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EDITORIAL

GUERNICA

"Guernica" is a powerful and iconic painting in 1937 by the Spanish artist Pablo Picasso It was created in response to the bombing of the town of Guernica during the Spanish Civil War. The painting was showcased at the Spanish Pavilion of the 1937 International Exposition in Paris.

When: The town of Guernica in the Basque region of Spain was bombed on April 26, 1937, by German and Italian warplanes supporting General Francisco Franco's Nationalist forces. Picasso began working on the painting shortly after the bombing and completed it in June 1937.

Why: Picasso, deeply affected by the devastating news of the bombing, felt compelled to create a work that would express his outrage and condemnation of the violence and suffering inflicted upon innocent civilians during war. "Guernica" became a powerful anti-war symbol and an embodiment of the anguish and horror caused by conflict.

The painting is highly symbolic, and different interpretations exist regarding the meaning of its elements. While Picasso did not provide specific explanations for each component, art historians and critics have offered various interpretations.

Significance of Elements: The painting is characterized by its chaotic and anguished composition, featuring distorted and fragmented figures. Several key elements in the painting have specific symbolic meanings:

Bull: The bull is a recurring symbol in Picasso's work, often representing brutality and violence. In "Guernica," the bull may symbolize the fascist forces behind the bombing.

Horse: The horse is a central and poignant element in the painting. It is depicted in a state of agony, its body pierced by a spear and its eye wide open in terror. The horse is often interpreted as a representation of the innocent victims of war, the suffering civilian population of Guernica.

Woman with Outstretched Arms: A grieving woman, possibly a mother is depicted with outstretched arms. She may represent the pain and despair of those affected by the bombing.

Broken Swords and Weapons: Broken and shattered swords and weapons scattered throughout the painting symbolize the futility and destructiveness of war. The sword in "Guernica" is often seen as a symbol of violence and aggression. Its placement near the center of the painting highlights the destructive force of war.

The Flower: The flower, sometimes interpreted as a lily or a poppy, is a contrast to the violence represented by the sword. It may symbolize hope, life, and resilience in the face of destruction.

The Man on the Floor: The figure lying on the ground, often interpreted as a wounded or dead soldier, represents the tragic human cost of war. This central figure embodies the suffering and pain experienced by innocent civilians caught in the crossfire.

The Man in the Window: The man in the window, sometimes identified as a grieving mother holding a dead child, may represent the anguish and despair of civilians affected by the war. The distorted and anguished expressions of the characters in the window reflect the horror and helplessness felt by those witnessing the devastation.

Distorted Figures: The distorted and fragmented figures throughout the painting convey a sense of chaos and the disintegration of humanity in the face of violence.

Guernica is considered one of the most powerful anti-war artworks of the 20th century, and its emotional impact and symbolism continue to resonate with audiences worldwide. The painting is now housed in the Museo Reina Sofia in Madrid, Spain.

It's important to note that Picasso intentionally left the interpretation of "Guernica" open-ended, allowing viewers to bring their own perspectives and emotions to the painting. The use of distorted and fragmented forms contributes to the overall sense of chaos and suffering. The painting is a powerful statement against the brutality of war and its impact on humanity.

Mirnaluci Paulino Ribeiro Gama
Ricardo Ribeiro Gama

Source:
Pablo Picasso org
Kahn Academy
Britannica.com
Museo Nacional Reina Sofia

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Our Cover: GUERNICA – Pablo Picasso (1937)

Source: Artwork Analysis: Guernica by Picasso

ORIGINAL ARTICLE
METAVIR SCORE: A PICTORIAL ESSAY EXPLORING ANATOMY, ULTRASONOGRAPHY, SONOELASTOGRAPHY, AND HISTOLOGY

METAVIR SCORE: UM ENSAIO PICTÓRICO EXPLORANDO ANATOMIA, ULTRASSONOGRAFIA, SONOELASTOGRAFIA E HISTOLOGIA

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Keywords: Liver; Ultrasound; Elastography; Histology; METAVIR score
Descritores: Fígado; Ultrassonografia; Elastografia; Histologia; Escore METAVIR

Abstract

Introduction: The METAVIR score was specifically elaborated and evaluated in chronic hepatitis C, is scoring system for evaluation the inflammatory activity and fibrosis on liver biopsies, although it ultrasound may indicate the fibrosis degree. **Objective:** To present a pictorial essay composing histological, sonographic, and sonoelastography images of the METAVIR fibrosis score based on a review of the literature. **Materials and Methods:** Using software for image composition, based on the ultrasound image of the liver with the various degrees of fibrosis, secondary to hepatitis C, we adapt to the anatomical image, the sonoelastography and the corresponding histology (METAVIR) and present a pictorial essay. **Results:** The correlation between the sonographic, anatomical, sonoelastography, and histological images corresponding to the METAVIR score are demonstrated. **Conclusion:** Ultrasonographic features and sonoelastography in evaluation hepatic fibrosis present in hepatitis C can correlate with histological features METAVIR score. **Endocrinol diabetes clin exp 2023/ 2431 - 2434.**

Resumo

Introdução: O escore METAVIR foi projetado e avaliado especificamente na hepatite C crônica. É um sistema de pontuação para a avaliação da atividade inflamatória e da fibrose em biópsias hepáticas, embora a ultrassonografia possa indicar o grau de fibrose. **Objetivo:** Apresentar um ensaio pictórico composto de imagens histológicas, ultrassonográficas e sonoelastográficas do escore de fibrose METAVIR com base em uma revisão da literatura. **Material e Métodos:** Utilizando um software de composição de imagens, com base na imagem ultrassonográfica do fígado com diferentes graus de fibrose, secundária à hepatite C, adaptamos a imagem anatômica, imagem sonoelastográfica e a histologia correspondente (METAVIR) e apresentamos um ensaio pictórico. **Resultados:** Demonstramos a correlação entre as imagens ultrassonográficas, anatômicas, sonoelastográficas e histológicas correspondentes com o escore METAVIR. **Conclusão:** As características ultrassonográficas e a sonoelastografia na avaliação da fibrose hepática presente na hepatite C podem ser correlacionadas com as características histológicas do escore METAVIR. **Endocrinol diabetes clin exp 2023 / 2431 - 2434.**

INTRODUCTION

The Hepatitis C virus was discovered in 1989 (1). Since its discovery, several studies have been conducted to evaluate its interaction with hepatocytes (2). The World Health Organization has set a goal of eliminating Hepatitis C by 2030, which is defined as a 65% reduction in mortality from HCV and a 90% reduction in new infections (3).

Liver biopsy is considered the gold standard for fibrosis assessment. The degree of fibrosis and inflammation is classified by the METAVIR score system, a semi-quantitative system primarily developed and studied in individuals with chronic Hepatitis C. The METAVIR score consists of a coding form with two letters and two numbers. The letter "A" encodes the degree of histological activity, with A0 indicating no activity, A1 indicating mild activity, A2 indicating moderate activity, and A3 indicating severe activity. The letter "F" encodes the degree of fibrosis, with F0 indicating no fibrosis, F1 indicating portal fibrosis without septa, F2 indicating portal fibrosis with a few septa, F3 indicating numerous septa without cirrhosis, and F4 indicating cirrhosis (4).

Assessing liver stiffness is crucial in the treatment of liver diseases, as the prognosis is directly linked to the progression of liver fibrosis. Ultrasound, a low-cost method that uses no ionizing radiation and is well accepted by patients, is an essential diagnostic imaging method for evaluating the liver. Sonographic studies have demonstrated a strong correlation between histological and ultrasound findings of liver fibrosis (5). Specific ultrasound findings such as irregularity or rippling of the liver surface, coarse echotexture, focal nodulations of the liver parenchyma, and diffuse periportal thickening are correlated with liver fibrosis at different stages (6).

Elastography, a non-invasive imaging technique developed in the 1990s, is based on the mechanical properties of tissues. It provides an alternative method to liver biopsy by measuring the stiffness correlated to liver fibrosis (7). Currently, there are two available ultrasound elastography techniques: strain imaging and shear wave imaging. Strain imaging involves applying external stress to the liver tissue, providing a qualitative assessment, while shear wave imaging applies dynamic stress using a vibrating mechanical device (8).

Despite the availability of various sophisticated imaging examinations, misinterpretations of images can still occur. The purpose of this study is to present a pictorial essay that combines histological, ultrasound, and elastography images

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of the METAVIR score of fibrosis based on a comprehensive literature review.

MATERIAL AND METHODS

Using image composition software, such as the basic Windows program "Paint," we have created a pictorial essay based on ultrasound images of the liver depicting various degrees of fibrosis and correlated them with corresponding histological images (METAVIR score). An ultrasound specialist and a pathologist conducted the correlation between the ultrasound images, focusing on the sonographic signs of liver fibrosis, and the review of histological specimens representing different degrees of liver fibrosis classified by the METAVIR score.

This study aims to enhance the theoretical understanding of pathologies in clinical practice. It is important to note that, according to the Research Ethics Committee of Brazil (CEP), CEP evaluation is not required for this particular study.

RESUTS AND DISCUSSION

METAVIR score F0

Anatomy

The liver is an organ located in the right hypochondrium, in direct contact with the gallbladder, stomach, and diaphragm. It is covered by Glisson's capsule and is almost entirely covered by the visceral peritoneum, along with peritoneal ligaments (9).

Ultrasonography

The ultrasound image of normal liver parenchyma shows little variation between individuals. The echotexture of normal liver parenchyma is homogeneously echogenic, slightly less echogenic than the spleen, and slightly brighter than the renal cortex when compared at the same depth level (10).

Sonoelastography

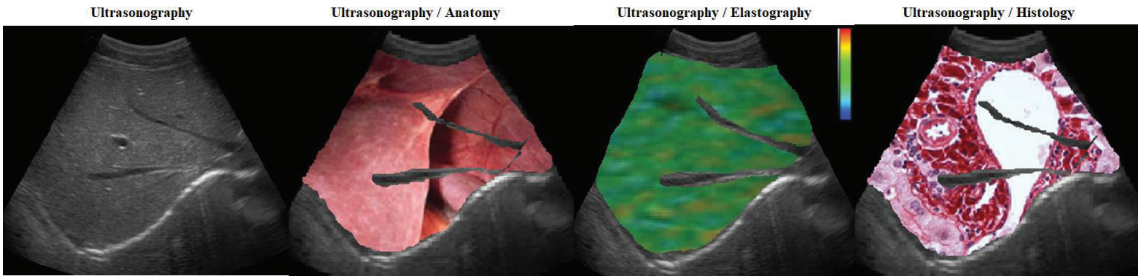
Based on several studies and the so-called 'rule of four' (5, 9, 13, and 17 kPa) for acoustic radiation force impulse (ARFI) techniques used to evaluate liver fibrosis of viral etiology, liver stiffness of 5 kPa (1.3 m/sec) or less has a high probability of being normal (11).

Histology

Histologically, the liver tissue is composed of hexagon--shaped lobules, and within these lobules, hepatocytes are aligned as cellular strands connecting the peripheral portal tracts with the central veins. The hepatic sinusoid, which corresponds to a specialized capillary system, is traversed by the hepatic artery and portal vein. The combination of hepatic canaliculi forms the bile ducts that, along with the hepatic artery and a branch of the portal vein, constitute the "portal triad" (12).

Figure 1 shows the composition of images that correspond to the normal liver in terms of ultrasound, anatomy, elastography, and histology.

Figure 1. Normal Liver.



Source: Research result

METAVIR score F1

Anatomy

From an anatomical standpoint, a fibrosis score of F1 according to the METAVIR score indicates minimal or incipient fibrosis in the liver, without significant anatomical changes compared to a non-fibrotic liver.

Ultrasonography

According to the METAVIR score, the F1 score shows mildly increased echogenicity in the walls of the main portal vein and reduced caliber of the portal vessels. In addition, there may be diffuse linear echogenicity resulting from mild periportal thickening and diffuse echogenicity in the hepatic periphery. These findings are observed on ultrasound examinations (13).

Sonoelastography

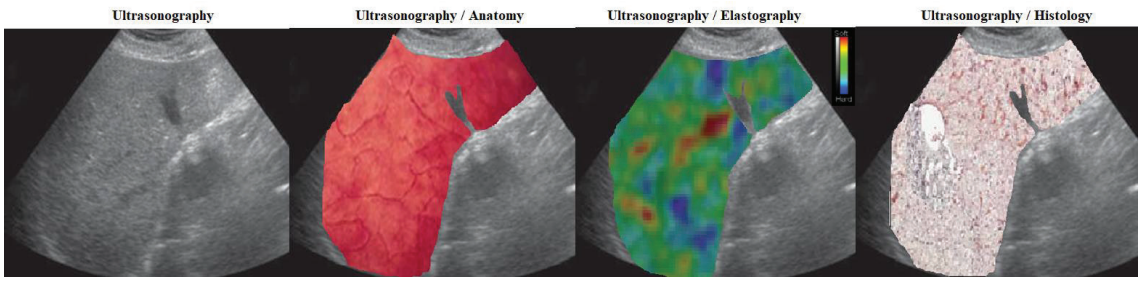
When using the ARFI technique to assess fibrosis score, a value of 5.3-7.4 kPa with a mean of 6.43 kPa (equivalent to 1.47 m/s) in sonoelastography indicates fibrosis with portal zone expansion, corresponding to METAVIR score F1 (14).

Histology

Histologically, the F1 stage of the METAVIR score is characterized by portal fibrosis without septa, which indicates incipient or minimal liver fibrosis (4).

Figure 2 displays images that represent each modality used to evaluate METAVIR score F1 (ultrasound, anatomy, elastography, and histology).

Figure 2. METAVIR score F1



Source: Research result

METAVIR score F2

Anatomy

From an anatomical standpoint, a fibrosis score of F1 accorMacroscopic anatomy of the liver reveals a granular surface appearance with regenerative nodules and fibrous tissue septa that divide the liver in a puzzle-like pattern.

Ultrasonography

Slight echogenic thickening of the walls of two or more peripheral portal branches is observed, with minimal thickening of the main portal vein wall and slight narrowing of the portal radicles. The gallbladder also shows wall thickening. Additionally, periportal fibrosis is more evident in this stage compared to the previous stage, and there are irregular narrowings in the lumen of the portal vessels (15).

Sonoelastography

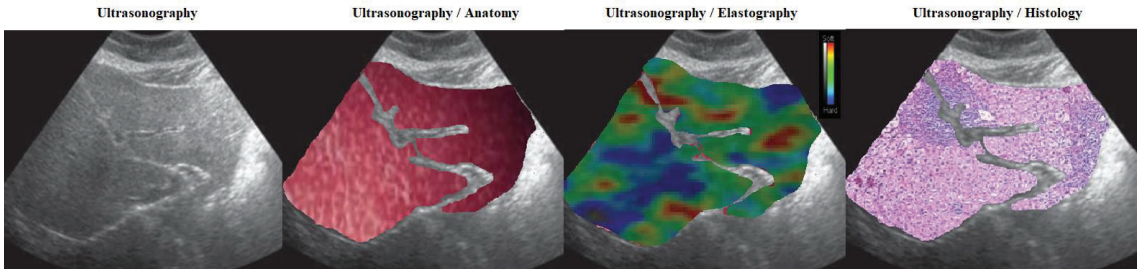
In the diagnosis of stage F2 liver fibrosis, the liver stiffness meters used in sonoelastography indicate the presence of fibrosis with expansion in most portal zones and occasional fibrosis with signaling fiber bridges. If the ARFI technique is used to evaluate liver stiffness, a range between 7.1 kPa (1.59 m/s) corresponds to the METAVIR F2 score (16).

Histology

The F2 stage of the METAVIR score presents anatomopathological characteristics of portal fibrosis with rare septa extending into the lobules, indicating moderate fibrosis (4).

Figure 3 includes images composition corresponding to the METAVIR F2 score for liver ultrasound, anatomy, elastography, and histology.

Figure 3. METAVIR score F2



Source: Research result

METAVIR score F3

Anatomy

The liver presents a pronounced nodularity on the external surface and a shiny capsule. Additionally, the organ shows reduced volume and a hardened consistency.

Ultrasonography

In severe fibrosis cases, ultrasonographic findings show significant periportal thickening with irregular distribution in most portal radicles, leading to marked narrowing of the central lumen. The thickening is particularly prominent at the bifurcation of the portal vein and extends towards the liver surface. The wall of the main portal vein thickens by 2 to 10 mm, as does the wall of the gallbladder (17).

Sonoelastography

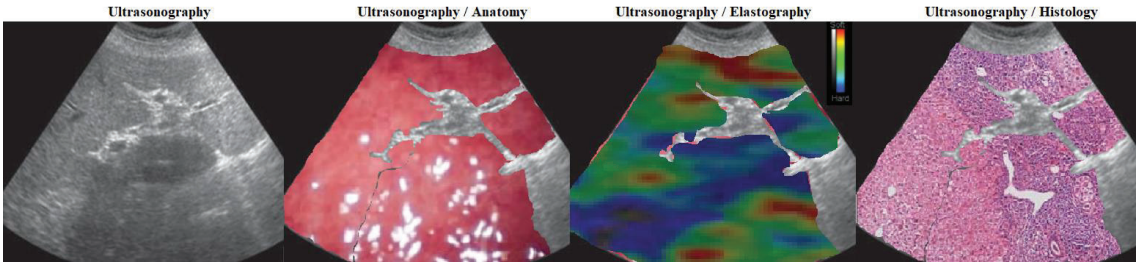
Utilizing the ARFI technique to assess fibrosis scores, sonoelastography indicates that liver fibrosis is characterized by the presence of numerous septa. Elasticity quantification reveals a value of 9.5 kPa and a shear wave velocity of 1.74 m/s, which corresponds to the METAVIR F3 score (18).

Histology

The F3 stage of the METAVIR score presents anatomopathological characteristics of numerous septa extending into the adjacent portal tracts or terminal hepatic venules, corresponding to severe fibrosis (4).

Figure 4 displays a composition of images corresponding to the METAVIR score F3 liver, showcasing ultrasound, anatomy, elastography, and histology.

Figure 4. METAVIR score F3



Source: Research result

METAVIR score F4

Anatomy

The external surface of the liver exhibits prominent nodularity and a shiny capsule. The organ undergoes significant reduction in volume, develops a hardened consistency, and its color may appear pale to brownish.

Ultrasonography

Ultrasonography plays a crucial role in the non-invasive diagnosis of liver cirrhosis. Echographic findings reflect the progression of hepatic fibrosis and include increased liver volume, a coarse or nodular texture of the hepatic parenchyma, and, in cases of portal hypertension, dilation of the portal vein with flow inversion, visualized using Doppler ultrasound. Therefore, ultrasonography is a cost-effective and easily accessible imaging modality for diagnosing liver cirrhosis (19).

Sonoelastography

Sonoelastography has consistently contributed to the improvement of cirrhosis diagnosis. When evaluating liver

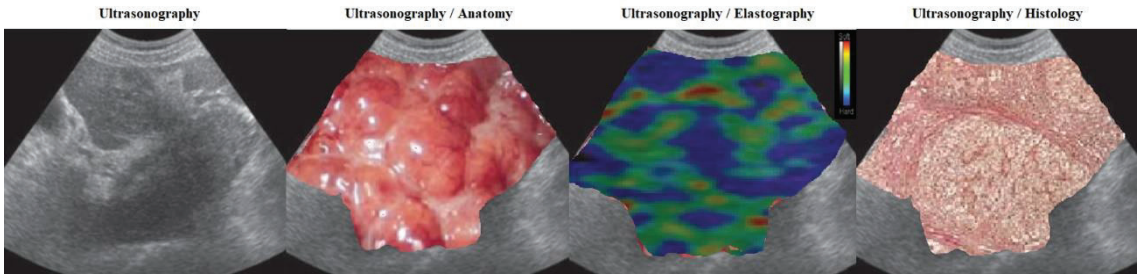
cirrhosis using the ARFI technique, sonoelastography reveals an elasticity quantification of 12.5 kPa and a shear wave velocity of 1.92 cm, corresponding to the METAVIR F4 score (20).

Histology

Cirrhosis, according to the Laennec histological classification, correlates with different stages of clinical severity. The METAVIR system modified this classification by subdividing the highest degree of fibrosis (F4) into 4A, 4B, and 4C to differentiate varying levels of cirrhosis severity. Recent advances in histopathological analysis, such as digital image analysis and molecular profiling, have provided additional insights into the heterogeneity and prognostic implications of cirrhosis subtypes (21).

Figure 5 displays a composition of images corresponding to the METAVIR score F4 liver, depicting ultrasound, anatomy, elastography, and histology.

Figure 5. METAVIR score F4



Source: Research result

CONCLUSION

Ultrasonographic features and sonoelastography in evaluating hepatic fibrosis present in hepatitis C can correlate with histological features of the METAVIR score.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. **Science**. 1989;244(4902):359-62.
2. Zeisel MB, Felmlee DJ, Baumert TF. Hepatitis C virus entry. **Curr Top Microbiol Immunol**. 2013;369:87-112.
3. World Health Organization Global Health Sector Strategy on Viral Hepatitis 2016–2021. Towards Ending Viral Hepatitis. [(Accessed on November 11, 2023]. Available online: https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf [Ref list].
4. Bedossa P, Poynard T. An algorithm for the grading of activ ity in chronic hepatitis C. The METAVIR Cooperative Study Group. **Hepatology.** 1996;24(2):289-93.
5. Nishiura T, Watanabe H, Yano K, Ito M, Abiru S, Fujimoto T, et al. Integrated fibrosis scoring by ultrasonography predicts the occurrence of hepatocellular carcinoma in patients with chronic hepatitis C virus infection. **J Med Ultrason**. 2011;38(1):13-9.
6. Zheng J, Guo H, Zeng J, Huang Z, Zheng B, Ren J, et al. Two-dimensional shear-wave elastography and conventional US: the optimal evaluation of liver fibrosis and cirrhosis. **Radiology**. 2015;275(1):290-300.
7. Agbim U, Asrani SK. Non-invasive assessment of liver fibrosis and prognosis: an update on serum and elastography markers. **Expert Rev Gastroenterol Hepatol**. 2019;13(4):361-74.
8. Ozturk A, Grajo JR, Dhyani M, Anthony BW, Samir AE. Principles of ultrasound elastography. **Abdom Radiol (NY)**. 2018;43(4):773-85.
9. Skandalakis JE, Skandalakis LJ, Skandalakis PN, Mirilas P. Hepatic surgical anatomy. **Surg Clin North Am**. 2004;84(2):413-35,
10. Khan SA, Yasmeen S, Adel H, Adil SO, Huda F, Khan S. Sonographic Evaluation of Normal Liver, Spleen, and Renal Parameters in Adult Population: A Multicenter Study. **J Coll Physicians Surg Pak**. 2018;28(11):834-39.
11. Barr RG, Ferraioli G, Palmeri ML, Goodman ZD, Garcia-Tsao G, Rubin J, et al. Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. **Radiology**. 2015;276(3):845-61.
12. Gerber MA, Thung SN. Histology of the liver. **Am J Surg Pathol.** 1987;11(9):709-22.
13. Li J, Qureshi M, Gupta A, Anderson SW, Soto J, Li B. Quantification of Degree of Liver Fibrosis Using Fibrosis Area Fraction Based on Statistical Chi-Square Analysis of Heterogeneity of Liver Tissue Texture on Routine Ultrasound Images. **Acad Radiol**. 2019;26(8):1001-1007.
14. Fraquelli M, Baccarin A, Casazza G, Conti CB, Giunta M, Massironi S, et al. Liver stiffness measurement reliability and main determinants of point shear-wave elastography in patients with chronic liver disease. **Aliment Pharmacol Ther**. 2016;44(4):356-65.
15. Zheng RQ, Wang QH, Lu MD, Xie SB, Ren J, Su ZZ, et al. Liver fibrosis in chronic viral hepatitis: an ultrasonographic study. **World J Gastroenterol**. 2003;9(11):2484-9.
16. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. **Gastroenterology**. 2005;128(2):343-50.
17. Wakui N, Nagai H, Yoshimine N, Amanuma M, Kobayashi K, Ogino Y, et al. Flash Imaging Used in the Post-vascular Phase of Contrast-Enhanced Ultrasonography is Useful for Assessing the Progression in Patients with Hepatitis C Virus-Related Liver Disease. **Ultrasound Med Biol**. 2019;45(7):1654-62.
18. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. **Clin Gastroenterol Hepatol**. 2007;5(10):1214–20.
19. Sharma S, Khalili K, Nguyen GC. Non-invasive diagnosis of advanced fibrosis and cirrhosis. **World J Gastroenterol**. 2014;20(45):16820-30.
20. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. **Hepatology**. 2005;41(1):48-54.
21. Rastogi A, Maiwall R, Bihari C, Ahuja A, Kumar A, Singh T, et al. Cirrhosis histology and Laennec staging system correlate with high portal pressure. **Histopathology**. 2013;62 (5):731-41.

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ORIGINAL ARTICLE
ECHOGENICITY UNIT: A MATHEMATICAL FORMULA BASED ON GRAYSCALE IMAGERY

UNIDADE DE ECOGENICIDADE: UMA FÓRMULA MATEMÁTICA BASEADA EM IMAGENS EM ESCALA DE CINZA

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Key words: Echogenicity unit; Grayscale; Mathematical model; Ultrasonography.
Descritores: Unidade de ecogenicidade; Escala de cinza; Modelo matemático; Ultrassonografia.

Abstract

Objective: To develop a mathematical formula for accurately calculates a unit of echogenicity based on the grayscale scale. **Material and Methods:** Data from grayscale images representing various levels of echogenicity were collected, ensuring coverage of both absence and maximum echogenicity. Each grayscale image was assigned a corresponding numerical value indicating its level of echogenicity. These echogenicity values were transformed into a normalized range from 0 to 100. A formula was derived to calculate the echogenicity unit. The derived formula was applied to a set of grayscale images with known echogenicity levels, and the resulting calculated echogenicity units were compared to the assigned values to ensure accuracy and reliability. **Result:** Based on the described methodology, the formula: **Echogenicity Unit** = (Echogenicity Value / 256) * 100 were derived. This formula assigns an echogenicity value between 0 and 100, where 0 represents the absence of echo and 100 indicates maximum echogenicity. The calculated echogenicity units were compared to the assigned values from the dataset to validate the formula's accuracy. **Conclusion:** This study developed a mathematical formula to create an echogenicity unit. This derived formula provided a standardized method to measure echogenicity levels in grayscale images. **Endocrinol diabetes clin exp 2435/ 2438-2402.**

Resumo

Objetivo: Desenvolver uma fórmula matemática para calcular com precisão uma unidade de ecogenicidade com base na escala de cinza. **Material e Métodos:** Foram coletados dados de imagens em escala de cinza que representam vários níveis de ecogenicidade, garantindo a cobertura tanto da ausência quanto da máxima ecogenicidade. Cada imagem em escala de cinza recebeu um valor numérico correspondente que indicava seu nível de ecogenicidade. Esses valores de ecogenicidade foram transformados em uma faixa normalizada de 0 a 100. Foi derivada uma fórmula para calcular a unidade de ecogenicidade. A fórmula derivada foi aplicada a um conjunto de imagens em escala de cinza com níveis conhecidos de ecogenicidade, e as unidades de ecogenicidade calculadas resultantes foram comparadas com os valores atribuídos para garantir precisão e confiabilidade. **Resultado:** Com base na metodologia descrita, foi derivada a fórmula: **Unidade de Ecogenicidade** = (Valor de Ecogenicidade / 256) * 100. Esta fórmula atribui um valor de ecogenicidade entre 0 e 100, onde 0 representa a ausência de eco e 100 indica máxima ecogenicidade. As unidades de ecogenicidade calculadas foram comparadas com os valores atribuídos do conjunto de dados para validar a precisão da fórmula. **Conclusão:** Este estudo desenvolveu uma fórmula matemática para criar uma unidade de ecogenicidade. Esta fórmula derivada forneceu um método padronizado para medir os níveis de ecogenicidade em imagens em escala de cinza. **Endocrinol diabetes clin exp 2023 / 2434 - 2438.**

INTRODUCTION

Ultrasonography is a non-invasive imaging technique widely used in medical practice for diagnostic purposes. One crucial aspect of ultrasound imaging is the interpretation of the grayscale images produced, also known as the B-mode or 2D mode (1). The grayscale provides valuable information about tissue characteristics and aids in the accurate diagnosis of various conditions (2).

Grayscale in ultrasound imaging refers to the range of shades of gray used to represent different tissue densities. The variation in grayscale is based on the amplitude of the reflected ultrasound waves. The darker shades represent fluids or hypoechoic structures, while the brighter shades represent dense or hyperechoic structures (3).

Grayscale imaging provides information about the texture of tissues. Images with a homogeneous grayscale pattern suggest normal tissue characteristics, while inhomogeneous patterns may indicate pathologies. The analysis of ultrasound texture has emerged as an important tool for distinguishing different lesions and their neoplastic nature (4).

Advancements in ultrasound technology have introduced various techniques to enhance grayscale imaging. These include harmonic imaging, tissue harmonic imaging, and spatial compounding. These techniques improve image quality, reduce artifacts, and provide more accurate diagnostic information (5).

Thus, grayscale in ultrasound imaging plays a vital role in the accurate diagnosis of various medical conditions. Understanding grayscale patterns and their significance is essential for radiologists and healthcare professionals involved in ultrasound imaging.

The grayscale levels in an ultrasound diagnostic equipment refer to the range of gray tones that can be displayed in an image and that varies from 0 (no echoes) to 256 (extremely high echogenicity), representing different levels of echogenicity. Echogenicity is a measure of how much the ultrasound beam is reflected back to the transducer, corresponding to tissue density and composition (6). The objective is to develop a mathematical formula that accurately calculates the unit of echogenicity based on the grayscale scale, enabling more quantitative and objective comparisons of tissue characteristics in diagnostic ultrasound imaging.

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MATERIAL AND METHODS

• ***Data Collection:*** The image acquisitions analyzed were obtained by the same examiner using dynamic equipment with a multifrequency convex transducer (3-5MHz). The overall gain of the device was set at 50%, allowing for greater flexibility in adjusting the gain curve to achieve uniform echogenicity at all depths of the images. Data from grayscale images representing various levels of echogenicity were collected, ensuring coverage of both absence and maximum echogenicity.

• ***Echogenicity Assessment:*** Each grayscale image was assigned a numeric value corresponding to its echogenicity level.

• ***Normalize Values:*** The echogenicity values were transformed into a normalized range from 0 to 100. This normalization was achieved by dividing each echogenicity value by the maximum possible value (256 in this case) and then multiplying it by 100.

• ***Formula Derivation:*** A formula was derived to calculate the echogenicity unit, which reflects a desired range where 0 represents absence of echo and 100 signifies maximum echogenicity.

• ***Formula Validation:*** The derived formula was applied to a set of grayscale images with known echogenicity levels. The resulting calculated echogenicity units were compared to the assigned values to ensure accuracy and reliability.

Since the study did not involve any human participants and only utilized an image database generated by the researchers, it was not required to be submitted to the research ethics committee for evaluation.

RESULTS

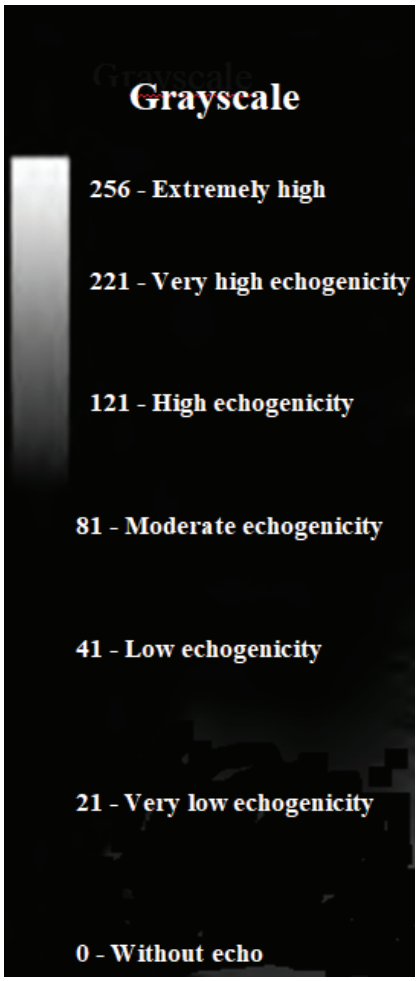
Based on the described methodology, the formula **"Echogenicity Unit** = (Echogenicity Value / 256) * 100" was derived. This formula assigns an echogenicity value between 0 and 100, where 0 represents the absence of echo and 100 indicates maximum echogenicity.

Human body tissues for each range of the described grayscale scale: 0-20: No echo), 21-40: Low echogenicity (weak echo), 41-80: Moderate echogenicity (moderate echo), 81-120: High echogenicity (strong echo), 121-220: Very high echogenicity (very strong echo), 221-256: Extremely high echogenicity (extremely strong echo) **Figure 1**.

By applying this formula to a set of grayscale images with known echogenicity levels, we were able to obtain accurate and reliable results. The calculated echogenicity units were compared to the assigned values from the dataset to validate the formula's accuracy. Thus, the derived formula provided a quantitative measure of echogenicity, allowing for objective analysis and comparison of the grayscale images **Figure 2**.

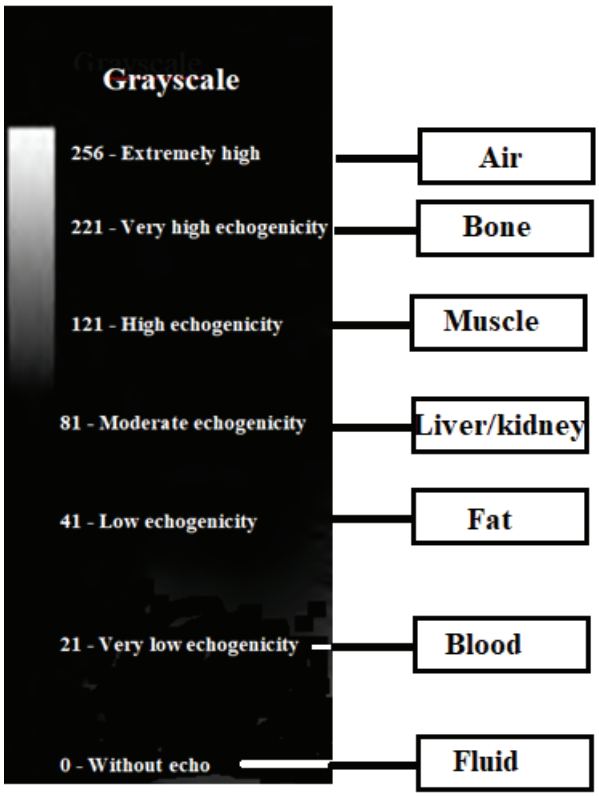
It is worth noting that in medical practice, grayscale scales may vary depending on the ultrasound machine and adjustments made by the operator. Additionally, tissues can have individual variations.

Figure 1. Grayscale representing various levels



Source: Research result

Figure 2. Tissue type and echogenicity



Source: Research result

DISCUSSION

The quantification of echogenicity in ultrasound has been challenging due to the subjective nature of visual interpretation. Our study focused on novel methodology for quantifying echogenicity using grayscale images. Thus, we have created a formula to calculate echogenicity units, demonstrating its accuracy and reliability, suggesting its potential application in clinical practice.

The spectrum of an acoustic echo signal, in terms of both its magnitude and frequency, is closely related to the structural and elastic properties of the medium with which it interacts. These properties include the size, shape, number, and organization of scattering sites within the medium. Thus, image processing techniques can be used to extract quantitative features, such as pixel intensity, texture, and shape, for the purpose of quantifying echogenicity. These features can be correlated with clinical outcomes or compared to subjective assessments by experts. The advantage of these approaches is their ability to automate the quantification process and reduce the subjectivity associated with visual interpretation. However, these methods often require complex algorithms and extensive computational resources, making them less accessible in routine clinical practice (7). In contrast, the methodology proposed in this study offers a simple and straightforward approach to echogenicity quantification. By assigning numerical values to grayscale images representing different levels of echogenicity and transforming them into a normalized range, a formula was derived to calculate the echogenicity unit.

Grayscale ultrasound imaging is a fundamental technique used in medical diagnostics to differentiate tissues based on their echogenicity (8). It was developed in the early 1960s, and its application to imaging by George Kossoff and William Garret in 1972, which allowed for improved contrast, revolutionized the field of ultrasound (9). By using a range of shades of gray to represent different levels of echogenicity, this imaging modality allows for intricate visualization of anatomical structures and detection of pathological changes (10). The grayscale in ultrasound imaging is critically important in distinguishing various tissues, such as solid organs, vessels, and cystic or fluid-filled structures (11). The grayscale in ultrasound imaging is a crucial tool that offers valuable insights into tissue characteristics, ultimately aiding in the precise diagnosis of numerous conditions. This article seeks to delve into the importance of grayscale in ultrasound imaging and its role in enhancing diagnostic accuracy. Utilizing a spectrum of the 256 shades of gray, we created a formula to determine an echogenicity unit.

By analyzing the ultrasound properties of tissues, including the attenuation coefficient, backscatter coefficient, and sound speed, it is possible to gain a deeper understanding of the tissue's condition and any potential pathologies. To determine the level of attenuation, it is necessary to compare the power spectra from at least two different depth regions (12). The overall attenuation is influenced by the combined effects of absorption and scattering along the ultrasound's path of propagation, which serve to decrease its intensity (13). As such, the total attenuation is a result of the cumulative impact of absorption and scattering along the propagation path, leading to a reduction in ultrasound intensity. The Hounsfield unit (HU) was developed to measure the attenuation coefficient of an X-ray beam as it passes through the human body. The HU, also known as the computed tomography, was named after Sir Godfrey Hounsfield, recipient of the Nobel Prize in Physiology or Medicine in 1979 (14). The value of a HU varies depending on the amount of X-ray photons absorbed by each type of human tissue. This scale is commonly used in computed tomography examinations (15). It is important to note that the methodology presented in this study has some limitations. Firstly, the dataset used to derive and validate the formula consisted of grayscale images with known echogenicity levels and varying acoustic attenuations depending on the tissue being assessed. While this ensured accuracy and reliability in the validation process, it may not fully represent the complexity and variability encountered in clinical practice. Additionally, the study focused on grayscale images, limiting its applicability to other imaging modalities, such as color Doppler or contrast--enhanced ultrasound.

Despite these limitations, the results of this study provide promising insights into the quantification of echogenicity using a simple and accessible approach. The derived formula offers a standardized and objective measure of echogenicity, which can enhance the accuracy and reproducibility of echogenicity assessments. This is particularly relevant in clinical decision--making, where reliable and quantitative information is essential for diagnosis, treatment planning, and monitoring of patients. The methodology presented in this study has the potential to improve the clinical utility of echogenicity quantification and should be considered for further investigation and validation.

CONCLUSION

In conclusion, this study presented a novel methodology for quantifying echogenicity in medical imaging using grayscale images. The results demonstrated the accuracy and reliability of the methodology, suggesting its potential application in clinical practice. When comparing the methodology and results to existing literature, the simplicity and accessibility of the proposed approach stood out as significant advantages. Overall, this study contributes to develop standardized and objective measures of echogenicity.

References

1. Dietrich CF, Bolondi L, Duck F, et al. History of Ultrasound in Medicine from its birth to date (2022), on occasion of the 50 Years Anniversary of EFSUMB. A publication of the European Federation of Societies for Ultrasound In Medicine and Biology (EFSUMB), designed to record the historical development of medical ultrasound. **Med Ultrason**. 2022;24(4):434-450.
2. Collinger JL, Fullerton B, Impink BG, Koontz AM, Boninger ML. Validation of grayscale-based quantitative ultrasound in manual wheelchair users: relationship to established clinical measures of shoulder pathology. **Am J Phys Med Rehabil**. 2010;89 (5):390-400.
3. Mancini L, Khehra A, Nguyen T, Barootchi S, Tavelli L. Echo intensity and gray-level co-occurrence matrix analysis of soft tissue grafting biomaterials and dental implants: an in vitro ultrasonographic pilot study. **Dentomaxillofac Radiol**. 2023:20230033.
4. Lindelius A, Törngren S, Sondén A, Pettersson H, Adami J. Impact of surgeon-performed ultrasound on diagnosis of abdominal pain. **Emerg Med J**. 2008;25 (8):486-91.
5. Uppal T. Tissue harmonic imaging. **Australas J Ultrasound Med**. 2010;13 (2):29-31.
6. Dambrosio F, Amy D, Colombo A. B-mode color sonographic images in obstetrics and gynecology: preliminary report. **Ultrasound Obstet Gynecol**. 1995;6 (3):208-15.
7. Shriki J. Ultrasound physics. **Crit Care Clin**. 2014;30 (1):1-24, v.
8. Garrett WJ, Kossoff G, Carpenter DA. Gray scale compound scan echography of the normal upper abdomen. **J Clin Ultrasound**. 1975;3 (3):199-204.
9. Kossoff G, Garrett WJ, Radovanovich G. Grey scale echography in obstetrics and gynaecology. Australas Radiol. 1974;18 (1):62-111.
10. Kossoff G. Basic physics and imaging characteristics of ultrasound. **World J Surg**. 2000;24 (2):134-42.
11. Knöttner R. 40 years of ultrasound real-time grayscale diagnostics. **Ultraschall Med**. 2006;27 (3):214-6.
12. Parker KJ, Lerner RM, Waag RC. Attenuation of ultrasound: magnitude and frequency dependence for tissue characterization. **Radiology**. 1984;153 (3):785-8.
13. Civale J, Bamber J, Harris E. Amplitude based segmentation of ultrasound echoes for attenuation coefficient estimation. **Ultrasonics**. 2021;111:106302.
14. Hounsfield GN. Computed medical imaging. Nobel lecture, Decemberr 8, 1979. J Comput Assist Tomogr. 1980;4 (5):665-74.
15. DenOtter TD, Schubert J. Hounsfield Unit. 2023 Mar 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.

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TOPICS IN MEDICAL CLINIC
ORIGINAL ARTICLE
ASSOCIATION OF INFLAMMATORY PARAMETERS WITH CLINICAL PROFILE IN SPONDYLOARTHRITIS PATIENTS

ASSOCIAÇÃO ENTRE PARÂMETROS INFLAMATÓRIOS E PERFIL CLÍNICO EM PACIENTES COM ESPONDILITE ANQUILOSANTE

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Key words: Spondyloarthritis; Disease activity; Clinical profile; Anti TNF-alpha
Descritores: Espondiloartrite; Atividade de Doença; Perfil Clínico; Anti-TNF alfa

Abstract

Background: Spondyloarthritis (SpA) are heterogeneous diseases with several forms of musculoskeletal involvement as well as extra articular manifestations. **Aim:** To study if the SpA inflammatory activity is linked to a particular disease phenotype. **Material and Methods:** One hundred and forty one patients with axial SpA (pure or mixed) with and without the main clinical manifestations (low back pain, buttock pain, cervicalgia, enthesitis, dactylitis, peripheral arthritis, uveitis and skin involvement) had their inflammatory activity [measured by ASDAS (Ankylosing Spondylitis disease Activity Score)-CRP (C reactive protein), ASDAS-ESR (erythrocyte sedimentation rate) and global judgment of the physician] as well as treatment requirement compared. The comparison group of patients (without the symptom) were tailored to pair the studied sample in gender, age and disease duration. **Results:** Patients with upper limb arthritis and skin psoriasis had higher ASDAS-CRP (p=0.01 and 0.04 respectively) and ASDAS-ESR (p=0.01 and 0.03 respectively) than those without it. Those with lower limb arthritis were judged to be worse by doctors' global evaluation (p=0.01). Patients with dactylitis required more biologic (p=0.02) and non-biologic treatment (p=0.02) and those with uveitis received more anti TNF-α drugs (p=0.006). **Conclusion:** Knowing a SpA patients' clinical profile may help the clinician to judge disease activity and/or treatment requirement. **Endocrinol diabetes clin exp 2023 / 2439 - 2442.**

Resumo

Justificativa: As espondiloartrites (SpA) são doenças heterogêneas com várias formas de envolvimento musculoesquelético, bem como manifestações extra-articulares. **Objetivo:** Estudar se a atividade inflamatória da SpA está ligada a um fenótipo da doença em particular. **Material e Métodos:** Cento e quarenta e um pacientes com Axial SpA tiveram sua atividade inflamatória [medida pelo ASDAS (Ankylosing Spondilitis Disease Activity Score)-CRP (proteína reativa C), ASDAS-ESR (taxa de sedimentação eritrócito) e julgamento global do médico, bem como a necessidade de tratamento comparados de acordo com a presença das principais manifestações clínicas (dor lombar, dor na nádega, cervicalgia, entesite, dactilite, artrite periférica, uveíte e envolvimento com a pele). O grupo de comparação dos pacientes (sem o sintoma) foi recortado para parear a amostra estudada em sexo, idade e duração da doença. **Resultados:** Pacientes com artrite do membro superior e psoríase da pele apresentaram maior ASDAS-CRP (p=0,01 e 0,04, respectivamente) e ASDAS-ESR (p=0,01 e 0,03, respectivamente) do que aqueles sem ele. Aqueles com artrite de membros inferiores foram julgados como piores pela avaliação global dos médicos (p=0,01). Pacientes com dactilite necessitaram de mais tratamento seja com biológicos (p=0,02) e não biológicos (p=0,02). Aqueles com uveíte receberam mais anti-TNF-α (p=0,006). **Conclusão:** Conhecer o perfil clínico de um paciente de SpA pode ajudar o médico a julgar a atividade da doença e/ou a exigência de tratamento. **Endocrinol diabetes clin exp 2023 / 2439 - 2442.**

INTRODUCTION

SpA (spondyloarthritis) are a group of rheumatic diseases that can be quite heterogeneous from the clinical point of view (1). Regarding musculoskeletal manifestations, they can be divided into disease with axial or with peripheral involvement or with a mixed pattern (axial and peripheral). In addition, extra articular features such as ocular, skin and gastrointestinal involvement may modulate their clinical expression (1).

It is well known that common pathophysiologic mechanism under musculoskeletal and extra-articular manifestations in SpA (2) are seen, but little is known about the influence of the clinical variability or presence of extra-articular features in the disease activity.

Judging disease activity is fundamental to tailor the treatment of a patient with rheumatic disease as inflammatory disease activity is responsible for the patients' future functional impair (3). Therefore, knowing if the presence of a determinate clinical profile is associated with more inflammation could help the clinician to choose therapeutic strategies. In the present study we analyzed if a special musculoskeletal complain as well as the presence of extra articular symptoms could help predict which SpA patient will have more disease activity.

MATERIAL AND METHODS

This is a cross-sectional study approved by the Committee of Ethics in Research of the three participant centers and all included individuals signed consent. To be included the patients must fill the ASAS classification criteria for SpA and to have axial involvement (pure axial or axial mixed with peripheral arthritis) (4). This was a convenience sample of SpA patients that come for regular consultation in a tertiary center and that agreed to participate in the study during the period of one year. Patients were invited to participate in the study according to appointment order. Epidemiological (gender, age, disease duration, smoking habits) and clinical (presence of lumbar and buttock pain, coxalgia, peripheral arthritis, dactilitis, enthesitis, ocular and skin involvement or psoriasis, presence of HLA B27)

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and treatment data was obtained through chart review. Clinical data was considered in cumulative way. ASDAS (Ankylosing Spondylitis Disease Activity Score)-CRP (C Reactive Protein) (5) and ASDAS-ESR (Erythrocyte Sedimentation Rate) (5) were measured at inclusion, simultaneously with a doctor's global judgment of disease activity through VAS (Visual Analogic Scale - from zero to 10, where 0 means no disease activity and 10 the worst scenario).

The parameters of disease activity (ASDAS-ESR, ASDAS--CRP, doctors VAS) were compared according to the presence or not of each clinical finding. For this, a sample of patients with the presence of the studied clinical finding and a tailored comparison sample (patients without the studied clinical finding) in order to be paired for gender, age and disease duration was selected.

Obtained data was analyzed in frequency and contingency tables. Fisher and chi-squared tests were used to compare nominal data and unpaired t test and Mann-Whitney test to compare numerical data. The software Graph Pad Prism 6.0 was used for calculations. The adopted significance was of 5%.

RESULTS

One hundred and forty-one patients were included: 71 with pure axial form and 70 with mixed (axial and peripheral) involvement. The patients mean age was of 49.5±12.6 years and the median disease duration was of 17 years (range 12-58). About 26.9 (38/141) were exposed to tobacco (smokers and ex-smokers). HLA B27 was present in 64/111 (57.6%).

In this sample. 132/141(93.6%) were using nonsteroidal anti-inflammatory drugs (AINHs); 83/141 (58.8%) were using glucocorticoids; 100/141(70.2%) were using methotrexate; 13/141 (9.2%) were using leflunomide and 76/141 (53.9%) were using anti TNF-α drugs.

1-Comparison of disease activity and treatment requirement in SpA patients according to musculoskeletal complaints:

The comparison of patients with lumbar pain (n=108;76.5%) with a sample of 33 patients without it paired for gender (p=0.14) , age (p=0.19) and disease duration (p=0.35) showed no differences in the comparison of ASDAS-PCR (p=0.24), ASDAS-ESR (p=0.09); doctor's VAS (p=-0.78) , use of conventional DMARDs (p=0.09) and anti TNF-α drugs (p=0.47).

The comparison of 39/141 (27.6%) patients with buttock pain with 86 patients without it paired for gender (p=0.43); age (p=0.62) and disease duration (p=0.17) showed no differences in the comparison of ASDAS-CRP (p=0.13), ASDAS-ESR (p=0.22) and doctor's VAS (p=0.37). Also, no differences in the requirement of conventional DMARDs (p=-60) and anti TNF-α drugs (p=0.68) were noted.

The comparison of patients with cervicalgia (n=62/141= 43.9%) with 79 patients without it paired for gender (p=0.99); age (p=0.12) and disease duration (p=0.35) demonstrated no differences in the ASDAS-CRP (p=0.61); ASDAS –ESR (p=0.66) and doctor's VAS (p=0.77), neither in the DMARDs (p=0.25) or anti TNF-α (p=0.88) use.

The comparison of patients with peripheral arthritis, dactylitis and enthesitis is on **table 1**. In this table, it is possible to see that patients with upper limb arthritis have higher ASDAS-ESR and ASDAS-CRP and used more conventional DMARDs. Those with lower limb arthritis have equivalent ASDAS-CRP and ESR but the doctor's global evaluation classified them with worse disease. Patients with dactylitis required more DMARDs and anti-TNF-α drugs and patients with enthesitis showed no difference with those without it.

TABLE 1- Comparison of inflammatory activity parameters, doctors global evaluation (vas) and treatment requirement according to the presence of arthritis, dactylitis and enthesitis.

	ARTHRITIS UPPER LIMB n= 59/82 (*)			ARTHRITIS LOWER LIMB n=81/55(*)			DACTYLITIS n= 24/117(*)			ENTHESITIS n= 54/87(*)		
Pairing	**Gender**	**Age**	**DD.**	**Gender**	**Age**	**DD.**	**Gender**	**Age**	**DD.**	**Gender**	**Age**	**DD.**
P value	0.85	0.93	0.35	0.46	0.28	0.87	0.43	0.87	0.17	0.52	0.27	0.55
	WITH	**WITHOUT**	**P**	**WITH**	**WITHOUT**	**P**	**WITH**	**WITHOUT**	**P**	**WITH**	**WITHOUT**	**P**
ASDAS CRP	2.59	2.07	**0.01**	2.10	2.36	0.64	2.20	2.20	0.70	2.23	2.15	0.51
Median (IQR)	(1.79-3.57)	(0.94-2.98)		(1.15-3.32)	(1.50-3.20)		(1.07-3.07)	(1.20-3.32)		(1.58-3.34)	(1.07-3.30)	
ASDAS ESR	2.95±1.19	2.51±1.00	**0.01**	2.71±1.15	2.68±1.02	0.87	2.37±1.04	2.76±1.10	0.11	2.77±1.13	2.65±1.08	0.52
Mean ± SD												
VAS Doctor	4	3.0	0.15	4	3.0	**0.01**	4	3	0.15	3	3	0.30
	(2-6)	(2.-5)		(2.5-6)	(1.0-5)		(2.2-6)	(2-5)		(1-5)	(2-6)	
DMARds (n)	48	52	**0.02**	61	35	0.14	22	78	**0.02** (§)	40	60	0.73
	(81.3%)	(63.4%)	(**)	(75.3%)	(63.3%)		(91.6%)	(66.6%)		(74.0%)	(68.9%)	
Anti TNF-α	32	44	0.94	43	31	0.70	18	58	**0.02**	33	43	0.25
(n)	(54.2%)	(53.6%)		(53.0%)	(56.3%)		(75%)	(49.55)	**(§§)**	(61.1%)	(49.4%)	

(*) refers to number of patients with the finding of studied sample/controls; n= number; IQR= interquartile rate; SD= standard deviation; DD.= disease duration.
ASDAS= Ankylosing Spondylitis Disease Activity Score; ESR= erythrocyte sedimentation rate; CRP= C reactive protein; VAS= Visual analogic scale; DMARds- Disease modifying anti-rheumatic drugs.
(**) OR=2.5; 95% CI=1.1-5.5; (§)- OR=5.2; 95%CI= 1.16-23.3; (§§)´OR=3.0; 95CI= 1.1-8.2.

2- Comparison of disease activity and treatment requirement in SpA patients according to extra articular manifestations.

The comparison of patients with uveitis and skin disease is on **table 2**. Only five (3.5% of the sample) had inflammatory bowel disease not allowing comparisons.

TABLE 2 - Comparison of inflammatory activity data, doctor's VAS and treatment requirement in Spa patients with and without uveitis and skin disease.

	UVEITIS N=31/87 (*)			SKIN DISEASE N=37/41 (*)		
Pairing	**Gender**	**Age**	**DD**	**Gender**	**Age**	**DD.**
P value	0.57	0.18	0.10	0.22	0.08	0.67
	With	**Without**	**P**	**With**	**Without**	**P**
ASDAS-CRP Median (IQR)	2.17 (1.33-2.82)	2.20 (0.94-3.30)	0.75	13.0 (7.5-19.0)	15.0 (8.5-18.0)	**0.04**
ASDAS-ESR Mean ± SD	2.50±1.12	2.74±1.06	0.28	3.01±1.23	2.46±0.85	**0.03**
DOCTOR'S VAS Median (IQR)	3 (0-5)	4 (2-5)	0.35	3.0 (2.0-5.0)	4.0 (2.0-5.5)	0.44
DMARDs users (n)	20 (64.5%)	70 (80.4%)	0.07	35 (94.5%)	25 (60.9%)	**0.0004 (§)**
Anti-TNF-α users (n)	24 (77.4%)	43 (49.4%)	**0.006** (**)	20 (54.0%)	26 (63.4%)	0.40

(*) refers to number of patients with the finding/ controls; n= number; IQR= interquartile rate; SD= standard deviation; DD.= disease duration; ASDAS= Ankylosing Spondylitis Disease Activity Score; ESR= erythrocyte sedimentation rate; CRP= C reactive protein; VAS= Visual analogic scale; DMARDs- Disease modifying anti rheumatic drugs.
(**) OR= 3.5; 95%CI=1.3-8.9; (§)- OR=11.2.7;(5%CI=2.3-53.1).

DISCUSSION

The results of this study show that SpA patients with upper limb arthritis have more disease activity measured by ASDAS--ESR and ASDAS-CRP and require more use of conventional DMARDS than those without it, but that this was not recognized by the global judgment made by the attending clinician. On the other hand, the physician considered patients with lower limb arthritis worse than those without it, but their inflammatory activity is considered the same by ASDAS-ESR and CRP. This is an interesting finding as it suggests that the attending physician probably values the lower limb complaints more than the upper ones. Contrary to our findings, Shali et al. (6) studying foot involvement in SpA patients found that this type of manifestation was associated with higher inflammation in blood tests (ESR and CRP). However, these authors studied the foot involvement as a whole, including in their observation entheseal disorders and not just arthritis. Ozaras et al., (7) studying feet function in SpA, could not correlate its impairment with inflammatory tests showing that foot involvement may not be directly affected from the disease activity but suffers influence of mechanical and ligament derangements. Probably such aspects influence the global health judgment by the physician. This also accentuates the need to evaluate foot involvement separately from global disease activity in order to improve patients' care.

The occurrence of dactylitis did not alter the measurements of disease activity but implicates in higher treatment requirement of both traditional DMARDs and biologic drugs. This manifestation results from inflammation in the finger flexor tendon sheaths (8), and according to some authors may be associated with synovitis (9). It is considered a severity marker in SpA mainly in the psoriatic form where it is more common (8). So, it is not surprising that such patients will need more treatment as demonstrated in the present study. Traditionally, dactilyitis are treated with nonsteroidal anti-inflammatory drugs and local corticosteroid injections; DMARDs and anti TNF-α drugs have also been used (8,10).

According to the present data, SpA patients with uveitis are more frequently treated with anti TNF-α drugs despite equal

disease activity than those without it. This is easily explained, as uveitis inflammatory activity does not reflect in the parameters evaluated by ASDAS. On the other hand, anti TNF-α drugs are frequently indicated in more severe cases of uveitis (11,12). Our data also shows that patients who developed uveitis do not have a more active articular disease and do not agree with the findings of Chen et al. (13) that observed association between uveitis with SpA activity and functional indexes. However, this latter author studied a different activity index - the BASDAI (Bath Ankylosing Spondylitis Disease activity index) – and a sample of patients with diverse ethnic background (from Taiwan). This may explain the differences found; it is well known that uveitis occurrence suffers genetic influence (14).

Skin involvement was associated with more inflammatory activity measured by both ASDAS-ESR and ASDAS-CRP and also with higher requirement of DMARDs. It is possible that the inflammatory process in the skin itself (15) increased the results of the inflammatory blood test resulting in higher values of activity indexes.

Limitations of this study are due to its cross-sectional design and to the small studied sample. However, it highlights the idea that the knowledge of SpA patients' clinical profile may help the clinician to judge disease activity and/or treatment requirement.

CONCLUSION

Concluding, in this sample it was detected that the occurrence of upper limb arthritis and skin psoriasis was linked to higher ASDAS-CRP and ASDAS-ESR than in those without it. Those with lower limb arthritis were judged to be worse by doctors' global evaluation. Patients with dactylitis required more biologic and non-biologic treatment and those with uveitis received more anti TNF-α drugs.

References

1. Terenzi R, Monti S, Tesei G, Carli L. One year in review 2017: Spondyloarthritis. **Clin Exp Rheumatol.** 2018; 36(1):1-14.
2. Paramarta JE, Baeten D. Spondyloarthritis: from unifying concepts to improved treatment. **Rheumatology** (Oxford). 2014;53(9):1547-59.
3. Kerschbaumer A, Baker D, Smolen JS, Aletaha D. The effects of structural damage on functional disability in psoriatic arthritis. **Ann Rheum Dis**. 2017;76(12):2038-2045.
4. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J et al. The development of assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. **Ann Rheum Dis**. 2009; 68:777-83.
5. Van der Heijde D, Lie E, Kvien TK, Sieper J, van den Bosch F, Listing J et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. **Ann Rheum Dis** 2009; 68:1811-8.
6. Sahli H, Bachali A, Tekaya R, Mahmoud I, Sedki Y, Saidane O, Abdelmoula L. Involvement of foot in patients with spondyloarthritis: Prevalence and clinical features. **Foot Ankle Surg**. 2017; pii: S1268-7731(17)31329-2.
7. Ozaras N, Havan 2, Poyraz 1, Rezvanı A, Aydın T. Functional limitations due to foot involvement in spondyloarthritis. **J Phys Ther Sci**. 2016; 28(7):2005-8.
8. Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. **J Rheumatol**. 2006; 33(7):1439-41.
9. Kane D, Greaney T, Bresnihan B, Gibney R, FitzGerald O. Ultrasonography in the diagnosis and management of psoriatic dactylitis. **J Rheumatol**. 1999; 26:1746-51.
10. Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. **J Rheumatol**. 2014; 41(11):2277-85.
11. LaMattina KC, Goldstein DA. Adalimumab for the treatment of uveitis. **Expert Rev Clin Immunol**. 2017;13(3):181-8.
12. Lee S, Park YJ, Lee JY. The Effect of Tumor Necrosis Factor-Alpha Inhibitors on Uveitis in Patients with Ankylosing Spondylitis. **J Korean Med Sci**. 2019 Nov 4;34(42):e278
13. Chen CH, Lin KC, Chen HA, Liao HT, Liang TH, Wang HP, Chou CT. Association of acute anterior uveitis with disease activity, functional ability and physical mobility in patients with ankylosing spondylitis: a cross-sectional study of Chinese patients in Taiwan. **Clin Rheumatol**. 2007; 26(6):953-7.
14. Wakefield D, Yates W, Amjadi S, McCluskey P. HLA-B27 Anterior Uveitis: Immunology and Immunopathology. **Ocul Immunol Inflamm.** 2016;24(4):450-9.
15. Chiang CC, Cheng WJ, Korinek M, Lin CY, Hwang TL. Neutrophils in Psoriasis. **Front Immunol**. 2019; 10:2376. e Collection 2019.

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TOPICS IN MEDICAL CLINIC
ORIGINAL ARTICLE
COMPARISON OF MALES AND FEMALES WITH ANKYLOSING SPONDYLITIS: A CROSS SECTIONAL STUDY IN A BRAZILIAN SAMPLE

ESPONDILITE ANQUILOSANTE EM HOMENS E MULHERES: UM ESTUDO TRANSVERSAL EM UMA AMOSTRA BRASILEIRA

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Key words: Ankylosing spondylitis; Spondyloarthritis; Females.
Descritores: Espondilite anquilosante; Espondiloartrites; Mulheres.

Abstract

Introduction: Ankylosing Spondylitis (AS) is a chronic rheumatic disease historically considered to be more common in men. However, recent data has suggested that females may have a higher rate of this disease than previously though. The diagnosis may be delayed in females because women may display a clinical profile different from men. **Objective:** To study comparatively males and females with AS in a Brazilian sample. **Material and Methods:** Cross-sectional study including AS patients studied for clinical and epidemiological data. Disease activity was measured by BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), ASDAS (Ankylosing Spondylitis Disease Activity Score) -ESR (Erythrocyte Sedimentation Rate), and ASDAS-CRP (C Reactive Protein). MASES (Maastrich Ankylosing Spondylitis Enthesitis Score) was used to estimate enthesitis; function was assessed by BASFI (Bath Ankylosing Spondylitis Functional Index) and ASQoL (Ankylosing Spondylitis Quality of Life questionnaire) was used to evaluate quality of life. **Results:** Ninety AS patients were included (36 females and 54 males) in a male/female proportion of 1.5 to 1. Males and females have the same age at first symptoms but females had diagnosis done later (p= 0.04). Females had more enthesitis (p=0.03) and males had more HLA-B27 (p=0.001) and a tendency to have more inflammatory low back pain (p=0.06). ASDAS -ESR, ASDAS-CRP and MASES were higher in females than males (with p= 0.01; 0.03 and 0.003 respectively) but BASFI and ASQoL showed no differences (p=ns). **Conclusion:** Compared to men, women had a later diagnosis of AS;they presented more enthesitis and inflammatory activity and less HLA-B27. **Endocrinol diabetes clin exp 2023 / 2443 - 2447.**

Resumo

Introdução: A espondilite anquilosante (EA) é uma doença reumática crônica considerada, historicamente, mais comum em homens. Entretanto dados recentes têm sugerido que mulheres têm muito mais EA do que se pensava anteriormente. O diagnóstico em mulheres pode ser retardado porque elas apresentam um perfil clínico diferente daquele dos homens. **Objetivo:** Estudar de maneira comparativa homens e mulheres com EA em uma amostra de pacientes brasileiros. **Material e Métodos:** Estudo transversal incluindo pacientes com EA analisados para perfil clínico e epidemiológico. A atividade de doença foi medida pelo BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), pelo ASDAS (Ankylosing Spondylitis Disease Activity Score) – VHS (velocidade de hemossedimentação), e pelo ASDAS-PCR (Proteina C reativa). MASES (Maastrich Ankylosing Spondylitis Enthesitis Score) foi usado para avaliar entesites; a funcionalidade foi medida pelo BASFI (Bath Ankylosing Spondylitis Functional Index) e o ASQoL (Ankylosing Spondylitis Quality of Life questionnaire) foi usado para medir qualidade de vida. **Resultados:** Noventa pacientes foram incluídos (36 mulheres e 54 homens) numa relação homem/mulher de 1.5 para 1. Homens e mulheres tinham a mesma idade ao primeiro sintoma, mas as mulheres tiveram o diagnóstico feito mais tardiamente (p=0.04). Mulheres tinham mais entesite (p=0.03) e homens tinham mais HLA B27 positivo (p=0.001) e uma tendência para ter mais queixas de dor lombar inflamatória (p=0.06). ASDAS-VHS, ASDAS PRC e MASES foram mais elevados nas mulheres que homens (p=0.01; 0,03 e 0,003 respectivamente) mas o BASFI e ASQoL não mostraram diferenças (p=ns). **Conclusão:** Comparadas com os homens, as mulheres têm um diagnóstico mais tardio da doença. Elas apresentam mais entesite e maior atividade inflamatória, mas menor positividade para o HLA-B27. **Endocrinol diabetes clin exp 2023 / 2443 - 2447.**

INTRODUCTION

Ankylosing Spondylitis (AS) is a chronic inflammatory disease characterized by spine involvement that causes inflammatory low back pain. Besides axial symptoms, patients with AS may have several extra spinal manifestations such as peripheral arthritis, enthesitis, uveitis, etc. (1) AS is a disease classically described in men although recent studies have shown that the occurrence of this disease in females is not so rare (2). AS sex ratio was described in older publications as 10:1 (3); in the more recent studies as 2.5:1–5:1 (2).

Despite this recognition, the diagnosis of AS in women may not be easy, as the disease may offer a different clinical pattern profile. The reasons for these differences are not well studied. From immunological point of view, females generate higher Th2 responses, whereas in males there is stronger Th17 response (4,5). According to animal studies, estrogens may have an anti-inflammatory effect on the spondyloarthritis (SpA) (4) and in menstruating females with AS, the estradiol levels is found to be lower in females with active AS than in those with inactive

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disease (6). No influences of X chromosome encoded genetic effects have been described so far (7).

Genetic and environmental influences such as microbial exposures in early childhood are important in the AS appearance (8,9). So, its prevalence and clinical profile may differ according to the studied population (10), highlighting the importance of local studies.

Herein we studied a sample of Brazilian patients aiming to know differences in clinical profile of AS between females and males.

MATERIAL AND METHODS

This study has cross-sectional design and was approved by the local Committee of Ethics in Research; all participants signed consent. To be included AS patients should fulfil the ASAS classification criteria for axial Spondyloarthritis (11). Included females and males were paired for age and disease duration. The study used a convenience sample of patients that come for regular consultation in a single tertiary Rheumatology Center and that agreed to participate in the study during the period of one year. The patient's chart was reviewed for epidemiological (gender, age, disease duration, smoking habits), clinical data (presence of lumbar and buttock pain, peripheral arthritis, enthesitis, ocular involvement, presence of HLA B27). Disease activity was assessed by BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (12), ASDAS (Ankylosing Spondylitis Disease Activity Score) -ESR (Erythrocyte Sedimentation Rate) (12), and ASDAS-CRP (C Reactive Protein) (12). MASES (Maastrich Ankylosing Spondylitis Enthesitis Score) was used to estimate enthesitis (13); function was assessed by BASFI (Bath Ankylosing Spondylitis Functional Index) (14) and ASQoL (Ankylosing Spondylitis Quality of Life questionnaire) (15) was used to evaluated quality of life.

Males and females were compared using chi-squared and Fisher test for nominal variables and unpaired t test and Mann Whitney for numerical data. The adopted significance was 5%.

RESULTS

Ninety patients were included: 54 (60%) males and 36 (40%) females in a proportion of 1.5:1. The main epidemiological and clinical data is on **Table 1**, showing that the commonest complain in the whole sample was inflammatory low back pain followed by enthesitis.

Table1- Descriptive data of studied sample (90 patients with Ankylosing Spondylitis)

Mean age (years)	49.3±10.3
Mean age at first symptom (years)	32.2±12.6
Mean age at diagnosis (years)	39.6±11.7
Current smokers (n)	14/89 – 15.7%
Inflammatory lumbar pain	69/90 – 76.6%
Buttock alternant pain	34/89 – 38.2%
Lower limb arthritis	28/90 -31.1%
Upper limb arthritis	21/90 – 23.3%
Enthesitis	48/90 – 53.3%
HLA B27	54/76 – 71.0%
Uveitis (n)	43/90 -47.7%
Median ASDAS PCR (IQR)	2.35 (1.67-3.01)
Median ASDAS ESR (IQR)	2.54 (1.76-4.02)
Median BASDAI	3.0 (1.92-5.27)
Median MASES	7 (1-12)
Median ASQoL	9.0 (4.5-13.5)
Median BASFI	4.46 (2.1-7.2)

ASDAS= Ankylosing Spondylitis Disease activity score; PCR= C reactive protein; ESR= erythrocyte sedimentation rate; BASDAI= Bath Ankylosing Spondylitis disease activity index; ASQoL= Ankylosing Spondylitis Quality of life questionnaire; BASFI= Bath Ankylosing Spondylitis functional index; MASES= Maastrich Ankylosing Spondylitis enthesitis score.

The comparison of epidemiological and clinical data between males and females is on **Table 2**. This table shows that males and females were equally old and, despite having the same age at first symptom, the diagnosis was done later in women than men. Enthesitis was more common in females while HLA-B27 was more common in males.

Table 2- Comparison of epidemiological and clinical data in males and females with Ankylosing Spondylitis

	Males	Females	P
Mean age ± SD (years)	50.0 ±9.1	48.3±12.0	0.44
Mean age ± SD at first symptom	30.9±12.1	34.0±13.0	0.20
Mean age ± SD at diagnosis	38.3±11.3	43.2±10.8	**0.04**
Current smokers (n)	11/54	3/35	0.23
Inflammatory lumbar pain (n)	45/54 -	24/36	0.06
Alternant buttock pain (n)	19/53	15/36	0.57
Lower limb arthritis (n)	20/54	8/36	0.13
Upper limb arthritis (n)	15/54	6/36	0.22
Enthesitis	24/54	24/36	**0.03 (*)**
Uveitis	24/54	19/36	0.43
HLA B27	39/46	15/30	**0.001 (**)**

(*) OR=2.5;95%CI=1,04- 6.0; (**) OR=5.5;95%IC=1.8-16.3.

The comparison of the results from inflammatory indexes, functional and enthesitis indexes and quality of life questionnaire are on **Table 3**. This table shows that females had worse performance in the ASDAS and MASES than males.

Table 3 – Comparison of disease activity, functional and enthesitis scores and quality of life between males and females with Ankylosing Spondylitis.

	Males	Females	P
BASDAI	2.8 (1.6-4.0)	3.8 (2.0-5.6)	0.09
ASDAS PCR	2.06 (1.50-2.87)	2.72 (1.99-3.47)	**0.01**
ASDAS ESR	2.19 (1.74-2.91)	3.42 (1.94-4.20)	**0.03**
BASFI	3.9 (1.82-6.97)	4.6 (2.05-6.87)	0.86
ASQoL	9.0 (3.7-13)	8.5 (4.2-13.7)	0.97
MASES	1.0 (0-4)	7.0 (2.5-12.0)	**0.003**

Values expressed in median (interquartile range). ASDAS= Ankylosing Spondylitis Disease activity score; PCR= C reactive protein; ESR= erythrocyte sedimentation rate; BASDAI= Bath Ankylosing Spondylitis disease activity index; ASQoL= Ankylosing Spondylitis Quality of life questionnaire; BASFI= Bath Ankylosing Spondylitis functional index; MASES= Maastrich Ankylosing Spondylitis enthesitis score.

In 46 patients the results of HLA B27 were available. Comparing male and females with positive HLA B27, the results are on **Table 4**; they were similar to the results obtained in the comparison of the whole sample.

Table 4- Comparison of males and females with ankylosing spondylitis HLA-B27 positives.

	Males HLA-B27 +	Females HLA-B27	p
Mean age± SD (years)	49.8±9.0	48.8±9.4	0.72
Mean age at first symptoms± SD (years)	29.8±11.7	35.6±11.9	0.11
Mean age at diagnosis± SD (years)	37.5±10.2	44.3±8.2	**0.03**
Inflammatory lumbar pain (n)	33/39 – 84.6%	10/15 – 66.6%	0.14
Alternant buttock pain (n)	10/38 – 26.3%	6/15 – 40%	0.32
Lower limb arthritis (n)	16/39 – 41.0%	4/15 -26.6%	0.36
Upper limb arthritis (n)	10/39 – 25.6%	2/15- 13.3%	0.47
Enthesitis	20/39 – 51.2%	10/15 – 66.6%	0.30
Uveitis	17/39 – 43.5%	11/15- 73.3%	0.07
BASDAI	2.82 (1.56-3.80)	5.45 (3.90- 6.00)	**0.02**
ASDAS PCR	1.98 (1.50-2.76)	3.41 (2.50-3.78)	**0.03**
ASDAS ESR	2.17 (1.74-3.11)	4.04 (2.85-4.90)	**0.01**
BASFI	3.85 (1.67-6.87)	4.70 (2.20-5.80)	0.95
ASQoL	8.25±4.61	8.40±5.64	0.92
MASES	2.0 (1.0-4.0)	11.0 (7.0-13.0)	**0.005**

ASDAS= Ankylosing Spondylitis Disease activity score; PCR= C reactive protein; ESR= erythrocyte sedimentation rate; BASDAI= Bath Ankylosing Spondylitis disease activity index; ASQoL= Ankylosing Spondylitis Quality of life questionnaire; BASFI= Bath Ankylosing Spondylitis functional index; MASES= Maastrich Ankylosing Spondylitis enthesitis score.

DISCUSSION

Our results have shown that, in this sample of patients with AS, the proportion male/female was 1.5/1 and that females had more enthesitis, a greater period from the first symptom until diagnosis, lower prevalence of HLA-B27 and a tendency towards less inflammatory lower back pain than males. Also, the ASDAS-ESR, ASDAS-CRP and MASES were higher in females than males. Despite higher inflammatory indexes in women than in men, the functional index and quality of life were similar in both sexes.

The delay in the diagnosis of AS in women when compared to men was recognized by others. A meta-analysis including 23,889 patients with SpA (with 32.3% women) showed that there is more delay in diagnosis among female than males (8.8 versus 6.5 years, respectively) (16). Some explanation of this finding is the under recognition of the occurrence of this disease in females by the medical community as AS is historically considered to be a male disease (17). Moreover, differences in the clinical picture may contribute for such delay; low frequency of inflammatory low back pain in women or high presence of widespread musculoskeletal pain caused by enthesitis that is frequently misdiagnosed as fibromyalgia are some of them (18).

In the current work higher values for disease activity in females than males measured by ASDAS-CRP, ASDAS-ESR and MASES were found. Rusmann et al. (17) in a systematic review of literature, observed that activity of the disease in females with axSpA was worse than in males but they did not identify differences when the ASDAS instrument was used. However, the data available on these later instruments was limited in the referred study.

The presence of HLA-B27 was found to be more common in males than females in this study and such observation replicates studies from Garrido-Cumbrera et al. (19). As HLA-B27 belongs to the set of classification criteria from ASAS for axial spondyloarthritis (11), it is easy to understand that men - that have more positive HLA B27 than women - have the disease classified more promptly. Corroborating this hypothesis, Feldtkeller et al. (20) observed that HLA-B27 negative patients with AS have a diagnosis delay when compared to HLA B27 positives. Interestingly, the presence of HLA-B27 did not attenuate the differences found between males and females in this sample. HLA-B27 is usually associated to a disease of early onset (21) and with the presence of uveitis (22). A work by Jong et al. (23) studying patients from Netherlands, could not find differences in males and females with SpA HLA-B27 positive –that is in agreement with the present study. However, the referred work also could not prove differences in male and females regardless of HLA -B27 presence. These results point to the importance of local studies to known clinical profile of EA patients. Not only the presence of diverse HLA-B27 alleles changes according to the studied region (24) but also environmental factors play a role on this context (25). One curious

finding in the present study was the high prevalence of uveitis in the whole sample but mainly in HLA-27 positive females. Uveitis have been described to be present in 32.2% of AS in a French sample (26) but only in 14.5% in a Brazilian series (27). The high prevalence observed presently could be credited to the presence of an outpatient ophthalmology clinic in the same hospital that is particularly interested in uveitis, directing such patients to rheumatologic care. Such finding highlights the importance of ophthalmologists in the recognition of AS. Also, the proportion of uveitis was higher in HLA-B27 positive females than males, although not statistically significant. This observation may be due to the fact that uveitis is an objective sign pointing to EA diagnosis otherwise missed in females with more unspecific complaints, such as widespread musculoskeletal pain.

This work is limited by its cross-sectional design and small sample, mainly of those with HLA-B27. However, it does reflect the real life of a rheumatology clinic from Southern Brazil and points to the lack of recognition of AS in females.

CONCLUSION

Concluding, in this sample a relation 1.5/1 in males/females with AS was found. Females had more enthesitis and delay in the diagnosis. Males had a tendency towards more inflammatory low back pain and HLA-B27 positivity. Inflammatory indexes were higher in women but the function and quality of life were similar in females and males. The presence of positive HLA-B27 did not attenuate these differences.

References

1. Magrey MN, Danve AS, Ermann J, Walsh JA. Recognizing Axial Spondyloarthritis: A Guide for Primary Care. **Mayo Clin Proc**. 2020; 95 (11):2499-2508.
2. Kennedy LG, Will R, Calin A. Sex ratio in the spondyloarthropathies and its relationship to phenotypic expression, mode of inheritance and age at onset. **J Rheumatol** 1993; 20:1900–4.
3. West H. The aetiology of ankylosing spondylitis. **Ann Rheum Dis**. 1949; 8:143–8.
4. Taneja V. Sex hormones determine immune response. **Front. Immunol**. 2018; 9, 1931.
5. Jeong H, Kim IY, Bae EK, Jeon CH, Ahn KS, Cha HS. Selective estrogen receptor modulator lasofoxifene suppresses spondyloarthritis manifestation and affects characteristics of gut microbiota in zymosan-induced SKG mice. **Sci Rep**. 2021; 11(1):11923.
6. Jimenez-Balderas FJ, Tapia-Serrano R., Madero-Cervera JI, Murrieta S, Mintz G. Ovarian function studies in active ankylosing spondylitis in women. Clinical response to estrogen therapy. **J. Rheumatol**. 1990; 17, 497–502.
7. Hoyle E, Laval SH, Calin A, Wordsworth BP, Brown MA. The X-chromosome and susceptibility to ankylosing spondylitis. **Arthritis Rheum**. 2000; 43(6):1353-5.
8. Akkoç N, Yarkan H, Kenar G, Khan MA. Ankylosing Spondylitis: HLA-B*27-Positive Versus HLA-B*27-Negative Disease. **Curr Rheumatol Rep**. 2017 ;19(5):26.
9. Wang R, Ward MM. Epidemiology of axial spondyloarthritis: an update. **Curr Opin Rheumatol**. 2018; 30(2):137-143.
10. Gallinaro AL, Ventura C, Barros PDS, Gonçalves CR. Spondyloarthritis: Analysis of a Brazilian series compared with a large Ibero-American registry (RESPONDIA group). **Bras J Rheumatol** 2010; 50(5):581-89.
11. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J et al. The development of assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. **Ann Rheum Dis**. 2009; 68:777-83.
12. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. **Ann Rheum Dis**. 2009; 68(Suppl II):ii1–ii44
13. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewé R, van ver Tempel H, Mielants H et al. Assessment of enthesitis in ankylosing spondylitis. **Ann Rheum Dis**. 2003 ; 62(2): 127–132.
14. Shinjo SK, Gonçalves R, Kowalski S, Gonçalves CR Brazilian-Portuguese version and applicability questionnaire of the mobility index for ankylosing spondylitis. **Clinics** (Sao Paulo). 2007 ;62(2):139-44.
15. Mateus C, Pimentel-Santos FM, Mourão AF, Barcelos A, Ribeiro C, Vieira-Sousa E, Sequeira G, et al. P33—Índices de qualidade de vida e seus determinantes em doentes com espondilite anquilosante. **Paper presented at the XVII Congresso Português de Reumatologia**, 2014, Algarve, Portugal.
16. Jovani V, Blasco-Blasco M, Ruiz-Cantero MT, Pascual E. Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and metaanalysis. **J Rheumatol**. 2017;44(2):174–83
17. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. **Curr Rheumatol Rep**. 2018; 20(6):35.
18. Aloush V, Ablin JN, Reitblat T, Caspi D, Elkayam O. Fibromyalgia in women with ankylosing spondylitis. **Rheumatol Int.** 2007;27(9): 865–8.
19. Garrido-Cumbrera M, Poddubnyy D, Gossec L, Mahapatra R, Bundy C, Makri S, et al. EMAS Working Group. Gender differences in patient journey to diagnosis and disease outcomes: results from the European Map of Axial Spondyloarthritis (EMAS). **Clin Rheumatol**. 2021; 40(7):2753-2761.
20. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. **Rheumatol Int**. 2003;23(2):61-6.
21. E Jaakkola , I Herzberg, K Laiho, M C N M Barnardo, J J Pointon, M Kauppi, et al. Finnish HLA studies confirm the increased risk conferred by HLA-B27 homozygosity in ankylosing spondylitis. **Ann Rheum Dis**. 2006 ;65(6):775-80.
22. Sharma SM, Jackson D. Uveitis and spondyloarthropathies. **Best Pract Res Clin Rheumatol.** 2017;31(6):846-862.
23. de Jong H, Paramarta JE, de Winter J, Baeten D, van de Sande M. Differences between females and males in axial spondyloarthritis: data from a real-life cross-sectional cohort. **Scand J Rheumatol**. 2020 Jan;49(1):28-32.
24. Khan MA. Polymorphism of HLA-B27: 105 subtypes currently known. **Curr Rheumatol Rep**. 2013;15(10):362.
25. Lindström U, Exarchou S, Lie E, Dehlin M, Forsblad-d'Elia H, Askling J, et al. Childhood hospitalisation with infections and later development of ankylosing spondylitis: a national case-control study. **Arthritis Res Ther**. 2016;18(1):240.
26. Wendling D, Prati C, Demattei C, Miceli-Richard C, Daures JP, Dougados M. Impact of uveitis on the phenotype of patients with recent inflammatory back pain: data from a prospective multicenter French cohort. **Arthritis Care Res** (Hoboken). 2012 ;64(7):1089-93.
27. Sampaio-Barros PD, Conde RA, Bonfiglioli R, Bértolo MB, Samara AM. Characterization and outcome of uveitis in 350 patients with spondyloarthropathies. **Rheumatol Int**. 2006; 26(12):1143-6.

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CASE REPORT AND LITERATURE REVIEW ACROMEGALY AND CANCER RISK: REVIEW AND CASE REPORT

ACROMEGALIA E RISCO DE CÂNCER: REVISÃO E RELATO DE CASO

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Key words: Acromegaly; Pituitary Adenoma; Risk of Neoplasia
Descritores: Acromegalia; Adenoma Pituitário; Risco de Neoplasia

Abstract

Introduction: Acromegaly is a rare endocrine disorder resulting from the overactivity of the pituitary gland, characterized by excessive secretion of growth hormone (GH). Its primary etiology is associated with GH-producing pituitary adenomas. The clinical presentation is marked by excessive growth of soft and bone tissues, leading to coarse facial features, enlargement of extremities, thickening of the skin, changes in internal organs, as well as an increased risk of developing malignant neoplasms. Diagnosis is confirmed by measuring GH and IGF-1 levels in the blood, along with radiological imaging that demonstrates the presence of the adenoma. Treatment includes transsphenoidal surgery for adenoma removal, medical therapy with somatostatin analogs or GH receptor antagonists, and, in resistant cases, radiotherapy. Multidisciplinary management is crucial for controlling symptoms and improving the quality of life for patients. **Objective:** The study aimed to highlight the incidence of neoplasms in patients with acromegaly. **Results and conclusion:** Patients with acromegaly face a higher risk of colorectal polyps and thyroid nodules, although the association with cancer is inconclusive. Some meta-analyses suggest a slight increase in cancer rates in this group, despite selection biases in some studies. Therefore, it is essential to screen for these conditions in patients with excess GH. Early diagnosis of neoplasms in these patients allows for appropriate intervention, increasing the life expectancy of these individuals. **Endocrinol diabetes clin exp 2023 / 2448 - 2450.**

Resumo

Introdução: A acromegalia é uma doença endócrina rara resultante do hiperfuncionamento da glândula pituitária, caracterizada pelo excesso de secreção de hormônio do crescimento (GH). Sua etiologia primária está associada a adenomas hipofisários produtores de GH. O quadro clínico é marcado por crescimento excessivo de tecidos moles e ósseos, levando a características faciais grosseiras, aumento das extremidades, espessamento da pele, alterações em órgãos internos, bem como aumento do risco de desenvolvimento de neoplasias malignas. O diagnóstico é confirmado pela medição dos níveis de GH e IGF-1 no sangue, bem como por imagens radiológicas que evidenciam a presença do adenoma. O tratamento inclui cirurgia transesfenoidal para remoção do adenoma, terapia medicamentosa com análogos de somatostatina ou antagonistas do receptor de GH e em casos resistentes, radioterapia. O manejo multidisciplinar é crucial para controlar os sintomas e melhorar a qualidade de vida dos pacientes. **Objetivo:** O estudo teve como objetivo evidenciar a incidência de neoplasias em pacientes com acromegalia. **Resultados e conclusão:** Pacientes com acromegalia enfrentam maior risco de pólipos colorretais e nódulos tireoidianos, embora a relação com câncer não seja conclusiva. Algumas meta-análises indicam ligeiro aumento nas taxas de câncer nesse grupo, apesar de vieses de seleção em alguns estudos. Portanto, é essencial rastrear essas condições em pacientes com excesso de GH. O diagnóstico precoce de neoplasias nesses pacientes permite abordagem adequada aumentando a expectativa de vida desses pacientes. **Endocrinol diabetes clin exp 2023 / 2448 - 2450.**

CASE REPORT

Patient V.C., male, 65 years old, has been under the care of the Endocrinology Department at Evangelico Mackenzie University Hospital in Paraná –Brazil for Type 2 Diabetes Mellitus (DM) since 1998. In 2015, during a consultation, facial changes were observed in the patient, including forehead protrusion, accentuation of nasolabial folds, prognathism, as well as enlargement of extremities and cutaneous papillomas (skin tags). Laboratory tests were then conducted, revealing an excess of growth hormone (GH) and insulin-like growth factor type 1 (IGF-1), with values of 13 mcg/L and 643 ng/mL, respectively.

The patient underwent a cranial magnetic resonance imaging (MRI) that showed an isointense nodule in T1 and T2 located in the sella turcica, measuring 19x18x16mm, consistent with a macroadenoma. Additionally, an increase in cervical volume was observed, leading to a thyroid ultrasound that demonstrated a thyroid nodule with suspicious characteristics of malignancy. After fine-needle aspiration biopsy (FNAB), (BETHESDA 5) the patient was referred for total thyroidectomy. The pathological examination of the thyroid nodule was consistent with Papillary Thyroid Carcinoma.

Subsequently, the patient underwent transsphenoidal surgery (TSS), which occurred without complications. Imaging and laboratory control tests performed after TSS showed disease remission throughout the follow-up. In 2022, 7 years after TSS, a routine colonoscopy revealed an extensive vegetative lesion in the hepatic angle of the colon. The patient was then referred to the digestive system surgery team, and a colectomy with ileo-transverse mechanical anastomosis was performed. The pathological examination was consistent with a villous adenoma and concomitant presence of submucosal polypoid fusocellular neoplasia and submucosal lipoma in the ascending colon.

Currently, the patient is under follow-up in the service with no new complications.

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DISCUSSION

Acromegaly is an insidious disease caused by excess production of growth hormone (GH) (1). Its prevalence is approximately 60 per 1,000,000, but studies suggest that this value may be underestimated, and diagnosis still occurs late (1,2).

The most common cause of acromegaly is secondary to somatotrophic pituitary adenomas, which lead to increased production of GH and typically have slow growth in patients over 50 years old and faster growth in younger individuals (3). The GH secreted stimulates the production of IGF-1 in the liver and other tissues, resulting in a multisystem disease characterized by somatic overgrowth, multiple comorbidities, premature mortality, and physical disfigurement (4).

Diagnosis is confirmed by detecting elevated levels of GH and IGF-1 through liquid immunoassay/spectrophotometry, coupled with visualization of the pituitary adenoma on magnetic resonance imaging. In rare situations where acromegalic patients do not exhibit an obvious tumor in pituitary magnetic resonance imaging, sectional images of the chest and abdomen can be used to detect possible ectopic sources (5).

Clinical manifestations may be related to mass effect, such as headache (48%) and visual deficits (48%); or excess GH--related, such as acral enlargement (86%) and maxillofacial alterations (74%) (6). Hyperprolactinemia may occur in approximately 30% of patients due to the co-secretion of prolactin and GH by the adenoma, with serum concentrations reaching values higher than 200 ng/mL. Hypogonadism may occur in up to 49% of men and 57% of women (7).

Acromegaly may be associated with other comorbidities. The most common ones include hypertension, diabetes mellitus, glucose intolerance, and sleep apnea. Additionally, joint damage with fractures despite normal bone densitometry can occur. Cardiovascular disease, caused by atherosclerosis leading to arterial and ventricular stiffening, may also be present (1).

Moreover, there may be an increased risk of neoplasia in patients with acromegaly. The association between GH/IGF-1 and cancer risk is complex. Experimental studies have shown that GH and IGFs have pro-mitogenic and antiapoptotic properties, playing a crucial role in growth, metabolism, cell cycle control, and chemoresistance (8).

Gullu et al. conducted a prospective study with 105 acromegaly patients (65 women, 40 men) to observe the incidence of neoplasms. All patients underwent colonoscopy, mammography, and ultrasound (US) of the thyroid and prostate, with malignancy detected in 15% of the patients. Thyroid cancer was found in 4.7%, being the most common, followed by breast cancer in 2.8%, colon cancer in 1.9%, lung cancer in 1.9%, uterine cervical cancer in 0.9%, myelodysplastic syndrome in 0.9%, cholangiocarcinoma in 0.9%, and multiple endocrine neoplasia (MEN) type 1 in 0.9% of the patients (9).

According to Esposito et al., an increased risk of benign tumors (more than twice) and malignant tumors (30% higher) was reported, especially colorectal and anal cancer (50% higher), as well as renal and ureteral cancer (four times higher) in acromegaly compared to the general Swedish population. The incidence of thyroid cancer did not increase in this study (only 3 cases were recorded in 1,296 acromegalics). The age at acromegaly diagnosis was significantly related to the increased cancer risk, while gender, hypopituitarism, and diabetes mellitus were not associated with a higher chance of developing cancer (10).

GH interferes with the microenvironment of the colon by suppressing tumor suppressor genes such as P53 and adenomatous polyposis coli (APC), causing a decrease in the expression of P21 and cellular apoptosis. Excess GH enables cell survival and motility, while the administration of a GH receptor blocker (pegvisomant) induces these tumor suppressor genes (p53 and APC) (11).

Colon adenomas appear more frequently in patients with acromegaly, especially those with uncontrolled disease (10). GH in colon cells reduces DNA repair and increases damage through a direct effect, independently of IGF-1, thus promoting chromosomal instability (12).

The Acromegaly Consensus Group guidelines recommend colonoscopy for early detection and treatment of premalignant colon polyps at the time of diagnosis (11).

Regarding differentiated thyroid cancer in patients with acromegaly, there is evidence of the role of genetic events in the onset of thyroid cancer without correlation with disease activity or GH/IGF-1 levels. Mian et al. proposed that the risk of thyroid cancer may be associated with BRAF mutations and overexpression of the aryl hydrocarbon receptor (AhR). Additionally, the BRAF V600E mutation was found in 70% of papillary thyroid cancers, and the aryl hydrocarbon receptor-interacting protein (AIP) was expressed more in papillary thyroid cancers, particularly those with BRAF mutations, than in normal tissue, regardless of acromegaly activity (13).

Other studies have shown a much lower prevalence of BRAF V600E mutations (14.3%) and NRAS mutations (21.4%) in acromegalic patients with thyroid cancer (14).

Moreover, experimental studies in animals with hypopituitarism have shown a lower incidence of malignancy and increased longevity (15). However, cases in the literature illustrate that even severe and isolated GH deficiency does not completely protect against the development of malignancy (16).

Recently, recommendations for screening thyroid and colorectal cancers in these patients were published (17). Considering that cancer is one of the leading causes of death in acromegaly patients (18), colonoscopy screening in acromegalic patients at the time of diagnosis has shown an increased risk of pre-neoplastic lesions of the colon and colorectal cancer compared to the general population, with insulin resistance being a risk factor for colonic polyps (19).

Medical treatment of acromegaly is a common initial approach to control symptoms and disease progression. It usually involves the use of medications such as somatostatin analogs, including octreotide, lanreotide, and pasireotide, which help suppress the excessive secretion of GH by the pituitary gland, or growth hormone antagonists such as pegvisomant, which acts directly on GH receptors, reducing IGF-1 levels. These medications help reduce excessive levels of GH in the body, alleviating typical symptoms of acromegaly, such as enlarged hands, feet, and facial features. They are often used as long-term treatment to maintain disease control, especially in patients who are not candidates for surgery or radiation therapy. Octreotide is administered as a monthly intramuscular injection. The recommended initial dose is 20 mg per month. If after two months of treatment blood levels of IGF-1 are still above normal the dose can be increased to 30 mg monthly and subsequently to 40 mg monthly. Lanreotide is available in various formulations in different countries, with the most commonly used being the deep subcutaneous form, administered in doses of 60 to 120 mg every four to six weeks (20). The typical initial dose of pasireotide is 40 mg administered by subcutaneous injection every 28 days. However, this dose can be adjusted to control GH and IGF-1 levels and ensure acromegaly symptoms are under control, ranging from 20 to 60 mg every 28 days. Pegvisomant is administered through daily subcutaneous injections. The recommended initial dose is 10 mg per day. Blood levels of IGF-1 should be monitored every four to six weeks, and the dose can be adjusted in 5 mg increments if necessary, with a maximum limit of 30 mg per day, to maintain IGF-1 levels within the normal range. Additionally, in some cases, administering the dose on alternate days has been shown to be effective based on preliminary data (21).

In more severe cases or when medical treatment is ineffective, surgery and radiotherapy become important options

for acromegaly treatment. Surgery, known as transsphenoidal adenomectomy, involves the removal of the pituitary tumor causing the excess growth hormone. In cases where surgery is not viable or does not completely remove the tumor, radiotherapy can be used to reduce the size of the residual tumor and control excessive hormone production (22). Both surgical and radiotherapy approaches aim to improve symptoms and the patient's quality of life, as well as prevent complications related to acromegaly.

FINAL COMMENTS

Acromegalic patients have a higher risk of colorectal polyps and thyroid nodules; however, there is still no pathological evidence suggesting a higher risk of cancer in these patients compared to the general population. Nevertheless, some meta-analyses suggest that cancer rates are slightly higher in this patient group, although biases in selection have been demonstrated in some of these studies.

Given this uncertainty about the actual impact of acromegaly on the development of neoplasms, we emphasize the importance of screening for these conditions in patients with excess growth hormone.

This case report illustrates an acromegalic patient who developed thyroid cancer and, after years of disease control, was also diagnosed with intestinal cancer, only identified early because the attending medical team regularly requested colonoscopies for screening. This proactive approach undoubtedly influenced the outcome of this case.

References

1. Ribeiro-Oliveira A Jr, Barkan A. The changing face of acromegaly-advances in diagnosis and treatment. **Nat Rev Endocrinol** 2012; 8:605.
2. Rosario PW. Frequency of acromegaly in adults with diabetes or glucose intolerance and estimated prevalence in the general population. **Pituitary** 2011; 14:217.
3. Melmed S. Medical progress: Acromegaly. **N Engl J Med** 2006; 355:2558.
4. Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. **J Clin Endocrinol Metab** 2014; 99:3933.
5. Ershadinia N, Tritos NA. Diagnosis and Treatment of Acromegaly: An Update. **Mayo Clin Proc**. 2022; Feb;97(2):333-346. doi: 10.1016/j.mayocp.2021.11.007. PMID: 35120696.
6. Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pituitary tumor registry: a novel clinical resource. **J ClinEndocrinol Metab** 2000; 85:168.
7. Katznelson L, Kleinberg D, Vance ML, et al. Hypogonadism in patients with acromegaly: data from the multi-centre acromegaly registry pilot study. **Clin Endocrinol (Oxf)** 2001; 54:183.
8. Kasprzak A 2021 Insulin-like growth factor 1 (IGF-1) signaling in glucose metabolism in colorectal cancer. **International Journal of Molecular Sciences** 22 6434. (https://doi.org/10.3390/ijms22126434)
9. Gullu BE, Celik O, Gazioglu N, Kadioglu P. Thyroid cancer is the most common cancer associated with acromegaly. **Pituitary** 2010; 13:242.
10. Esposito D, Ragnarsson O, Johannsson G & Olsson DS Incidence of benign and malignant tumors in patients with acromegaly is increased: a nationwide population-based study. **J Clin Endocrinol** Metab 2021;106 3487–3496. (https://doi.org/10.1210/clinem/dgab560)
11. Chesnokova V, Zonis S, Zhou C, Recouvreux MV, Ben-Shlomo A, Araki T, Barrett R, Workman M, Wawrowsky K, Ljubimov VA, et alGrowth hormone is permissive for neoplastic colon growth. **PNAS**. 2016;113E3250–E3259. (https://doi.org/10.1073/pnas.1600561113)
12. Chesnokova V, Zonis S, Barrett RJ, Gleeson JP & Melmed S Growth hormone induces colon DNA damage independent of IGF-1. **Endocrinology** 2019;160 1439–1447. (https://doi.org/10.1210/en.2019-00132)
13. Mian C, Ceccato F, Barollo S, Watutantrige-Fernando S, Albiger N, Regazzo D, de Lazzari P, Pennelli G, Rotondi S, Nacamulli D, et al. AHR over-expression in papillary thyroid carcinoma: clinical and molecular assessments in a series of Italian acromegalic patients with a long-term follow-up. **PLoS ONE** 2014; 9 e101560. (https://doi.org/10.1371/journal.pone.0101560)
14. Aydin K, Aydin C, Dagdelen S, Tezel GG & Erbas T Genetic alterations in differentiated thyroid cancer patients with acromegaly. **Exp Clinl Endocrinol Diabetes** 2016; 124 198–202. (https://doi.org/10.1055/s-0035-1565061)
15. Bartke A, List EO & Kopchick JJ The somatotropic axis and aging: benefits of endocrine defects. **Growth Hormone and IGF Research** 2016; 27 41–45.)
16. Aguiar-Oliveira MH, Oliveira FT, Pereira RM, Oliveira CR, Blackford A, Valenca EH, Santos EG, Gois-Junior MB, Meneguz Moreno RA, Araujo VP, et al. 2010 Longevity in untreated congenital growth hormone deficiency due to a homozygous mutation in the GHRH receptor gene. **J Clin Endocrinol Metab** 2010; 95 714–721. (https://doi.org/10.1210/jc.2009-1879)
17. Terzolo M, Puglisi S, Reimondo G, Dimopoulou C & Stalla GK Thyroid and colorectal cancer screening in acromegaly patients: should it be different from that in the general population? **European Journal of Endocrinology** 2020;183 D1–D13. (https://doi.org/10.1530/EJE- 19-1009)
18. Bolfi F, Neves AF, Boguszewski CL & Nunes-Nogueira VS Mortality inacromegaly decreased in the last decade: a systematic review and meta-analysis. **European Journal of Endocrinology** 2018; 179 59–71. (https:// doi.org/10.1530/EJE-18-0255)
19. Battistone MF, Miragaya K, Rogozinski A, Agüero M, Alfieri A, Ballarino MC, Boero L, Danilowicz K, Diez S, Donoso M, et al. Increased risk of preneoplastic colonic lesions and colorectal carcinoma in acromegaly: multicenter case-control study. **Pituitary** 2021; 24 96–103. (https://doi.org/10.1007/s11102-020-01090-8)
20. Dal J, Leisner MZ, Hermansen K, Farkas DK, Bengtsen M, Kistorp C, Nielsen EH, Andersen M, Feldt-Rasmussen U, Dekkers OM, Sørensen HT, Jørgensen JOL. Cancer Incidence in Patients With Acromegaly: A Cohort Study and Meta-Analysis of the Literature. **J Clin Endocrinol Metab**. 2018; Jun 1;103(6):2182-2188. doi: 10.1210/jc.2017-02457. PMID: 29590449.
21. Delhougne B, Deneux C, Abs R, et al. The prevalence of colonic polyps in acromegaly: a colonoscopic and pathological study in 103 patients. **J Clin Endocrinol Metab** 1995; 80:3223.
22 Melmed S, Colao A, Barkan A, et al. Guidelines for acromegaly management: an update. **J Clin Endocrinol Metab** 2009; 94:1509.

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