva, sendo a forma de apresentação mais frequente a surto-remissão (SR).[2] Manifesta-se em adultos jovens, entre 20 e os 50 anos,[3] com uma incidência aproximadamente três vezes superior no sexo feminino.[4] O seu curso é

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Recebido/*Received*: 03/07/2023 - **Aceite/*Accepted*:** 30/10/2023 - **Publicado/*Published*:** 03/01/2024

marcado por uma importante incapacidade funcional, com deterioração da qualidade de vida dos doentes e um impacto económico significativo para a sociedade.[1]

A ressonância magnética (RM), incorporada desde 2001 nos critérios diagnósticos da EM,[5] assume-se como o exame complementar de eleição nesta entidade, pela elevada sensibilidade e especificidade na deteção de lesões desmielinizantes,[6,7] permitindo a avaliação objetiva da carga global da doença.[8] Os meios de contraste com gadolínio (GBCAs) surgem, neste exame, como os agentes de contraste mais utilizados, integrando atualmente a prática clínica para propósitos de diagnóstico, prognóstico e monitorização.[9] O seu papel no estabelecimento do diagnóstico da EM é essencial e consensualmente recomendado,[10,11] uma vez que a informação dada pelas lesões que captam gadolínio (GD) permite a demonstração da disseminação no tempo, segundo os critérios de McDonald de 2017,[12] sendo igualmente importante na exclusão de diagnósticos diferenciais.[9,11,13]

Por outro lado, é controversa a imprescindibilidade do contraste na monitorização da atividade da doença, resposta ao tratamento e respetivas complicações. Dado que os doentes com EM realizam múltiplos exames de RM com contraste, desde muito jovens e durante vários anos de seguimento, justifica-se uma revisão das indicações dos GBCAs no seguimento de rotina desta patologia, acrescendo para este debate a discussão em curso, na comunidade científica, sobre a segurança do GD.

O objetivo deste artigo é reunir as recomendações atuais relativas à utilização dos GBCAs nas RM de controlo dos doentes com EM, de modo a definir um protocolo de monitorização efetivo e seguro a implementar na prática clínica, ponderando os riscos e benefícios envolvidos.

MÉTODOS

Para a presente revisão da literatura, foi realizada uma pesquisa, na base de dados PubMed, com a seguinte fórmula: "'Multiple Sclerosis' AND 'Magnetic Resonance Imaging' AND ('Contrast Media' OR 'Gadolinium')". Foram incluídos artigos publicados entre janeiro de 2013 e janeiro de 2023, com versão completa disponível, escritos em língua inglesa ou portuguesa, abrangendo a segurança do GD e a utilização do mesmo na RM de controlo dos doentes adultos com diagnóstico estabelecido de EM. Excluíram-se estudos pré-clínicos em modelos animais, bem como recomendações direcionadas a populações-alvo com caraterísticas particulares, nomeadamente idade pediátrica, gravidez, pós-parto e lactação. A análise de 256 artigos incluídos no intervalo de pesquisa definido permitiu a exclusão de 169 pelo título/resumo e 33 após leitura integral. Foram ainda adicionados 32 artigos de interesse com base na seleção inicial, perfazendo um total de 86 estudos revistos.

DEPOSIÇÃO CEREBRAL DE GADOLÍNIO

Os GBCAs são agentes de contraste paramagnéticos introduzidos em 1988 na prática clínica.[14] Podem ser classificados em lineares ou macrocíclicos, de acordo com a estrutura molecular do ligando a que o ião de GD se encontra quelado, e em iónicos ou não iónicos, consoante a carga do complexo formado. Nos compostos macrocíclicos, o ligando apresenta uma forma de anel rígido que envolve completamente o ião de GD no seu centro; enquanto nos compostos lineares a estrutura molecular que envolve o ião é mais aberta e flexível, conferindo uma menor proteção ao GD, que sofre assim um maior risco de dissociação – razão pela qual os GBCAs lineares possuem, de um ponto de vista molecular, menor estabilidade. Os efeitos secundários associados à sua administração endovenosa são mínimos, tendo sido considerados seguros aquando da sua introdução.[14]

Porém, no ano de 2006 foi recomendada a suspensão dos GBCAs lineares nos doentes com insuficiência renal grave, pela associação com fibrose sistémica nefrogénica, uma entidade rara, mas com elevada morbimortalidade, e cuja incidência diminuiu consideravelmente após esta restrição.[15] O Colégio Americano de Radiologia determinou, assim, uma divisão dos GBCAs em função do seu risco nefrogénico, sendo este risco mínimo (inferior a 0,07%) no grupo II, que inclui maioritariamente compostos macrocíclicos (gadobutrol, gadoteridol e gadoterato de meglumina) e também um composto linear (gadobenato de dimeglumina).[16]

Relativamente aos doentes com função renal normal, a discussão sobre a segurança dos GBCAs emergiu apenas em 2014, com a deteção de alterações imagiológicas compatíveis com a presença de depósitos de GD no SNC em doentes submetidos a múltiplas RM com GBCAs lineares,[17] confirmados em estudos *post-mortem*.[18] Estes doentes exibiam, na sequência de RM cerebrais ponderadas em T1 sem contraste, uma maior intensidade de sinal, sobretudo no núcleo dentado e globo pálido, correlacionada positivamente com o número prévio de administrações de contraste.[17] A referida hiperintensidade de sinal foi reportada pela primeira vez em 2009, como marcador de neurodegenerescência da EM, pela correlação positiva com variáveis clínicas e imagiológicas de severidade da doença.[19] Contudo, é atualmente consensual a atribuição destes achados à administração de contraste,[17,20,21] um fator confundente não contemplado anteriormente. Estas conclusões foram igualmente suportadas recorrendo à análise quantitativa proporcionada pelas técnicas de relaxometria em T1 e T2.[18,22,23]

Ainda que a retenção de GD seja preponderante no núcleo dentado, seguido do globo pálido, vários autores admitem uma acumulação cerebral disseminada, envolvendo inclusivamente regiões como a substância nigra,[24] a ponte

ou o tálamo.[18]

Apesar de as publicações iniciais terem sugerido a formação de depósitos de GD em doentes que receberam seis ou mais injeções de GBCAs lineares[17,25] e das autoridades de saúde americanas terem alertado para o mesmo efeito com o mínimo de quatro doses,[26] estudos mais recentes apontam que tal possa ocorrer com apenas uma administração.[27,28] Vários aspetos do comportamento do GD no organismo permanecem por esclarecer,[29] havendo evidência contraditória relativamente à permanência no tempo dos depósitos cerebrais[18,27,30,31] e investigações a sugerir a possibilidade do osso funcionar como reservatório do contraste, por apresentar níveis nove ou mais vezes superiores aos encontrados no globo pálido,[30] potenciando a recirculação nos tecidos.[18,30]

A acumulação de GD depende também da estrutura molecular do GBCAs administrado, sendo consensual uma retenção superior com os compostos lineares não iónicos, comparativamente aos lineares iónicos[32] e dos GBCAs lineares comparativamente aos macrocíclicos.[21,33] O efeito do uso exclusivo dos GBCAs macrocíclicos permanece por clarificar. A numerosa evidência da segurança destes agentes,[23,27,28,34-37] com base na ausência de alterações imagiológicas compatíveis com depósitos de GD, contrasta com os dados apresentados por Stojanov *et al*[38] que demonstram uma correlação positiva entre a administração cumulativa de gadobutrol e a retenção de contraste. Embora esta investigação[38] tenha sido amplamente criticada na comunidade científica pelas suas limitações metodológicas e de apresentação de resultados,[28] as conclusões merecem uma análise cuidada, dado que outros autores reportaram hiperintensidade de sinal com gadoterato de meglumina ou gadobutrol, ainda que sem significância estatística.[39] A retenção de GD após administração de agentes macrocíclicos no tecido cerebral foi ainda demonstrada por espectrometria de massa, em concentrações, todavia, 20 vezes menores comparativamente a GBCAs lineares não iónicos.[30]

A evidência supramencionada motivou, em 2017, a suspensão de todos os GBCAs lineares utilizados na EM,[40] permanecendo apenas os macrocíclicos em uso pela sua maior estabilidade e menor risco de desconjugação e retenção nos tecidos.

Nos estudos que procuraram, até à data, avaliar a integridade tecidual das estruturas afetadas pelos depósitos de gadolínio, nomeadamente do núcleo dentado, recorrendo a RM com 23-sódio,[41] a RM ponderada em difusão (DWI)[33] ou a ultrassonografia transcraniana,[42] não foram observadas alterações.

Em doentes com EM, a retenção de GD imagiológica foi associada a menor desempenho na fluência verbal,[23,43] menor velocidade de processamento da informação[23] e maior incapacidade funcional avaliado por EDSS (do inglês *Expanded Disability Status Scale*),[24,27] apesar desta última ter sido refutada por outros estudos.[23,44,45] Contudo, estas investigações padecem de limitações importantes como amostras reduzidas e ferramentas de avaliação que não englobam todas as funções específicas das estruturas com maior deposição de GD. Admite-se, adicionalmente, que a investigação conduzida na EM possa ter como importante fator confundente a própria fisiopatologia da doença, pautada por neurodegenerescência, incapacidade progressiva e deterioração cognitiva, mesmo após a correção de fatores de gravidade da doença na interpretação dos dados.

Noutros contextos clínicos não se observou na literatura uma demonstração de sintomatologia atribuível à exposição cumulativa a GBCAs, nomeadamente toxicidade cerebelosa[46] ou parkinsonismo.[47]

Alguns autores atribuíram a nomenclatura 'doença da deposição do GD' aos sintomas inespecíficos e generalizados, não diretamente relacionados com os locais de mais frequente acumulação de GD, autorreportados por alguns doentes horas ou até dois meses após exposição a GBCAs endovenosos.[48] Destacam-se neste contexto as dores ósseas/articulares, cefaleias e alterações visuais/auditivas,[49] não obstante as limitações metodológicas das publicações em foco.

Em suma, à data desta revisão, nenhum efeito biológico ou consequência clínica, com relação causal estabelecida foi inequivocamente atribuído à acumulação a longo prazo dos GBCAs no SNC.[50,51] Face ao estado de arte e enquanto se aguardam novos ensaios prospetivos de grandes dimensões, a Agência Europeia de Medicamentos (EMA) e a organização reguladora equivalente nos Estados Unidos, Food and Drug Administration (FDA), recomendam limitar

- Foram detetados depósitos cerebrais de gadolínio (GD), nomeadamente no núcleo dentado e globo pálido, em doentes submetidos a múltiplas ressonâncias magnéticas (RM) com agentes de contraste, de forma proporcional ao número de administrações.
- A retenção é superior com compostos lineares não iónicos, seguindo-se os lineares iónicos e por fim os macrocíclicos, com evidência controversa em relação aos últimos.
- Não são conhecidos efeitos biológicos ou consequências clínicas inequivocamente atribuídos à acumulação a longo prazo do GD no SNC.
- Recomenda-se a limitação destes agentes de contraste exclusivamente a circunstâncias clínicas em que seja indispensável a informação adicional que providenciam.

os GBCAs à menor dose possível e exclusivamente a circunstâncias clínicas em que a informação que providenciam seja indispensável.[40,50]

A Sociedade Internacional de RM em Medicina recomenda aos clínicos uma boa documentação dos GBCAs administrados e encoraja, quando justificável nos projetos de investigação, a obtenção de consentimento informado com informação relativamente ao estado de arte da deposição do GD.[29]

LESÕES NA ESCLEROSE MÚLTIPLA ATIVA

As lesões desmielinizantes clássicas da EM possuem uma forma redonda/ ovóide, com mais de 3 mm e distribuem-se no SNC tipicamente por localizações periventriculares (sendo comum a configuração em dedos de Dawson), justacorticais/corticais, infratentoriais, no corpo caloso e na medula espinhal.[9]

A identificação do estado de 'doença ativa' na EM, caraterizado pela progressão da inflamação e neurodegenerescência, é essencial para otimizar decisões terapêuticas e prevenir incapacidade acumulada. A 'doença ativa' pode ser definida pela presença de surtos clínicos ou, mais frequentemente, de acordo com critérios imagiológicos, por lesões captantes de GD ou lesões novas/ aumentadas nas sequências ponderadas em T2.[7,15,52]

A avaliação da captação de GD deve ser realizada na ponderação em T1 de RM, adquirida pelo menos cinco minutos após administração de contraste. Na atividade inflamatória aguda ocorre focalmente uma disrupção/aumento da permeabilidade da barreira hematoencefálica, que é então atravessada pelo GD.[7,9] Esta captação de GD permite inferir o tempo de instalação da lesão, uma vez que o realce apenas persiste por duas a seis semanas.[3,6,53,54] Assim, mesmo com intervalos de monitorização relativamente curtos (seis meses a um ano), a atividade da doença não poderá ser exclusivamente avaliada pela captação de GD, devendo ser também informada pela presença de novas lesões hiperintensas nas sequências ponderadas em T2 ou aumento de lesões prévias.[3,54,55] A sua presença traduz a persistência do processo inflamatório e destruição tecidual focal, que teve lugar algures no tempo entre a realização de dois exames de RM, indicando assim ocorrência de progressão da doença nesse intervalo. Embora ambas as lesões sejam usadas para definir doença ativa, apenas as lesões com captação de contraste representam a fase ativa da inflamação focal, com as lesões T2 novas/aumentadas a capturar um estádio mais tardio e irreversível do mesmo processo inflamatório.[15,54,55]

LESÕES T2 NOVAS/AUMENTADAS NA MONITORIZAÇÃO DA ATIVIDADE DA DOENÇA

Na última década, diversos estudos retrospetivos (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20467/15278) foram conduzidos com o objetivo de avaliar a concordância entre os achados imagiológicos sugestivos de doença ativa na EM, em sequências de RM com e sem GD. Embora com diferentes protocolos imagiológicos e limitações como a natureza retrospetiva ou as amostras reduzidas, selecionadas e homogéneas de doentes com EM SR, as conclusões das investigações mencionadas são unânimes: há uma baixa incidência (1,1% a 15,0%) de lesões que realçam com contraste sem correspondente aumento da carga lesional (traduzido por lesões novas/aumentadas) em sequências não contrastadas (T2-FLAIR/DIR/T2-STIR).[3,7,8,52,56-59] Estas lesões seriam explicadas por fenómenos de reativação inflamatória de lesões pré-existentes,[7] e teriam um papel questionável na gestão clínica do doente, sendo a captação de contraste um fenómeno precoce e transitório, com baixa probabilidade de ser detetado por rotina.

Face a estes resultados, é consensual o contributo limitado do GD na definição de doença ativa, em RM de rotina, em indivíduos clinicamente estáveis, com carga lesional baixa a moderada[8] e sem evidência de novas lesões/aumentadas nas sequências não contrastadas.[3,7,52,56-59]

A implementação prática de protocolos de uso condicionado de GD, com decisão em tempo real sobre a aplicação de contraste (consoante o aumento da carga lesional em T2-FLAIR), sustentou ainda a viabilidade do uso exclusivo das lesões T2 novas/aumentadas para propósitos de mo-

- O estado de doença ativa, na EM, é definido pela presença de surtos clínicos ou alterações na RM sugestivas de atividade inflamatória, nomeadamente lesões com captação de gadolínio e lesões em T2 novas/aumentadas.
- A presença de uma lesão ativa com captação de GD traduz atividade inflamatória aguda recente, uma vez que o realce permanece por duas a seis semanas.
- As lesões novas/aumentadas em T2/FLAIR que surgem entre dois exames de RM representam uma fase tardia e irreversível do processo inflamatório focal.
- A percentagem de lesões captantes de GD sem tradução nas sequências T2/FLAIR sem contraste é muito reduzida e com impacto questionável na gestão dos doentes, tornando plausível a adoção exclusiva das lesões novas/aumentadas em T2/FLAIR no seguimento de rotina da EM.
- A implementação de protocolos com limitação do GD na EM aumentaria o conforto do doente e teria um impacto económico positivo.

nitorização da atividade da doença, com dispensa da administração do GD em 86,9% dos doentes.[60] As vantagens da limitação deste agente suplantam o potencial ganho de segurança, permitindo a redução de custos diretos e indiretos associados aos GBCAs, o aumento da disponibilidade da RM, a redução do tempo de execução da mesma e o aumento do conforto e satisfação do doente.[60,61]

LESÕES QUE REALÇAM COM GD E MONITORIZAÇÃO DA ATIVIDADE DA DOENÇA

Apesar das recomendações das autoridades de saúde no sentido de limitar a administração de GD nos exames de RM, a informação adicional fornecida pelo contraste ainda justifica o seu uso em determinados contextos clínicos.

Perante uma elevada carga lesional (mais de 20 lesões)[8] ou lesões crónicas difusas/confluentes nas sequências ponderadas em T2 (Fig. 1), a identificação de nova atividade de doença em áreas da substância branca com alterações pré-existentes é difícil e está sujeita a uma grande variabilidade interobservador, pelo que é consensual, nesta situação, a maior sensibilidade e reprodutibilidade do estudo contrastado na definição de doença ativa.[7,8,10,11,15,55,62]

Uma vez que o GD fornece informação sobre a janela temporal em que as lesões desmielinizantes ocorreram, perante intervalos entre RM prolongados, nomeadamente superiores a um ano, e sobretudo quando os exames foram executados em condições técnicas não equiparáveis, as lesões T2/FLAIR possuem isoladamente um valor diminuto na gestão do doente, podendo mesmo sugerir outras comorbilidades confundidoras, como patologias vasculares.[15]

Vários autores sugerem ainda o valor acrescido do GD antes e depois do início/alteração de qualquer terapêutica modificadora de doença (TMD), dada a maior sensibilidade das lesões que captam GD na quantificação da atividade

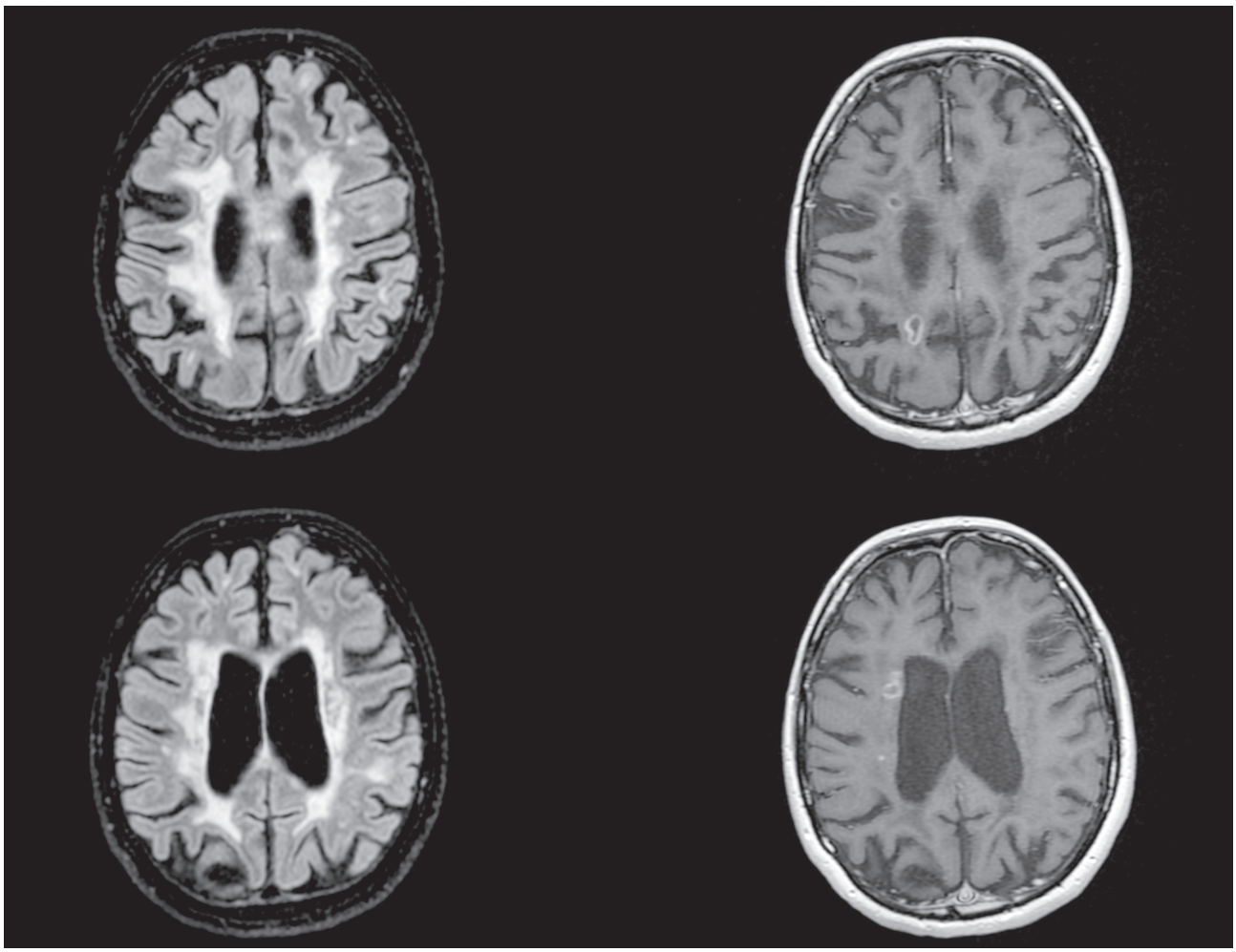

Figura 1 – Aquisições de RM, nos mesmo planos, antes (esquerda) e após (direita) administração de GD endovenoso. À direita individualizam-se múltiplas lesões com realce em anel/nodular, traduzindo atividade inflamatória aguda no seio das áreas de desmielinização confluente, representadas à esquerda pelo hipersinal nas sequências FLAIR.

- A utilização de GD permanece imprescindível nas seguintes circunstâncias clínicas:
  - Elevada carga lesional ou lesões crónicas difusas/confluentes em T2;
  - Intervalos entre RM prolongados (superiores a dois anos);
  - Obtenção de uma RM de referência quando as anteriores não estão disponíveis, antes e após início de nova terapêutica;
  - Informação sobre atividade imagiológica recente necessária para decisões terapêuticas/aferição de prognóstico;
  - Diagnóstico diferencial de surto clínico.
- As lesões ativas na medula espinhal são menos comuns que as cerebrais e tipicamente sintomáticas, razões pelas quais a RM da medula espinhal não é recomendada como exame de rotina no seguimento dos doentes.
- As técnicas e marcadores emergentes de inflamação crónica e leptomeníngea carecem de validação adicional e ainda não são recomendados na prática clínica.

inflamatória recente e avaliação da resposta ao tratamento,[52,56,58] sobretudo perante TMD menos eficazes, que teriam uma resposta subestimada com base unicamente nas lesões em T2/FLAIR.[54,55] As lesões ativas em T1 após contraste têm ainda um papel decisivo na aferição do prognóstico, associando-se a índices superiores de incapacidade a longo prazo.[7,54,63]

Ainda no que concerne à decisão terapêutica, Dallera *et al* demonstraram uma maior probabilidade de escalar para TMD de alta eficácia nos doentes que executaram RM cerebral e/ou da medula espinhal com GD, comparativamente aos que prescindiram do agente de contraste.[64] Esta diferença sofria uma diminuição significativa com o tempo (decréscimo de 63% aos dois anos),[64] podendo ser explicada pela maior atividade subclínica expectável numa fase precoce de tratamento, justificando a importância acrescida do GD e de uma monitorização imagiológica mais exigente em doentes mais jovens e com EM SR.[6,65,66] Outros investigadores realçaram uma probabilidade superior de alterar a TMD em curso perante a presença concomitante de lesões definidoras de doença ativa em T1 e T2, comparativamente com as T2 isoladamente,[58] um dado não acompanhado da informação clínica necessária para o valorizar, mas cuja interpretação poderá prender-se com a maior confiança dos clínicos na informação fornecida pelo realce com contraste na sustentação das suas decisões terapêuticas.

Por fim, qualquer deterioração clínica súbita ou inesperada, que coloque diagnóstico diferencial com pseudo surtos ou outras etiologias que possam mimetizar um agravamento da atividade inflamatória da EM, justifica a informação adicional do contraste.[8,11,56,59]

Relativamente às lesões captantes de GD na medula espinhal, a literatura admite o seu contributo na monitorização da atividade de doença subclínica[67] e escalada para terapêuticas de alta eficácia.[64] No entanto, por estas lesões ocorrerem até 10 vezes menos que as cerebrais, e possuírem tradução sintomática frequente, a RM da medula espinhal não se encontra recomendada por rotina para efeitos de monitorização de doentes estáveis.[68]

NOVAS TÉCNICAS DE RM E MARCADORES IMAGIOLÓGICOS

Nos últimos anos, surgiram diferentes técnicas quantitativas que procuram ser alternativas às aquisições convencionais de RM com GD,[69] assim como marcadores imagiológicos de atividade inflamatória crónica e leptomeníngea, cuja fisiopatologia ainda requer estudos adicionais.

A inflamação leptomeníngea, tipificada pelo realce nas sequências de RM contrastadas (nomeadamente na sequência FLAIR), foi associada à desmielinização subpial e atrofia cortical na EM.[70,71] Contudo, não se trata de um marcador específico desta doença,[72] e alguns autores relatam um comportamento estável ao longo dos anos e ausência de correlação com as lesões ativas/volume lesional na substância branca, tratamentos em curso ou exacerbações da doença.[70]

No que concerne à inflamação crónica na EM, e com elevada especificidade nesta patologia,[9] destacam-se as lesões crónicas ativas (*smoldering lesions*). Estas traduzem-se maioritariamente por um halo paramagnético nas imagens ponderadas em suscetibilidade (*iron rim lesions*) e/ou por um crescimento lento e progressivo (*slowly expanding lesions*),[73] correlacionando-se com formas de doença mais graves e progressivas.[74,75]

MONITORIZAÇÃO DAS COMPLICAÇÕES DO TRATAMENTO

O papel da RM na EM estende-se às complicações decorrentes do estado de imunossupressão gerado pelas próprias TMD. Estas complicações englobam infeções oportunistas e comorbilidades não infeciosas, como neoplasias primárias e secundárias, doenças autoimunes, encefalopatia posterior reversível e acidentes vasculares cerebrais.[10,55,66]

Pela incidência e relevância clínica, destaca-se neste contexto a leucoencefalopatia multifocal progressiva (LMP), uma infeção oportunista do SNC, com elevada morbimortalidade, causada pela reativação do vírus latente John Cunningham, com tropismo para oligodendrócitos, células neuronais e astrócitos.[76] Na EM, a LMP foi inicialmente

- A leucoencefalopatia multifocal progressiva (LMP) é uma complicação temível no decurso da imunossupressão gerada por terapêuticas modificadoras de doença usadas na EM.
- A RM cerebral permite a deteção desta entidade num estádio precoce e assintomático, melhorando o prognóstico.
- O rastreio da LMP por RM pode ser realizado apenas com sequências não contrastadas (T2 FLAIR e DWI), uma vez que as lesões precoces com captação de GD são raras.
- Por outro lado, na monitorização desta entidade e da sua evolução para o síndrome inflamatório de reconstituição imunológica (IRIS), a captação de GD em diferentes padrões é um dos achados mais preponderantes.

reportada com a utilização do natalizumab,[77] tendo já sido associada a outras TMD,[55,78] pelo que se preconiza uma farmacovigilância sistemática com RM cerebral nos doentes sob esta terapêutica.[79] É possível deste modo a deteção da LMP no período de latência assintomático, que dura em média cinco meses, associando-se a menor carga viral e melhor prognóstico.[77] Os achados imagiológicos clássicos de LMP são lesões da substância branca hiperintensas em T2-FLAIR e hipointensas em T1, que atingem preferencialmente o lobo frontal, seguido do lobo parietal e occipital, e que se distinguem das lesões desmielinizantes clássicas da EM pela hiperintensidade de sinal em DWI e ausência de captação de contraste, efeito de massa ou distribuição perivascular.[78,80] As lesões que realçam com GD são raras, até 43%[79] no momento do diagnóstico da LMP,[76,79] sendo consensual atualmente a maior sensibilidade das sequências não contrastadas T2-FLAIR e DWI no rastreio desta entidade.[55,78]

Dias ou semanas após a cessação do natalizumab, poderá ocorrer, com a recuperação da imunocompetência, a síndrome inflamatória de reconstituição imunológica (IRIS, do inglês *immune reconstitution inflammatory syndrome*), que pode ser visto no *continuum* da LMP. Carateriza-se, paradoxalmente, por uma deterioração clínica com agravamento ou surgimento de novos sinais imagiológicos inflamatórios na RM,[76] sendo a captação de contraste um dos achados mais preponderantes.[78] A apresentação imagiológica típica consiste no aumento de tamanho das lesões LMP pré-existentes, na captação irregular/ em padrão punctiforme de contraste na periferia das lesões[76] e ainda na presença de caraterísticas inflamatórias como distribuição perivascular, edema cerebral e efeito de massa.[78]

RECOMENDAÇÕES ATUAIS

De modo a uniformizar a atuação clínica no seguimento dos doentes com EM, recomenda-se a utilização de campos magnéticos iguais ou superiores a 1,5T nos exames de RM cerebral, idealmente 3T,[10,11] com protocolos semelhantes aos aplicados nos exames de referência e, idealmente, no mesmo equipamento.[54] Relativamente à RM da medula espinhal, a realização do exame em equipamento 3T não se traduz em ganho de informação comparativamente ao 1,5T.[10]

Apesar de alguns autores defenderem a implementação clínica da dose cumulativa de GD 0,2 mmol/kg, argumentando maior sensibilidade e confiança na deteção de lesões com atividade inflamatória aguda e fenótipos de doença ativa ($p < 0,001$ em ambos os casos),[81] a dose de 0,1 mmol/kg mantem-se recomendada.[10] Os GBCAs macrocíclicos de baixo risco, nomeadamente gadoteridol, gadobutrol e gadoterato de meglumina, deverão ser opções preferenciais.[40,50,82]

Desde o início do debate sobre a segurança do GD, várias recomendações de grupos de peritos foram publicadas, reconhecendo gradualmente o GD como não essencial.[83] Inicialmente, foi sugerido um período de estabilidade imagiológica e clínica de pelo menos cinco anos para prescindir da administração de GD na RM.[84] Posteriormente, esse período foi reduzido para dois anos,[62,85] ressalvando-se três contextos em que a informação adicional do GD seria essencial: deterioração clínica rápida e inexplicada, deteção de elevada atividade de doença subclínica (carga lesional) e exclusão de diagnóstico alternativo à EM.[62,85]

As recomendações mais atuais, de 2020[82,86] e 2021,[10] vão ao encontro da literatura anteriormente mencionada e preconizam, de forma consensual, a utilização exclusiva das lesões T2 novas/ aumentadas (em sequências 3D T2-FLAIR, idealmente) na demonstração de atividade subclínica em RM cerebral de controlo da EM.[10,11,82] No entanto, caso se verifique elevada carga lesional/ lesões crónicas difusas/confluentes ou uma RM anterior recente não estiver disponível (um a dois anos de intervalo) e em condições técnicas equiparáveis, a inclusão de sequências contrastadas no protocolo imagiológico é recomendada.[10,11,54,85]

Antes do início/alteração de qualquer TMD deve ser realizada uma RM cerebral com GD para avaliar a atividade inflamatória recente e assim suportar a decisão terapêutica,[15,82] sobretudo se as indicações formais do tratamento assim o exigirem.[10] Na RM de referência '*rebaseline*' realizada três/seis meses a um ano após o início de TMD, as recomendações divergem. O consenso internacional europeu e norte-americano admite a utilização de sequências não contrastadas neste contexto, caso não se verifique elevada atividade de doença ou atividade clínica inesperada na altura da RM de referência,[10] enquanto os peritos franceses,[82] em concordância com outros autores,[52,56,58]

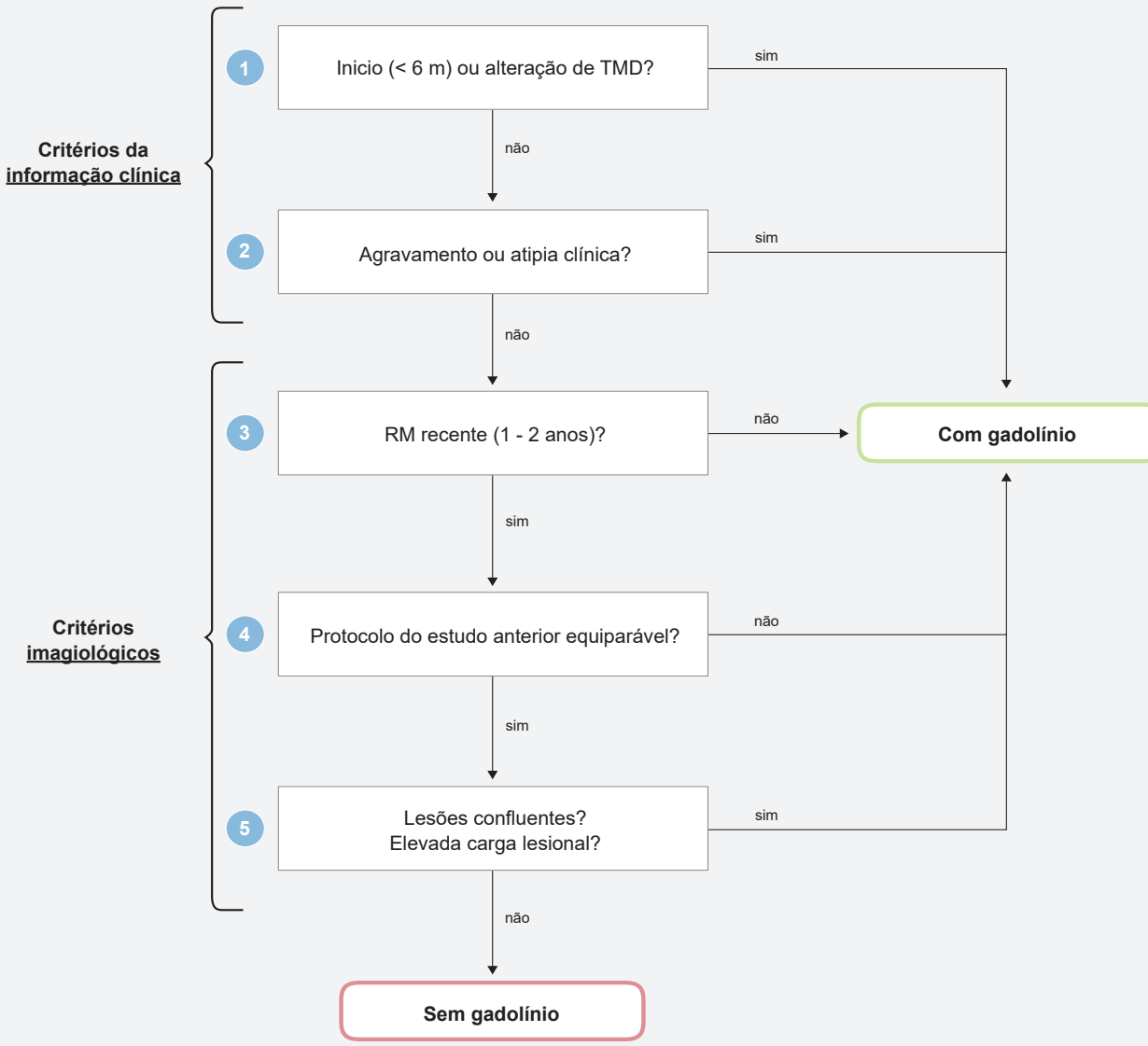

Figura 2 – Fluxograma ilustrativo do seguimento de rotina com ressonância magnética dos doentes com esclerose múltipla
TMD: terapêutica modificadora de doença; RM: Ressonância Magnética

consideram a inclusão de contraste ainda essencial nesta circunstância. É de ressalvar que, perante TMD menos eficazes na redução da atividade inflamatória como o acetato de glatirâmero e o interferão beta, admite-se, consensualmente, a opção por sequências de RM após contraste no primeiro ano de seguimento.[10,54,55]

A RM cerebral e/ou da medula espinhal com contraste está indicada perante agravamentos clínicos inesperados e/ou de evolução rápida, que coloquem dúvidas de diagnóstico diferencial entre a ocorrência de um surto clínico, um pseudo surto ou outra etiologia,[10,11,62,82,85] sendo admitida como opcional por alguns autores na avaliação da gravidade de um surto clínico.[82]

No que se refere ao rastreio da LMP nos doentes sob natalizumab, a RM cerebral pode ser executada unicamente com aquisições 3D FLAIR de alta qualidade e DWI, sendo obrigatória a inclusão de sequências T1 após contraste depois do surgimento de lesões sugestivas de LMP em rastreio, sobretudo para exclusão de evolução para IRIS.[10,55,79,82]

De notar que os novos marcadores imagiológicos em debate na comunidade científica, como a inflamação leptomeníngea e as lesões crónicas ativas, bem como as técnicas de RM quantitativas, não se encontram ainda

preconizados por rotina.[10]

Na Fig. 2 apresentamos a nossa proposta de abordagem pragmática da decisão de inclusão ou não de gadolínio na monitorização de rotina da EM, de fácil aplicação na prática clínica, desde o pedido imagiológico até à execução do exame, e que sintetiza as recomendações atuais descritas nesta revisão.

CONCLUSÃO

É exequível e segura a limitação do uso de agentes de contraste com gadolínio nas ressonâncias magnéticas de controlo na esclerose múltipla, dada a elevada sensibilidade das lesões T2 novas/aumentadas na monitorização da atividade de doença subclínica. Contudo, a informação adicional do contraste torna-o indispensável em determinadas circunstâncias, nomeadamente perante lesões difusas/confluentes nas sequências ponderadas em T2, intervalos entre exames de ressonância magnética prolongados, diagnóstico diferencial de surto clínico, antes e após o início de uma TMD e na monitorização do síndrome inflamatório de reconstituição imunológico.

CONTRIBUTO DOS AUTORES

AMSC: Conceção do estudo, revisão bibliográfica, redação do manuscrito.

DJP: Conceção do estudo e revisão crítica do manuscrito.

SRMB: Conceção do estudo, revisão crítica do manuscrito, supervisão.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

DJP recebeu pagamentos de Roche para consultadoria e reuniões e/ou viagens.

SB recebeu pagamentos de Novartis, Biogen, Roche, Merck, Sanofi, Janssen e Bristol Meyers Squibb para consultadoria, palestras, reuniões e/ou viagens.

AC declara não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Carta ao Editor referente a "Prevalência e Fatores Preditivos do Aleitamento Materno Exclusivo nos Primeiros Seis Meses de Vida"

Letter to the Editor concerning "Prevalence and Predictive Factors of Exclusive Breastfeeding in the First Six Months of Life"

Palavras-chave: Aleitamento Materno; Lactentes; Mães; Portugal
Keywords: Breast Feeding; Infants; Mothers; Portugal

Caro Editor,

O artigo "Prevalência e Fatores Preditivos do Aleitamento Materno Exclusivo nos Primeiros Seis Meses de Vida"[1] publicado em junho de 2023 na vossa revista, da autoria de Branco *et al*, com o objetivo de avaliar a prevalência e os fatores que influenciam o aleitamento materno nos primeiros seis meses de vida em Portugal e de comparar os resultados com um estudo prévio realizado em 1999 na mesma área geográfica,[2] valida anteriores resultados que revelam que Portugal tem índices de aleitamento materno exclusivo aos seis meses de vida inferiores aos recomendados por entidades internacionais [e.g., Organização Mundial de Saúde (OMS) e Fundo das Nações Unidas para a Infância (UNICEF)]. Efetivamente, na Região Europeia da OMS, encontramos algumas das taxas mais baixas de aleitamento materno exclusivo nos primeiros seis meses de vida, onde somente 13% dos lactentes são alimentados exclusivamente com leite materno.[3] Sendo os benefícios do aleitamento materno – tanto para o lactente quanto para a mãe – sobejamente conhecidos,[4] acredito, enquanto médico de família, que se torna decisivo superar os desafios para a sua implementação e promover o aleitamento materno através de sistemas de apoio. Em particular, deve-se atuar nos fatores socioculturais apontados tanto no estudo de Branco *et al* (2023) quanto no estudo anterior de 1999, tais como a menor escolaridade e o retorno da mãe ao seu local de trabalho.[1]

Crenças, normas e tradições culturais podem afetar o aleitamento materno devido a equívocos ou estigmas que desencorajam as mães de amamentar os seus filhos. São exemplos as convicções do leite materno ser fraco ou insuficiente para o lactente, ou as repercussões negativas da amamentação para o corpo das mães.[5] Logo, a educação pré-natal com a transmissão de informações corretas sobre os benefícios do aleitamento materno exclusivo e a desmistificação de mitos e crenças poderá levar a um maior sucesso na amamentação, como demonstrado em estudos anteriores.[5] No campo da educação salienta-se o importante papel que a enfermagem de família tem nas Unidades Funcionais dos Cuidados de Saúde Primários, a qual poderá ter contribuído para as diferenças encontradas no estudo de Branco *et al*[1] em relação ao aleitamento materno em grávidas vigiadas por médicos de família *versus* médicos obstetras privados. Este aconselhamento qualificado, bem como a capacitação das mães por profissionais de saúde com formação (enfermeiros ou outros) devem manter-se no período pós-natal, de forma a apoiarem as mães a ultrapassarem as dificuldades da amamentação.

Em relação ao retorno da mãe ao local de trabalho, Portugal tem políticas laborais que apoiam as mães com período de licença de maternidade, mas ainda tem um longo caminho a percorrer no estímulo de uma cultura de trabalho incentivadora à amamentação por mães que trabalham antes dos seis meses de idade do/a filho/a. É por isso importante apostar na flexibilização dos horários de trabalho, na definição de intervalos para amamentação, e criar espaços tranquilos e dedicados ao aleitamento materno com privacidade e higiene adequadas.

Só com a implementação de estratégias que forneçam formação e apoio às mães e propiciem ambientes favoráveis à amamentação nos locais de trabalho é que se poderá aumentar significativamente as taxas de aleitamento materno em Portugal.

CONFLITOS DE INTERESSE

O autor declara não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Recebido/*Received*: 16/06/2023 - **Aceite/*Accepted*:** 18/10/2023 - **Publicado *Online*/*Published Online*:** 15/11/2023 - **Publicado/*Published*:** 03/01/2024

https://doi.org/10.20344/amp.20305

Addressing Sexual Health in Oncology Patients

Abordagem da Saúde Sexual em Doentes Oncológicos

Keywords: Neoplasms/complications; Sexual Dysfunction, Physiological; Sexual Dysfunctions, Psychological
Palavras-chave: Disfunções Sexuais Fisiológicas; Disfunções Sexuais Psicológicas; Neoplasias/complicações

To the Editor,

Cancer is the second leading cause of death in Portugal and in 2020 there were 25 306 new cases of cancer in women (with breast cancer as the leading cause) and 32 436 new cases in men (with prostate cancer as the leading cause).[1]

Cancer-related sexual dysfunction is highly prevalent (affecting around 50% of survivors of breast and gynecological cancer, 90% of men with prostate cancer, and 20% of survivors of other cancers) by the nature of the disease and its treatments, through changes in body image, self-perception and relationships due to illness.[2,3] Sexual morbidity is associated with poor quality of life, distress, depression, and anxiety, even though it is often overlooked by healthcare providers.[3]

Physicians should address sexual difficulties upon initial diagnosis and review them during follow-up. The PLISSIT (Permission Limited-Information Specific-Suggestions Intensive-Therapy) model of sexual counseling helps clinicians to gather information, relate it to their level of competence, and refer patients to sex therapists if needed.[4]

The main sexual complaints of oncology patients' are disorders of sexual response, body image, intimacy and relationships, vasomotor symptoms, and genital symptoms.[2] Psychological counselling is recommended for all sexual problems.[3]

Sexual response difficulties, including decreased desire, decreased arousal or anorgasmia can be addressed through regular stimulation for both sexes, and phosphodiesterase type 5 inhibitors (PDE5Is) for erectile dysfunction.[2,5] For men who do not respond to PDE5Is, the alternatives include vacuum erection devices (VED), intracavernous injection therapy, and penile prosthesis.[5]

Couple-based interventions are recommended in intimacy/relationships and body image disorders, associated with ostomy, alopecia, mastectomy, or others.[2]

Women's vasomotor symptoms can be relieved with the use of hormone therapy until the average age of menopause (around 51 years). For women unable (hormone-sensitive breast cancer) or unwilling to use it, some possible alternatives are paroxetine, venlafaxine, gabapentin, and clonidine. In men, vasomotor symptoms should be addressed with symptomatic medications: venlafaxine, medroxyprogesterone acetate, cyproterone acetate, and gabapentin.[2,3]

Genital symptoms are frequent in women. Vaginal/vulvar atrophy or dyspareunia can be managed with the daily use of vaginal moisturizers and lubricants during sexual activity. In refractory cases, low-dose vaginal estrogen medication can be tried (dehydroepiandrosterone or ospemifene in postmenopausal women without history of breast cancer). Vaginal dilators are indicated in vaginismus and pelvic floor (Kegel) exercises may help mitigate lower urinary tract symptoms.[2,3] In men, VED daily use is recommended to prevent penis length loss.[2]

In conclusion, it is imperative for physicians to address sexual health in oncology care.

AUTHOR CONTRIBUTIONS

MA: Conception and writing of the manuscript.
DD, IF: Critical review and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 09/10/2023 - **Aceite/*Accepted*:** 20/11/2023 - **Publicado/*Published*:** 03/01/2024

https://doi.org/10.20344/amp.20671

Saúde Mental nos Cuidados de Saúde Primários: Uma Realidade Longe do Ideal

Mental Health in Primary Health Care: A Reality Far from Ideal

Palavras-chave: Cuidados de Saúde Primários; Perturbações Mentais; Portugal; Prestação de Cuidados de Saúde; Psicologia Clínica
Keywords: Delivery of Health Care; Mental Disorders; Portugal; Primary Health Care; Psychology, Clinical

Caro Editor,

Lemos com bastante interesse o artigo "Prescrição de Benzodiazepinas e outros Sedativos na Administração Regional de Saúde de Lisboa e Vale do Tejo de 2013 a 2020: Um Estudo Retrospetivo".[1] Sabemos que Portugal está entre os países da União Europeia com maior prevalência de sintomas associados a problemas psicológicos, com destaque para a insónia, ansiedade e depressão.[2]

Nos Cuidados de Saúde Primários (CSP) o médico de família (MF) tem, em muitos casos, o primeiro contacto com o utente e está numa posição privilegiada de intervenção.

A doença mental está associada a elevados custos económicos, não só por ser uma das principais causas de absentismo laboral, como também pela despesa que acarreta nomeadamente no tratamento e internamento em estádios mais avançados.

O investimento na área da saúde mental tem sido encarado como uma prioridade pelo Governo português.[3] No entanto, enquanto 'profissionais no terreno' ainda nos deparamos com a ausência de medidas concretas e benéficas para os utentes.

O reforço dos recursos humanos e a criação de equipas multidisciplinares e comunitárias de saúde mental seriam fundamentais para uma resposta adequada.

É evidente a escassez de psicólogos no Serviço Nacional de Saúde (SNS). O rácio 1 psicólogo por 5000 habitantes, definido para a população portuguesa, encontra-se longe de ser atingido,[4] verificando-se atualmente no SNS uma proporção de 1 psicólogo para 9700 habitantes.[5] As assimetrias a nível nacional obrigam-nos a olhar com especial atenção para o bom exemplo da Região Autónoma da Madeira. Trata-se de uma região com elevada prevalência de doença mental e com um dos melhores rácios psicólogo/habitante: cerca de 1 psicólogo por 3900 habitantes,[6] números que desejaríamos alcançar em todo o território. Naturalmente, a maior acessibilidade a estes profissionais permite um melhor acompanhamento dos utentes e a aplicação de critérios de referenciação mais abrangentes.

Por outro lado, a dificuldade no acesso a consultas de Psicologia reforça ainda mais a importância do MF: no rastreio e intervenção precoce quando detetados problemas de saúde mental, no acompanhamento e na gestão dos doentes, e no uso da terapêutica ao seu alcance (quer farmacológica quer não farmacológica), em complementaridade com a referenciação fundamentada para Psicologia nos CSP ou para cuidados secundários, nas situações devidamente justificadas.

Com esta reflexão pretendemos alertar para a necessidade de melhoria no acesso aos cuidados de saúde mental nos CSP, com redução dos tempos de espera para consultas de Psicologia no SNS, e para a necessidade de criação de programas específicos com maior foco no diagnóstico precoce da doença mental no adulto, na criança e no adolescente.

CONTRIBUTO DOS AUTORES

BA: Revisão da literatura, elaboração e revisão do manuscrito.

MR: Elaboração e revisão do manuscrito.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos

pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Recebido/*Received*: 24/08/2023 - **Aceite/*Accepted*:** 14/11/2023 - **Publicado *Online*/*Published Online*:** 07/12/2023 - **Publicado/*Published*:** 03/01/2024

https://doi.org/10.20344/amp.20596

Paracetamol Induced Acute Interstitial Nephritis: A Pediatric Case Report

Nefrite Intersticial Aguda Induzida pelo Paracetamol: Um Caso Clínico Pediátrico

Keywords: Acetaminophen/adverse effects; Child; Nephritis, Interstitial/chemically induced
Palavras-chave: Acetaminofen/efeitos adversos; Criança; Nefrite Intersticial/induzida quimicamente

Dear Editor,

Acute interstitial nephritis (AIN) is characterized by the presence of inflammatory infiltrates and edema in the renal interstitium, and is usually associated with an acute deterioration in renal function (acute kidney injury – AKI).[1] AIN can have multiple causes, but it is most frequently drug-induced. Even though the list of drugs that can trigger AIN keeps growing, antimicrobial agents and non-steroidal anti-inflammatory drugs are the most common.[1]

We report the case of a 14-year old girl who developed biopsy-proven AIN with a temporal association with paracetamol exposure. The patient presented two weeks after receiving daily treatment for an upper-respiratory infection with paracetamol, in therapeutic doses. The patient had low-grade fever, weight loss (approximately 7% of total body weight), and polyuria, without nocturia or other changes in urine. No other drugs were taken. The physical examination was normal, including normal blood pressure. The patient was diagnosed with AKI (serum creatinine 3.88 mg/dL; glomerular filtration rate 23.8 mL/min/1.73 m^2), mild leukocituria (15 leukocytes/ µL), no hematuria, non-nephrotic proteinuria, and glycosuria, with normal glycemia. Globally enlarged kidneys with a moderate diffuse increase in parenchymal echogenicity were observed in renal ultrasound. A kidney biopsy showed tubulitis and an intense interstitial inflammatory infiltrate, with numerous eosinophils and no granulomas, which was suggestive of AIN (Fig. 1). Infectious and autoimmune causes were excluded. After re-exposure to paracetamol for pain following the biopsy, the patient became febrile, began vomiting, and exhibited an urticaria-like rash. Blood tests showed eosinophilia (6% eosinophils; 770/µL) and worsening renal function. Paracetamol-induced AIN was suspected. Prednisolone was started (1 mg/kg/day) and complete eviction of paracetamol was recommended. Ibuprofen was suggested as an alternative if a painkiller or antipyretic was needed.

The symptoms completely resolved, and the renal function recovered completely one month after the eviction of paracetamol. Steroids were progressively tapered. The patient maintains a normal renal function seven months after the diagnosis.

Any drug can potentially induce AIN.[1] However, very few cases of AIN after therapeutic doses of paracetamol have

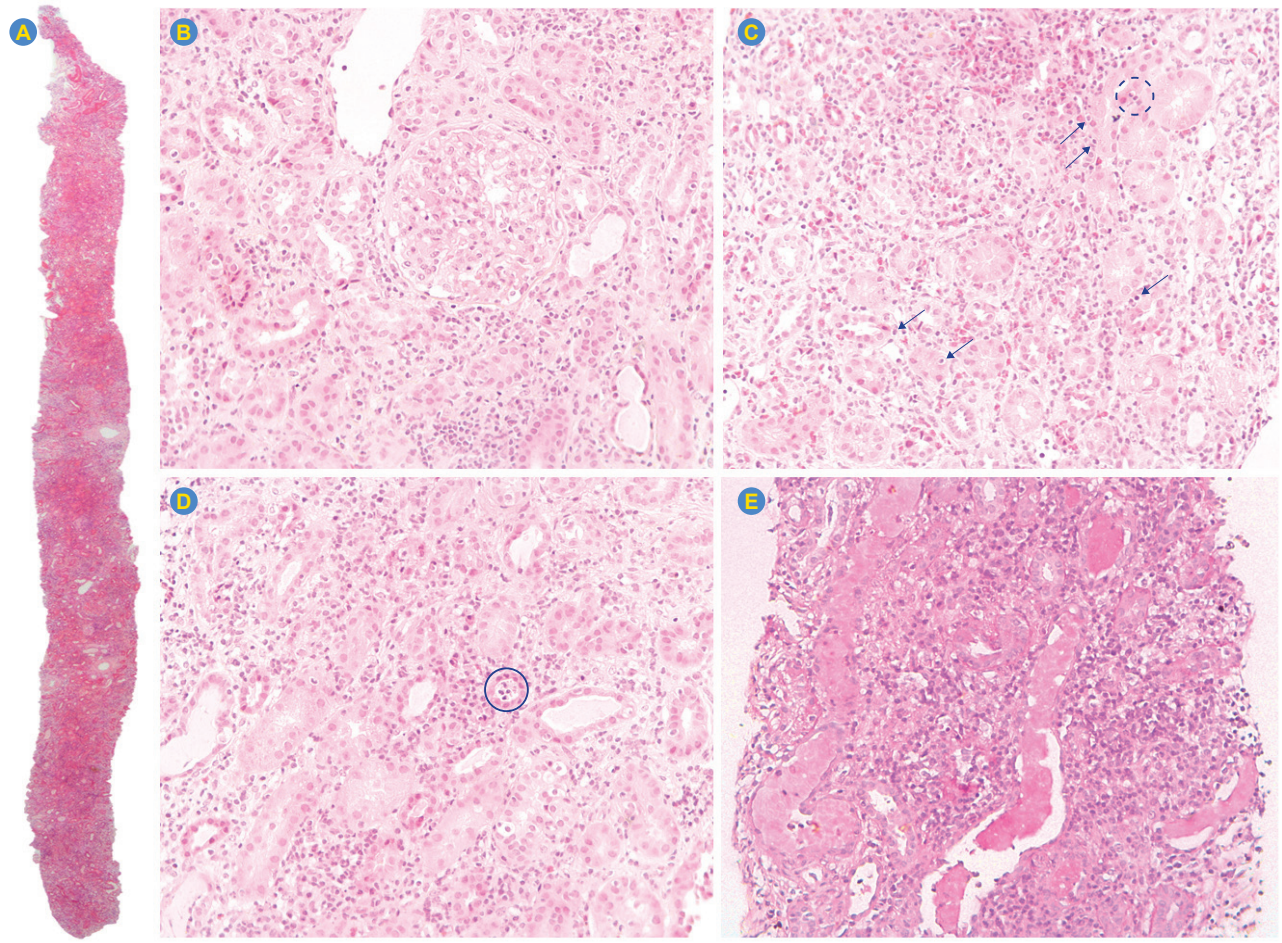

Figure 1 – Histological sections of the renal biopsy, measuring 10 mm, which include the cortex and medulla (A – H&E). About five renal glomeruli were examined and showed no morphological changes (B – H&E). The renal interstitium was expanded by a severe inflammatory infiltrate mainly composed of lymphocytes and plasma cells, along with a significant number of granulocytes, particularly numerous eosinophils (C – H&E). Degenerative tubular changes with tubulitis are observed, with occasional intraepithelial lymphocytes (C - arrows) and neutrophils (C – dashed circle). Some of the renal tubules display intratubular granulocytes (D – circle, H&E) and urinary hyaline casts (E – PAS).

been reported.[2] The clinical presentation is non-specific.[3] Not all patients have a complete recovery of renal function even if the inciting agent is removed.[3,4] The most important therapeutic measure is the early removal of the responsible drug. The role of corticosteroids remains controversial.[5] In conclusion, AIN caused by paracetamol is rare. The diagnosis is challenging because of the heterogeneous clinical picture and the inexistence of reliable non-invasive diagnostic procedures. It is important to keep a high clinical suspicion and the early suspension of the causative drug is crucial for the prognosis.

AUTHOR CONTRIBUTIONS

PJM: Data acquisition and analysis, writing of the manuscript.

RMC: Data acquisition and analysis.

PCR, ARS: Critical review of the manuscript.

JES: Critical review and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 06/09/2023 - **Aceite/*Accepted*:** 03/11/2023 - **Publicado/*Published*:** 03/01/2024

https://doi.org/10.20344/amp.20563

High-Pressure Fluid Injection Injury: The Importance of a Prompt Diagnosis

Lesões por Injeção de Fluído a Alta Pressão: A Importância do Diagnóstico Atempado

Keywords: Amputation, Surgical; Decompression, Surgical; Hand Injuries
Palavras-chave: Amputação Cirúrgica; Descompressão Cirúrgica; Lesões da Mão

Dear Editor,

Hand and forearm injuries caused by high-pressure fluid injection are underreported and often diagnosed late.[1,2] In certain professional activities such as construction work, there is an increased risk of these injuries, especially in the index finger of the non-dominant limb, due to the use of tools such as paint guns or air compressors.[3]

This article reports the case of a 57-year-old man, who presented to the emergency department with a punctiform wound on the volar surface of his left index finger, caused by a plaster gun (Fig. 1A). The incident had occurred approximately 12 hours prior to seeking medical attention, and the patient complained of pain and local swelling, but there were no apparent signs of tenosynovitis. A radiograph of the hand showed extensive infiltration of plaster throughout the subcutaneous tissues from the metacarpal to the distal interphalangeal joint of the same finger.

After identifying the apparent extent and severity of the injury, urgent surgical exploration of the wound and attempted debridement using dilution with normal saline were performed. There was complete adhesion of the plaster to the neurovascular bundle, which was inseparable, and therefore only partial removal was possible (Fig. 1B). In addition, empirical intravenous antibiotic therapy with amoxicillin and clavulanic acid was initiated during the preoperative period.

The patient had a good postoperative course, with no signs of infection or ischemia throughout the follow-up period. At eight weeks post-trauma, there was complete resolution of symptoms, and the patient was able to resume his professional activity.

When faced with a high-pressure fluid injection injury, early assessment and treatment are essential since these injuries can have devastating consequences even though their external appearance can often seem innocuous.[4] The rates of amputation described in the literature can exceed 50%, even when injuries are treated within the first six hours.[5] In cases where amputation is avoided, the resulting sequelae prevent more than half of individuals from returning to their professional activities. Injected substances can progress through tissues along paths of least resistance, such as neurovascular bundles, triggering inflammatory reactions that contribute to tissue irrigation compromise and eventual necrosis. In addition, the presence of a portal of entry, combined with local ischemia, promotes infection.[1,3]

High-pressure fluid injection injuries are a surgical emergency. Prompt diagnosis is very important to avoid serious complications such as amputation. Given the severity of this condition and the associated consequences, clear and thorough communication with patients is crucial.

AUTHOR CONTRIBUTIONS

FS, MR: Conception and design of the work, data acquisition, analysis, and interpretation, drafting of the work.

MJL: Data analysis and interpretation, drafting of the work.

AS: Critical review of the manuscript.

VV: Critical review and approval of the final version of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed

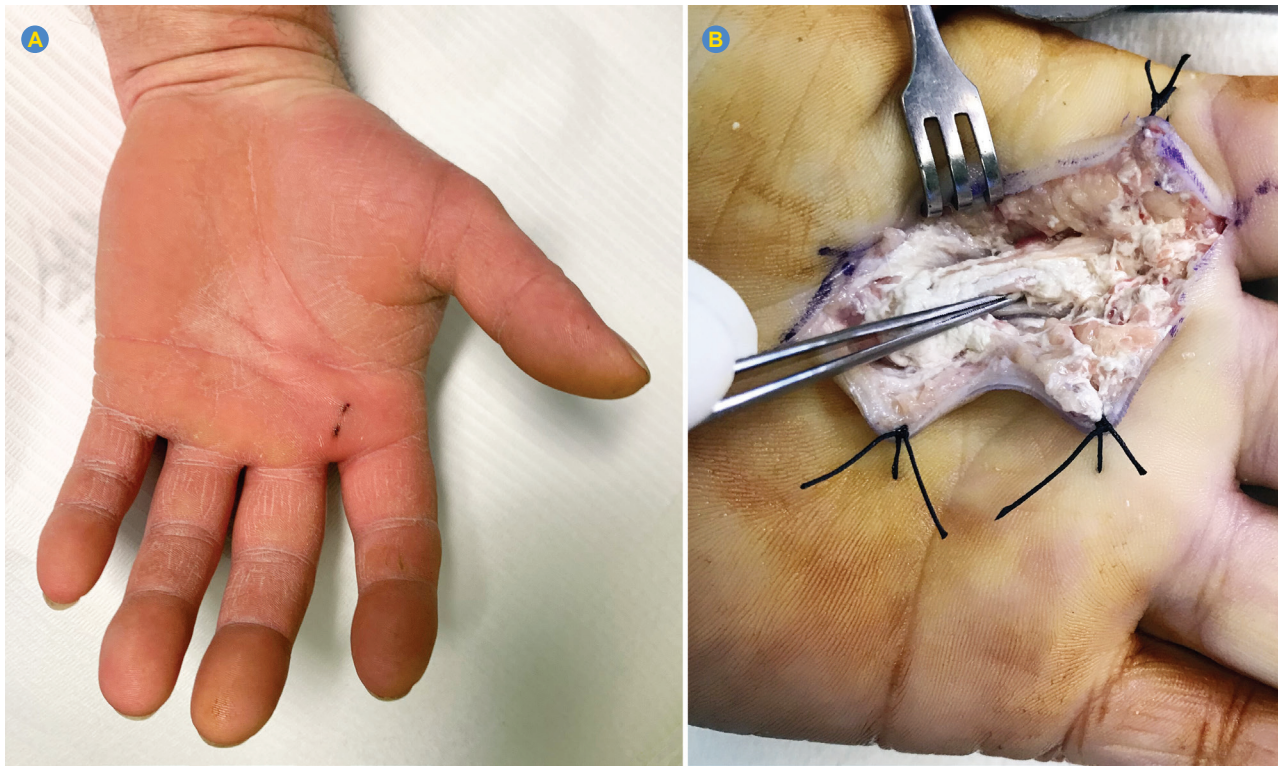

Figure 1 – Punctiform wound on the volar surface of index finger (A). Thick and adhesive consistency of plaster adherent to the neurovascular bundle (B).

according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 15/09/2023 - **Aceite/*Accepted*:** 22/11/2023 - **Publicado/*Published*:** 03/01/2024

https://doi.org/10.20344/amp.20635

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