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EDITORIAL

ORIGINAL ARTICLES

REVIEW ARTICLES

CLINICAL CASES

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EDITORIAL

Diabetes mellitus 2 in Mexico: challenge for the health system

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Diabetes mellitus 2 (DM2), the most common form of the disease (90%), is one of the main causes of morbidity, disability, and death in Mexico and in the world. By 2021, the International Diabetes Federation[1] estimated that there were 537 million adults aged 20-79 with the disease, which by 2030 would reach 643 million, and by 2045, 783 million. It is estimated that three out of four adults with T2D live in low- and middle-income countries.

As a cause of disease in Mexico, in 2022 it ranked eleventh, with almost half a million cases. The highest percentage was recorded in the 50-59 age group, followed by the 65 and older age group. Almost two-thirds of the cases (65.2%) were observed in people aged 50 years and older[2] (Table 1).

On the other hand, in terms of new cases, the incidence was higher in women than in men, and the highest figure was recorded in the 60-64 age group (Fig. 1).

Regarding its prevalence, The *Encuesta Nacional de Salud y Nutrición* (ENSANUT) 2022 reported that 22.1% of the population had pre-diabetes and that this was more frequent in the groups with the lowest education and socioeconomic level. In turn, the prevalence of diabetes already diagnosed was 12.8% and that of undiagnosed diabetes was 5.8%[3].

Diabetes mellitus ranked second as a cause of death in Mexico in 2023, both globally and by sex. The disease is among the top 10 causes of death from the age of 25. By sex, 50.6% of deaths corresponded to women and 49.4% to men. By age group, it was observed that those aged 65 and over had the highest frequency of deaths. Of the deaths due to diabetes mellitus, 75.9% corresponded to non-insulin-dependent cases and 2.8% to insulin-dependent diabetes mellitus. The highest mortality rates per 100,000 inhabitants (adjusted for age) were recorded in Tabasco (123.3), Puebla (111.2), and Veracruz de Ignacio de la Llave (109.0), whereas the lowest corresponded to Sinaloa, Sonora, and Baja California Sur, with figures of 48.3, 52.8, and 56.1, respectively[4].

With respect to the importance of DM2, it stands out, in addition to the fact that it leads to death, that it is associated with the development of cardiovascular disease, cerebrovascular disease, kidney disease, blindness, and amputations of lower limbs, which is why it is the main cause of disability in the country[3]. Any of these complications individually, and often in combination, represent an enormous challenge for the affected people, their families, and the health system for daily life. In addition, the limitations they impose on work and social activities, in general, as well as the expenses involved in the consumption of medications, and replacement therapies (for example, of kidney function or the use of prostheses). Without the support of the social security system, out-of-pocket spending is unpayable in the medium or short term, depending on the personal situation. ENSANUT 2022 reported that 21.4% of people with pre-diabetes were not entitled to social security, whereas this occurred with 13.5% of people with diabetes, highlighting that 40.7% had no previous diagnosis.

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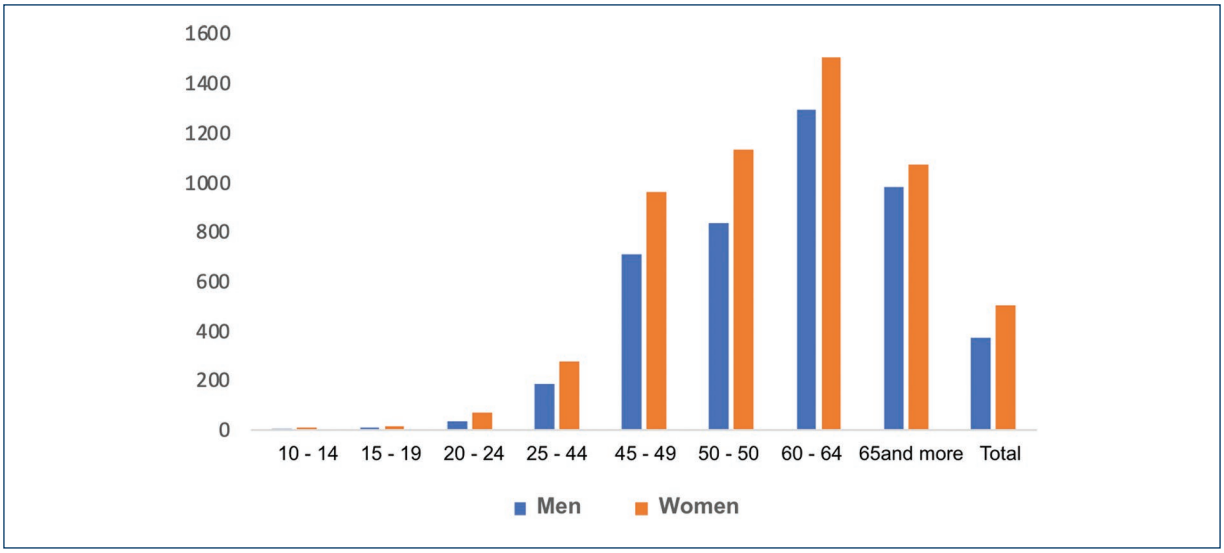

Figure 1. Incidence* of diabetes mellitus 2 by age group and sex. Mexico 2022.
*Rate/100,000 persons in the relevant age group (*prepared by the authors based on the Morbidity Yearbook: https://epidemiologia.salud.gob.mx/anuario/2022/principales/nacional/grupo_edad.pdf.*)

Table 1. Cases of diabetes mellitus 2 by age group in Mexico 2022

Age group (years)	No. of cases	%
10 and 14	694	0.1
15 and 19	1308	0.3
20 and 24	5567	1.2
25 and 44	89754	18.8
45 and 49	67559	14.2
50 and 59	132072	27.7
60 and 64	70663	14.8
65 year más	108408	22.7
Se ignora	575	0.1
Total	476600	100.0

Morbidity Yearbook: https://epidemiologia.salud.gob.mx/anuario/2022/principales/nacional/grupo_edad.pdf

The Pan American Health Organization's analysis of the burden of disease caused by DM2 in the Region of the Americas for 2019 reported that Mexico ranked second in mortality, third in years of life lost due to premature deaths, and seventh in years lived with disability[5].

Although progress has been made in the knowledge of the pathophysiology of the disease, more pharmacological groups have been developed for the management of hyperglycemia, and a greater variety of types of insulin are available, the truth is that the problem is far from being controlled. This suggests that the approach based on the care of existing cases does not give the expected results, since there is no cure, and metabolic control is not adequate. Although the patterns of consumption of food and beverages, as well as the performance of physical activity, are very important intermediate determinants in the genesis of overweight and obesity, as triggers of DM2, intervention strategies must be oriented to the structural determinants of the problem.

Public health policies represent one of the most relevant tools in this regard, to exercise effective control over the supply and distribution of healthy foods and restrict the marketing of ultra-processed products, which, in addition to having little or no nutritional value, are dense in energy, contain high concentrations of salt and trans fats. They constitute another risk due to the diversity of additives that are added to them, whose effects are observed, for example, in directly producing insulin resistance and affecting the composition and diversity of the intestinal microbiota, which metabolically regulates the absorption of nutrients.

The educational component of health promotion must comply with the incorporation or reinforcement of knowledge, attitudes, and behaviors with the conviction of its usefulness in health care, and not be limited to providing information, leaving the responsibility to the

population to carry out the recommendations proposed, since, in this way, people are blamed for their health situation, by not complying with what is prescribed.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript.

References

1. International Diabetes Federation. Datos y cifras. [Internet] Available from: https://idf.org/es/about-diabetes/diabetes-facts-figures
2. Anuario de Morbilidad. [Internet] Available from: https://epidemiologia.salud.gob.mx/anuario/2022/principales/nacional/grupo_edad.pdf
3. Basto-Abreu A, López-Olmedo N, Rojas-Martínez R, Aguilar-Salinas CA, Moreno-Barda GL, Carnalla M, et al. Prevalencia de prediabetes y diabetes en México: Ensanut 2022. Salud Pública Mex. 2023;65:S163-8.
4. Instituto Nacional de Estadística y Geografía (INEGI) [Internet]. Available from: https://www.inegi.org.mx/contenidos/saladeprensa/boletines/2024/EDR/EDR2023_ene-dic.pdf
5. Organización Panamericana de la Salud. La carga de la diabetes mellitus en la Región de las Américas, 2000-2019 [Internet]. Washington, D.C.: Organización Panamericana de la Salud; 2021. Available from: https://www.paho.org/es/enlace/carga-enfermedad-por-diabetes

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ORIGINAL ARTICLE

Profile of proinflammatory markers in pregnant women who died of severe COVID-19

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Abstract

Introduction: *In December 2019, four cases of pneumonia of unknown origin were reported to the World Health Organization (WHO) in China, caused by SARS-CoV-2. In March 2020, the WHO declared the beginning of the COVID-19 pandemic. In COVID-19, a relevant component is vulnerable groups, such as pregnant women representing a special group due to their high mortality secondary to COVID-19.* **Objective:** *Describe the association between proinflammatory markers and survival in pregnant women with critical COVID-19, in the intensive care unit (ICU) of the General Hospital of Cholula from January 2020 to 2021.* **Materials and methods:** *This is an analytical and cross-sectional observational retrospective study conducted on pregnant women admitted to the ICU. Pregnant women, between 18 and 35 years old, at 30-40 weeks gestation diagnosed with critical COVID-19 were included.* **Results:** *It was observed that pregnant women with critical COVID-19 showed increased values of C-reactive protein, leukocytes, D-dimer, and DHL compared to surviving pregnant patients with critical COVID-19; however, no statistical significance was observed for platelet number and fibrinogen.* **Conclusion:** *In the case of pregnant women who died from critical COVID-19, there was a significant increase in inflammatory markers, in contrast to what was observed in other studies, no changes in the number of platelets or fibrinogen were observed.*

Keywords: *Critical COVID-19. Pregnant women. Proinflammatory cytokines.*

Introduction

In December 2019, four cases of pneumonia of unknown origin were reported to the World Health Organization (WHO) in Wuhan, China, later it was identified that this pneumonia was caused by a new virus, called SARS-CoV-2; which spread around the world. Consequently, on March 12, 2020, the WHO declared the beginning of the COVID-19 pandemic[1].

In the case of the COVID-19 pandemic, a relevant component of the potentially affected population was vulnerable groups, of which pregnant women represented a susceptible group because they are, especially affected by respiratory diseases, significantly increasing morbidity and mortality in this population group[2,3]. Although the spectrum of respiratory diseases is wide from mild to severe forms, the importance of COVID-19 infection is especially serious as approximately one-third of affected women died as a result of the disease[4,5].

The SARS-CoV-2 virus is an encapsulated single-stranded RNA virus, which infects the cells of the respiratory tract through its binding to the angiotensin-converting enzyme-2 receptor, this receptor is predominantly expressed in type II pneumocytes; however, various extrapulmonary cells are also located such as myocytes, endothelial cells, esophageal epithelial cells, neurons, glial cells, podocytes, and proximal renal epithelial cells[6]. SARS-CoV-2 infection is followed by

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intracellular replication and secondarily host cell pyroptosis, the products released during cell lysis, which include ATP and nucleic acids are recognized by molecular patterns associated with damage, which initiate an inflammatory response in neighboring cells. Among the proinflammatory molecules directly involved in the induction of the immune response are interleukin (IL)-6, IL-18, chemokine 10, and interferons (IFN)-1, these factors function as chemoattractants for monocytes, macrophages, and T lymphocytes, inducing the formation of a positive feedback loop enhancing the inflammatory response in the lung parenchyma and facilitating superinfection by resident microorganisms. This severe inflammation is responsible for the high morbidity and mortality rates characteristic of SARS-CoV-2 infection[7].

An important aspect in the context of SARS-CoV-2 infection is the fact that pregnant women are more susceptible to acquiring infection by this virus, related to the various physiological adaptations induced during pregnancy, among the factors involved in gestational rhinitis which is the result of estrogen-mediated hyperemia. Favoring an increase in local tissue perfusion and an increase in mucus production, these modifications would not only facilitate infection by the COVID-19 virus but could also mask the coryza present in SARS-CoV-2 infection.

In addition, it has been observed that in pregnant women there are various changes in respiratory dynamics, which are the result of the growth of the pregnant uterus, among these are: an increase in the demand for O_2 by the mother binomial, gestational anemia as a result of the plasma volume observed during the 1st 30 weeks of gestation and high fetal consumption of oxygen. These phenomena could favor the presence of dyspnea, which could mask the symptoms of respiratory distress characteristic of SARS-CoV-2 infection.

However, changes in respiratory volumes are also observed during pregnancy, such as decreased functional residual capacity, decreased end-expiratory volume, and residual volume, which together could predispose to respiratory failure in SARS-CoV-2-infected patients[8]. Together, all the factors mentioned above could favor the delay in the recognition of the signs and symptoms of COVID-19 in pregnant women, increasing morbidity and mortality in this group of patients observed during the pandemic.

One of the most important aspects of SARS-CoV-2 infection, which negatively impacts the evolution of COVID-19 infection in pregnant women, is the fact that these patients deploy an immune response dependent on the activation of Th1 lymphocytes, this type of response is associated with a significant increase in the secretion of proinflammatory cytokines, such as IFN-gamma, IL-1beta, IL-6, and IL-12, which is observed within the first 2 weeks of the onset of SARS-CoV-2 infection, generating significant damage to the lung parenchyma[9], it has been observed that the increase in IL-6 was associated with an increase in the mortality rate of patients with COVID-19[10].

Given the aforementioned background, the objective of this study is to describe the association between the concentrations of proinflammatory markers and the survival and death of pregnant patients with severe COVID-19 in the intensive care service of the General Hospital of Cholula from January 2020 to January 2021.

Materials and methods

This is a retrospective, cross-sectional study carried out in pregnant patients who were admitted to the intensive care service of the General Hospital of Cholula in the period from January 2020 to January 2021. The study period was chosen based on the complete records existing in the hospital unit. Pregnant patients diagnosed with severe COVID-19, aged between 18 and 35 years, with 30-40 weeks of gestation, without previous data of severe disease, APACHE scores were not included due to this data were only described in < 15% of the population studied.

The sample size was calculated based on the population of pregnant women who met the inclusion requirements with a complete record (total population of 39 patients) using the formula for finite samples with a confidence level of 95% and an error of 5%, obtaining a final sample of 36 patients. The proinflammatory markers that were determined in each group were: C-reactive protein (CRP), leukocytes, D-dimer, fibrinogen, and platelets, which were measured every 72 h or until the death or discharge of the patient due to improvement, at the end of the averages were made for each marker. Once the total sample was obtained, two study groups were integrated, the group of pregnant women who survived severe COVID-19 (n = 18) and the group made up of pregnant women who died from severe COVID-19 (n = 18). In all cases, the diagnosis was established by the treating physician and confirmed in the clinical file. All pregnant patients included in the study had their COVID-19 infection confirmed by a positive polymerase chain reaction (PCR) test.

The statistical analysis plan included averages, percentages, and standard deviation between the different groups.

Table 1. Clinical characteristics of pregnant women with severe COVID-19

Variable	Survival (n = 13)	Deceased (n = 25)	Relative risk (RR)
Age (years)	30	32	0.83
BMI (kg/m^2)	24	31	2.24
PAM (mm Hg)	78	80	0.65
SDG	34	37	1.04

BMI: body mass index; PAM: medial arteria pressure; SDG: week of gestation.

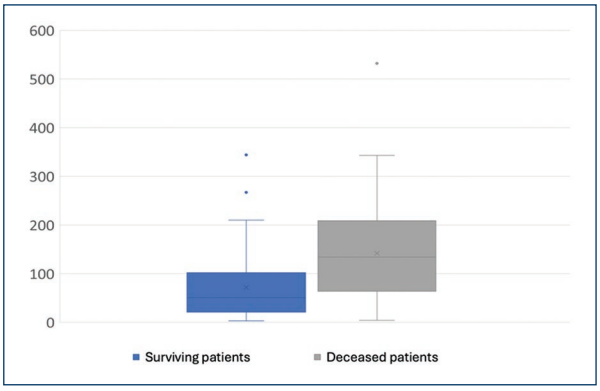

Figure 1. C-reactive protein levels in living and deceased patients due to critical COVID-19.

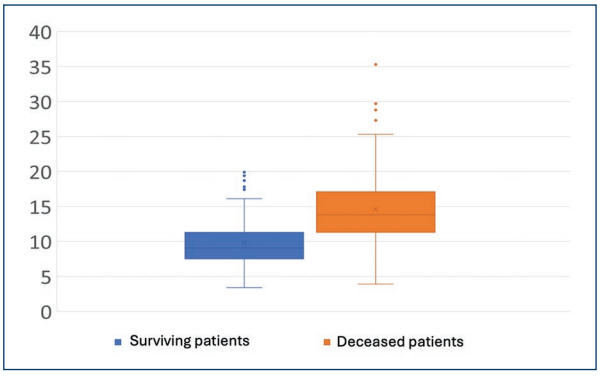

Figure 2. Leukocytes in living and deceased patients with critical COVID-19.

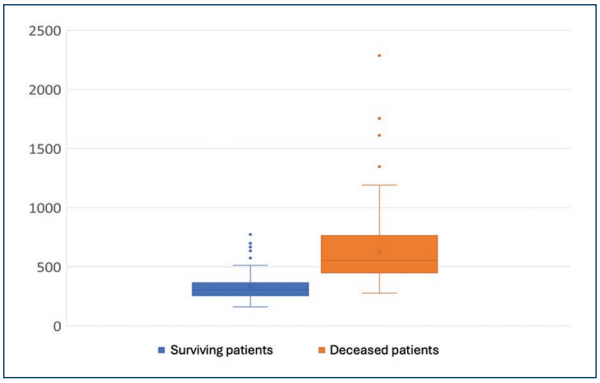

Figure 3. Lactic dehydrogenase in living and deceased patients with critical COVID-19.

The informed consent form was not used because we worked with clinical records; however, the information collected from each patient was handled confidentially, avoiding the use of the full name and social security number, replacing it with folios. It is worth mentioning that the choice of patients and the proinflammatory markers included in the study were related to the availability of complete records and the availability of reagents, respectively.

Results

The two groups involved in the study did not show significant differences in terms of age, body mass index, blood pressure, and weeks of gestation; however, overweight women showed a higher risk of death from severe COVID-19 compared to non-overweight pregnant women, which did not reach statistical significance (Table 1).

Of the total sample number (n = 36), 38% of pregnant women survived severe COVID-19 infection, whereas 62% with severe COVID-19 died. Our study showed that pregnant women who died from critical COVID-19 showed an increase in serum concentrations of CRP compared to pregnant women who survived 210 ± 12 mg/L versus 100 ± 16 mg/L (Fig. 1). In the same way, it was observed that the number of leukocytes was significantly higher among pregnant women who died from critical COVID-19 compared to survivors 14,350 ± 1200 versus 8796 ± 436 (Fig. 2). Regarding lactic dehydrogenase (LDH), it was observed that pregnant women who died from severe COVID-19 showed a significant increase in HDL concentrations compared to those of surviving pregnant women (700 ± 68 IU/L vs. 350 ± 49 IU/L) (Fig. 3).

Our results showed that the number of platelets did not show significant differences between deceased pregnant women or survivors with severe COVID-19 (278000 ± 370 mm^3 vs. 312000 ± 489 mm^3) (Fig. 4).

Our study also evaluated serum fibrinogen concentrations, observing that, such as the number of platelets, there were no significant differences in serum fibrinogen concentrations between surviving pregnant women or

those who died from severe COVID-19 (850 ± 125 versus 830 ± 75 g/L) (Fig. 5). Finally, our study quantified D-dimer concentrations, observing that non-surviving pregnant women with critical COVID-19 showed a significant increase in D-dimer compared to surviving pregnant women (4500 ± 879 ng/mL vs. 3000 ± 376 ng/mL) (Fig. 6).

Discussion

The objective of this study was to describe the relationship between various inflammatory markers, such as CRP, number of leukocytes, fibrinogen, LDH, platelets, and dimer among pregnant patients who were admitted to intensive care, who survived or died after critical COVID-19 infection.

In this sense, there are few reports in Mexico of the effect of severe COVID-19 infection on pregnant women. The present study shows that the mortality percentage of pregnant women who were admitted to the Hospital General de Cholula (HGCH) intensive care unit (ICU) was 62% and on the contrary, only 32% survived the same condition, which is in relation to the Mexican average for 2021 shown by López-Rodríguez et al.[11]. In addition, our study showed a significant increase in CRP concentrations, which was associated with higher mortality among pregnant women infected with severe COVID-19 (210 ± 12 mg/L vs. 100 ± 16 mg/L, *p < 0.05.), which is in relation to previous reports described by Tan et al.[12]. In relation to the previous point, PCR quantifications can be very useful from various points of view, on the one hand it provides valuable information regarding inflammation associated with inflammation in this particular case, after COVID-19 infection given its high sensitivity, specificity and low cost and on the other hand it has been shown that PCR could work as a potential predictor of thrombotic events, since there is recent evidence that has shown that the circulating pentameric form of PCR is capable of generating two isoforms with prothrombotic potential, which directly activate the complement system facilitating platelet aggregation, so one of the useful strategies in the future would be to evaluate the PCR-complement system relationship in patients infected with COVID-19 to establish more accurately the development of thromboembolic phenomena, which could be an important factor in the death of pregnant women with critical COVID-19 admitted to the ICU of the HGCH[13].

On the other hand, our work showed that pregnant patients who did not survive COVID-19 infection had a higher number of neutrophils compared to surviving pregnant women (14, 350 ± 1200 vs. 8796 ± 436, *p < 0.05), this finding was related to several studies in which it was observed that high concentrations of chemoattractant cytokines (IL-18) could attract a greater number of neutrophils generated during SARS-CoV-2 infection.

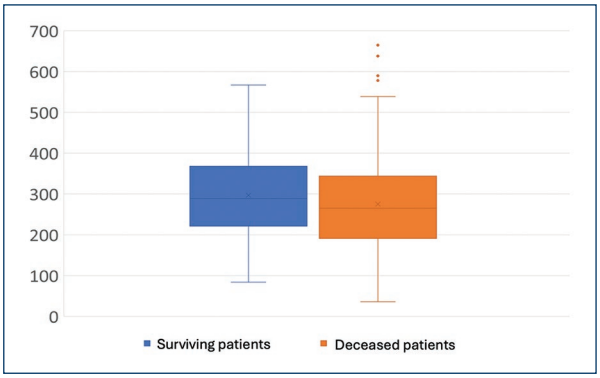

Figure 4. Platelets in living and deceased patients due to critical COVID-19.

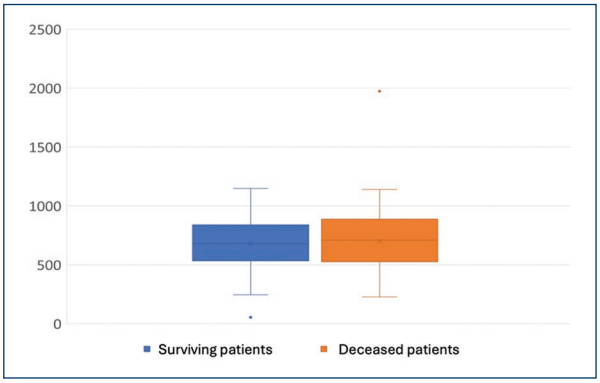

Figure 5. Fibrinogen in living and deceased patients due to critical COVID-19.

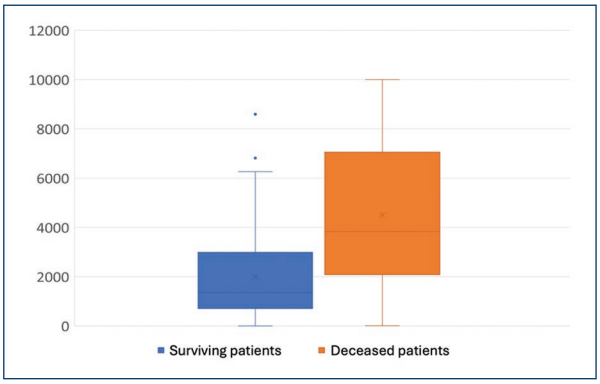

Figure 6. Dimer in living and deceased patients with critical COVID-19.

Favoring, on the one hand, the production of oxygen-free radicals and on the other favoring an exaggerated response of neutrophils after exposure to an infectious agent characterized as NETosis, this being a mechanism of "cell death" inducing the formation of extracellular traps within which the infectious agent is contained and destroyed and simultaneously due to its content (elastases, myeloperoxidase, gelatinases, and lysozyme C) secondary tissue damage[14,15]. Among the limitations of our studies regarding this point was that the hospital's protocols during the pandemic did not allow necropsies to be performed on patients who died from COVID-19, making it impossible to assess tissue damage by microscopy.

On the other hand, although LDH occupies an important place in glucose metabolism, its final product lactate is crucial in cellular metabolism when the partial pressure of oxygen is decreased, so recently LDH has been placed as a predictor marker of severity in some conditions such as acute respiratory distress syndrome and specifically in COVID-19, since the characteristic of both pathologies is the compromise tissue oxygenation secondary to lung damage. In the present study, it was observed that pregnant women who did not survive SARS-CoV-2 infection had higher serum LDH concentrations compared to survivors 700 ± 68 versus 350 ± 49 IU/L, *p < 0.05. In relation to this point, the increase in LDH in non-surviving pregnant patients infected by SARS-CoV-2 COVID-19 could mean that high lactate concentrations in the pathophysiological context of the disease would participate both as a chemical marker of disease severity, as well as a marker of severe cell damage, which could significantly modify the immune response of these patients favoring phenomena such as cytokine production proinflammatory and secondary tissue damage. However, more work is needed in experimental models of COVID-19 to determine *in vivo* the role of this enzyme in pregnancy, which is outside the scope of our study[16-18].

An important finding in our study was the fact that, unlike other studies, we did not find significant differences between platelet count and fibrinogen concentrations among pregnant women who died or survived severe SARS-CoV-2 infection (278000 ± 370 vs. 312000 ± 489 respectively *p > 0.05)[19,20]. In this regard, when studying a population in which various physiological adaptations occur during pregnancy, it is likely that platelet count and fibrinogen concentration may be modified compared with other population groups. Cines and Levine found that between 4.4% and 11.6% of pregnant women experienced gestational thrombocytopenia defined as a platelet count of < 150,000, noting that these variations in platelet count could be the result of increased plasma volume, as well as greater platelet destruction, which begins during the third trimester of pregnancy[21], in the same way, these modifications in plasma volume in pregnant women could favor fibrinogen dilution, in addition, the rapid evolution of severe COVID-19 infection in patients admitted to the HGCH ICU could be an additional factor for which no significant changes were observed in these variables. A limitation of our study could be related to the sample number, which was affected by the high number of incomplete records, as well as the availability of reagents to quantify the variables measurable in this study.

Finally, like other studies, our work showed that pregnant women who did not survive severe COVID-19 infection had significantly higher concentrations of D-dimer compared to surviving pregnant women 4500 ± 879 versus 3000 ± 376 ng/mL, *p < 0.05. Previously, D-dimer has been shown to be an important marker associated with a high risk of thromboembolic events, disease severity, and mortality risk[22].

Therefore, our findings are important, as they describe the relationship of various inflammatory markers in a population that has been little studied, but in which COVID-19 had a very important negative impact.

Conclusion

There are few reports in the literature about the characteristics of COVID-19 in pregnant women and in particular in pregnant women who died or survived severe COVID-19 infection in our country. Our work describes the characteristics of various inflammatory markers in the course of SARS-CoV-2 infection in pregnant women admitted to the HGCH ICU, which could help to typify the risk of a disease that will remain among a population with multiple comorbidities such as the Mexican population in rural areas. However, limitations of our work such as a small sample number and the changing availability of laboratory reagents for the quantification of proinflammatory markers could inaccurately reflect the results of our study.

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References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382:1199-207.
2. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol. 2011;205:10-8.
3. Yates L, Pierce M, Stephens S, Mill AC, Spark P, Kurinczuk JJ, et al. Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant. Health Technol Assess. 2010;14:109-82.
4. Calvert C, John J, Nzvere FP, Cresswell JA, Fawcus S, Fottrell E, et al. Maternal mortality in the covid-19 pandemic: findings from a rapid systematic review. Glob Health Action. 2021;14:1974677.
5. Ríos-Silva M, Murillo-Zamora E, Mendoza-Cano O, Trujillo X, Huerta M. COVID-19 mortality among pregnant women in Mexico: a retrospective cohort study. J Glob Health. 2020;10:020512.
6. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis. 2021;40:905-19.
7. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine Growth Factor Rev. 2020;53:66-70.
8. Chen M, Zeng J, Liu X, Sun G, Gao Y, Liao J, et al. Changes in physiology and immune system during pregnancy and coronavirus infection: a review. Eur J Obstet Gynecol Reprod Biol. 2020;255:124-8.
9. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021;93:250-6.
10. Rodríguez-Hernández MÁ, Carneros D, Núñez-Núñez M, Coca R, Baena R, López-Ruiz GM, et al. Identification of IL-6 signalling components as predictors of severity and outcome in COVID-19. Front Immunol. 2022;13:891456.
11. López-Rodríguez G, Galván M, Galván-Valencia O. Comorbilidades asociadas a mortalidad materna por COVID-19 en México. Gac Méd Méx. 2021;157:618-22.
12. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with CT findings and predicts severe COVID-19 early. J Med Virol. 2020;92:856-62.
13. Dix C, Zeller J, Stevens H, Eisenhardt SU, Shing KS, Nero TL, et al. C-reactive protein, immunothrombosis and venous thromboembolism. Front Immunol. 2022;13:1002652.
14. Borges L, Pithon-Curi TC, Curi R, Hatanaka E. COVID-19 and neutrophils: the relationship between hyperinflammation and neutrophil extracellular traps. Mediators Inflamm. 2020;2020:8829674.
15. Masso-Silva JA, Moshensky A, Lam MT, Odish MF, Patel A, Xu L, et al. Increased peripheral blood neutrophil activation phenotypes and neutrophil extracellular trap formation in critically ill coronavirus disease 2019 (COVID-19) patients: a case series and review of the literature. Clin Infect Dis. 2022;74:479-89.
16. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol. 2021; 17:11-30.
17. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LF. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020; 20:363-74.
18. Gupta GS. The lactate and the lactate dehydrogenase in inflammatory diseases and major risk factors in COVID-19 patients. Inflammation. 2022;45:2091-123.
19. Bonaventura A, Vecchié A, Dagna L, Martinod K, Dixon DL, Van Tassell BW, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. Nat Rev Immunol. 2021; 21:319-29.
20. Birnhuber A, Fließer E, Gorkiewicz G, Zacharias M, Seeliger B, David S, et al. Between inflammation and thrombosis: endothelial cells in COVID-19. Eur Respir J. 2021;58:2100377.
21. Cines DB, Levine LD. Thrombocytopenia in pregnancy. Blood. 2017; 130:2271-7.
22. Eljilany I, Elzouki AN. D-Dimer, fibrinogen, and IL-6 in COVID-19 patients with suspected venous thromboembolism: a narrative review. Vasc Health Risk Manag. 2020;16:455-62.

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ORIGINAL ARTICLE

Bortezomib, thalidomide, and dexamethasone versus thalidomide and dexamethasone for response rates in multiple myeloma patients: a retrospective study

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Abstract

Introduction: *The most current treatment of multiple myeloma is based on a combination of drugs, including immunomodulators and proteasome inhibitors. The bortezomib, thalidomide, and dexamethasone (VTD) and thalidomide and dexamethasone (TD) regimens are commonly used as a first-line treatment due to limited resources.* **Objective:** *To compare the proportion of favorable responses, survival, and time to the next treatment between two different treatment approaches.* **Materials and methods:** *Retrospective study based on medical records of patients with multiple myeloma, eligible for stem cell transplantation, who received, first-line, the VTD or TD combination.* **Results:** *A total of 83 patients were analyzed. The average age was 57 years. The most common type of MM was immunoglobulin G kappa (79.5%), and 51.8% had an International Staging System score of 3. At diagnosis, 28.9% had renal failure, and 42.2% had albumin levels < 3 g/dL. 37.3% were treated with the TD regimen, whereas 62.7% received the VTD regimen. It was considered that 53% had a favorable response. However, patients treated with ETV showed a higher proportion of responses (54.8% vs. 39.3%, p = 0.011). Regarding survival, no differences were identified between the two treatments (Log Rank 0.076) or between the times until the next treatment (Log Rank 0.288).* **Conclusion:** *The VTD scheme was superior to the TD scheme, presenting response ratios similar to other series worldwide. This makes it a viable option for patients with limited financial resources.*

Keywords: *Multiple myeloma. Bortezomib. Thalidomide. Acute phase response. Survival.*

Introduction

Multiple myeloma is a neoplasm characterized by the presence of plasma cell clones that produce an abnormal immunoglobulin (component M), which leads to osseous destruction, anemia, renal function deterioration, and hypercalcemia[1]. It represents around 10% of the hematological neoplasms and mainly affects individuals over 60 years old[2]. Its treatment has experienced a rapid evolution; chemotherapy has been displaced by drugs that activate the immune system, redirecting it in a specific manner to identify and eliminate malignant plasma cells[3,4]. At present, the most effective treatment consists of a combination of drugs (double, triple, or quadruple), which include immunomodulatory agents (lenalidomide and thalidomide), proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), and monoclonal antibodies (daratumumab and isatuximab), followed by high doses of chemotherapy and hematopoietic stem cell transplantation[5,6].

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In the Latin American context, and despite the clinical and biological characteristics of the diagnosis which are similar to those in other regions of the world[7], there are great differences, due to, mainly, the limited access to specialized centers and a considerably late diagnosis[8,9]. The Hispanic population faces additional vulnerabilities, such as the low level of participation in clinical trials, and the limited access to new specific therapeutic strategies, such as CAR-T cells, compared to the Anglo population[10].

This has led most of the patients to be treated with drugs which are more readily available at a more affordable cost. Among the drugs used in the region, thalidomide and lenalidomide are used as immunomodulators, bortezomib is used as a proteasome inhibitor, combined as a triplet and, in some cases, as a quadruple, along with the monoclonal antibodies anti-CD38[11].

A rarely discussed aspect that is present in every health-care system is financial toxicity, which affects individuals with a lower educational level mainly, having a significant impact on the quality of life[12].

Finally, a late diagnosis leads to more patients presenting complications, some irreversible, such as kidney failure or the presence of acute extramedullary disease. In addition, more patients are diagnosed at very advanced stages in the region (International Staging System [ISS] 3), which makes the comparison of results of various clinical studies difficult.

In Mexico, multiple myeloma is still considered an uncommon disease with significant underreporting, since very few centers have the necessary tools for the diagnosis, as well as the required drugs to complete first-line treatment[13].

The main purpose of this real-life study was to describe the characteristics of patients with multiple myeloma treated at the reference center in Mexico City, identifying the severity and the rate of favorable responses to both treatments available.

Materials and methods

This retrospective study involves research on the clinical records of patients diagnosed with multiple myeloma treated at Hospital General de México between 2020 and 2023. We included the clinical records of patients who were considered eligible for transplant due to their functional status and who were given some treatment strategy comprising a combination of drugs (double or triple). The excluded criteria included: 1. Incomplete clinical records, 2. Clinical records of patients who abandoned treatment or could not continue with the treatment due to economic or distance issues; 3. Clinical records of patients who presented severe sepsis before the beginning of either treatment (Fig. 1).

Two treatment schemes were analyzed – thalidomide 100 mg-200 mg PO daily alone or in combination with dexamethasone 40 mg PO every 24 h on days 1-4, 8-11 of each cycle, and treatment based on bortezomib 1.3 mg/m^2 SC on days 1, 4, 8, 11 to the thalidomide and dexamethasone (TD) scheme for a total of six treatment cycles[14,15] bortezomib, thalidomide, and dexamethasone (VTD).

The response criteria were established in accordance with the International Multiple Myeloma Working Group criteria. Patients with a greater than partial response (very good partial response and response complete) were considered responders.

The combination of albumin and beta2 microglobulin (ISS score) was used for risk stratification. Renal function deterioration was considered with a creatinine > 2 mg/dL at diagnosis[16]. In cases where cytogenetic results were available, they were described within the general characteristics.

Statistical analysis

The demographic characteristics of the study were presented using median (range) for quantitative variables and cases n, [%] for categorical variables. Non-parametric analysis was used for every variable since they did not follow a normal distribution according to the Shapiro-Wilk test. The difference between the groups was calculated using a Mann-Whitney U test for the quantitative variables and Chi-squared tests for the categorical variables. To determine the relationship between the main variables and the main outcomes (time until the next treatment and overall survival), we calculated the odds ratio. In addition, we used Kaplan–Meier estimates to analyze the time until the next treatment and overall survival. Regardless of the median value, differences between groups were analyzed with a Log-Rank test, and the data were presented in median values. We established a $p < 0.05$ as a statistical difference. We conducted all statistical analyses using the SPSS version 25 (SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) software and generated figures using GraphPad Prisma version 7.

Ethical considerations

As per the second title of the General Health Law on Health Research, specifically in Chapter I, article 17,

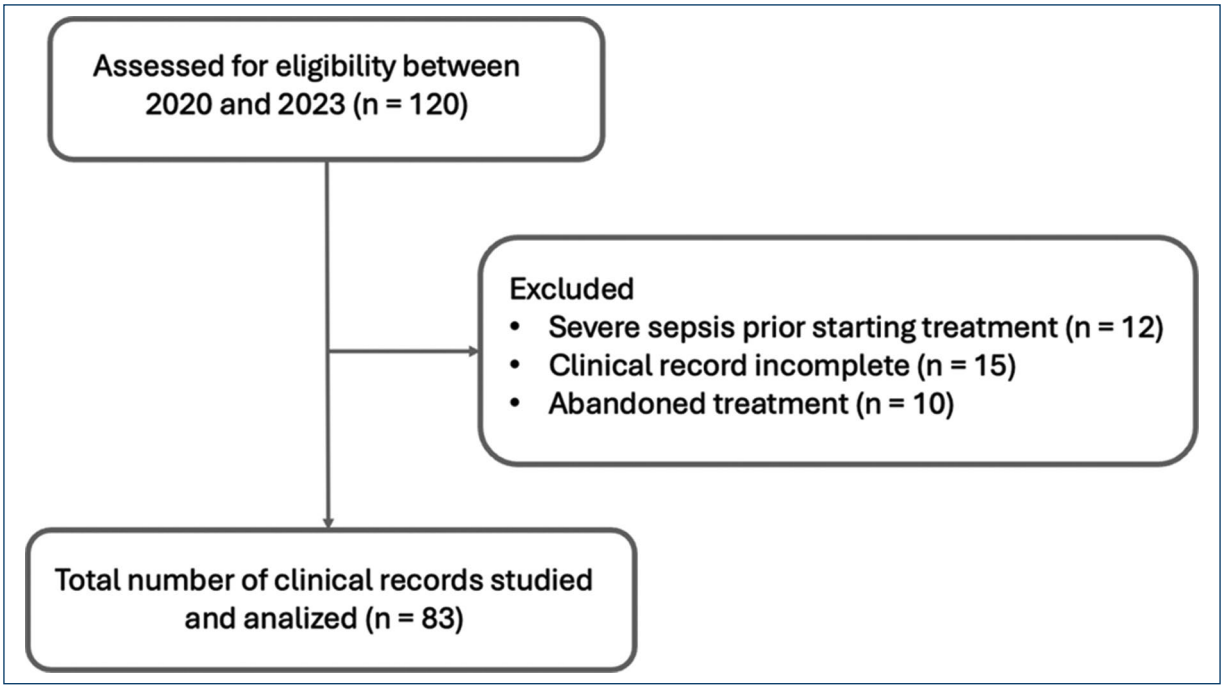

Figure 1. Clinical records selected.

the research study poses no risk to the human patient. The researchers involved in the study confirm that all ethical aspects of privacy and confidentiality have been met while dealing with retrospective information. In addition, the information gathered will be solely used for academic and research purposes. It is also important to note that the researchers involved in this study have no economic, pharmaceutical, political, or social interest in said research.

Results

Patients' general characteristics

A total of 83 patients with a diagnosis of multiple myeloma were studied between January 2020 and June 2023, 54.2% (n = 45) belonged to the male gender and 45.8% (n = 38) to the female gender, and the average age was 57 years (ranging between 34 and 90 years old), not finding a significant difference between genders (p = 0.667, 95% confidence interval [IC]).

The average time for diagnosis was 375 days (with a range from 260 to 490 days, 95% IC), but 24.1% (n = 20) were diagnosed a year after the symptoms began.

Most of the cases were referred by a primary healthcare physician (n = 23, 27.7%), whereas a limited number of cases were referred by a specialist (nephrologist [n = 5, 6%], orthopedist [n = 11, 11.2%], internist [n = 19, 22.9%], oncologist [n = 3, 3.6%] or hematologist [n = 3, 3.6%]). In 16.9% (n = 14) of the cases, the referral happened at the emergency department. In terms of comorbidities, the main ones were diabetes mellitus (n = 11, 12.4%) as well as hypertension (n = 9, 10.8%).

Clinical considerations

The main symptom was pain (n = 72, 86.7%), appearing mainly in the lumbar region, followed by anemia (n = 55, 66.3%), and renal function deterioration (n = 42, 50.6%). Among bone lesions, the majority corresponded to lytic lesions (n = 39, 47%), fractures (n = 24, 28.9%), or the presence of extramedullary disease (n = 14, 16.9%).

In terms of the functional state, 54.2% (n = 45) presented an electrocorticography (ECOG) above 1 (ECOG 2: n = 23, 27.7%, ECOG 3: n = 18, 21.7%, ECOG 4: n = 4, 4.8%). When analyzing the frailty index, 30.1% (n = 25) was considered functional, whereas 37.3% (n = 31) was considered intermediate, and 32.5% (n = 27) was considered frail.

Biological characteristics

When analyzing the different subtypes of clonality, the immunoglobulin G (IgG) type was the most frequent

variant (79.5%) (IgG kappa: n = 33, 39.8% and IgG lambda: n = 26, 31.3%), followed by the IgG variant (n = 7, 8.4%), the IgA variant (unrestricted IgA: 3, 3.6%, IgA kappa: 7, 8.4/, and IgA lambda: 3, 3.6%), and a case of IgE kappa type (1.2%).

In terms of the risk, when combining the ISS risk score (albumin and macroglobulin B2), most cases corresponded to an ISS 3 (n = 43, 51.8%), an ISS 2 (n = 28, 33.7%), and an ISS 1 (n = 12, 14.5%).

Regarding the cytogenetics, the most frequent finding was a normal karyotype (n = 36, 43.4%); in 39 of the cases the karyotype was not assessable (47%), and in 6% (n = 5) it did not present development. In a limited number of samples (n = 3), it was possible to identify some type of abnormality.

Within the abnormalities in the laboratory, 47% (n = 39) presented a level of hemoglobin below 10 g/dL, 28.9% (n = 24) debuted with a level of creatinine above 2 mg/dL, and close to a third of the cases (n = 35, 42.2%) presented a level of albumin below 3g/dL when diagnosed. The main characteristics of the patients are described in table 1.

Types of treatment and responses

Both combinations analyzed were thalidomide–dexamethasone (n = 31, 37.3%), and bortezomib–thalidomide–dexamethasone (n = 52, 62.7%).

In conjunction with the oncological treatment, 16.9% of the cases were combined with radiotherapy, and 45.6% (n = 38) received an addition to the treatment of zoledronic acid or denosumab.

Response to the treatment

When analyzing the overall responses, 45.7% (n = 38) presented a favorable response (full remission or very good partial response), whereas 54.3% (n = 45) presented a non-optimal response (partial response, progression, or stable disease). Of the total cases, 33.7% were considered to have progression criteria. When analyzing the responses to each of the treatments, patients treated through the triplet (VTD) presented a higher rate of favorable responses compared to the patients who received a scheme based exclusively on thalidomide (59.6% vs. 22.5%, p = 0.001, 95% IC). Similarly, the cases treated with the TD scheme presented progression with a higher frequency than the VTD scheme (54.8% vs. 21.1%, p = 0.011, 95% IC). When comparing the effectiveness of both treatments, the time until the next treatment, the patients treated with the TD scheme presented a prolonged time until the following treatment compared to the VTD scheme (536 vs. 479 days, p = 0.38 95% IC) despite the fact that the cases treated with the TD scheme included a higher range of cases with progression. In Fig. 2A and B, the general comparison and detailed range of the responses between both treatments are presented.

Overall survival and associated risk factors

The average survival time was 662 days, with a survival of 3 years in 41% of cases. When comparing the survival according to the type of treatment, no difference between TD or VTD (Log Rank 0.076) was registered, and, despite patients with TD presenting a higher risk of progression, this difference was not reflected in the time until the next treatment (Log Rank 0.288). The overall survival and time until the following treatment are presented in Fig. 3A and B. Fig. 4A and B could include a forest plot on the main variables and the need to initiate the next line of treatment; however, only the triplet (VTD) had an impact on the ratio of favorable responses OR: 0.19 (IC 95% 0.075-0.523; p < 0.001).

Discussion

This real-life study presents the experience of both main combinations used for the treatment of patients with multiple myeloma considered eligible for a transplant. After the introduction of the generic formulation of bortezomib, the inclusion of bortezomib in the TD scheme became more attainable, allowing to treat the majority of patients with triplets (VTD). Other treatments, such as the usage of monoclonal antibodies or stronger drugs such as lenalidomide or carfilzomib, were more limited and destined for patients with social health insurance, used mainly in subsequent lines of treatment[17,18].

Thalidomide is one of the first drugs considered an immunomodulator (IMiD), used at first as a sedative to prevent nausea in pregnant women, it is now one of the most popular drugs for the treatment of MM due to its anti-inflammatory effect in the microenvironment as a stimulant for various lymphocyte subpopulations (CD4+ and CD8+), increasing the levels of IL-2 and interferon γ[19,20]. At present, new and stronger drugs have emerged such as lenalidomide or pomalidomide which, combined with proteasome inhibitors (VRd or KRd) or monoclonal antibodies (elotuzumab-Rd, daratumumab-Rd, isatuximab–pomalidomide–dexamethasone), have become a better option in those patients

Table 1. Demographic characteristics of the study population

Variants	TD (n = 31)	VTD (n = 52)	p
Age (years)	58.00 (49.00-90.00)	52.00 (34.00-80.00)	0.038
Gender (M:F)	18:13	27:25	0.377
Time to diagnosis, n (%) < 6 months > 6 months	 09 (29.0) 22 (71.0)	 30 (57.7) 22 (42.3)	0.010
Type of myeloma, n (%) IgA IgA kappa IgA lambda IgE kappa IgG IgG kappa IgG lambda	 02 (06.5) 02 (06.5) 01 (03.2) 01 (03.2) 04 (12.9) 13 (41.9) 08 (25.8)	 04 (07.6) 05 (09.6) 02 (03.8) 00 (00.0) 03 (05.8) 20 (38.5) 18 (34.6)	
Anemia, n (%) Presence Absence	 19 (61.3) 12 (38.7)	 36 (69.2) 16 (30.8)	0.307
Pain, n (%) Presence Absence	 27 (87.1) 04 (12.9)	 45 (86.5) 07 (13.5)	0.610
Kidney failure, n (%) Presence Absence	 16 (51.6) 15 (48.4)	 26 (50) 26 (50)	0.534
Bone status, n (%) No lesions Lytic lesions Fractures Plasmocytoma	 03 (09.7) 13 (41.9) 11 (35.5) 04 (12.9)	 03 (05.8) 26 (50.0) 13 (25.0) 10 (19.2)	
Frailty score, n (%) Functional Not functional	 21 (67.7) 10 (32.3)	 37 (71.2) 15 (28.8)	0.465
IMPEDE score, n (%) High Low	 21 (67.7) 10 (32.3)	 24 (46.2) 28 (53.8)	0.046
ISS, n (%) 1 2 3	 02 (06.5) 09 (29.0) 20 (64.5)	 10 (19.2) 19 (36.5) 23 (44.2)	
Response to 1st treatment, n (%) Response No response	 09 (29.0) 22 (71.0)	 35 (67.3) 17 (32.7)	0.001
Leukocytes (× 10^3/µL)	5.20 (2.10-15.20)	5.40 (2.37-28.30)	0.980
Hemoglobin (mg/dL)	11.10 (2.80-15.20)	9.60 (4.50-15.20)	0.321
Platelets (× 10^3/µL)	191.00 (9.00-616.00)	221.00 (37.00-493.00)	0.411
Creatinine (mg/dL)	1.00 (0.50-9.40)	1.31 (0.30-12.50)	0.513
Albumin (mg/dL)	2.70 (1.70-4.20)	3.30 (1.96-5.00)	0.029

(Continues)

Table 1. Demographic characteristics of the study population *(continued)*

Variants	TD (n = 31)	VTD (n = 52)	p
LDH (mg/dL)	201.00 (60.00-415.00)	197.50 (5.10-500.00)	0.976
GFR (mL/min/m^2)	74.00 (06.00-109.00)	52.00 (04.00-144.00)	0.479

The Mann-Whitney U test was used for non-parametric variables and is expressed in median (range), and the $\chi 2$ test for qualitative variables and is expressed in absolute values (%). Statistical significance was considered with a $p < 0.05$.
M: male; F: female; IMPEDE: immunomodulatory agent, body mass index, pelvic hip or femur fracture, erythropoietin stimulating agent, dexamethasone/doxorubicin, Asian ethnicity/race; ISS: International staging system; LDH: lactic dehydrogenase; GFR: glomerular filtration rate; IgG: immunoglobulin G.

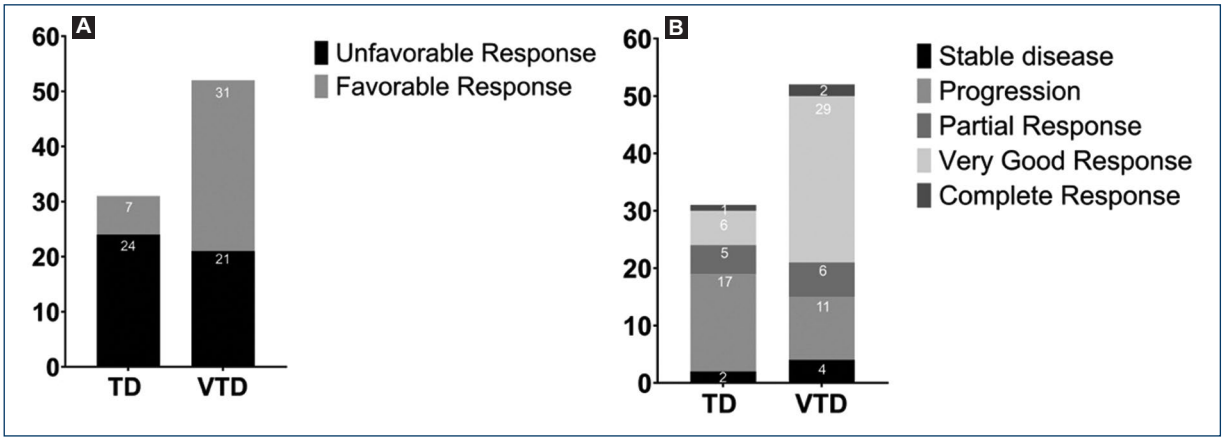

Figure 2. A: the overall ratio of favorable and unfavorable responses and **B:** detailed classified responses between groups.

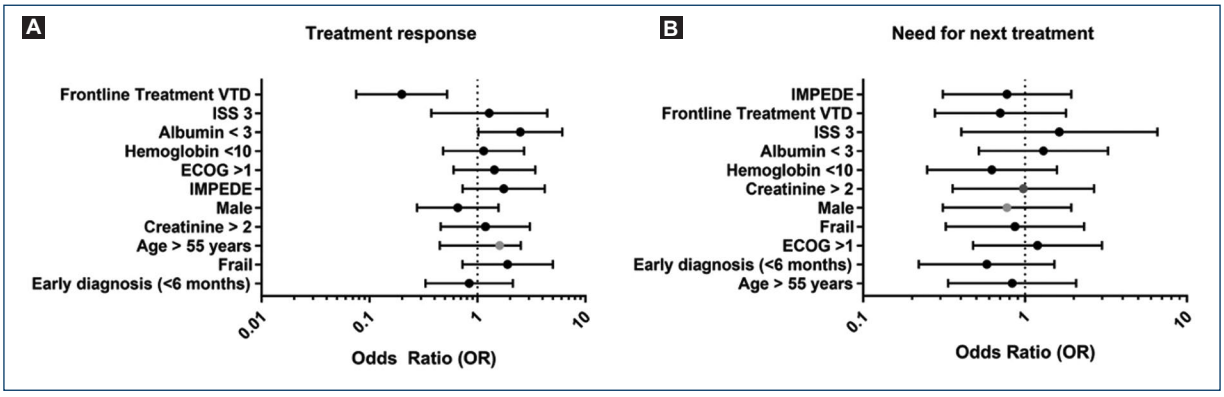

Figure 3. A: overall survival using Kaplan-Meier and **B:** time to next treatment using Kaplan-Meier.

in relapse or resistant to the first treatment or who are not eligible for a transplant[21,22].

Due to the accessibility and cost, both thalidomide and bortezomib are the drugs used with more frequency, be it as a triplet (VTD) or as a double (TD). Despite these combinations having been displaced by more effective combinations, it is important to understand the ratio of favorable responses and their duration, especially since the drugs used are generic. In Turkey, Mersin et al. evaluated the responses to generic bortezomib when compared to the original without finding a difference in the responses or adverse events[23].

In this study, the greater ratio of favorable responses was found in the group treated with bortezomib (67.3%),

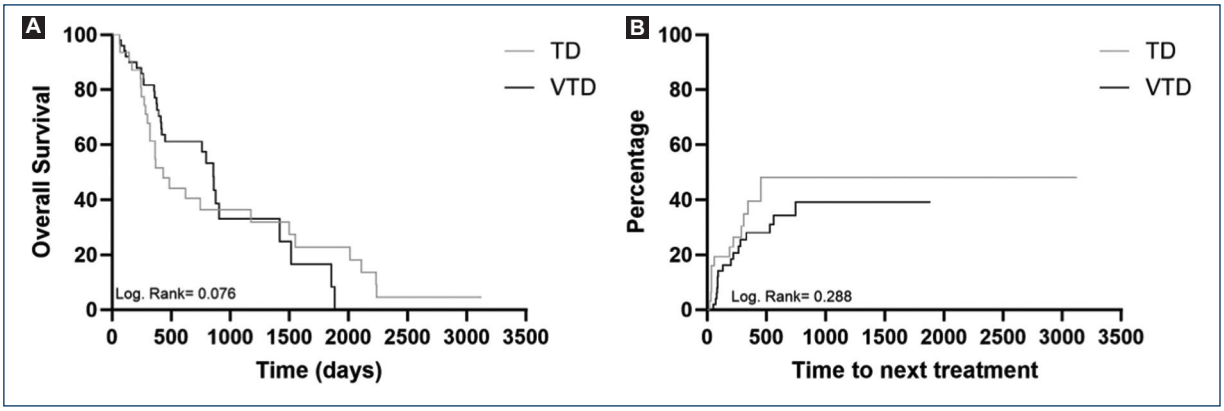

Figure 4. A: forest plot on treatment response and **B:** need for next treatment.

although the percentage of complete responses remained low (3.8%). These data are consistent with the available evidence on combinations based on bortezomib in various clinical trials (APEX, GIMEMA-MM-03-05, and HOVON-65)[24,25].

Since its introduction, bortezomib has presented a synergy with both immunomodulatory agents as well as with chemotherapy (cyclophosphamide and melafan) in various trials, improving the survival and the response to an autologous transplant[26,27]. Another aspect of the combination of an IP with an immunomodulator is its safety profile since the combination of drugs such as anthracyclines (doxorubicin and idarubicin) were more toxic and never better than the double[28].

One of the important aspects of our series is that a significant difference in the overall survival between the treatment regimens (TD vs. VTD) was not found; this had already been described in the first series that compared these combinations before an autologous transplant, where the main benefit was found in the favorable response ratio[29].

When analyzing the group of patients treated with VTD and comparing it to the response ratio in studies where a monoclonal antibody was included (CASSIOPEIA study; VTD vs. daratumumab-VTD), the ratio of favorable responses (RC+VGPR) of the VTD scheme was similar to our series (56.1% vs. 67.3%), but the percentage of full remissions registered for the clinical trial was slightly greater (8.9% vs. 3.8%)[30].

When trying to select the first-line treatment that is more effective without combining it with monoclonal antibodies, Rosiñol et al. analyzed the data from several patient databases treated with VRd (PETHEMA, GEM2012 and IFM2009) or VTD (PETHEMA, GEM2005 and IFM2013-04), who presented a greater benefit with the use of VRd, in particular when reaching a negative measurable residual disease[31]. Similar to the Cassiopeia study (VTD vs. D-VTD), the VRd combination was also challenged with the combination of the monoclonal antibodies anti-CD38. In the GRIFFIN study, Voorhees et al. studied the effect of VRd versus D-VRD; in patients eligible for transplant, they proved an advantage both in the ratio of complete responses (CR/CRs) at the end of the induction (19.2% for D-VRd vs. 13.3% with VRd), with measurable residual disease (21.2% vs. 5.8%), and survival free of progression[32]. When analyzing the results of the different first-line combinations (VTD, VRd, and CyBorD), no significant differences were identified between the ratio of favorable responses (above the partial response), which suggests that VTD remains an effective triplet as a first-line scheme in patients who are eligible for a transplant.

Finally, the greatest benefit at the first line is achieved with the inclusion of the monoclonal antibody anti-CD38 (daratumumab), which allows a greater ratio of complete responses, as well as a greater ratio of negative measurable residual disease as opposed to the schemes based exclusively on IP or immunomodulators[33].

Conclusion

With this real-life data, we conclude that the combination of VTD presents similar evidence in terms of the response to other series around the world, including the results from clinical trials (Cassiopeia study); even when most of the drugs were generic, the responses were superior to the TD combination, without having an influence on survival. When the combination with daratumumab is not available, VTD is a useful first-line option for patients eligible for a transplant.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript.

References

1. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. JAMA. 2022;327:464-77.
2. Rajkumar SV. Multiple myeloma: every year a new standard? Hematol Oncol. 2019;37 Suppl 1:62-5.
3. Soekojo CY, Chng WJ. Treatment horizon in multiple myeloma. Eur J Haematol. 2022;109:425-40.
4. Nishida H, Yamada T. Monoclonal antibody therapies in multiple myeloma: a challenge to develop novel targets. J Oncol. 2019;2019:6084012.
5. Branagan A, Lei M, Lou U, Raje N. Current treatment strategies for multiple myeloma. JCO Oncol Pract. 2020;16:5-14.
6. Goldschmidt H, Ashcroft J, Szabo Z, Garderet L. Navigating the treatment landscape in multiple myeloma: which combinations to use and when? Ann Hematol. 2019;98:1-18.
7. Curado MP, Oliveira MM, Silva DR, Souza DL. Epidemiology of multiple myeloma in 17 Latin American countries: an update. Cancer Med. 2018;7:2101-8.
8. Mateos MV, Ailawadhi S, Costa LJ, Grant SJ, Kumar L, Mohty M, et al. Global disparities in patients with multiple myeloma: a rapid evidence assessment. Blood Cancer J. 2023;13:109.
9. Mela Osorio MJ, Pavlovsky C, Pavlovsky MA. Inequalities in access to treatment in Argentina: differences in management of CLL and multiple myeloma? Semin Hematol. 2023;60:209-14.
10. Kanapuru B, Fernandes LL, Fashoyin-Aje LA, Baines AC, Bhatnagar V, Ershler R, et al. Analysis of racial and ethnic disparities in multiple myeloma US FDA drug approval trials. Blood Adv. 2022;6:1684-91.
11. Tietsche de Moraes Hungria V, Chiattone C, Pavlovsky M, Abenoza LM, Agreda GP, Armenta J, et al. Epidemiology of hematologic malignancies in real-world settings: findings from the Hemato-Oncology Latin America observational registry study. J Glob Oncol. 2019;5:1-19.
12. Fiala MA, Silberstein AE, Schroeder MA, Stockerl-Goldstein KE, Vij R. The dynamics of financial toxicity in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2023;23:266-72.
13. Ruiz-Argüelles GJ, Gómez-Almaguer D. Lessons learned treating patients with multiple myeloma in resource-constrained settings. Curr Hematol Malig Rep. 2021;16:40-4.
14. Boccadoro M, Blade J, Attal M, Palumbo A. The future role of thalidomide in multiple myeloma. Acta Haematol. 2005;114 Suppl 1:18-22.
15. Kapoor P, Ramakrishnan V, Rajkumar SV. Bortezomib combination therapy in multiple myeloma. Semin Hematol. 2012;49:228-42.
16. Kyrtsonis MC, Maltezas D, Tzenou T, Koulieris E, Bradwell AR. Staging systems and prognostic factors as a guide to therapeutic decisions in multiple myeloma. Semin Hematol. 2009;46:110-7.
17. De la Peña-Celaya JA, Aguilar-Luevano J, Alcivar-Cedeño LM, Álvarez-Vera JL, Anaya-Cuellar I, Añorve-Hernández E, et al. Mexican concensus of multiple myeloma. Gac Med Mex. 2020;156 Suppl 1:S1-45.
18. De Moraes Hungria VT, Martínez-Baños DM, Peñafiel CR, Miguel CE, Vela-Ojeda J, Remaggi G, et al. Multiple myeloma treatment patterns and clinical outcomes in the Latin America Haemato-Oncology (HOLA): observational study, 2008-2016. Br J Haematol. 2020;188:383-93.
19. Zhu YX, Kortuem KM, Stewart AK. Molecular mechanism of action of immune-modulatory drugs thalidomide, lenalidomide and pomalidomide in multiple myeloma. Leuk Lymphoma. 2013;54:683-7.
20. Weber D. Thalidomide and its derivatives: new promise for multiple myeloma. Cancer Control. 2003;10:375-83.
21. Shah UA, Mailankody S. Emerging immunotherapies in multiple myeloma. BMJ. 2020;370:m3176.
22. Sharma NS, Choudhary B. Good cop, bad cop: profiling the immune landscape in multiple myeloma. Biomolecules. 2023;13:1629.
23. Mersin S, Gedük A, Mehtap Ö, Tarkun P, Ünal S, Polat MG, et al. Evaluation of a generic bortezomib molecule in newly diagnosed multiple myeloma patients. Turk J Hematol. 2021;38:211-7.
24. Scott K, Hayden PJ, Will A, Wheatley K, Coyne I. Bortezomib for the treatment of multiple myeloma. Cochrane Database Syst Rev. 2016;4:CD010816.
25. Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010;28:2259-66.
26. Figueiredo A, Atkins H, Mallick R, Kekre N, Kew A, McCurdy A. Cyclophosphamide-bortezomib-dexamethasone compared with bortezomib-dexamethasone in transplantation-eligible patients with newly diagnosed multiple myeloma. Curr Oncol. 2020;27:e81-5.
27. Schütz NP, Ochoa P, Duarte P, Remaggi G, Yantorno S, Corzo A, et al. Real world outcomes with bortezomib thalidomide dexamethasone and cyclophosphamide bortezomib dexamethasone induction treatment for transplant eligible multiple myeloma patients in a Latin American country. A retrospective cohort study from Grupo Argentino de Mieloma Múltiple. Hematol Oncol. 2020;38:363-71.
28. Sekine L, Ziegelmann PK, Manica D, Da Fonte Pithan C, Sosnoski M, Morais VD, et al. Frontline treatment for transplant-eligible multiple myeloma: a 6474 patients network meta-analysis. Hematol Oncol. 2019;37:62-74.
29. Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet. 2010;376:2075-85.
30. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394(10192):29-38.
31. Rosiñol L, Hebraud B, Oriol A, Colin AL, Ríos Tamayo R, Hulin C, et al. Integrated analysis of randomized controlled trials evaluating bortezomib + lenalidomide + dexamethasone or bortezomib + thalidomide + dexamethasone induction in transplant-eligible newly diagnosed multiple myeloma. Front Oncol. 2023;13:1197340.
32. Voorhees PM, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood 2020;136:936-45.
33. Bazarbachi AH, Al Hamed R, Malard F, Bazarbachi A, Harousseau JL, Mohty M. Induction therapy prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma: an update. Blood Cancer J. 2022;12:47.

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ORIGINAL ARTICLE

Epidemiological panorama of type 2 diabetes in Mexico: differences by state and social determinants

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Abstract

Introduction: *Type 2 diabetes mellitus (T2DM) is a public health problem with an impact on individuals and society.* **Objective:** *The study aimed to describe the rates of variation and the rate of growth of the prevalence and mortality of T2DM in the states of Mexico, in relation to the figures of multidimensional poverty and indicators of social deprivation, the Human Development Index, the Gini Coefficient and GDP per capita.* **Material and methods:** *An ecological study was carried out with information from official open access sources in Mexico, the prevalence and mortality of T2DM were analyzed. The entities were grouped according to their rates of change, and their growth rates were analyzed according to the socio-economic context. A correlation analysis was performed between the rate of variation of mortality and the prevalence of T2DM with the percentage of the population living in extreme poverty.* **Results:** *Both indicators have increased in all entities at different rates. The poorest states, with the lowest Human Development Index and GDP and the highest Gini coefficient have been the most affected. The correlation showed that, the higher the level of extreme poverty, the higher the increase in mortality and the prevalence of T2DM.* **Conclusion:** *If the care strategy is not modified, this accelerated increase will mainly affect the poorest entities, which, due to their access to health services and living conditions, will have more far-reaching consequences.*

Keywords: *Type 2 diabetes. States. Social determinants of health. Mortality and prevalence.*

Introduction

In Mexico, between 2000 and 2016, mortality from Type 2 diabetes mellitus (T2DM) increased by 5%; it is estimated that, worldwide, it is the main cause of blindness, kidney failure, heart attack, cerebrovascular event, and amputation of lower limbs[1]. About 10.5% of adults between 20 and 79 years of age have this disease and by 2030 and 2045, there will be 643 and 783 million people with T2DM, respectively. In addition, 94.0% of this increase is expected to occur in low- and middle-income countries[2]. This research focuses on T2DM, which accounts for about 90% of all diabetes cases and 70% of deaths[3]. In this study, it is argued that both the increase in prevalence and mortality due to T2DM[3] are the result of a complex network of social determinants of health (SDH), which, according to the World Health Organization (WHO), are "the circumstances in which people are born, grow, work, live, and age, including the broader set of forces and systems that influence the conditions of daily life"[4]. The analysis of these

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determinants lies in identifying how inequities in the distribution of social goods are manifested by generating unfair differences in the health status of social groups[5,6].

Once the diagnosis has been made, the main objective of the health system is to ensure effective control of diabetes. In Mexico, both strategies and programs have focused on direct causes, such as risk factors (which, by definition, according to authors such as Jenicek[7], are modifiable conditions), and, on the other hand, they have not been able to have an impact on the detection and control of the disease (which depend more on prognostic factors). Some explanations for this refer to the inaccessibility of health services (geographical, economic, and/or cultural), and the poor quality of care they offer[8-10].

The percentage of the population aged 20 years and over with a previous medical diagnosis of diabetes in 2018 was 10.3%[11]. In 2016, the total prevalence of diabetes was 13.7% (9.5% diagnosed, 4.1% undiagnosed); 68.2% of the individuals diagnosed had glycemic imbalance, compared to 94.5% in 2006[12]. This reflected a decrease in the figures; however, the proportion of people with glycemic decontrol continues to be high. According to the ENSANUT 2021[13], the prevalence of people aged 20 years and over with a previous medical diagnosis of T2DM was 10.2%. However, from venous blood samples, it was found that this prevalence was 15.8%, (that is, the percentage of people who were unaware that they had the disease), thus, the overall prevalence was 26%. The objective of this study was to describe the rates of change and the growth rate of the prevalence and mortality due to T2DM in the states of Mexico, in relation to the figures of multidimensional poverty and indicators of social deprivation, the Human Development Index, the Gini Coefficient and GDP per capita.

Material and methods

An ecological study[14] was carried out to analyze the behavior of prevalence and mortality in Mexico, by state. The data were obtained from official open access sources. The prevalence by state was collected from the National Health and Nutrition Surveys (ENSANUT) 2000, 2012, 2016, 2018, 2020, and 2021 of the National Institute of Public Health[15], mortality, from the death registry of the National Institute of Statistics and Geography (INEGI)[3,16,17] and to calculate the rates, the population projections of the National Population Council (CONAPO) were used[18]. The health data were contrasted with multidimensional poverty figures and indicators of social deprivation, from the National Council for Social Development Policy (CONEVAL) 2020[19], with the Human Development Index (HDI)[20], the Gini Coefficient[21], and GDP *per capita*[22], during the period 2000-2020.

The rates of change in prevalence and mortality were calculated to analyze their growth rates in the States. That is, the positive change in the percentage of a variable between two different moments of time was analyzed**.** The entities were grouped into four groups (G) according to the position that they occupied in both years studied: G1, occupied the last positions of prevalence and mortality in both years; G2, went from low to high or medium levels; G3, high levels in the 1st year and low levels in the last year, and G4, were positioned in the first places in both years:

$$Cluster\ 1 = Entity\ (Position\ t1\ {}^{32}_{20}\ \wedge\ Position\ t2\ {}^{32}_{20})$$

$$Cluster\ 2 = Entity\ (Position\ t1\ {}^{20}_{32}\ \wedge\ Position\ t2\ {}^{1}_{19})$$

$$Cluster\ 3 = Entity\ (Position\ t1\ {}^{1}_{19}\ \wedge\ Position\ t2\ {}^{20}_{32})$$

$$Cluster\ 4 = Entity\ (Position\ t1\ {}^{1}_{19}\ \wedge\ Position\ t2\ {}^{1}_{19})$$

Where:

t1= 2000

t2 = 2018 in the case of prevalence and 2019 in the case of mortality, and the superindex and subindex numbers refer to the position they occupied in both years. Finally, a correlation analysis was made between the rate of change in mortality (2000-2019) and the rate of change in the prevalence of diabetes (2000-2018) with the percentage of the population in a situation of extreme poverty in 2020.

Results

Pattern and rate of growth of T2DM prevalence by state in Mexico from 2000 to 2018 and socioeconomic indicators

The lowest prevalence of T2DM in Mexico went from 3.2% in 2000 to 7.4% in 2018 and the highest prevalence, from 7.9% in 2000 to 14.0% in 2018. The highest prevalences in 2000 were observed in the north-east of the country, which continued in 2018 and were also added to southeastern entities such as Veracruz, Tabasco, and Campeche, and those of Hidalgo, Morelos, and Mexico City (Fig. 1).

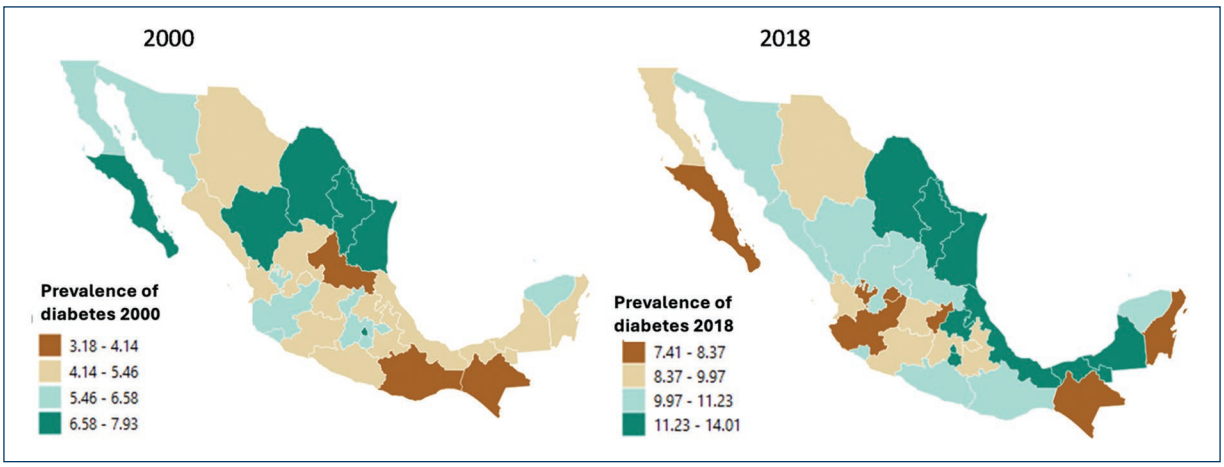

Figure 1. Mexico: prevalence of diagnosed diabetes, 2000-2018
(authors' elaboration based on data from the National Institute of Public Health's ENSANUT 2000 and 2018).

Between the 2 years, the growth rate of T2DM prevalence ranged from 219.5% in Oaxaca to 15.0% in Baja California Sur (BCS) and Jalisco (JAL). Within the G1, Chiapas and Quintana Roo stood out for presenting the lowest levels of prevalence in both years. In the G2, Campeche, Guerrero, Oaxaca, and Tabasco stood out, states that during the year 2000 showed the lowest prevalences and in 2018 occupied the first places. In the G3, entities such as Jalisco and BCS went from high to low prevalence between 2000 and 2018.

Finally, in the G4, entities such as Tamaulipas, Nuevo León, Coahuila, Mexico City and Sonora, were located within the 10 with the highest levels of diabetes in both years. Some of the G2 states, such as Chiapas, Guerrero and Oaxaca, whose growth was greater than 110.0%, had an HDI below the national average, the Gini above the average, which reflects greater inequality and the GDP per capita below the national average, with the exception of Campeche and Tabasco (Table 1).

Mortality due to T2DM in Mexico

From 2000 to 2019, it went from 47.2 deaths to 82.9/100,000 inhabitants (75.6% increase) (Fig. 2). In 1990, it caused 6.1% of deaths, while in 2019, it corresponded to 15.7% of the total deaths registered. Between 1998 and 2019, the rate for men and women practically doubled, reaching 84.3 and 81.5, respectively[16,17].

Pattern and pace of growth of mortality were due to T2DM by state in Mexico from 2000 to 2019 and socioeconomic indicators.

In the year 2000, the highest mortality was concentrated in the central, Bajío, and North-east areas of the country and in Mexico City with 74.5 deaths/100,000 inhabitants, in contrast to Quintana Roo where a rate of 16 was recorded. In 2019, an increase was observed in South-east entities such as Veracruz, Tabasco, and Oaxaca, as well as Puebla, Tlaxcala, Morelos and Mexico (Fig. 3).

The growth rate ranged from 16.0% in Sonora to 236.0% in Quintana Roo, the latter with an accelerated growth rate. Within the G1, there were entities with low mortality in both years, such as Quintana Roo and Sinaloa. In the G2 were Tabasco and Oaxaca, which went from position 25 and 28 in 2000 to first and tenth place in mortality in 2019, respectively. In the G3 were located entities that went from high to low mortality such as Querétaro and Jalisco. Finally, in the G4, Mexico City, Veracruz and Puebla stood out, which were among the 10 entities with the highest mortality in both years. Some G2 entities, which were characterized by a very accelerated growth in mortality, in 2020 showed a low HDI (0.759 or less)[19], with a Gini coefficient of IDH[20] above the national average and a GDP per capita lower than the national average[21] (Table 1).

In other G4 entities such as Mexico City and several in the north-east of the territory, mortality grew at a low rate and the HDI was higher than the national average, its Gini coefficient was below the national average, which reflects lower inequality and its GDP per capita above the national average with the exception of Nayarit and Tamaulipas.

Table 1. Entities with an accelerated rate of growth in mortality and prevalence of type 2 diabetes mellitus, socioeconomic indicators, poverty and social deprivation. Mexico 2020

Mortality growth > 150%	IDH* 2020 Below the national (0.756)	Gini** 2020 Above the national average (0.449)	PIB*** 2019 Lower than the national average (3.8)
G1 Quintana Roo 236.8% G2 Campeche 168.5% G2 Tabasco 189% G2 Guerrero 185%, G2 Oaxaca 167%, G2 Chiapas 154.4%	Quintana Roo, Campeche, Guerrero, Oaxaca, and Chiapas	Campeche, Guerrero, Oaxaca, and Chiapas	Quintana Roo, Guerrero, Oaxaca, and Chiapas
Prevalence Growth > 110.0%			
Oaxaca 219.5% Campeche 205.9% San Luis Potosí 162% Chiapas 145% Tabasco 140.6% Zacatecas 137.6% Hidalgo 135% Veracruz 125% Guerrero 110.8%	Oaxaca, Campeche, Chiapas, Hidalgo, Veracruz, and Guerrero	Oaxaca, Campeche, Chiapas, and Guerrero	Chiapas, Guerrero, Hidalgo, and Oaxaca
Extreme poverty 2020[a]	Food insecurity 2020[b]	Income below the extreme poverty line by income 2020[c]	Educational lag[d]
Chiapas, Guerrero, and Oaxaca	Tabasco, Guerrero, and Oaxaca	Veracruz, Morelos, Chiapas, Guerrero, Oaxaca, Quintana Roo, Campeche, and Tabasco	Chiapas, Oaxaca, Veracruz, and Guerrero

*HDI: human development index. Summary measure composed of life expectancy, education and GDP.
**Gini. Coefficient that measures inequality, the closer it is to 1, the greater the concentration of income and the greater the inequality.
***GDP: gross domestic product. It is the standard measure of the value added created by the production of goods and services in a country during a given period. Maximum value 1, the closer it is to 1, the higher the level of development.
[a]Extreme poverty 2020. Population that has three or more deprivations, out of six possible, within the Social Deprivation Index and that, in addition, is below the minimum well-being line.
[b]Food insecurity 2020. Moderate or severe food insecurity, or population that presented a limitation in the frequency of food consumption.
[c]Income below the extreme poverty line by income. Population that cannot access a basic food basket.
[d]Educational lag. Population aged 18 years and over had a secondary education level or less.

Social determinants and T2DM

A correlation analysis was performed between the variation in mortality (r = 0.78) and prevalence of diabetes (r = 0.53) and the percentage of the population in extreme poverty. The association was positive and significant, that is, the higher the level of extreme poverty in the states, the higher the growth rate of both indicators (Figs. 4 and 5). In 2020, states with accelerated growth rates in mortality and prevalence of T2D (RACMP T2DM) were in a situation of extreme poverty, had insufficient income to have a healthy diet, with a moderate or severe degree of food insecurity, or had a limitation in the frequency of food consumption. They had an income below the extreme poverty line and showed high values in terms of educational backwardness (Table 1 and Fig. 6).

Discussion

The increase in the prevalence and mortality of T2DM is a structural health problem caused by a combination of various SDCs, which have not been addressed in a conclusive manner. In the country, in 2020, the percentage of the population in extreme poverty was 8.5%, which implies that one in almost 12 people in Mexico had an insufficient income to have adequate food. Likewise, in 2020, around 28.6 million people had a moderate or severe degree of food insecurity, or had a limitation in the frequency of food consumption[21]. Income, expenditure and access to food can be observed through the percentage of the population that has an income below the extreme poverty line, in 2020, this was 17.2%, which implies that two out of almost 10 people could not access a basic food basket.

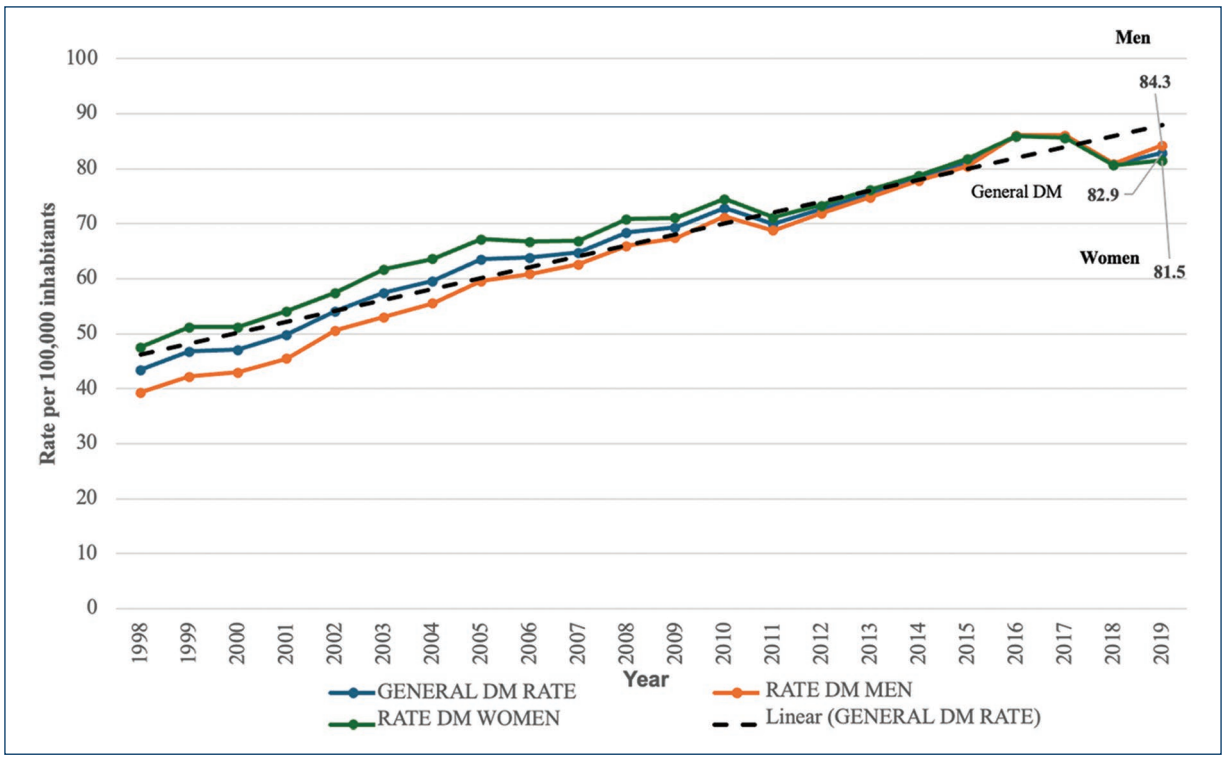

Figure 2. Mortality rate for diabetes mellitus (E10-E14) in Mexico by sex, year 1998-2019
(prepared by the author with information from National Institute of Statistics and Geography. Mortality statistics, 1998 to 2019. CONAPO: Population Projections, 1990-2010 and 2010-2030. Rate per 100,000 inhabitants).

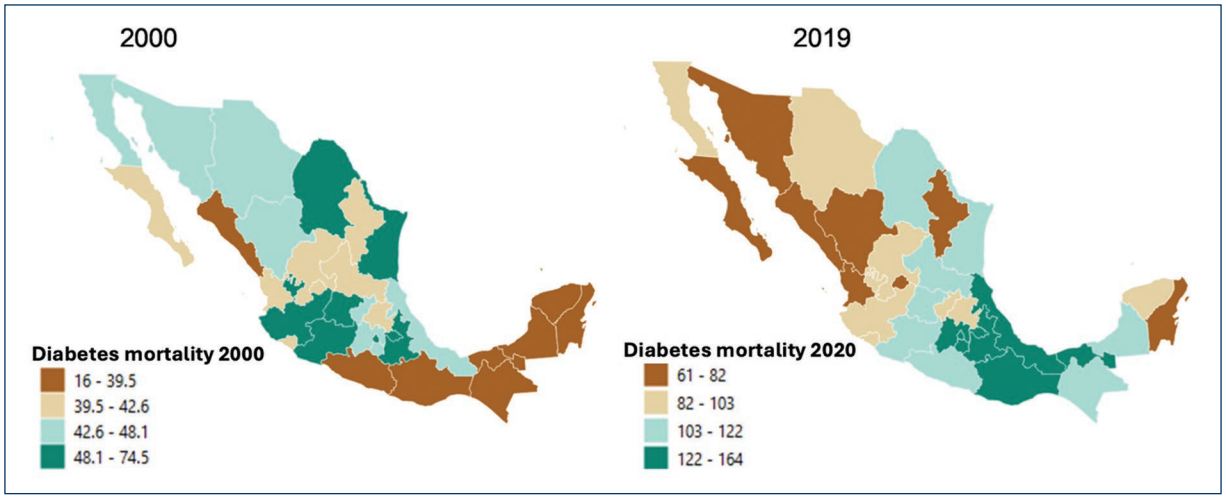

Figure 3. Mexico: diabetes mellitus mortality rate per 100,000 inhabitants 2000-2019
(authors' elaboration based on data from the National Institute of Statistics and Geography death registry and CONAPO population projections).

Another related social determinant is education, in the country, the literacy rate in people aged 15 years and over, in 2020, it was 95.2% and 54.9% of the population aged 18 and over had a secondary education level or less[23]. At the national level, in this year, the educational lag was 19.2%.

The heterogeneous increase in mortality and prevalence of T2DM among the entities is related to their

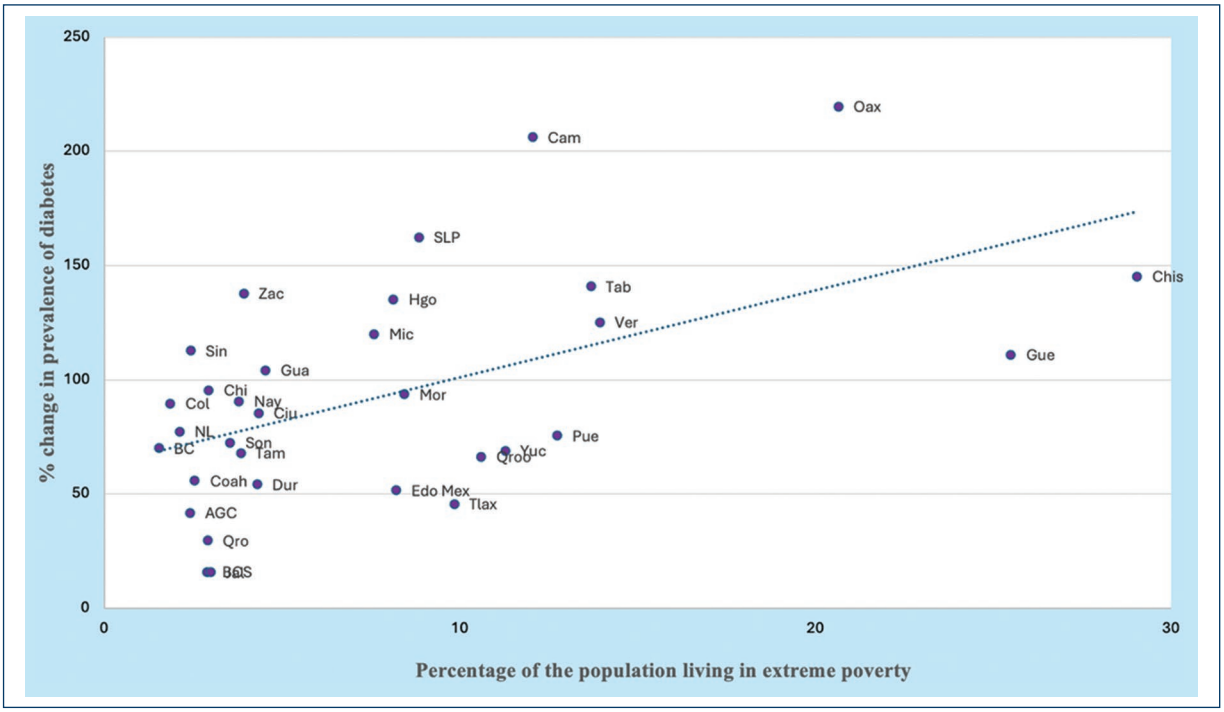

Figure 4. Correlation between the rate of change in the prevalence of type 2 diabetes mellitus (2000-2018) with the percentage of the population in extreme poverty in 2020
(authors' elaboration based on poverty data from CONEVAL and ENSANUT 2018 from the National Institute of Public Health).

socioeconomic differences. The southeastern states such as Chiapas, Oaxaca, Guerrero, Quintana Roo stand out, which showed the highest growth rates in both indicators. More than 50% of its population was in high conditions of food insecurity, in addition to lack of access to nutritious and quality food. In states such as Campeche and Tabasco, it is striking that the impact of oil activity is not reflected in the population.

In the above context, it is notorious that, according to the ENSANUT 2021[22], there are more people who are unaware that they have T2DM than those who already have an established diagnosis, representing, together with people who are already sick, a quarter of the population aged 20 years and over. It is evident that in Mexico there is an insufficient health system in terms of the timely detection of the disease, and a first level of care that requires resuming strategies such as primary healthcare that contribute to strengthening the prevention of diseases such as diabetes.

On the other hand, for the purposes of this work, the fact of appreciating a different behavior of prevalence than expected in some states (G3) stands out. It should be remembered that the magnitude of this indicator depends on the number of new cases and the duration of the disease[24]. As it is a chronic, non-reversible health problem, the observed decrease in prevalence in the study period would have to be the result of a reduction in the incidence, which implies having acted on the factors that generate it, and, therefore, constitute a success in the preventive programs implemented, or be the effect of a reduction in the duration of the disease, which, in turn, would be the result of higher mortality. Neither of the two possible explanations is satisfactory; therefore, it is necessary to continue analyzing this complex behavior. For example, in Jalisco, mortality from T2DM decreased, but the mechanisms related to this result are unknown.

Poverty was traditionally associated with malnutrition and food shortages. It is currently also linked to obesity, T2DM, and other metabolic diseases[25]. One explanation for the above is that in recent decades a diet based on ultra-processed, energy-dense, low-cost products has been adopted, which has been associated with low

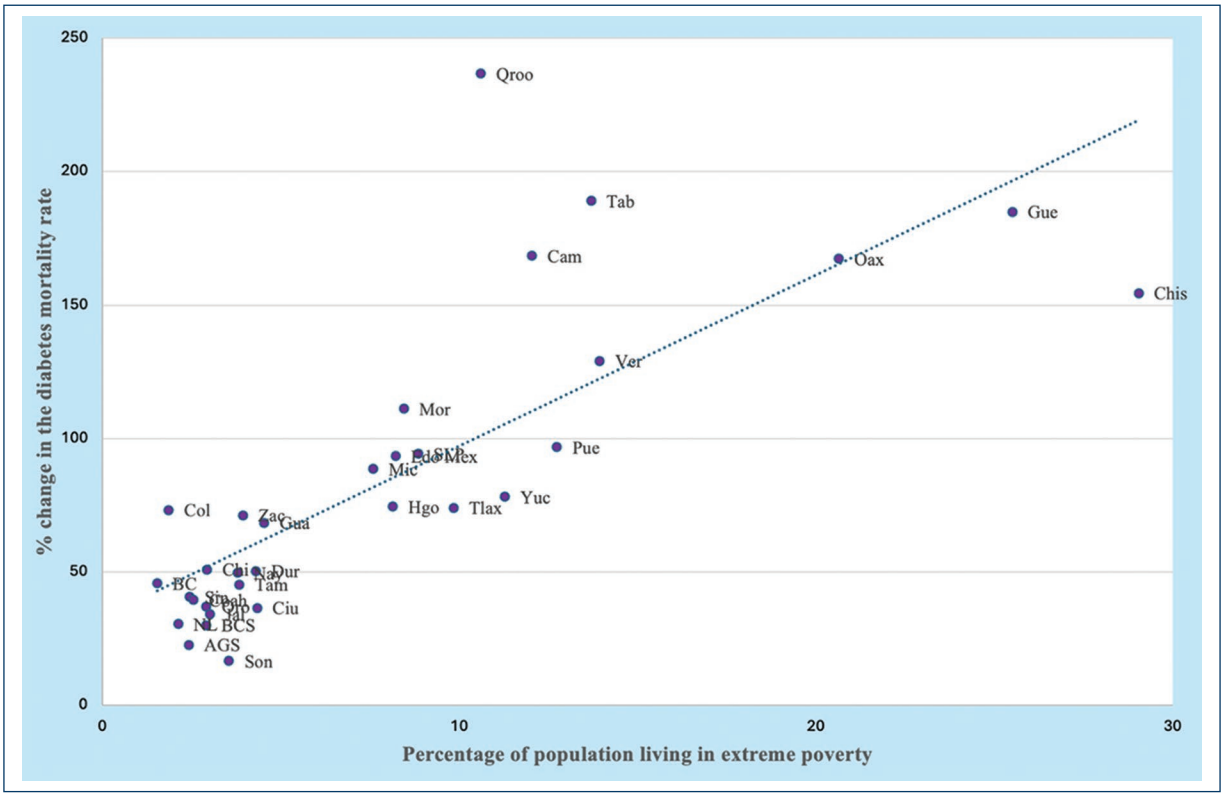

Figure 5. Correlation between the rate of change in mortality due to Type 2 diabetes (2000-2019) and the percentage of the population in extreme poverty in 2020
(authors' elaboration based on poverty data from CONEVAL and the National Institute of Statistics and Geography death registry).

income and poor educational level[26,27], as shown in this study. Adequate levels of income and schooling condition favorable behaviors that translate into seeking preventive care for diseases, as well as the adoption of healthy behaviors[28,29], such as the consumption of an adequate diet, the practice of physical activity, the performance of screening tests, and, if the disease is already present, therapeutic attachment, the execution of glycemic control tests, participation in support groups, among others.

On the other hand, as Laurell[30] points out, the processes of social determination do not act like the classic biological, physical, or chemical agents in the generation of a particular disease, since they do not have an etiological specificity, as Bradford-Hill proposed in his causality criteria[7], nor do they mechanically obey a dose-response relationship. However, several authors, such as Marmot[31] and Krieger[32], have documented the existence of a gradient of mortality and life expectancy with respect to the socioeconomic conditions of the population, using, respectively, concepts such as social class (although it does not strictly correspond to the Marxist notion, from which it comes), and the incorporation of social experiences into the body. That are expressed biologically.

The data observed in the present study regarding the behavior of prevalence and mortality due to T2DM also suggest the existence of this gradient.

Conclusion

Based on the analysis carried out, it is hypothesized that the care of T2DM in Mexico, focused on biological and behavioral factors and pharmacological treatment, has left aside key elements such as DSS, which could contribute to slowing its increase. If the strategy is not modified, this accelerated increase will mainly affect the poorest states and certainly rural areas (which were not analyzed in this study) which, due to their access to health services and living conditions, will have more far-reaching consequences[33].

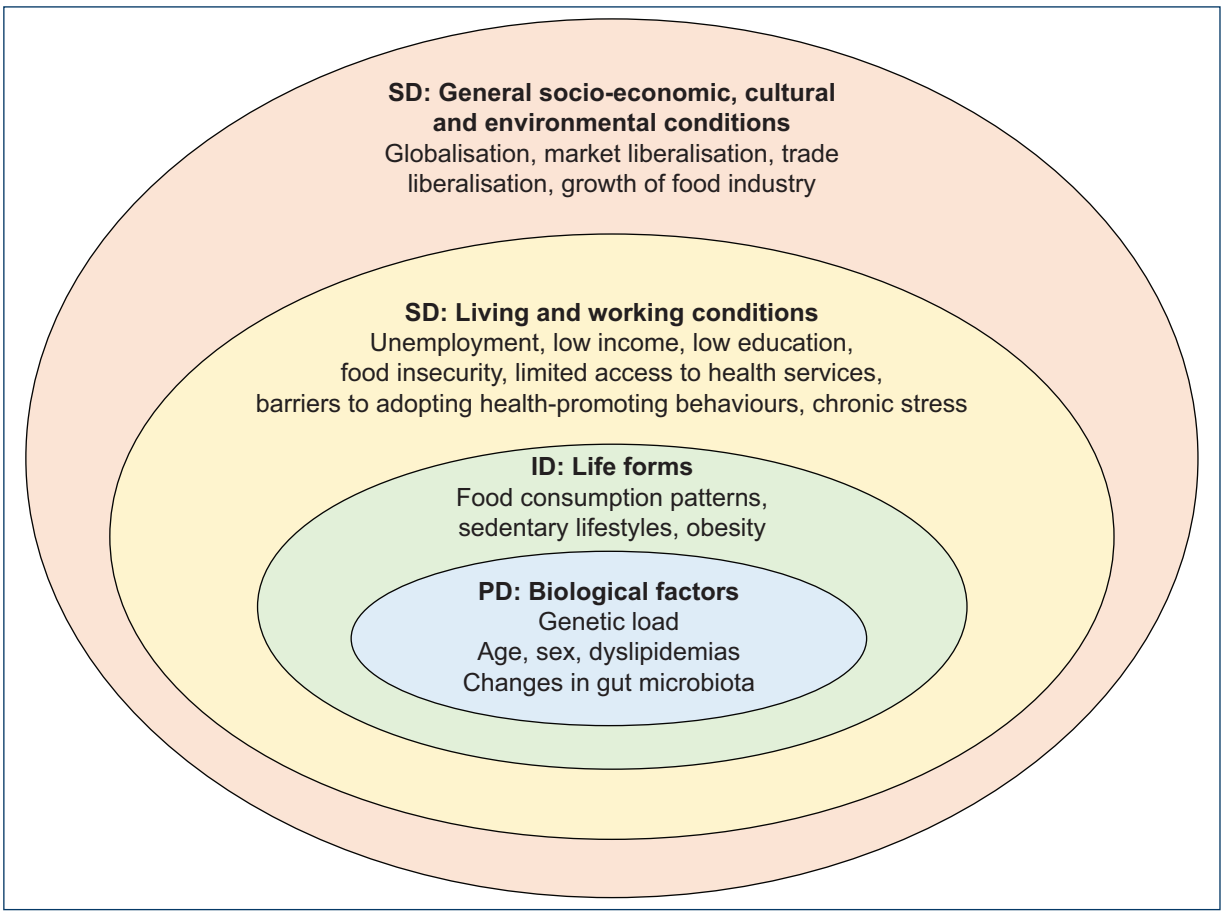

Figure 6. Social determinants of health and Type 2 diabetes mellitus.
SD: structural determinants; ID: intermediate determinants; PD: proximal determinants.

What was observed in this study with respect to the selected socioeconomic indicators raises the need to continue exploring the causal complexity of this disease. The working group is aware of the danger involved in analyzing social conditions and processes as if they were risk factors; however, information is presented that points to the fact that these processes are presented in the case of T2DM. It is not enough to point out the existence of associations, we must move on to the explanation of why they exist. As has been pointed out: the causes of the causes must be sought[30], that is, public policies and specifically health policies must be reanalyzed.

Limitations

The very nature of an ecological study makes it impossible to know the simultaneous distribution, at the individual level, of a condition (or risk factor) with the presence of damage to health.

In this type of study, the magnitude of the association of two sociodemographic variables tends to be greater than in studies that work with individual information, which can give rise to a multicollinearity problem. It should also be remembered that these designs are a very useful tool in Public Health for the generation of hypotheses and for the evaluation of preventive and/or control interventions[13].

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. World Health Organization. Diabetes, Fact Sheets. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes [Last accessed on 2020 Oct 10].
2. IDF Diabetes Atlas. Global Fact Sheet. 10th ed. International Diabetes Federation; 2021. Available from: https://diabetesatlas.org [Last accessed on 2022 May 11].
3. Instituto Nacional de Estadística y Geografía (INEGI). Tabulados Interactivos-Genéricos. Available from: https://www.inegi.org.mx/app/tabulados/interactivos/?px=mortalidad_04&bd=mortalidad [Last accessed on 2022 Mar 01].
4. Determinantes Sociales de la Salud. Organización Panamericana de la Salud/Organización Mundial de la Salud. Available from: https://www.paho.org/es/temas/determinantes-sociales-salud
5. Wilkinson RG. Unhealthy Societies: The Afflictions of Inequality. United Kingdom: Taylor & Francis Group; 1996. p. 16-7.
6. Whitehead M. The concepts and principles of equity and health. Int J Health Serv. 1992;22:429-45.
7. Jenicek M. Búsqueda de las Causas de la Aparición de la Enfermedad. Barcelona: Masson S.A.; 1996. p. 165-82.
8. Sánchez-Torresa DA. Accesibilidad a los servicios de salud: debate teórico sobre determinantes e implicaciones en la política pública de salud. Rev Med Inst Mex Seguro Soc. 2017;55:82-9.
9. Secretaría de Salud. El Impacto de las Políticas Públicas Sobre Diabetes Mellitus Available from: https://www.gob.mx/salud/articulos/el-impacto-de-las-politicas-publicas-sobre-diabetes-mellitus-169335?idiom=es [Last accessed on 2020 Apr 26].
10. Secretaría de Salud. Estrategia Nacional para la Prevención y el Control del Sobrepeso, la Obesidad y la Diabetes. 2013. Available from: https://www.gob.mx/salud/cenaprece/documentos/estrategia-nacional-para-la-prevencion-y-el-control-del-sobrepeso-la-obesidad-y-la-diabetes-136837
11. Secretaría de Salud, Instituto Nacional de Salud Pública, Instituto Nacional de Estadística y Geografía. Encuesta Nacional de Salud y Nutrición 2018. Presentación de Resultados. 2018. p. 42. Available from: https://ensanut.insp.mx/encuestas/ensanut2018/doctos/informes/ensanut_2018_presentacion_resultados.pdf
12. Basto-Abreu A, Barrientos-Gutiérrez T, Rojas-Martínez R, Aguilar-Salinas CA, López-Olmedo N, De la Cruz-Góngora V, et al. Prevalencia de diabetes y descontrol glucemico en Mexico: resultados de la Ensanut 2016. Salud Pública Mex 2020;62:50-9.
13. Encuesta Nacional de Salud y Nutrición 2021 Sobre Covid-19. Resultados Nacionales. Instituto Nacional de Salud Pública. Available from: https://www.insp.mx/novedades-editoriales/encuesta-nacional-de-salud-y-nutricion-2021-sobre-covid-19-resultados-nacionales [Last accessed on 2022 Oct 01].
14. Morgenstern H. Ecologic studies. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. 3rd ed. Philadelphia, PA: Wolters Kluver-Lippincott-Williams and Wilkins; 2012. p. 596-619.
15. Instituto Nacional de Salud Pública, Secretaría de Salud. Encuesta Nacional de Salud y Nutrición (Ensanut). Available from: https://ensanut.insp.mx [Last accessed on 2022 Oct 25].
16. Instituto Nacional de Estadística y Geografía (INEGI). Características de las Defunciones Registradas en México Durante 2019. Comunicado de Prensa Núm. 480/20, 29. Aguascalientes: Instituto Nacional de Estadística y Geografía; 2020.
17. Instituto Nacional de Estadística y Geografía (INEGI). Consulta de: Defunciones Generales. Available from: https://www.inegi.org.mx/sistemas/olap/proyectos/bd/continuas/mortalidad/mortalidadgeneral.asp [Last accessed on 2021 Jun 20].
18. Consejo Nacional de Población (CONAPO). Proyecciones de la Población de México y de las Entidades Federativas, 1950-2070. Gobierno de México. Available from: https://datos.gob.mx/busca/dataset/proyecciones-de-la-poblacion-de-mexico-y-de-las-entidades-federativas-2020-2070 [Last accessed on 2022 Oct 30].
19. CONEVAL. Anexo Estadístico 2020. Available from: https://www.coneval.org.mx/medicion/mp/paginas/ae_pobreza_2020.aspx [Last accessed on 2022 Oct 01].
20. IDH. Programa de las Naciones Unidas para el Desarrollo (PNUD). Informe de Desarrollo Humano Municipal 2010-2020: Una Década de Transformaciones Locales para el Desarrollo de México. Available from: https://www.undp.org/es/mexico/publicaciones/informe-de-desarrollo-humano-municipal-2010-2020-una-decada-de-transformaciones-locales-en-mexico-0
21. Índice de Gini - México. Data. Available from: https://datos.bancomundial.org/indicator/si.pov.gini?locations=mx
22. Instituto Nacional de Estadística y Geografía (INEGI). Tabulados. Sistema de Cuentas Nacionales de México. Producto Interno Bruto por Entidad Federativa. Cifras a 2019 Revisadas. Available from: https://www.inegi.org.mx/app/tabulados/default.aspx?pr=17&vr=7&in=2&tp=20&wr=1&cno=2 [Last accessed on 2022 Oct 01].
23. Banco Mundial. Datos. Tasa de Alfabetización, Total De Adultos (% de Personas de 15 Años o Más). Available from: https://datos.bancomundial.org/indicator/se.adt.litr.zs [Last accessed on 2022 Oct 01].
24. Gordis L, editor. The ocurrence of disease I: Disease surveillance and measures of morbidity. Epidemiology. 5th ed. Canada: Elsevier-Saunders; 2014. p. 38-60.
25. Moreno-Altamirano L, García-García JJ, Soto-Estrada G, Capraro S, Limón-Cruz D. Epidemiología y determinantes sociales asociados a la obesidad y la diabetes tipo 2 en México. Rev Médica Hosp Gen Méx. 2014;77:114-23.
26. Olson CM, Strawderman MS. The relationship between food insecurity and obesity in rural childbearing women. J Rural Health 2008;24:60-6.
27. Organización de las Naciones Unidas para la Alimentación y la Agricultura. El Estado de la Seguridad Alimentaria y la Nutrición en el Mundo 2022. Available from: https://www.fao.org/3/cc0639es/online/sofi-2022/cost-affordability-healthy-diet.html [Last accessed on 2023 Feb 24].
28. García, B. Las carencias laborales en México: Conceptos e indicadores. In: Pacheco GE, editor. Trabajos Atípicos y Precarización Del Empleo. 1st ed. Mexico: CEDUA, El Colegio de México; 2011. p. 81-113.
29. Rezago Educativo por Estado, Coneval. Available from: https://www.coneval.org.mx/medicion/mp/documents/mmp_2018_2020/notas_pobreza_2020/nota_tecnica_sobre_el_rezago%20educativo_2018_2020.pdf
30. López AO, Escudero JC, Carmona ML. Los determinantes sociales de la salud: una perspectiva desde el taller latinoamericano de determinantes sociales sobre la Salud, ALAMES. Soc Med 2008;3:323-35.
31. Marmot M. Multinivel approaches to undertanding social determinants. In: Berkman LF, Kawachi I, editors. Social Epidemiology. USA: Oxford University Press; 2000. p. 349-67.
32. Krieger N. Discrimination and health. In: Berkman LF, Kawachi I, editors. Social Epidemiology. USA: Oxford Uniiversity Press; 2000. p. 36-75.
33. Jiménez-Corona A, Aguilar-Salinas CA, Rojas-Martínez R. Diabetes mellitus tipo 2 y frecuencia de acciones para su prevención y control. Salud Publica Mex 2013;55:S137-43

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REVIEW ARTICLE

Biological therapy in the reduction of cardiovascular risk in patients with psoriasis

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Abstract

Psoriasis is a chronic inflammatory disease that primarily affects the skin, and its complications include a predisposition to atherosclerosis and cardiovascular disease (CVD), with this risk related to the severity of psoriasis. The mechanisms by which psoriasis predisposes to CVD are not clear. They are attributed to persistent chronic inflammation, which is a common factor in both diseases. However, timely recognition of psoriasis and initiation of systemic therapy may improve the prognosis of the disease. The hypothesis that the inflammatory cascade activated in psoriasis contributes to the atherosclerotic process provides a basis for suggesting that anti-inflammatory therapy that ameliorates psoriasis activity would also reduce CVD risk. Biological therapy that inhibits certain proinflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-12/23, and IL-17, has a direct effect on the development of psoriasis and, in addition to reducing the risk of developing psoriasis, may improve vascular damage. However, the available information is not entirely conclusive, and further studies are needed to define the true role of these drugs in the prevention and prognosis of CVD in patients with severe forms of psoriasis and with various comorbidities. This review analyzes recent studies that suggest a protective effect of biologic therapies in the risk of CVD in patients with psoriasis.

Keywords: *Psoriasis. Biological therapy. Cardiovascular diseases. Proinflammatory cytokines.*

Introduction

Psoriasis is a chronic inflammatory skin disease characterized by an increase in the speed of hematopoiesis that causes hyperplasia of the epidermis, clinically resulting in the formation of indurated erythematous squamous plaques[1]. Psoriasis vulgaris is far from being a disease with an exclusive impact on the skin, it is a systemic disease that seriously affects the general condition of the individual and can lead to serious complications, even leading to the death of the patient[2]. The causes of the disease are unknown, although its pathogenesis includes genetic and immunological aspects, and is also associated with different external factors that can exacerbate psoriasis, such as psychological stress, changes in environmental climate, infectious diseases, medications, physiological states such as pregnancy, among others[3]. The prevalence of the disease varies according to the geographical area, although it is accepted that the global prevalence is approximately 2%[4]; In Mexico, it is estimated that the prevalence is in line with that referred to worldwide.

Psoriasis predisposes to the development of cardiovascular disease (CVD) (25% increase in relative risk), with a relationship directly proportional to the severity of the disease[5]. The risk increases if the patient has other comorbidities associated with CVD such as obesity, dyslipidemia, hypertension, diabetes mellitus, and metabolic syndrome[4]. Chronic and persistent inflammation (PCI),

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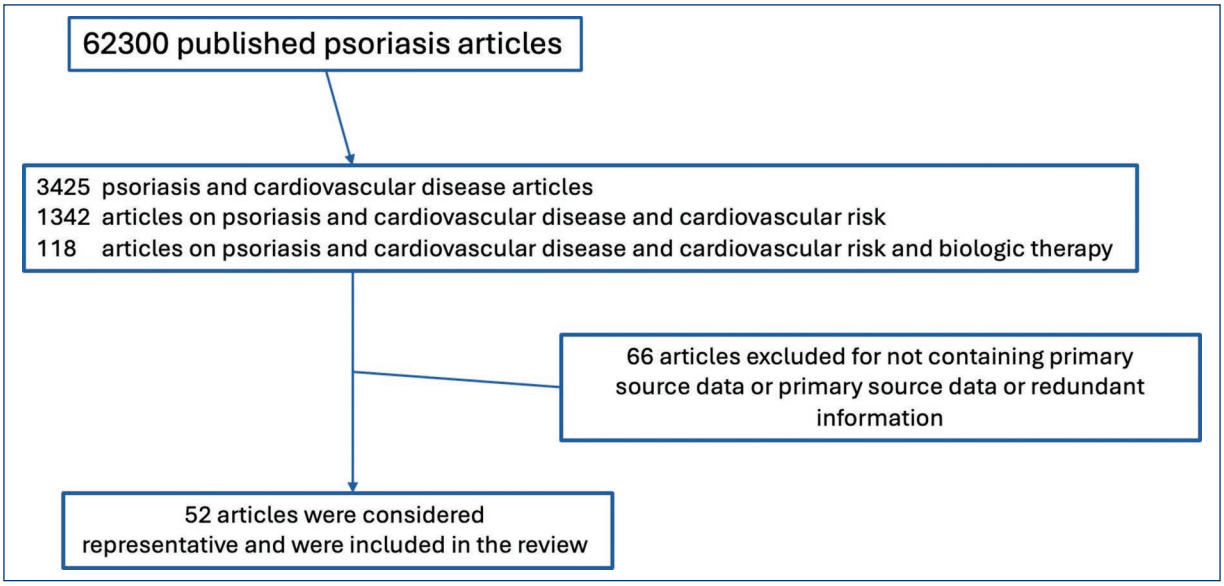

Figure 1. Search criteria and selection of the most representative articles.

which involves proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon γ (IFN-γ), interleukin (IL)-6, IL-8, IL-12, IL-17A, and IL-18, is a common factor in these diseases, including psoriasis[6]. This PCI directly contributes to the development of endothelial dysfunction, favoring atherosclerosis and CVD[7].

The CVDs that increase in prevalence in patients with psoriasis are mainly acute myocardial infarction and ischemic heart disease, in addition to thromboembolic disease and cerebrovascular events[8]. This makes it necessary to routinely review the cardiovascular health status of the patient with psoriasis and determine the strategy to be followed, which includes modifications in the patient's lifestyle, treatment of comorbidities, and control of PCI associated with psoriasis.

The development of biological therapy has considerably changed the evolution of psoriasis. Recently, it has been suggested that this therapy can effectively reduce cardiovascular risk[9]. This review will discuss the most recent studies suggesting a protective effect of biologic therapies on CVD risk in patients with psoriasis.

Material and methods

A narrative review, through searching PubMed, EMBASE, MEDLINE, and Web of Science up to January 2023, was conducted to identify all studies documenting the use of biologic therapy in patients with psoriasis and evaluating cardiovascular risk modification.

The following search terms were used alone or in combination with the Boolean operators "AND," "OR:" "Psoriasis," "Biological therapy," "cardiovascular risk," "therapy" and "proinflammatory cytokines." We did not apply any temporal (except for the date of closure of the search), study design, or language restrictions. We focused on full-text articles but considered abstracts if relevant (Fig. 1).

Results and discussion

The psoriasis-atherosclerosis-CVD (PAC) triad

The common factor that the components of the PAC triad have is PCI, a factor that also contributes to the development of other comorbidities such as metabolic syndrome, obesity, dyslipidemia, and diabetes mellitus[4]. This PCI is one of the triggers of psoriasis in genetically predisposed individuals; as part of the natural history of the disease, psoriasis can contribute to the development of endothelial dysfunction and atherosclerosis, directly influencing the appearance of CVD, which can manifest itself in less than a decade of development of psoriasis, a process that is part of the so-called "psoriatic march"[10] (Fig. 2).

Although endothelial dysfunction can be associated with different diseases such as hypertension, diabetes, insulin resistance, and dyslipidemia, in the case of patients with psoriasis, this dysfunction occurs even in

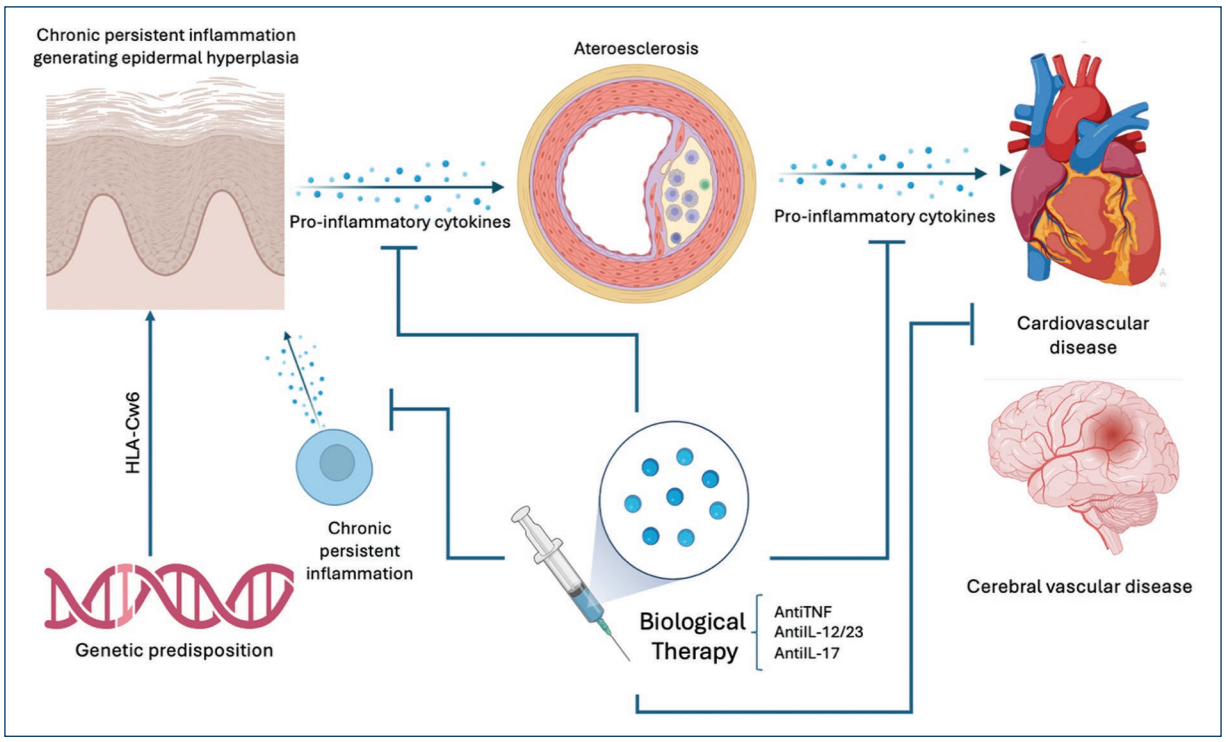

Figure 2. Sequence of pathophysiological events of the PAC triad that begins with genetic predisposition and the development of persistent chronic inflammation that favors the appearance of psoriasis and that, through the elevation of proinflammatory cytokines, contributes to the development of endothelial dysfunction, atherosclerosis, and increased cardio-cerebrovascular risk. It is suggested that the intervention of biologic therapy in the selective control of key cytokines such as tumor necrosis factor, IL-23, and IL-17, involved in the pathogenesis of the PAC triad, could decrease the risk of the aforementioned outcome.

IL: interleukin; PAC: psoriasis-atherosclerosis-cardiovascular disease.

the absence of such comorbidities, with psoriasis being an independent risk factor for CVD, 9 however, it is clear that the presence of these comorbidities substantially increases the risk of CVD, leading to a fatal outcome[11].

It has been observed that the life expectancy of patients with severe psoriasis is 6 years shorter than in healthy subjects; in addition, the risk of acute myocardial infarction and cerebral vascular disease is higher in patients with severe psoriasis than in those with mild-to-moderate form[12].

In an effort to reduce the risk of CVD in patients with psoriasis, Garshick and Berger[13], using an algorithm that determined the risk of CVD in patients with psoriasis, proposed that if the patient was at high risk of CVD, statins should be considered, but not for low-risk patients, where only CVD risk factors had to be identified and controlled.

Insulin resistance and elevated leptin levels in patients with psoriasis are associated with an increased risk of CVD due to endothelial dysfunction, and this risk increases in direct proportion to the severity of psoriasis. It is imperative to implement more rigorous control measures to address this issue. These factors have the potential to promote atherosclerosis by directly influencing immune responses in vascular tissue. Consequently, this can lead to PCI and a harmful cycle that may ultimately result in CVD and an increased risk of mortality[14]. Other factors involved in the outcome of the PAC triad are dyslipidemia (oxidized low-density lipoprotein that is highly atherogenic, alterations in the reverse transport of high-density lipoprotein cholesterol, and hypertriglyceridemia)[15] and the increase in the density of epicardial adipose tissue that promotes coronary heart disease,[16] representing risk factors for CVD and consequently increasing the risk of death if not identified and controlled in time.

PCI, the common denominator of the PAC triad, is directly mediated by proinflammatory cytokines such as TNF-α, IL-23, and IL-17A, the latter through the IL-17 receptor that stimulates the production of granulocyte colony-stimulating factor and IL-6, causing vascular damage that contributes to atherosclerosis and CVD. Therefore, it is suggested that treatment aimed at

Table 1. Main studies evaluating the effect of biologic therapy on the development of cardiovascular disease in patients with psoriasis

Author Reference	Country/year	Drug	Patients	Relative risk (95% CI)
Abaubara et al.[25]	U.S.A./2010	TNFi	12,224	0.68 (0.5-0.94)
Wu et al.[26]	U.S.A./2012	TNFi	1,673	0.56 (0.37-0.83)
Ahlehoff et al.[27]	Denmark/2013	TNFi	693	0.42 (0.13-1.31)
Wu et al.[28]	U.S.A./2013	TNFi	976	0.61 (0.41-0.91)
Ahlehoff et al.[29]	Denmark/2015	TNFi	959	0.46 (0.22-0.98)
Shaaban and Al-Mutairi[30]	Kuwait/2016	TNFi	1058	4.88 (2.5-7.2)*
Wu et al.[31]	U.S.A./2018	TNFi	11,410	0.77 (0.60-0.99)
Wu et al.[32]	U.S.A./2017	TNFi	9148	0.55 (0.45-0.67)
Rungapiromnan et al.[33]	U.K./2016	TNFi	5205	OR 0.67 (0.10-4.63)
Ryan et al.[34]	U.S.A./2011	TNFi	1078	–0.0005 (–0.01-0.009)**
Ahlehoff et al.[29]	Denmark/2015	IL-12/23i	178	1.52 (0.47-4.94)
Rungapiromnan et al.[33]	U.K./2016	IL-12/23i	2310	OR 4.48 (0.24-84.77)
Ryan [34]	U.S.A./2011	IL-12/23i	771	0.012 (–0.001-0.026)**
Reich et al.[42]	U.K./2011	IL-12/23i	1582	0.44 (0.27-0.67)
Tzellos et al.[43]	Germany/2012	IL-12/23i	3179	OR 4.23 (1.07-16.75)
Poizeau et al.[44]	France/2020	IL-12/23i	9290	OR 4.17 (1.19-14.59)
Papp et al.[45]	U.S.A./2013	IL-12/23i	3117	IR (45 mg) 0.56/100 SY IR (90 mg) 0.36/100 SY
Gordon et al.[46]	U.S.A./2012	IL-12/23i	981	Exposure-adjusted rate: 1.06/100SY, (0.43-2.18).
Rungapiromnan et al.[33]	U.K./2016	IL-17i	2549	OR 1.00 (0.09-11.09)
Gottlieb et al.[49]	U.S.A./2022	IL-17i	8819	IR 0.4/100 PY (no increase over time)
Van De Kerkhof et al.[50]	The Netherlands/2016	IL-17i	3430	IR: 0.42/100 SY (300 mg dose) IR: 0.35/100 SY (150 mg dose)

*Incidence rate of myocardial infarction per 1000 person-years (95% CI).
**Risk difference, events per person-year (95% CI).
OR: *odds ratio*; IR: incidence rate; SY: subject-year of exposure; PY: per year; CI: confidence interval; TNF: tumor necrosis factor; IL: interleukin.

blocking these cytokines could be beneficial not only for the control of psoriasis but also of atherosclerosis and the development of CVD[17].

Effect of biologic therapy on PCI/PAC

Table 1 summarizes the main studies evaluating the effect of biologic therapy on the development of CVD in patients with psoriasis.

It has been suggested that PCI in psoriasis contributes to the atherosclerotic process and that modification of the former may contribute to reducing atherosclerosis and consequently the risk of CVD. The different treatments available for the management of psoriasis in different degrees of severity such as topical therapy, phototherapy, and systemic immunosuppressants can largely control the disease, some of them can even increase the already high cardiovascular risk in patients with the disease. Some exceptions are obvious, such as the effect of methotrexate that can decrease cardiovascular risk[18].

Studies evaluating the protective effect of biological therapy on CVD are scarce in patients with psoriasis, although not in other diseases, and expectations for control of cardiovascular comorbidity have increased markedly, as they reduce the likelihood that patients with psoriasis will develop CVD, although their role in vascular damage processes remains controversial. Probably due

to the inconsistency of clinical data on its efficacy against increased cardiovascular risk[18]. At present, biologic drugs included in the therapeutic regimen for psoriasis target three main targets: TNF, IL-12/IL-23, and IL-17.

A recent study found that suppression of some proinflammatory cytokines could reduce the risk of CVD, as has been observed with inhibition of IL-1β and subsequent reduction of CVD recurrence[19]. In addition to this effect, biologic therapy may reduce coronary inflammation; therefore, biologic therapy predominantly targeting TNF-α, IL-23, and IL-17 may influence PCI and thus lessen the impact of the PAC triad in psoriasis patients[20]. In the case of IL-17 inhibitors such as secukinumab, ixekizumab, and brodalumab, the first two blocking IL-17A, while the third blocks the IL-17 receptor[21], could also impact the activation of neutrophils, crucial for psoriasis and PCI, in addition to the fact that these cells interact with the damaged endothelium and contribute to the development of atherosclerosis and CVD[22].

Recent studies, including two meta-analyses, suggest that treatment with anti-TNF-α reduces the risk of CVD and acute myocardial infarction[23-34]. The cardioprotective effect of some biological therapies, mainly anti-TNF, has been observed in patients with other auto-inflammatory diseases such as rheumatoid arthritis, where it improved endothelial function and reduced the risk of CVD by 70%[35]. Among the most commonly used TNF anti-TNFs in the management of psoriasis is adalimumab, which effectively reduces PCI, although with a variable impact on vascular inflammation and endothelial dysfunction[36].

Recent systematic reviews did not show a significant effect of TNF inhibitors on subclinical indicators of atherosclerosis in psoriasis or other chronic inflammatory diseases (including indicators of arterial stiffness, carotid intima-media thickness, endothelial dysfunction measured as forearm blood flow-mediated dilation, and aortic vascular inflammation)[37,38], however, this could occur by different routes such as remission of the primary disease or reduction of the prothrombotic tendency[37].

On the other hand, IL-23, a proinflammatory cytokine that induces the differentiation of Th17 and Th22 cells, is a key player in the pathogenesis of psoriasis, and its blockade is effective in the control of psoriasis and psoriatic arthritis[39]. We carry out this blockade in clinical practice with four drugs, including ustekinumab (the most commonly used), guselkumab, tildrakizumab, and risankizumab, the first inhibiting both IL-23 and IL-12, while the last three are selective toward IL-23[40]. IL-23 has been linked to the development of atherosclerosis, and its elevated serum levels are predictors of mortality in patients with CVD[41].

IL-23 also mediates the production of granulocyte-macrophage colony-stimulating factor which promotes the development of atherosclerosis and increases oxidative stress that contributes to the PAC triad[41]. There is still little evidence on the cardioprotective effect of anti-IL23[42-46], so more studies are needed in this regard.

IL-17 inhibitors have shown efficacy in the treatment of psoriasis, being comparable in their effect and even more effective than anti-TNF and anti-IL-23[47]. The cardioprotective effect of antiIL-17A has been documented in previous studies[6,48-50]. Considering the inhibition of the proatherogenic, proinflammatory, pro-oxidant, and prothrombotic effects of IL-17,48 however, more studies are needed to evaluate the impact of biological therapy on atherosclerosis, since previous studies have proposed that IL-17 could even have a protective effect against atherosclerosis and that its serum levels do not correlate with carotid intimal thickness[18].

Regarding the effect of antiIL-17A on vascular dysfunction, the results are contradictory; a previous study with secukinumab showed that the addition of the biologic did not modify endothelial function in the first 12 weeks of use in patients with psoriasis and vascular dysfunction, but later until 52 weeks[51]. While in another recent study, it was observed that the addition of anti-IL-17 therapy reduced the thickness of non-calcified plaque in patients with psoriasis, improving endothelial function[52].

Conclusion

Psoriasis is a systemic disease that increases the risk of CVD, and this increases in direct proportion to the severity of psoriasis. Therefore, biological therapies are an option to block proinflammatory signaling pathways common in these diseases. Biological therapies in their different modalities could reduce the risk of developing CVD, however, the available information is not entirely conclusive, so more studies are needed to define the real role of these drugs in CVD, mainly in patients with severe forms of psoriasis.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The author declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The author declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Liu C, Chen H, Liu Y, Huang H, Yu W, Di T, et al. Immunity: psoriasis comorbid with atherosclerosis. Front Immunol. 2022;13:1070750.
2. Parab S, Doshi G. An update on emerging immunological targets and their inhibitors in the treatment of psoriasis. Int Immunopharmacol. 2022;113:109341.
3. Vičić M, Kaštelan M, Brajac I, Sotošek V, Massari LP. Current concepts of psoriasis immunopathogenesis. Int J Mol Sci. 2021;22:11574.
4. Bu J, Ding R, Zhou L, Chen X, Shen E. Epidemiology of psoriasis and comorbid diseases: a narrative review. Front Immunol. 2022; 13:880201.
5. Zhang L, Wang Y, Qiu L, Wu J. Psoriasis and cardiovascular disease risk in European and East Asian populations: evidence from meta-analysis and Mendelian randomization analysis. BMC Med. 2022;20:421.
6. Trovato E, Rubegni P, Prignano F. Place in therapy of anti-IL-17 and 23 in psoriasis according to the severity of comorbidities: a focus on cardiovascular disease and metabolic syndrome. Expert Opin Biol Ther. 2022;22:1443-8.
7. Anyfanti P, Margouta A, Goulas K, Gaveiilaki M, Lazaridou E, Patsatsi A, et al. Endothelial dysfunction in psoriasis: an updated review. Front Med (Lausanne). 2022;9:864185.
8. Orlando G, Molon B, Viola A, Alaibac M, Angioni R, Piaserico S. Psoriasis and cardiovascular diseases: an immune-mediated cross talk? Front Immunol. 2022;13:868277.
9. Doumas M, Katsiki N, Papademetriou V. Psoriasis and cardiovascular disease: two sides of the same coin? Angiology. 2018;69:5-9.
10. Furue M, Kadono T. "Inflammatory skin march" in atopic dermatitis and psoriasis. Inflamm Res. 2017;66:833-42.
11. Liu L, Cui S, Liu M, Huo X, Zhang G, Wang N. Psoriasis increased the risk of adverse cardiovascular outcomes: a new systematic review and meta-analysis of cohort study. Front Cardiovasc Med. 2022; 9:829709.
12. Correa TL, Quitete MA, De Azevedo LT, Fraga IA, Teixeira LC. Myocardial infarction, stroke, and psoriasis: a systematic review of observational studies. Ann Cardiol Angeiol (Paris). 2023;72(2):101574.
13. Garshick MS, Berger JS. Psoriasis and cardiovascular disease-an ounce of prevention is worth a pound of cure. JAMA Dermatol. 2022; 158:239-41.
14. Yan H, Yu B, Tian J, Xia D, Xu Y, Li C. Serum leptin and adiponectin: indicators of cardiovascular disease secondary to psoriasis. Indian J Dermatol. 2022;67:109-14.
15. Miao C, Li J, Li Y, Zhang X. Obesity and dyslipidemia in patients with psoriasis: a case-control study. Medicine (Baltimore). 2019; 98:e16323.
16. Ellis CN, Neville SJ, Sayyouh M, Elder JT, Nair RP, Gudjonsson JE, et al. Epicardial adipose tissue volume is greater in men with severe psoriasis, implying an increased cardiovascular disease risk: a cross-sectional study. J Am Acad Dermatol. 2022;86:535-43.
17. Michalak-Stoma A, Bartosińska J, Raczkiewicz D, Kowal M, Kosak J, Gujski M, et al. Multiple cytokine analysis of Th1/Th2/Th9/Th17/Th22/ Treg cytokine pathway for individual immune profile assessment in patients with psoriasis. Med Sci Monit. 2022;28:e938277.
18. Andújar I, Esplugues JV, García-Martínez P. Looking beyond the skin: pathophysiology of cardiovascular comorbidity in psoriasis and the protective role of biologics. Pharmaceuticals (Basel). 2022; 15:1101.
19. Baragetti A, Catapano AL, Magni P. Multifactorial activation of NLRP3 inflammasome: relevance for a precision approach to atherosclerotic cardiovascular risk and disease. Int J Mol Sci. 2020;21:4459.
20. Wang X, Kaiser H, Kvist-Hansen A, McCauley BD, Skov L, Hansen PR, et al. IL-17 pathway members as potential biomarkers of effective systemic treatment and cardiovascular disease in patients with moderate-to-severe psoriasis. Int J Mol Sci. 2022;23:555.
21. Lanna C, Lambiase S, Gaeta Shumak R, Borselli C, Cosio T, Dattola A, et al. Why targeted therapeutics have provided benefit in psoriasis: looking at IL-17 biology. Expert Rev Clin Pharmacol. 2022;15:1209-24.
22. Sileno S, Beji S, D'Agostino M, Carassiti A, Melillo G, Magenta A. microRNAs involved in psoriasis and cardiovascular diseases. Vasc Biol. 2021;3:R49-68.
23. Champs B, Degboé Y, Barnetche T, Cantagrel A, Ruyssen-Witrand A, Constantin A. Short-term risk of major adverse cardiovascular events or congestive heart failure in patients with psoriatic arthritis or psoriasis initiating a biological therapy: a meta-analysis of randomised controlled trials. RMD Open. 2019;5:e000763.
24. Ursini F, Leporini C, Bene F, D'Angelo S, Mauro D, Russo E, et al. Anti-TNF-alpha agents and endothelial function in rheumatoid arthritis: a systematic review and meta-analysis. Sci Rep. 2017;7:5346.
25. Abuabara K, Lee H, Kimball AB. The effect of systemic psoriasis therapies on the incidence of myocardial infarction: a cohort study. Br J Dermatol. 2011;165:1066-73.
26. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. Arch Dermatol. 2012;148:1244-50.
27. Ahlehoff O, Skov L, Gislason G, Lindhardsen J, Kristensen SL, Iversen L, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. J Intern Med. 2013;273:197-204.
28. Wu JJ, Poon KY, Bebchuk JD. Association between the type and length of tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. J Drugs Dermatol. 2013;12:899-903.
29. Ahlehoff O, Skov L, Gislason G, Gniadecki R, Iversen L, Bryld LE, et al. Cardiovascular outcomes and systemic anti-inflammatory drugs in patients with severe psoriasis: 5-year follow-up of a Danish nationwide cohort. J Eur Acad Dermatol Venereol. 2015;29(6):1128-34.
30. Shaaban D, Al-Mutairi N. The effect of tumor necrosis factor inhibitor therapy on the incidence of myocardial infarction in patients with psoriasis: a retrospective study. J Dermatolog Treat. 2018;29(1):3-7.
31. Wu JJ, Sundaram M, Cloutier M, Gauthier-Loiselle M, Guérin A, Singh R, et al. The risk of cardiovascular events in psoriasis patients treated with tumor necrosis factor-α inhibitors versus phototherapy: an observational cohort study. J Am Acad Dermatol. 2018;79:60-8.
32. Wu JJ, Guérin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-α inhibitors versus methotrexate. J Am Acad Dermatol. 2017;76:81-90.
33. Rungapiromnan W, Yiu ZZ, Warren RB, Griffiths CE, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomized controlled trials. Br J Dermatol. 2017;176:890-901.
34. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA. 2011;306:864-71.
35. Deyab G, Hokstad I, Aaseth J, Smastuen MC, Whist JE, Agewall S, et al. Effect of anti-rheumatic treatment on selenium levels in inflammatory arthritis. J Trace Elem Med Biol. 2018;49:91-7.
36. Wegner J, Karbach S, Drosos I, Schnorbus B, Muxel S, Schmidt F, et al. TNF-α blockade may lead to improvement of vascular function in psoriasis patients. Exp Dermatol. 2022;31:237-41.
37. Knowles L, Nadeem N, Chowienczyk PJ. Do anti-tumour necrosis factor-α biologics affect subclinical measures of atherosclerosis and arteriosclerosis? A systematic review. Br J Clin Pharmacol. 2020;86: 837-51.
38. González-Cantero A, Ortega-Quijano D, Álvarez-Díaz N, Ballester MA, Jimenez-Gomez N, Jaen P, et al. Impact of biological agents on imaging and biomarkers of cardiovascular disease in patients with psoriasis: a systematic review and meta-analysis of randomized placebo-controlled trials. J Invest Dermatol. 2021;141:2402-11.
39. Ruggiero A, Megna M, Fabbrocini G, Ocampo-Garza SS. Anti-IL23 biologic therapies in the treatment of psoriasis: real-world experience versus clinical trials data. Immunol Res. 2023;71:328-55.
40. Vu A, Ulschmid C, Gordon KB. Anti-IL 23 biologics for the treatment of plaque psoriasis. Expert Opin Biol Ther. 2022;22:1489-502.
41. Marovt M, Marko PB, Pirnat M, Ekart R. Effect of biologics targeting interleukin-23/-17 axis on subclinical atherosclerosis: results of a pilot study. Clin Exp Dermatol. 2020;45:560-4.
42. Reich K, Langley RG, Lebwohl M, Szapary P, Guzzo C, Yeilding N, et al. Cardiovascular safety of ustekinumab in patients with moderate to severe psoriasis: results of integrated analyses of data from phase II and III clinical studies. Br J Dermatol. 2011;164:862-72.

43. Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol. 2013; 27:622-7.
44. Poizeau F, Nowak E, Kerbrat S, Nautout BL, Droitcourt C, Drici MD, et al. Association between early severe cardiovascular events and the initiation of treatment with the anti-interleukin 12/23p40 antibody ustekinumab. JAMA Dermatol. 2020;156:1208-15.
45. Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol. 2013;168:844-54.
46. Gordon KB, Langley RG, Gottlieb AB, Papp KA, Krueger GG, Strober BE, et al. A phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. J Invest Dermatol. 2012;132:304-14.
47. Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. Br J Dermatol. 2017;177:1014-23.
48. Piros ÉA, Szabó Á, Rencz F, Brodszky V, Szalai K, Galajda N, et al. Impact of interleukin-17 inhibitor therapy on arterial intima-media thickness among severe psoriatic patients. Life (Basel). 2021;11:919.
49. Gottlieb AB, Deodhar A, Mcinnes IB, Baraliakos X, Reich K, Schreiber S, et al. Long-term safety of secukinumab over five years in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis: update on integrated pooled clinical trial and post-marketing surveillance data. Acta Derm Venereol. 2022;102:adv00698.
50. Van de Kerkhof PC, Griffiths CE, Reich K, Leonardi CL, Blauvelt A, Tsai TF, et al. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016;75:83-98.e4.
51. Von Stebut E, Reich K, Thaçi D, Koenig W, Pinter A, Köber A, et al. Impact of secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. J Invest Dermatol. 2019;139:1054-62.
52. Elnabawi YA, Dey AK, Goyal A, Groenendyk JW, Chung JH, Belur AD, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. Cardiovasc Res. 2019;115:721-8.

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REVIEW ARTICLE

Meconium aspiration syndrome, fetal heart rate, and stillbirth. Literature review

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Abstract

Meconium aspiration syndrome (MAS) is a medical condition that can affect newborn babies. It occurs when a newborn inhales meconium, which is the first stool (feces) that a baby passes in the womb. Normally, meconium is expelled after birth, but in some cases, it is released into the amniotic fluid and can be inhaled by the baby before or during delivery. This can lead to a range of respiratory problems and complications. The severity of MAS can vary, with some infants experiencing mild symptoms and others facing more severe respiratory distress. Babies with MAS may have symptoms such as rapid breathing, grunting, bluish or grayish skin color (cyanosis), and chest retractions (drawing in of the chest wall with each breath). Severe cases of MAS may require treatment in a neonatal intensive care unit. The prognosis for babies with MAS varies depending on the severity of the condition and the promptness of treatment. Most infants recover with appropriate medical care, but in severe cases, complications can occur. It is important for health-care providers to closely monitor and provide care to babies with MAS to ensure the best possible outcomes. We present a document that results from the consultation of an updated bibliography on MAS, including aspects related to its pathophysiology and complications and the considerations to be taken into account by the obstetric service.

Keywords: *Meconium aspiration syndrome. Perinatal asphyxia. Stillbirth.*

Methods

A literature review was carried out with the keywords meconium aspiration syndrome (MAS), perinatal asphyxia, and stillbirth. The search included literature from the most recent 10 years, using the PUBMED databases, 65 articles with the topic linked to the keywords were selected, and then 28 manuscripts from those that included the items to be treated in the review (fetal distress vs. non-reassuring fetal state (NFRS), heart rate and fetal hypomotility, decreased fetal movements (DFM) and its risks, labor and fetal distress, fetal death, and its etiology) were selected.

Introduction

Most obstetric damage and risks to the health of the mother and child can be successfully prevented, detected, and treated through the application of standardized procedures for care, including the use of the risk approach and the performance of eminently preventive activities and the elimination or rationalization of some practices that, if carried out routinely, increase the risks. The proposed actions tend to favor the normal development of each of the stages of the gestational process and prevent the appearance of complications, improve maternal and child survival, and quality of life,

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and additionally contribute to providing care with greater warmth[1-3].

MAS is one of the most common causes of respiratory distress in neonates. The incidence is still high in the developing world. MAS is one of the most common causes of respiratory distress in a neonate which is associated with common maternal risk factors, especially in primigravida, which includes urinary tract infection, hypertension, and oligohydramnios. A study was conducted in Nepal, and a cross-sectional descriptive study was done among neonates admitted to the neonatal intensive care unit (NICU) with a diagnosis of MAS. The early outcome of those neonates was studied. Out of 140 neonates with a mean birth weight of 2865 + 543 g, 73.6% were male, of which 76.4% were referred cases, whereas 23.6% were inborn. Of them, 69.3% had a history of the thin type of meconium, whereas 30.7% had the thick type of meconium during delivery. Of all mothers, 74.3% were primigravida, 4.3% had an intrapartum fever of unknown source, 11.4% suffered from urinary tract infection, and 2.8% had hypertension. Premature rupture of membrane had occurred among 7.9%, and oligohydramnios was found in 10%. Half of them (50.7%) had a spontaneous vaginal delivery, 44.3% had a cesarean section, whereas 4.8% had assisted delivery. Around one-third of the neonates (37.1%) were given supplemental oxygen through nasal prongs, 25.7% through head box, 27.1% through continuous positive airway pressure, and 10% intubated. Around half of the neonates (42.1%) had no complications. Complications noted were sepsis, birth asphyxia, seizures, and polycythemia in 35%, 14.3%, 5.7%, and 2.9%, respectively. Mortality occurred among 5.0% of them[4].

Some stillbirths caused by placental abruption are potentially preventable. To prevent stillbirths caused by placental abruption, improvements should be implemented in obstetric management and assessment of fetal well-being, as well as in establishing a regional perinatal emergency transport system[5].

In the search for factors and conditions associated with fetal death, several types of exposures have been investigated, the study conducted in the United Kingdom published in 2023 found the following: In a population of women who had a stillbirth ≥ 28 weeks' gestation (n = 238) and women with an ongoing pregnancy at the time of interview (n = 597), a secondary analysis of data from the Midlands and North of England Stillbirth case-control study only included participants domiciled within 20 km of fixed air pollution monitoring stations. Pollution exposure was calculated using pollution climate modeling data for NO_2, NOx, and $PM_{2.5}$. The association between air pollution exposure and stillbirth risk was assessed using multivariable logistic regression adjusting for household income, maternal body mass index (BMI), maternal smoking, index of multiple deprivation quintile, and household smoking and parity. There was no association with whole pregnancy ambient air pollution exposure and stillbirth risk, but there was an association with pre-conceptual NO_2 exposure (adjusted odds ratio [aOR] 1.06, 95% confidence interval [CI] 1.01-1.08/$\mu g/m^3$). Risk of stillbirth was associated with maternal smoking (aOR 2.54, 95% CI 1.38-4.71), nulliparity (aOR 2.16, 95% CI 1.55-3.00), maternal BMI (aOR 1.05, 95% CI 1.01-1.08) and placental abnormalities (aOR 4.07, 95% CI 2.57-6.43). In conclusion, levels of ambient air pollution exposure during pregnancy in the UK, all of which were beneath recommended thresholds, are not associated with an increased risk of stillbirth. Periconceptual exposure to NO_2 may be associated with increased risk, but further work is required to investigate this association[6].

Exposure to high levels of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO increases the risk of stillbirth, and the most susceptible gestational period to ambient air pollution exposure was in the third trimester. Further toxicological and prospective cohort studies with improved exposure assessments are needed to confirm the causal link between air pollutants and stillbirth[7].

Fetal distress versus NFRS

NRFS is associated with significant maternal complications, in the form of increased need for blood transfusions, intensive care unit (ICU) admissions, and increased infection and readmission rates. Strategies for minimizing maternal complications need to be proactively considered in the management of NRFS[8].

One of the largest clinical trials on this topic was conducted using the following methodology: a large retrospective cohort study of 27,886 women who delivered between January 2013 and December 2016 in a single health system was studied. Inclusion criteria included (1) women over the age of 18 at the time of admission; (2) singleton pregnancy; (3) live birth; and (4) gestational age ≥ 37 weeks at the time of admission. NRFS was defined as umbilical cord pH ≤ 7.00, fetal bradycardia, late decelerations, and/or umbilical artery base excess ≤ –12. Univariate and multivariate logistic regression and propensity score analyses were performed, and propensity score aORs (AORPS) were derived. $p < 0.05$ were considered statistically significant. Primary outcomes

are maternal blood transfusion, maternal readmission, maternal ICU admission, and cesarean delivery in relation to umbilical artery pH, fetal bradycardia, and late decelerations. Results: umbilical artery pH ≤ 7 was associated with maternal blood transfusion (AORPS 6.83 [95% CI 2.22-21.0, p < 0.001]), maternal readmission (AORPS 12.6 [95% CI 2.26-69.8, p = 0.0039]), and cesarean delivery (AORPS 5.76 [95% CI 3.63-9.15, p < 0.0001]). Fetal bradycardia was associated with transfusion (AORPS 2.13 [95% CI 1.26-3.59, p < 0.005]) and maternal ICU admission (AORPS 3.22 [95% CI 1.23-8.46, p < 0.017]). Late decelerations were associated with cesarean delivery (AORPS 1.65 [95% CI 1.55-1.76, p < 0.0001]), clinical chorioamnionitis (AORPS 2.88 [95% CI 2.46-3.37, p < 0.0001]), and maternal need for antibiotics (AORPS 1.89 [95% CI 1.66-2.15, p < 0.0001]). Umbilical artery base excess ≤ –12 was associated with readmission (AORPS 6.71 [95% CI 2.22-20.3, p = 0.0007]), clinical chorioamnionitis (AORPS 1.89 [95% CI 1.24-2.89, p = 0.0031]), and maternal need for antibiotics (AORPS 1.53 [95% CI 1.03-2.26, p = 0.0344]). Conclusion of the study: NRFS is associated with significant maternal complications, in the form of increased need for blood transfusions, ICU admissions, and increased infection and readmission rates. Strategies for minimizing maternal complications need to be proactively considered in the management of NRFS[8].

Heart rate and fetal hypomotility

With the objective of assessing this condition, artificial intelligence, inspired by clinical decision-making procedures in delivery rooms, can correctly interpret cardiotocographic (CTG) tracings and distinguish between normal and pathological events. In a study, a method based on artificial intelligence was developed to determine whether a cardiotocogram shows a normal response of the fetal heart rate (FHR) to frequency of uterine contractions (UCF) predicts a FHR response, under the assumption that the fetus is still in good condition and based on how that specific fetus has responded so far. It hypothesizes that this method when having only learned from fetuses born in good condition, is incapable of predicting the response of a compromised fetus or an episode of transient fetal distress. The (in)capability of the method to predict the FHR response would then yield a method that can help assess fetal condition when the obstetrician is in doubt. CTG data of 678 deliveries during labor were selected based on a healthy outcome just after birth. The method was trained on the CTG data of 548 fetuses in this group to learn their heart rate response. Subsequently, it was evaluated on 87 fetuses, by assessing whether the method was able to predict their heart rate responses. The remaining 43 cardiotocographies were segment-by-segment annotated by three experienced gynecologists, indicating normal, suspicious, and pathological segments, while having access to the full recording and neonatal outcome. The comparison between abnormalities detected by the method (only using past and present input) and the annotated CTG segments by gynecologists (also looking at future input) yields an area under the curve of 0.96 for the distinction between normal and pathological events in majority-voted annotations. The developed method can distinguish between normal and pathological events in near real-time, with a performance close to the agreement between three gynecologists with access to the entire CTG tracing and fetal outcome[9].

DFM and its risks

The presence of DFM is a marker associated with increased risk for a fetus. However, DFM is associated with increased odds of an infant being born small for gestational age (SGA), obstetric intervention, early-term birth, and a composite of adverse perinatal outcomes. The biggest trial related to this topic was conducted as follows: among 101,597 women with pregnancies that met the inclusion criteria, 8821 (8.7%) presented at least once with DFM, and 92,776 women (91.3%) did not present with DFM (i.e., the control population). Women presenting with DFM, compared with those presenting without DFM, were younger (mean [SD] age, 30.4 [5.4] years vs. 31.5 [5.2] years; p < 0.001), more likely to be nulliparous (4845 women [54.9%] vs. 42 210 women [45.5%]; p < 0.001) and have a previous stillbirth (189 women [2.1%] vs. 1156 women [1.2%]; p < 0.001), and less likely to have a previous cesarean delivery (1199 women [13.6%] vs. 17 444 women [18.8%]; p < 0.001). During the study period, the stillbirth rate was 2.0 per 1000 births after 28 weeks' gestation. Presenting with DFM was not associated with higher odds of stillbirth (9 women [0.1%] vs. 185 women [0.2%]; aOR, 0.54; 95% CI, 0.23-1.26, p = 0.16). However, presenting with DFM was associated with higher odds of a fetus being born SGA (aOR, 1.14; 95% CI, 1.03-1.27; p = 0.01) and the composite adverse perinatal outcome (aOR, 1.14; 95% CI, 1.02-1.27; p = 0.02). Presenting with DFM was also associated with higher odds of planned early-term birth (aOR, 1.26; 95% CI, 1.15-1.38; p < 0.001), induction of labor (aOR, 1.63; 95% CI,

1.53-1.74; p < 0.001), and emergency cesarean delivery (aOR, 1.18; 95% CI, 1.09-1.28; p < 0.001)[10].

Labor and fetal distress

Keeping in mind the large number of inflammatory mediators that are potentially released during labor, several studies have been conducted, one of the most transcendental is the following: to investigate the correlation between the intrapartum CTG findings "suggestive of fetal inflammation" ("SOFI") and the interleukin (IL)-6 level in the umbilical arterial blood a prospective cohort study conducted at a tertiary maternity unit and including 447 neonates born at term. IL-6 levels were systematically measured at birth from a sample of blood taken from the umbilical artery. The intrapartum CTG traces were retrospectively reviewed by two experts who were blinded to the postnatal umbilical arterial IL-6 values as well as to the neonatal outcomes. The CTG traces were classified into "suggestive of fetal inflammation (SOFI)" and "no evidence of fetal inflammation (NEFI) according to the principles of physiologic interpretation of the CTG traces. The CTG was classified as "SOFI: if there was a persistent FHR increase > 10% compared with the observed baseline FHR observed at the admission or the onset of labor without any preceding repetitive decelerations. The occurrence of composite adverse outcome (CAO) was defined as NICU or special care baby unit admission due to one or more of the following: metabolic acidemia, Apgar score at 5 min ≤ 7, the need for neonatal resuscitation, respiratory distress, tachypnea/polypnea, jaundice requiring phototherapy, hypotension, body temperature instability, poor perinatal adaptation, suspected, or confirmed early neonatal sepsis. To compare the umbilical IL-6 values between the cases with intrapartum CTG traces classified as "SOFI" and those classified as "NEFI"; to assess the correlation of umbilical IL-6 values with the neonatal outcome. 43 (9.6%) CTG traces were categorized as "SOFI"; IL-6 levels were significantly higher in this group compared with the "NEFI" group (82.0 [43.4-325.0] pg/mL vs. 14.5 [6.8-32.6] pg/mL; p < 0.001). The mean FHR baseline assessed 1 h before delivery and the total labor length showed an independent and direct association with the IL-6 levels in the umbilical arterial blood (p < 0.001 and p = 0.005, respectively). CAO occurred in 33 (7.4%) cases; IL-6 yielded a good prediction of the occurrence of the CAO with an AUC of 0.72 (95% CI 0.61-0.81). Intrapartum CTG findings classified as "SOFI" are associated with higher levels of IL-6 in the umbilical arterial blood[11].

There are significant differences in perinatal outcomes when fetuses were exposed to evolving intrapartum hypoxic stress culminating in an abnormal baseline FHR variability, which was preceded by repetitive decelerations, followed by an increase in the baseline heart rate. Therefore, the knowledge of fetal physiological response to evolving hypoxic stress can be reliably used to determine fetal compensation[12].

The absence of cycling is associated with intrapartum maternal pyrexia, and fetuses with the absence of cycling are more likely to have poorer perinatal outcomes measured by Apgar ≤ 7 at 5 min, despite no association with fetal acidosis[13].

Contrary to continued use in some clinical areas, we found no evidence of benefit for the use of the admission CTG for low-risk women on admission in labor. Furthermore, the probability is that admission CTG increases the cesarean section rate by approximately 20%. The data lacked the power to detect possible important differences in perinatal mortality. However, it is unlikely that any trial, or meta-analysis, will be adequately powered to detect such differences. The findings of this review support the recommendation that the admission CTG not be used for women who are at low risk of admission in labor. Women should be informed that admission CTG is likely associated with an increase in the incidence of cesarean section without evidence of benefit[14].

Fetal death (stillbirth)

India contributes the highest absolute number of stillbirths in the world. This systematic review and meta-analysis were conducted to synthesize the burden, timing, and causes of stillbirths in India. Forty-nine reports from 46 studies conducted in 21 Indian states and union territories were included. It was found that there was no uniformity/standardization in the definition of stillbirths and in the classification system used to assign the cause. The share of antepartum stillbirths was estimated to be two-thirds whereas the remaining were intrapartum stillbirths. Maternal conditions and fetal causes were found to be the leading cause of stillbirth in India. The maternal condition was assigned as the most common cause (25%) followed by fetal (14%), placental cause (13%), congenital malformation (6%), and intrapartum complications (4%). Approximately 20% of the stillbirths were assigned as unknown or unexplained[15]. One of the biggest studies conducted with the aim of identifying stillbirth risk conditions was done. The study population of 131,514 pregnancies

included 131,037 live births and 477 (0.36%) stillbirths. There are four main findings of this study. First, 92.5% (441/477) of stillbirths were antepartum and 7.5% (36/477) were intrapartum, and 59.2% (261/441) of antepartum stillbirths were observed in association with placental dysfunction, and 40.8% (180/441) were unexplained or due to other causes. Second, placental dysfunction accounted for 80.1% (161/201) of antepartum stillbirths at < 32 weeks gestation, 54.2% (52/96) at 32 + 0 to 36 + 6 weeks, and 33.3% (48/144) at ≥ 37 weeks. Third, the risk of placental dysfunction-related antepartum stillbirth increased with increasing maternal weight and decreasing maternal height, was 3-fold higher in African-american than in Caucasian women, was 5.5-fold higher in parous women with previous stillbirth than in those with previous live birth, and was increased in smokers, in women with chronic hypertension and parous women with a previous pregnancy complicated by pre-eclampsia, and/or birth of a small-for-gestational-age baby. Fourth, in screening for placental dysfunction-related antepartum stillbirth by a combination of maternal risk factors, estimated fetal weight (EFW), and uterine artery (UtA)-pulsatility index (PI) in the validation dataset, the DR at a 10% FPR was 62.3% (95% CI, 57.2-67.4%) and the AUC was 0.838 (95% CI, 0.799-0.878); these results were consistent with those in the dataset used for developing the algorithm and demonstrate high discrimination between affected and unaffected pregnancies. Similarly, the calibration slope was 1.029 and the intercept was −0.009, demonstrating good agreement between the predicted risk and observed incidence of placental dysfunction-related antepartum stillbirth. The performance of screening was better for placental dysfunction-related antepartum stillbirth at < 37 weeks' gestation compared to at term (DR at a 10% FPR, 69.8% vs. 29.2%). Screening at mid-gestation by a combination of maternal risk factors, EFW and UtA-PI can predict a high proportion of placental dysfunction-related stillbirths and, in particular, those that occur preterm. Such screening provides poor prediction of unexplained stillbirth or stillbirth due to other causes[15,16].

EFW, UtA PI, umbilical artery (UA) PI, fetal middle cerebral artery PI, mean arterial pressure, serum placental growth factor, and soluble fms-like tyrosine kinase-1 for screening at 30-34 weeks gestation, biomarkers of impaired placentation and fetal hypoxemia provide a good prediction of PE, SGA, and fetal distress before labor, but poor or no prediction of stillbirth and adverse events in labor or after birth[17].

The survival of a fetus in utero is dependent on several factors. These factors can be broken down into the well-being of the host in its environment, the function of the uteroplacental unit, the condition of the environment in which the fetus lives, and the absence of lethal fetal factors. A single insult or a combination of factors may affect the function of these life-sustaining factors and lead to a stillbirth. The ability to maintain and support a pregnancy is dependent on multiple physiologic, hormonal, and anatomical adaptations[18].

The integrity of the uteroplacental unit may be compromised by structure, function, genetic anomalies, or insults such as hemorrhage or infection. Placental findings could include (1) single umbilical cord insertion, (2) velamentous umbilical cord insertion, (3) furcate umbilical cord insertion, (4) circummarginate insertion of the placental membranes, (5) circumvallate insertion of the placental membranes, (6) terminal villous immaturity, (7) terminal villous hypoplasia, (8) terminal villous hyperplasia, (9) acute chorioamnionitis of placental membranes, (10) acute chorioamnionitis of the chorionic plate, (11) acute funisitis, (12) acute umbilical cord arteritis, (13) acute umbilical cord phlebitis, (14) chorionic plate acute vasculitis of the fetal blood vessels, (15) chorionic plate vascular degenerative changes, (16) acute villitis, (17) chronic villitis, (18) avascular villi, (19) retroplacental hematoma, (20) parenchymal infarction, (21) intraparenchymal (intervillous) thrombosis, (22) perivillous fibrin deposition, (23) intervillous fibrin deposition, (24) placental weight, and (25) ratio placental weight/birth weight[18].

Etiology of fetal death

Placental abnormalities can also be found in stillbirths without evidence of impaired growth. Symphysis-fundal height, used to estimate serial fetal growth at prenatal visits, has a low sensitivity and specificity for detecting SGA infants. Placental factors such as a placental abruption are found in 6% of stillbirths[19].

Diabetes increases stillbirth risk up to 5 times. The highest rate for stillbirth is in the 38th week for type 1 diabetes and in the 39th week for type 2 diabetes, with type 2 diabetes, the risk for stillbirth was two-fold higher if the birth weight was over the 95th%[20].

Non-obese women have a stillbirth risk of 5.5/1000. The risk is 8/1000 for a BMI of 30-39.9 kg/m^2 and 11/1000 for a BMI > 40 kg/m^2. Overweight women with BMI 25-29.9 kg/m^2 have an OR 1.37 (95% CI: 1.02-1.85), and class IV obese women with BMI > 50 kg/m^2 have an OR 5.04 (95% CI: 1.79-14.07)[21].

The risk of stillbirth is augmented by advanced maternal age due to an increased risk for aneuploidy and medical complications of pregnancy. Even after controlling for these risk factors, maternal age over 35 has an increased risk for stillbirth, which is accentuated by nulliparity. At age 40, the risk is 1/116 for a nullipara and 1/304 for a multipara[22].

Smoking tobacco increases the risk of stillbirth, both antepartum and intrapartum (15/1000). The odds ratio for stillbirth associated with alcohol use is 1.36 (95% CI: 1.05-1.76). There is a 1.5 OR for stillbirth associated with opioid use in pregnancy (95% CI: 1.3-1.8) and a 5.1 OR for stillbirth associated with methamphetamine use in pregnancy (95% CI: 3.7-7.2)[23].

Chronic hypertension increases stillbirth risk 3-times. Hypertension is a common condition that complicates pregnancy; incidence is 9.6% (95% CI: 6.9-12.1)[19].

Congenital defects, defined as physical or biochemical abnormalities, occur in 1/33 of pregnancies and are associated with a higher risk of stillbirth. The detection of congenital defects prenatally may impact antenatal surveillance policy in hopes of reducing the risk of stillbirth. Stillbirth risk is 11/1000 for bladder exstrophy and 490/1000 for the limb-body-wall complex; even for isolated congenital defects not affecting major organs, the risk of stillbirth increases. The risk for stillbirth associated with cleft lip with cleft palate is 10/1000, transverse limb deficiencies are 26/1000, longitudinal limb deficiencies are 11/1000, and amniotic band-associated limb defects are 110/1000. The increased stillbirth risk for sacral agenesis is 13/1000, isolated spina bifida 24/1000, and holoprosencephaly 30/1000 may be underestimated due to failure to account for elective termination of pregnancy[24].

Infection as a cause of stillbirth may be underrepresented because signs and symptoms of infection are often undetected, and evaluation for infection is often not conducted. Stillbirth related to infection varies from 5% to 22%. In developed countries, infection accounts for 19% of stillbirths before 28 weeks, but only 2% of stillbirths at term. When an infection is the cause of stillbirth, spontaneous preterm delivery is common. A US cohort study demonstrated infection as the probable or possible cause of stillbirth in 12.9% of cases. Predominant bacteria cultured included *Escherichia coli* 29%, group B *Streptococcus* 12%, *Enterococcus* 12%, and rarely *Listeria monocytogenes*. The placental evaluation found evidence of infection in 99% of culture-positive cases. Non-bacterial organisms causing stillbirth included cytomegalovirus 8%, parvovirus 3%, syphilis 2%, and herpes simplex virus 2%. Infection is unlikely the cause of stillbirth unless it results in significant autopsy or placental findings. Serologic screening for toxoplasmosis, chlamydia, rubella, or herpes is usually not indicated when these infections are not detected on placental or autopsy examination. Malaria should be screened for in endemic areas. Human immunodeficiency virus increases the risk of stillbirth[25].

Antiphospholipid syndrome (APS), in addition to thrombotic events, has been linked to stillbirth since 1984. To diagnose APS, one clinical criterion plus one laboratory criterion must be met. The anticardiolipin antibodies, anti-β2 glycoprotein 1 antibody, or the lupus anticoagulant, have to be above the 99th% and present on two occasions at least 12 weeks apart. In some cases, these antibodies may not be detected due to the limitations of current assays. These antibodies may be found in 5% of people without clinical symptoms. Stillbirth risk is highest when all three laboratory criteria are positive and lowest when the lupus anticoagulant is negative. Recently, anti-β2 glycoprotein 1 domain-1 antibody has been linked to late pregnancy morbidity. Lupus anticoagulant positivity at baseline was associated with an odds ratio of 8.3 (95% CI: 3.6-19.3) for adverse pregnancy outcomes[26].

Intrahepatic cholestasis may affect 0.1%-2% of pregnant women. Cases of fetal arrhythmias have been documented in pregnancies complicated by cholestasis. Most of these stillborns have signs of acute anoxia but no signs of growth restriction or long-term uteroplacental compromise[27].

Conclusion

The prognosis for infants with MAS depends on the severity of the condition and the promptness of medical intervention. Most infants with mild-to-moderate MAS recover with appropriate care and do not experience long-term complications. However, severe cases can be life-threatening and may result in long-term respiratory issues or other health problems. Timely medical attention and support are crucial in managing MAS. The goal of antepartum surveillance is to identify any issues promptly so that appropriate medical interventions can be initiated to optimize the health of the fetus and the expectant mother. This close monitoring can help reduce the risk of complications, including stillbirth and perinatal asphyxia, and improve the chances of a healthy pregnancy and delivery.

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References

1. Official Mexican Guideline Nom-007-SSA2-2016, for the Care of Women During Pregnancy, Childbirth and Puerperium, and of the Newborn Person. Mexico: Ministry of Health; 2016. Available form: https://www.gob.mx.nom-007-ssa2-2016.pdf
2. Clinical Guidelines for Prenatal Control IMSS 028-08. Mexico: Ministry of Health; 2009. Available from: https://www.calameo.com/gpc-control/renatal/con/enfoque/de/riesgo
3. Clinical Practice Guideline Prenatal Control with Patient-Centered Care, Evidence, and Recommendations. Master Catalog of Clinical Practice Guidelines. Mexico: Mexican Institute of Social Security; 2017. Available from: https://imss.gob.mx/sites/all/statics/guiasclinicas/028ger.pdf
4. Bhandari I, Karmacharya-Malla K, Chaudhary BR, Ghimire P. Early outcome of neonates admitted with meconium aspiration syndrome. J Nepal Health Res Counc. 2023;21:165-9.
5. Kasahara M, Koshida S, Tokoro S, Katsura D, Tsuji S, Murakami T, et al. Potential prevention of stillbirth caused by placental abruption: a regional population-based study in Japan. J Matern Fetal Neonatal Med. 2024;37:2321485.
6. Hammer L, Heazell AE, Povey A, Myers JE, Thompson JM, Johnstone ED. Assessment of the association between ambient air pollution and stillbirth in the UK: results from a secondary analysis of the MiNESS case-control study. BJOG. 2024;131:598-609.
7. Yang S, Tan Y, Mei H, Wang F, Li N, Zhao J, et al. Ambient air pollution the risk of stillbirth: a prospective birth cohort study in Wuhan, China. Int J Hyg Environ Health. 2018;221:502-9.
8. Alhousseini A, Farr C, Ogunyemi D, Wharton K, Fawaz A, Bazzi N, et al. Delivery of a fetus with a non-reassuring status is associated with significant maternal morbidity. Gynecol Obstet Invest. 2023;88:359-65.
9. Melaet R, de Vries IR, Kok RD, Guid-Oei S, Huijben IA, van Sloun RJ, et al. Artificial intelligence based cardiotocogram assessment during labor. Eur J Obstet Gynecol Reprod Biol. 2024;295:75-85.
10. Turner JM, Flenady V, Ellwood D, Coory M, Kumar S. Evaluation of pregnancy outcomes among women with decreased fetal movements. JAMA Netw Open. 2021;4:e215071.
11. Di Pasquo E, Fieni S, Chandraharan E, Dall'Asta A, Morganelli G, Spinelli M, et al. Correlation between intrapartum CTG findings and interleukin-6 levels in the umbilical cord arterial blood: a prospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2024;294:128-34.
12. Jia YJ, Chen X, Cui HY, Whelehan V, Archer A, Chandraharan E. Physiological CTG interpretation: the significance of baseline fetal heart rate changes after the onset of decelerations and associated perinatal outcomes. J Matern Fetal Neonatal Med. 2021;34:2349-54.
13. Pereira S, Lau K, Modestini C, Wertheim D, Chandraharan, E. Absence of fetal heart rate Cycling on the Intrapartum Cardiotocograph (CTG) is associated with intrapartum pyrexia and lower Apgar scores. J Matern Fetal Neonatal Med. 2022;35:7980-5.
14. Devane D, Lalor JG, Daly S, McGuire W, Cuthbert A, Smith V. Cardiotocography versus intermittent auscultation of fetal heart on admission to labour ward for assessment of fetal wellbeing. Cochrane Database Syst Rev. 2017;1:CD005122.
15. Sharma B, Aggarwal N, Suri V, Siwatch S, Kakkar N, Venkataseshan S. Facility-based stillbirth surveillance review and response: an initiative towards reducing stillbirths in a tertiary care hospital of India. J Perinat Med. 2022;50:722-8.
16. Sharma B, Lahariya C, Majella MG, Upadhyay A, Yadav S, Raina, A, et al. Burden, differentials and causes of stillbirths in India: a systematic review and meta-analysis. Indian J Pediatr. 2023;90:54-62.
17. Valiño N, Giunta G, Gallo DM, Akolekar R, Nicolaides KH. Biophysical and biochemical markers at 30-34 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound Obstet Gynecol. 2016;47:194-202.
18. Bukowski R, Hansen NI, Pinar H, Willinger M, Reddy UM, Parker CB, et al. Altered fetal growth, placental abnormalities, and stillbirth. PLoS One. 2017;12:e0182874.
19. Zile I, Ebela I, Rumba-Rozenfelde I. Maternal risk factors for stillbirth: a registry-based study. Medicina (Kaunas). 2019;55:326.
20. Mackin ST, Nelson SM, Wild SH, Colhoun HM, Wood R, Lindsay RS, et al. Factors associated with stillbirth in women with diabetes. Diabetologia. 2019;62:1938-47.
21. Jacob L, Kostev K, Kalder M. Risk of stillbirth in pregnant women with obesity in the United Kingdom. Obesity Res Clin Pract. 2016;10:574-9.
22. Urhoj SK, Andersen PK, Mortensen LH, Davey Smith G, Nybo Andersen AM. Advanced paternal age and stillbirth rate: a nationwide register-based cohort study of 944,031 pregnancies in Denmark. Eur J Epidemiol. 2017;32:227-34.
23. Miller CB, Wright T. Investigating mechanisms of stillbirth in the setting of prenatal substance use. Acad Forensic Pathol. 2018;8:865-73.
24. Heinke D, Nestoridi E, Hernandez-Diaz S, Williams PL, Rich-Edwards JW, Lin AE, et al. Risk of stillbirth for fetuses with specific birth defects. Obstet Gynecol. 2020;135:133-40.
25. Page JM, Bardsley T, Thorsten V, Allshouse AA, Varner MW, Debbink MP, et al. Stillbirth associated with infection in a diverse U.S. cohort. Obstet Gynecol. 2019;134:1187-96.
26. Chighizola CB, Pregnolato F, Andreoli L, Bodio C, Cesana L, Comerio C, et al. Beyond thrombosis: anti-β2GPI domain 1 antibodies identify late pregnancy morbidity in anti-phospholipid syndrome. J Autoimmun. 2018;90:76-83.
27. Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology. 2014;59:1482-91.

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REVIEW ARTICLE

Hernia uterine inguinale as an intraoperative diagnosis of male pseudohermaphroditism: case report

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Abstract

Persistent Müllerian duct syndrome is a very rare form of pseudohermaphroditism characterized by the presence of structures deriving from persistent Müllerian duct in a patient phenotypically and occasionally genotypically expressed as a normal male. Utero Inguinal Hernias are a rare entity, which in the female population reaches 1% of incidence. However, in the male population, it is directly associated with abnormalities of sexual differentiation. We present the exceptional case of a male patient with no previous diagnosis of intersexuality who is scheduled for a right inguinal repair of a hernia. During the operative management, structures compatible with the uterus, fallopian tubes, and ovaries were identified in the hernial sac. Reduction of the hernial content to the peritoneal cavity was performed and the inguinal defect was resolved with placement of a prosthetic mesh by Lichtenstein technique.

Keywords: *Inguinal hernia. Disorders of sexual development 46 XY. Male infertility. Herniorrhaphy.*

Introduction

Uterine inguinale hernias are a rare entity, reaching 1% of incidence in the female population. However, in the male population, it is directly associated with abnormalities of sexual differentiation or intersex conditions such as male pseudohermaphroditism or also called Type I Müllerian duct persistence syndrome, with no more than 150 cases described worldwide. Intersex states usually have an early manifestation that allows multidisciplinary intervention, but cases of silent courses are reported in phenotypically male patients whose only clinical signs are infertility or cryptorchidism and whose diagnosis is made accidentally during an inguinal hernioplasty or an orchidopexy[1,2]. The following is the case of an adult male patient, infertile, with right homolateral cryptorchidism, who was scheduled on an outpatient basis for a right

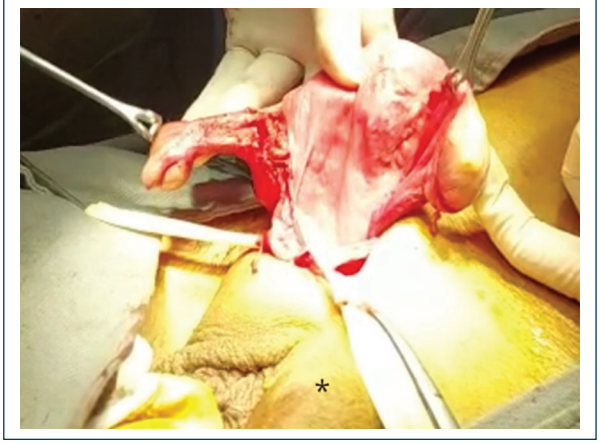

Figure 1. Inguinotomy and content of hernial sac compatible with Müllerian structures (uterus, fallopian tubes, and ovaries). Caudally male reproductive structures, testicles, and penis (*).

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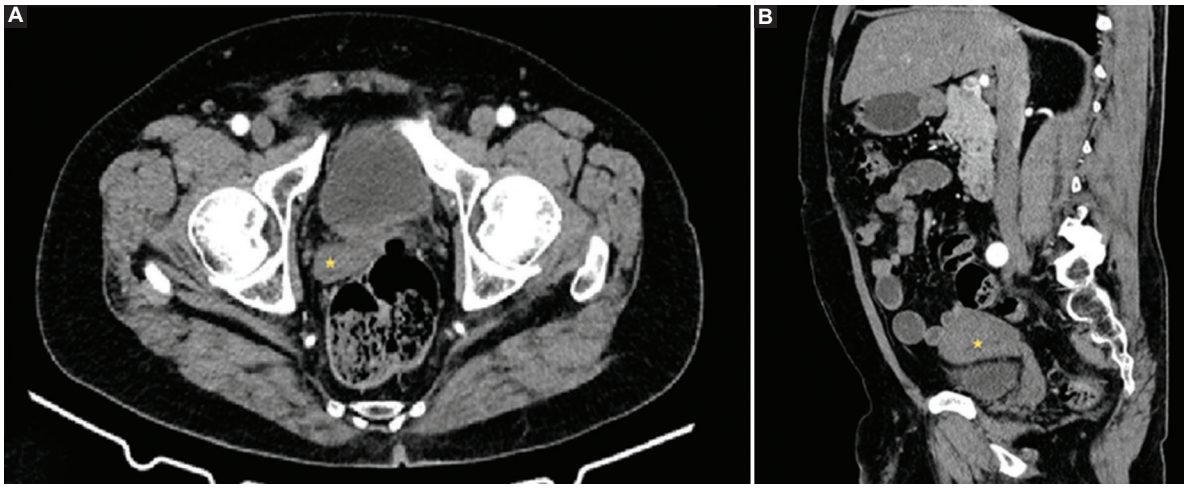

Figure 2. Contrast abdominal computed tomography in arterial phase in axial and sagittal planes
A and **B**: respectively showing evidence of muscular soft tissue density mass (30 HU) in retrovesical space in contact with pelvic structures (yellow star).

inguinal hernioplasty and whose intraoperative findings described the presence of macroscopically Müllerian structures such as uterus, fallopian tube and ovaries running inside the operated inguinal hernial sac.

Case report

We present the case of a 64-year-old male patient, infertile, with a long-standing right inguinoscrotal hernia. He had a soft tissue ultrasound where an inguinal and umbilical hernial defect was documented with no additional findings. The patient also presented a diagnosis of right homolateral cryptorchidism and nodular images in the right testicle with normal Doppler analysis. A right inguinal hernioplasty was scheduled on an outpatient basis. The surgical approach was performed through an oblique inguinotomy incision. An indirect inguinoscrotal hernia with sliding of contents into the hernia sac compatible with structures macroscopically compatible with the uterus, fallopian tubes, and involuted ovaries was observed (Fig. 1).

Reduction of the contents of the inguinal hernial sac and hernioplasty with the placement of prosthetic mesh with the Lichtenstein technique was performed. In the post-operative period, the patient had no complications and underwent an axial tomography of the abdomen and total pelvis which confirmed the intraoperative findings described above (Fig. 2A and B).

Discussion

Persistent Müllerian duct syndrome (PMDS) is a very rare form of pseudohermaphroditism characterized by the presence of structures deriving from persistent Müllerian duct in a patient phenotypically and occasionally genotypically expressed as a normal male[3-5]. It was initially described by Nilson in 1939, and since then approximately 150 related cases have been published[6,7]. To have an appropriate male differentiation, the production of anti-Müllerian Hormone is needed, which induces the regression of the Müllerian structures, allowing the differentiation of the Wolf's ducts and the formation of the vas deferens, epididymis, and seminal vesicles, which together with testosterone allow the adequate organization of the male reproductive system[8,9]. Its etiology is not entirely clarified; however, it is related to a lack of synthesis and release of Müllerian inhibitory factor (MIF) or its receptor (MIFr). MIF is secreted by Sertoli cells in fetal tissue from the 7th gestational week and is responsible for the regression of the Müllerian ducts in male fetuses. These patients are usually of 46 XY karyotype and besides presenting infertility or cryptorchidism, they can be asymptomatic until they are taken for surgical intervention and accidentally realize the recognition of organs macroscopically similar to the uterus and fallopian tubes, exceptionally during an inguinal herniorrhaphy or an orchidopexy[10-12]. The presence of macroscopically uterine-like structures, with an ovary, in an inguinal hernial sac is due to the persistence of the paramesonephric duct in the male also called as PMDS type I[13-15]. In patients with true hermaphroditism, both ovarian and testicular tissue will be found in one or both gonads. In female patients classified as pseudohermaphrodites, the gonads are ovarian, but the reproductive

organ has a masculine tendency. Pseudohermaphroditism may not be identified until puberty and even, as in the current clinical case, in the context of an elderly patient with an active sexual life, sometimes even with preserved reproductive capacities[16]. Currently, there are reports of laparoscopic management of male pseudohermaphroditism in pediatric patients with exeresis of the Müllerian structures, justified by the risk of malignization and infertility[17,18]. In cases of concomitant cryptorchidism, a division of the intra-abdominal uterine tissue attached to the testicle is considered to allow an adequate downward trajectory into the tunica vaginalis and then the remaining Müllerian structures are resected by an anterior inguinotomy[19].

Conclusion

Müllerian duct persistence syndrome Type I is described as an extremely rare pathology that is generally diagnosed intraoperatively when performing orchidopexy or inguinal hernioplasty in patients with phenotypically male characteristics. Given that preoperative findings of physical examination and ultrasonography of the inguinal region, whose ability to discriminate the structures contained in the hernial sac is precarious, it is unlikely that a preoperative identification of the pathology is performed in the patient with silent intersex clinic[20]. In the current case, through outpatient programming of a right inguinal hernioplasty, intraoperative identification of the Müllerian structures, which were not excised in the first surgical stage, was carried out. The defect of the indirect inguinal hernia was repaired by inserting a prosthetic mesh through the Lichtenstein technique without complications and was sent to complement studies with the genetics and endocrinology service, as well as to follow-up controls by the general surgery service. We consider of great importance to take into account that, in spite of being a very rare pathology, it can mean a therapeutic challenge for the multidisciplinary group in charge during the performance of an inguinal hernioplasty in men.

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Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

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References

1. Enriquez D, Rittler M, Pomata J, Brunetto O. Genitales ambiguos: incidencia, presentación de un caso clínico, orientación diagnóstica y recomendaciones. Rev Hosp Mat Inf Ramón Sardá. 1998;17:25-30.
2. Bonarriba Beltrán CR, Fernández L, Alonso D, García-Montes F. Male Pseudohermaphroditism: ambiguous genitalia. Arch Esp Urol. 2016;69:444-5.
3. Carvajal López A, Naranjo Aristizabal FA, Flórez Arango N, Carvajal López AM, Valencia Gómez YM. Hernia inguinal con útero y anexos como contenido del saco herniario: reporte de caso y revisión de la literatura. Rev Hispanoam Hernia. 2017;5:173.
4. Farina M, Espinola C, Bernal M, Villalba J. Hernia uterina inguinal. Cir Esp. 2007;82:247-8.
5. Isurugi K. Male pseudohermaphroditism. Jpn J Urol. 1994;85:1189-212.
6. Nilson O. Hernia uteri inguinalis bein Manne. Acta Chir Scand. 1939;83:231-49.
7. Zdravković D, Milenković T, Sedlecki K, Guć-Sćekić M, Rajić V, Banićević M. Causes of ambiguous external genitalia in neonates. Srp Arh Celok Lek. 2001;129:57-60.
8. Dávila SR, Ordóñez EA, García DI, Mondragón ME. Pseudohermafroditismo masculino. An Méd Asoc Méd Cent Méd ABC. 2007;52:148-51.
9. Nimkarn S, Likitmaskul S, Sangacharoenkit P, Pathomvanich A, Sawathiparnich P, Wacharasindhu S, et al. Ambiguous genitalia: an overview of 22 years experience and the diagnostic approach in the Pediatric Department, Siriraj Hospital. J Med Assoc Thail Chotmaihet Thangphaet. 2002;85:S496-505.
10. Jha BK, Garg R, Soni RK, Singh K, Aneja H. Hernia uteri inguinale: a travesty of nature. Indian J Surg. 2019;81:192-4.
11. Ponnatapura J. Hernia uteri inguinalis in ovotesticular disorder of sexual differentiation: a rare complication and role of imaging. Indian J Radiol Imaging. 2018;28:41-4.
12. Hughes IA, Williams DM, Batch JA, Patterson MN. Male pseudohermaphroditism: clinical management, diagnosis and treatment. Horm Res. 1992;38:77-81.
13. Gujar NN, Choudhari RK, Choudhari GR, Bagali NM, Mane HS, Awati JS, et al. Male form of persistent Mullerian duct syndrome type I (hernia uteri inguinalis) presenting as an obstructed inguinal hernia: a case report. J Med Case Reports. 2011;5:586.
14. Joshi RR, Rao S, Desai M. Etiology and clinical profile of ambiguous genitalia an overview of 10 years experience. Indian Pediatr. 2006;43:974-9.
15. Al-Maghribi H. Congenital adrenal hyperplasia: problems with developmental anomalies of the external genitalia and sex assignment. Saudi J Kidney Dis Transplant. 2007;18:405-13.
16. Özbey H, Etker S. Disorders of sexual development in a cultural context. Arab J Urol. 2013;11:33-9.
17. Turaga KK, St. Peter SD, Calkins CM, Holcomb GW, Ostlie DJ, Snyder CL. Hernia uterus inguinale: a proposed algorithm using the laparoscopic approach. Surg Laparosc Endosc Percutan Tech. 2006;16:366-7.
18. Yuksel B, Saygun O, Hengirmen S. Persistent müllerian duct syndrome associated with irreducible inguinal hernia, bilateral cryptorchidism and testicular neoplasia: a case report. Acta Chir Belg. 2006;106:119-20.
19. Sherwani AY, Shah AQ, Wani AM, Bashir AC, Bashir AK, Sofi FA, et al. Hysterectomy in a male? A rare case report. Int J Surg Case Rep. 2014;5:1285-7.
20. Ramanathan S, Palaniappan Y, Sheikh A, Ryan J, Kielar A. Crossing the canal: looking beyond hernias - spectrum of common, uncommon and atypical pathologies in the inguinal canal. Clin Imaging. 2017;42:7-18.

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CLINICAL CASE

Amyand hernia: an incidental finding and literature review

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Abstract

Amyand hernia (AH) is an uncommon pathology occurring in any age range. The symptoms are those of a complicated or uncomplicated inguinal hernia. Diagnosis is intraoperative and may be accompanied by ultrasound and computed tomography. A 56-year-old male presented to the clinic for right inguinal hernia. He underwent right inguinal plasty and a vermiform appendix was found within the contents of the hernia sac. AH with appendicitis or without appendicitis is often a rare incidental finding, so its treatment is not well established and is a challenging decision for the surgeon.

Keywords: *Amyand hernia. Inguinal hernia. Acute appendicitis, Appendectomy.*

Introduction

In 1735, Claudius Amyand discovered a vermiform appendix (VA) within an inguinal hernia in an 11-year-old boy and performed appendectomy through the inguinal incision; hence the name Amyand hernia (AH). It is estimated to be an extremely rare pathology with an incidence of approximately 1% of inguinal hernia cases[1]. Its symptoms are non-specific, as it can manifest symptoms of an uncomplicated inguinal hernia up to symptoms of a complicated inguinal hernia when acute appendicitis is presented[2]. Diagnosis is usually made intraoperatively; however, nowadays, there are suggestive data in imaging methods such as computed tomography (CT) and ultrasound (USG). Because it is a rare entity, treatment has not been well established and often depends on the patient's condition (age and comorbidities), surgical findings, and the surgeon's criteria[3].

The aim of this article is to present a clinical case of incidental AH without evidence of appendicitis, as well as a review of the literature.

Case history

A 58-year-old male patient attended general surgery for right inguinal hernia. The patient reported an increase in volume of 1 month's evolution, denies pain in the inguinal region, and denies data of intestinal obstruction. Chronic degenerative history denied, non-pathological personal history, and positive ethylism. Surgical history: left inguinal plasty with mesh + left orchiectomy in February 2023. Physical examination revealed a tumor in the right inguinal region with increase on Valsalva manoeuvre, painless on palpation, reducible. Pre-surgical laboratory tests were performed, all within normal parameters, and elective right inguinal plasty surgery was scheduled. The patient underwent this surgery by making an oblique incision in the right inguinal region, during the transoperative period a 6 × 3 cm hernia sac was observed and during dissection the 6 × 1 cm VA was found with no evidence of inflammation (Figs. 1 and 2); it was decided to perform an appendectomy using the pouchet technique (Fig. 3) and subsequently, the McVay technique was

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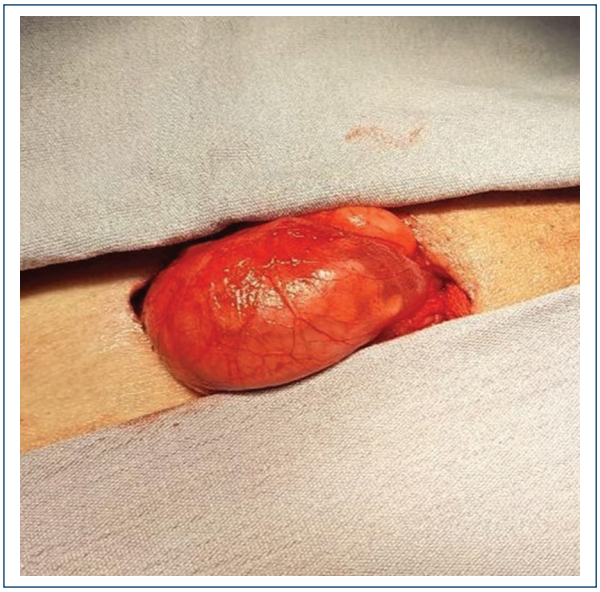

Figure 1. Inguinal hernial sac with intestinal content and omentum.

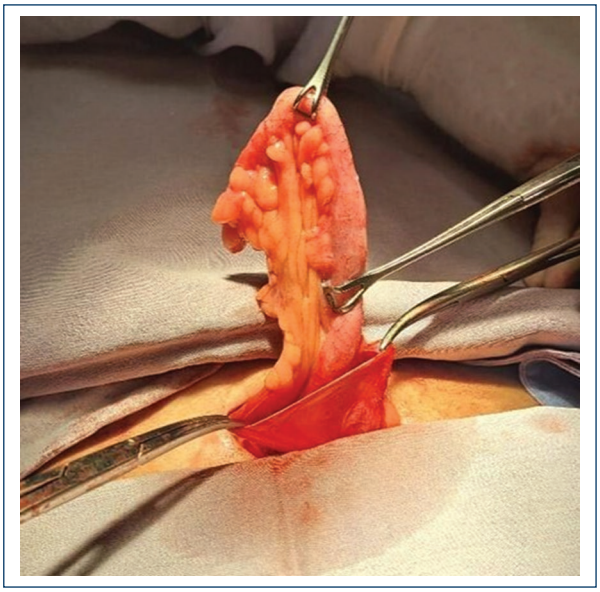

Figure 2. Vermiform appendix without signs inflammation extracted from the inguinal hernia.

used to repair the hernia. The patient remained in hospital for 2 days with antibiotic therapy and analgesia, with no signs of complications.

Discussion

Abdominal hernias are everyday pathologies in the surgeon's practice, and of these, the most common is the inguinal hernia[4,5]. HA is an inguinal hernia containing the VA, with an estimated incidence ranging from 0.19% to 1.7%[1]. An inflamed VA within the inguinal hernia is a rarer entity with an estimated incidence of 0.07-0.13%. Its presentation occurs in any age group with reported cases ranging from 4 days to 92 years, although some reviews and authors state that there is a bimodal distribution, the former in infants and the latter in > 70 years[2,6]. This occurs because in the pediatric population, there is a persistence of the vaginal process, and in the third age population, there is an enlargement of the internal inguinal ring. It is more common in men than women, and the presentation is more common on the right side due to the anatomical position, although cases reported on the left side are usually related to intestinal malrotation, situs inversus or mobile cecum[6,7].

The pathophysiology of appendicitis in AH is unclear; there have been theories that agree on the migration of the VA into the inguinal canal, and therefore, there are four possible outcomes: incarceration by the internal inguinal ring and inflammation; development of adhesions evolving into an irreducible, injury-prone hernia; increased intra-abdominal pressure leading to appendiceal compression and obstruction of the appendix; finally, a non-reducible appendix causing venous stasis, bacterial overgrowth, and translocation[6].

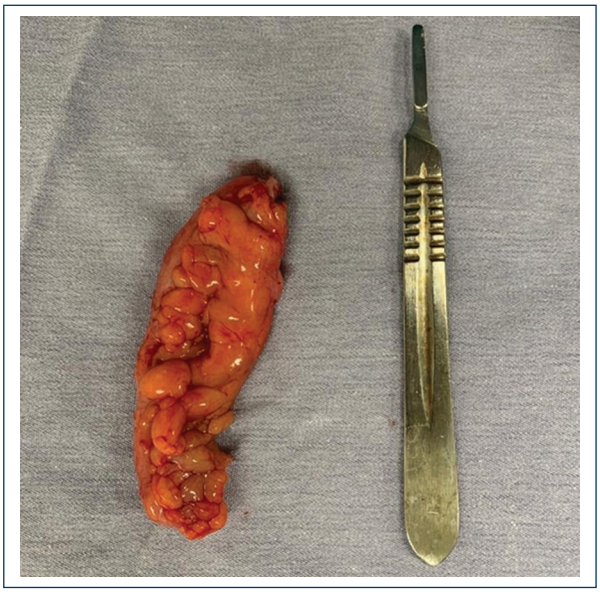

Figure 3. Vermiform appendix size 6 × 1 cm, resection with pouchet technique.

Detecting an AH is clinically challenging because the signs and symptoms are non-specific. It may present as

a painful or painless lump in the inguinal region, which increases with the Valsalva maneuver and may be reducible or irreducible, and yet with these data, the first thing we think of is an inguinal hernia. On the other hand, an acute process may manifest with an irreducible tumor, pain in the inguinal region, erythema, and edema, but this would make us think of an irreducible or incarcerated inguinal hernia, and differential diagnoses such as acute appendicitis, orchiepididymitis, hydrocele, and testicular torsion[2,5,6].

Diagnosis is mostly incidental and intraoperative; the VA can be found inflamed or non-inflamed; the reason why imaging studies are not performed is that complicated and uncomplicated inguinal hernias are regularly clinically diagnosed. USG is an operator-dependent imaging study, but it is accessible and inexpensive; findings that raise suspicion of AH, non-compressible tubular structure in the hernial sac in connection with the cecum and wall thickening can be found. CT is the imaging study of choice for better visualisation; an AH is suspected when the cecum is closed to the internal inguinal ring, and there is evidence of a thickened appendix, and tubular structure in the hernial sac[3,6].

The Losanoff and Basson classification proposes the management of AH in different clinical situations. For type 1 AH, the appendix is normal and reduction or appendectomy (depending on age), hernioplasty with mesh is advised. Type 2 is acute appendicitis located in the sac, with management of appendectomy and endogenous repair with or without biological mesh. Type 3 is acute appendicitis with sepsis beyond the hernial sac, with laparotomy appendectomy and endogenous repair without mesh placement. Type 4 is acute appendicitis and other abdominal pathology; management depends on the clinical scenario and hernia repair can be performed at a later stage[8].

At present, there are many dilemmas regarding the use of mesh for hernia repair and whether or not appendectomy should be performed in a VA without inflammation.

Appendectomy is justified in the case of inflammation and when a left AH is presented to avoid atypical presentations and diagnostic delay leading to complications in the future. Nowadays, it is unclear whether there is any benefit to prophylactic appendectomy. Some authors recommend appendectomy for everyone regardless of the condition of the appendix and patient characteristics. Other literature says that performing appendectomy in children is not recommended because it is a lymphoid organ and has an impact on their immune system. On the other hand, manipulating the VA to return it to the abdominal cavity can cause appendicitis secondary to manipulation and increase the risk of hernia recurrence[1,6,9].

The use of mesh for hernia repair is another point of controversy in the medical literature. Based on the afore mentioned classification, the use of synthetic mesh is recommended only when an appendectomy is not performed because the mesh must be placed in a clean cavity to reduce the risk of infection, and performing appendectomy turns a clean surgery into a clean-contaminated one. Systematic reviews have shown that the risk of infection with synthetic mesh is minimal, so the use of synthetic mesh is advised even when appendectomy is performed or there is evidence of appendicitis without perforation[6,9].

The World Society for Emergency Surgery published guidelines on emergency repair of complicated abdominal hernias in 2020. The section on complicated or strangulated inguinal hernia establishes the approval of using synthetic mesh for hernia repair even in cases of intestinal resection, in our case, it can be applied for AH; with an acceptable morbidity rate and few sequelae related to surgical site infection. The use of synthetic mesh is only contraindicated when the field is considered contaminated-dirty (effusion, peritonitis or intestinal perforation); in this case, primary repair or use of biological mesh can be considered, although it is difficult to access due to its high cost[10].

Mortality of appendicitis in AH depends on late diagnosis, and the extent of sepsis can reach up to 30%; however, it has decreased with the new era of antibiotics and early surgical management by up to 5%[4,5].

Conclusion

AH is undoubtedly a disease with a very low incidence, and therefore, it is difficult to establish guidelines for its treatment. At present, the use of synthetic mesh for hernia repair is advised. However, the decision will always depend on the surgeon, surgical findings and clinical conditions of the patient. The best evidence we have are systematic reviews of clinical cases, therefore, an invitation is made to continue reporting this pathology to improve statistics and treatment guidelines.

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References

1. Gao Y, Zhang T, Zhang M, Hu Z, Li Q, Zhang X. Amyand's hernia: a 10-year experience with 6 cases. BMC Surg. 2021;21:315.
2. Kyang LS, See V, Nguyen H. Irreducible inguinal hernia and acute appendicitis: a case of Amyand's hernia. ANZ J Surg. 2020;90:2100-101.
3. Corvatta F, Rodriguez Santos F, Mazzini F, Fuente I. Amyand's hernia complicated with appendicitis. Rev Fac Cien Med Univ Nac Córdoba. 2021;78:330-3.
4. Assad MA, Boushal TA, Halawani ZW, Alruwaili RS, Alkuwaiti YH, Alghamdi AM, et al. Amyand hernia with acute appendicitis: a rare type of hernia. Cureus. 2021;13:e18720.
5. Aldosari DM, Alaboon NK, Mojammami MY, Aqeeli MO, Aldhafeeri OA, Theban AA, et al. Inguinal hernia containing an inflamed appendix: a case of Amyand hernia. Cureus. 2022;14:e21121.
6. Manatakis DK, Tasis N, Antonopoulou MI, Anagnostopoulos P, Acheimastos V, Papageorgiou D, et al. Revisiting Amyand's hernia: a 20-year systematic review. World J Surg. 2021;45:1763-70.
7. Diego Alonso E, Ayuso Velasco R, Cebrián Muiños C, Moreno Zegarra C, Liras Muñoz J. Left Amyand's hernia associated with omphalocele. Cir Pediatr. 2020;33:143-5.
8. Losanoff JE, Basson MD. Amyand hernia: a classification to improve management. Hernia. 2008;12:325-6.
9. Papaconstantinou D, Garoufalia Z, Kykalos S, Nastos C, Tsapralis D, Ioannidis O, et al. Implications of the presence of the vermiform appendix inside an inguinal hernia (Amyand's hernia): a systematic review of the literature. Hernia. 2020;24:951-9.
10. De Simone B, Birindelli A, Ansaloni L, Sartelli M, Coccolini F, Di Saverio S, et al. Emergency repair of complicated abdominal wall hernias: WSES guidelines. Hernia. 2020;24:359-68.

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CLINICAL CASE

Management of Allen II digital tip injury with cross flap in a specialized hand surgery center in Mexico

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Abstract

The cross-finger flap is a procedure used to cover defects in the proximal and middle phalanges by transposition of tissue from adjacent healthy fingers with good esthetic and functional results. We present the case of a patient who suffered a fingertip crush injury. Reconstruction of the digital tip of the fourth finger was performed with the digital cross flap of the third finger, taking and application of full thickness thenar skin graft, and was followed up for 2 months. The evolution was favorable, obtaining an adequate esthetic and functional result. This technique can be performed by surgeons without much experience in hand surgery.

Keywords: *Finger cruciate flap. Microsurgery. Reconstruction. Trauma.*

Introduction

Hand injuries account for 5-10% of all emergency department visits. There are different treatment modalities for certain fingertip injuries. Treatment options full-thickness skin grafting and both local and regional soft tissue, as well as skin flaps. All these options strive for the same common goals: the restoration of a sensitive and pain-free fingertip in a fully mobile finger of the maximum possible length, rapid healing, and a limited duration of functional disability[1,2]. The cross-finger flap is a 2-stage procedure first published by Gurdin and Pangman in 1950 but was used by Cronin as the original procedure since 1945. The flap is taken from the dorsum of an adjacent finger, usually at the level of the middle phalanx, and is used to cover a pulp amputation unfavorable to flying. The cross-toed flap is reliable and can cover extensive pulp loss from the fingers and thumb[3,4]. The main goal of treating this type of injury is to restore the length, appearance, function, and feel of the finger[5,6]. Possible complications that may occur in this type of procedure are scarring, deficiency in flexion and/or extension of the finger, stiffness, and loss of finger length[7,8].

Case presentation

A 49-year-old male patient with a history of smoking since he was 18 years old. His condition began on May 19, 2023, at 3 p.m. when he changed a tire on his car, the hydraulic jack lost its resistance and caused crushing trauma to the fourth finger of his right hand, he presented intense pain and bleeding, so he went to the emergency department. On physical examination: right hand with oval-shaped wound 22 mm high by 15 mm wide, irregular borders, located on the volar surface of the distal phalanx of the fourth finger, which began 2 mm above the flexion fold of the distal interphalangeal joint and ended in the dorsal region with loss of 40% of the plate and nail bed. He compromised skin and subcutaneous cellular tissue, full thickness (Wolfe-Krause), presented bone exposure of the head of the distal

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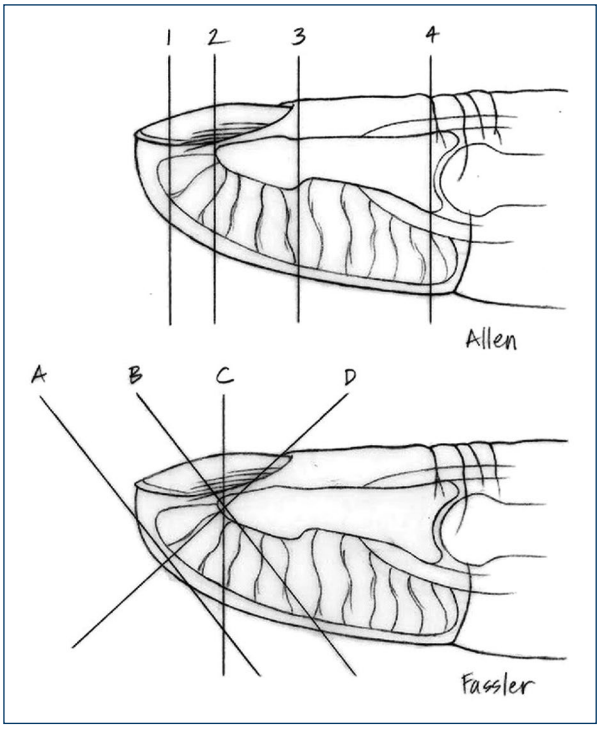

Figure 1. Allen and Fassler classification.

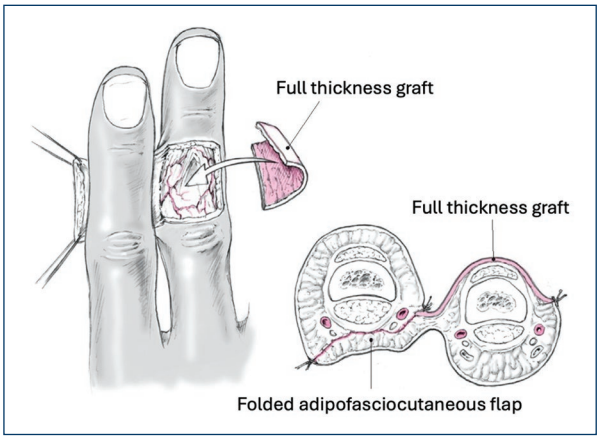

Figure 2. The flap donor area is covered by a full-thickness graft.

phalanx, and loss of skin coverage in the pulp. An X-ray was taken that showed oblique amputation proximal to distal, from volar to dorsal of the distal portion of the head of the distal phalanx of the fourth finger. The other fingers of the right hand are without compromise in motor skills and sensitivity. The diagnosis of trauma due to crushing of the fourth finger of the right hand and digital tip injury was integrated: Allen II, Fassler B (Fig. 1). Since no viable artery was located, it was decided to

Figure 3. Transoperative. Cross-flap fixation is observed to cover the loss of skin coverage of the digital tip of the fourth finger.

perform reconstruction of the digital tip of the fourth finger with a crossed digital flap of the third finger and the collection and application of a full thickness thenar skin graft. Under local median, radial, ulnar nerve block of the right hand with 2% lidocaine and epinephrine 1 mg/mL. Antisepsis was performed with chlorhexidine, sterile drapes were placed. The flap collection site was marked on the dorsal surface of the middle phalanx of the third finger with a 20 × 15 mm ulnar base. A graft was taken from the hypothenar region, a 25 × 20 mm marking was performed, and a full-thickness graft was lifted (Fig. 2). Cross-flap fixation was continued to cover the loss of skin coverage of the digital tip of the fourth finger, the cutaneous edges of the wound were remodeled into the digital tip of the fourth finger, it was fixed to the surrounding skin with simple stitches with 5-0 nylon and then a full-thickness fenestrated graft was placed at the flap donor site. It was set with single points with nylon 4-0 (Fig. 3). A tie-over was placed on the skin graft. Hemostasis and adequate skin coverage were confirmed. A resting flying splint was placed on the third and fourth fingers and the surgical procedure was terminated without complications (Figs. 4 and 5).

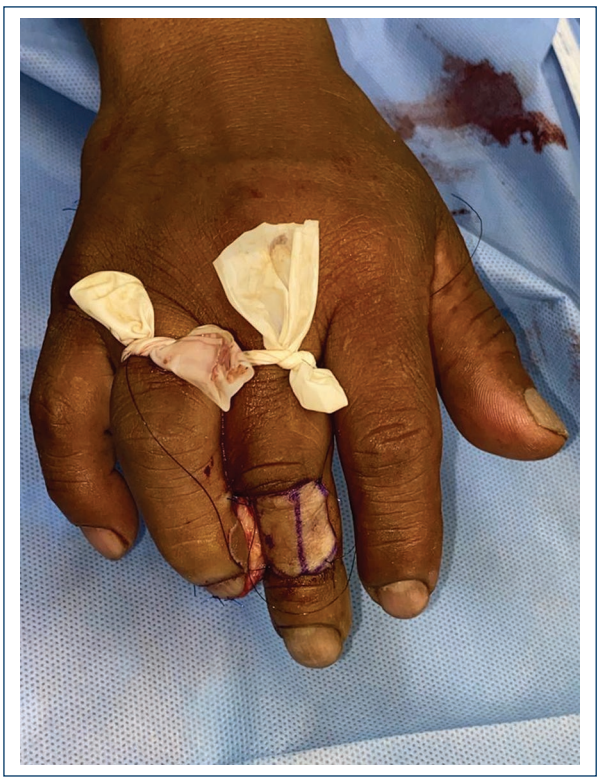

Figure 4. Immediate post-surgery of the dorsal aspect of the right hand. Adequate coloration of the flap is observed.

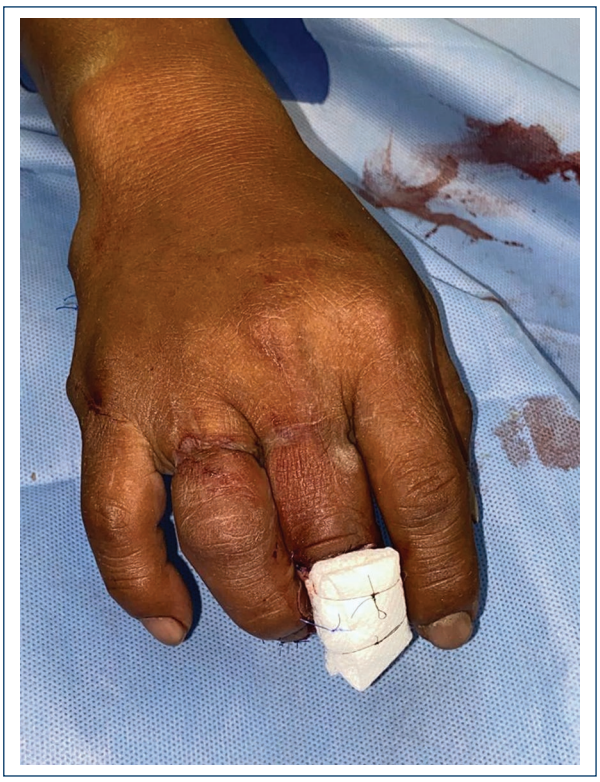

Figure 5. Immediate post-operative period. A resting flying splint was placed on the third and fourth fingers and the surgical procedure was terminated without complications.

The patient was kept under daily surveillance, and a favorable evolution was observed with adequate capillary filling and coloration of the donor area. When the patient had been in the case for 10 days, the cotton loop that compressed the graft was removed, and 90% integration was observed. 19 days after the initial procedure, the second intervention was performed under local anesthesia with a block of both fingers, which consisted of separating the third and fourth fingers by means of an incision in the flap, having good coloration and with a favorable evolution (Figs. 6 and 7). At his follow-up appointment 1 month after surgery, the patient was performing all his daily activities, without any limitation.

Discussion

The survival rate of reimplanted fingers is 45-65% in crush injuries, which is much lower compared to more common amputations. In avulsion lesions, it is often difficult to estimate the degree of tissue injury, even with the aid of a surgical microscope[5,6]. The main criticism of the cross-toed flap is that it is a 2-stage procedure, uses an uninjured finger, and can lead to stiffness of the donor finger. Although the flap is not an innervated flap, it has been shown that this flap can achieve good sensory recovery and good outcomes with younger patients. In addition, a handful of studies reported that they did not have a reduced range of motion of the donor finger. Flap division can be done safely at 2-3 weeks with very few reports of flap necrosis. It is postulated that early flap division can reduce the degree of stiffness in the donor and recipient finger[3,4]. Understanding the usefulness of various fingertip reconstruction options, as well as the advantages and disadvantages of each technique, is critical to maximizing patient outcomes with these complex lesions. The plan must be individualized. The knowledge, experience, and creativity of the treating surgeon are essential to achieve good functional and esthetic results and ensure high patient satisfaction[1,2]. Cross-flap flaps are an applicable method that can achieve an esthetic and functional appearance very close to normal; it can be performed by surgeons who o not have a large learning curve and by those who do not master microsurgery techniques[7,8].

Conclusion

The patient in our medical center presented a functional and esthetic final result. The technique mentioned

Figure 6. Post-surgical 19 days after the procedure and after finger separation.

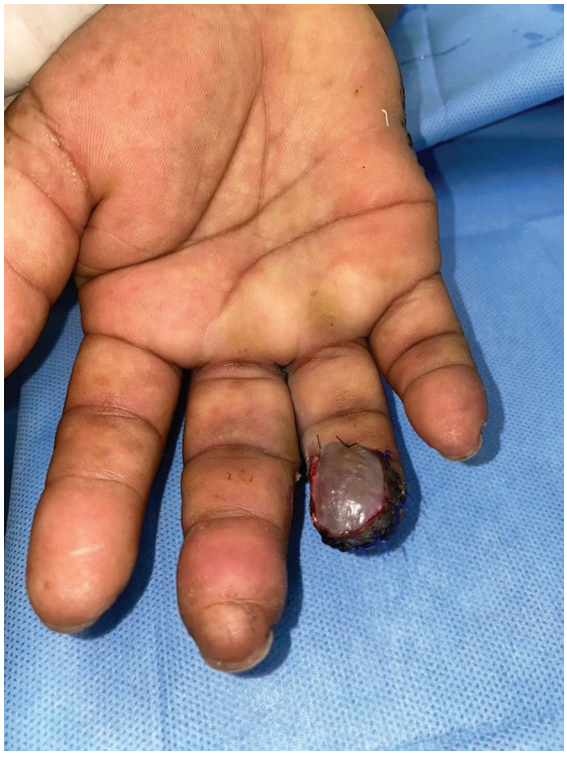

Figure 7. Post-surgical at 19 days after finger separation. The flap is observed with adequate coloration.

has been used for several years but due to its ignorance or lack of time by doctors, it is not practiced regularly. This good prognosis was obtained with comprehensive pre-operative planning since this type of lesion has a high success rate.

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References

1. Polatsch DB, Rabinovich RV, Beldner S. The double thenar flap: a technique to reconstruct 2 fingertip amputations simultaneously. J Hand Surg. 2017;42(4):396.e1-5.
2. van den Berg WB, Vergeer RA, van der Sluis CK, Ten Duis HJ, Werker PM. Comparison of three types of treatment modalities on the outcome of fingertip injuries. J Trauma Acute Care Surg. 2012;72(6):1681-7.
3. Lim JX, Chung KC. VY advancement, thenar flap, and cross-finger flaps. Hand Clin. 2020;36(1):19-32.
4. Kwon YJ, Ahn BM, Lee JS, Park YG, Ryu HJ, Ha YC. Reconstruction of two fingertip amputations using a double thenar flap and comparison of outcomes of surgery using a single thenar flap. Injury. 2017;48(3):481-5.
5. Chen S, Wen G, Cheng L, Chai Y. Mangled finger salvage using cross-finger revascularization. J Orthop Surg Res. 2020;15(1):104.
6. Chen SY, Wang CH, Fu JP, Chang SC, Chen SG. Composite grafting for traumatic fingertip amputation in adults: technique reinforcement and experience in 31 digits. J Trauma. 2011;70(1):148-53.
7. Mata-Sansores LE, Huerta-Rivadeneyra FJ. Colgajo cruzado de dedo. Cir Plást. 2023;33(1):50-4.
8. Atasoy E. The reverse cross finger flap. J Hand Surg. 2016;41(1):122-8.

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CLINICAL CASES

Recurrence of juvenile gigantomastia secondary to virginal hypertrophy: case report

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Abstract

Virginal mammary hypertrophy is a non-frequent benign medical affection, seen in teenagers, mainly during puberty. It consists on excessive bilateral or unilateral mammary growth, provoking physical and psychological dysfunctionality. Actually, there is no established algorithm for treatment, and the options available are based on published case reports. These options mainly include subcutaneous mastectomy, reduction mammoplasty and medical treatment with tamoxifen. In this article, we present the case of a prepubescent 12-year-old patient, who has not reached menarche yet. She presents excessive mammary growth suggestive of virginal mammary hypertrophy. She is addressed by a multidisciplinary group including oncologic surgeon, endocrinologist, gynecologist, and esthetic and reconstructive plastic surgeon. We decide to carry out surgical management, by performing a reduction mammoplasty with superior pedicle, obtaining satisfactory temporary results. Three months later, she presents new mammary growth, reaching 80% of the preoperatory volume. We decide surgical reintervention, carrying out a subcutaneous bilateral skin and nipple-sparing mastectomy, with immediate implant reconstruction as definitive treatment. Any case of juvenile gigantomastia merits multidisciplinary management,involving specialties such as endocrinology, psychology,pediatrics, and plastic and reconstructive surgery.

Keywords: *Gigantomastia. Mammary gland surgical reconstruction. Recurrence. Mammoplasty. Mastectomy.*

Introduction

Breast development during adolescence is an important factor in the transition to adulthood[1]. Breast overgrowth in adolescents was first described in 1910 by Henry Albert, who names this pathology as juvenile hypertrophy or virginal breast hypertrophy[2]. It is a rare, benign, and sporadic condition that affects adolescents, mainly during puberty.

There are different terms that describe this entity in the medical literature, such as virginal hypertrophy, juvenile gigantomastia (JG), or juvenile macromastia[3].

Within juvenile infant breast pathology, virginal breast hypertrophy accounts for 12.5% of all breast diseases in adolescents, while gigantomastia has a prevalence of 1 in 25,000 women and affects only 3.5/1000 adolescents[3]. The etiology is unknown; however, in the case of patients without comorbidities, with normal hormone levels, it is believed that it is hypersensitivity of the breast tissue to estrogen, resulting in diffuse breast growth[4].

Under this hormonal hypothesis, the use of drugs such as tamoxifen, danazol, or bromocriptine is justified, however, the safety and efficacy in the short and long term is unknown[5,6]. For this reason, the most recommended treatment in most cases is reduction mammoplasty, which is the option with the lowest recurrence rates[3].

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The most challenging aspect in the management of JM, or juvenile breast hypertrophy, is the effectiveness of definitive management, as its challenging natural history and refractory nature to surgery are well documented[7]. We report the case of a 12-year-old girl with bilateral juvenile breast hypertrophy of large dimensions, which was recurrent to the initial surgical management.

Case report

A 12-year-old female patient presented with JG with massive and progressive bilateral breast growth, with a 6-month evolution (Fig. 1). She presents local manifestations of breast overweight such as mastodynia. In addition, added symptoms such as neck pain and severe low back pain limit their interpersonal relationships, causing social distancing. The only important antecedent was pubarche at 11 years of age, without menarche. No other history of relevance to the condition, and he does not take medication on a regular basis.

On physical examination, an ectomorphic patient was found, weighing 45.7 kg and height of 1.52 m with a BMI of 19.8 kg/m^2. Measurement of bilateral nipple-to-nipple fork distance of 32 and 33 cm, nipple-to-inframammary fold distance of 15 cm. Disproportionately large, asymmetrical breasts, with Grade 4 ptosis, expanded, dilated subcutaneous veins, diffuse erythema, hard and firm consistency, no palpable masses, no nipple secretions or axillary lymphadenopathy.

Luteinizing hormone, follicle-stimulating hormone, prolactin, thyroid function tests, and cortisol within normal parameters. Breast ultrasound results without masses, only interstitial edema. We performed a bilateral mammoplasty surgery for the reduction of the supermedial pedicle, with a total breast resection of 6167 g (2906 g of right breast tissue and 3261 g of left breast tissue), integrating this resection to the equivalent of 13.3% of your total body weight (Figs. 2 and 3). The pathological report reported diffuse proliferation of the mammary stroma with abundant deposits of collagen, lymphocyte infiltrate, mast cells and extravasated erythrocytes. Dilated capillaries and ducts were identified, with a decrease in breast adipose tissue and the epithelial component. There were no morphological data of malignancy, confirming a diagnostic suspicion of virginal breast hypertrophy.

Her post-operative evolution was characterized by progressive breast growth, reaching gigantomastia in just 3 months after the previous breast reduction surgery.

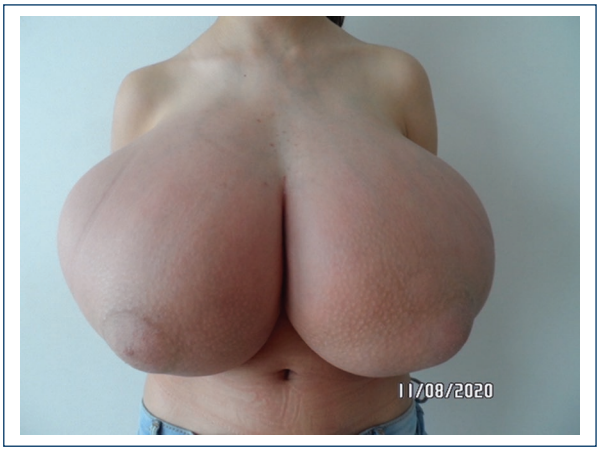

Figure 1. 11-year-old female, 11.08.2020 pre-operative.

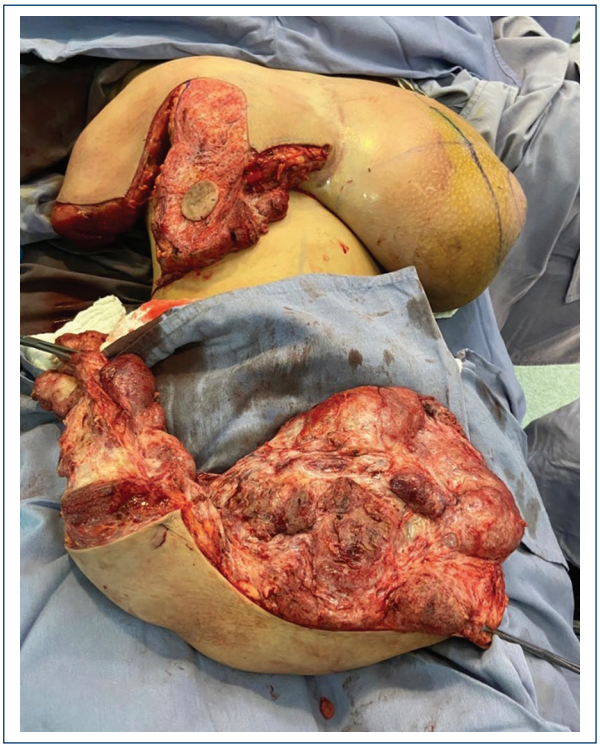

Figure 2. Surgical management with superomedial pedicle reduction mammoplasty. Right resection of 2906 g.

Therefore, it was decided to perform a bilateral subcutaneous mastectomy, with immediate breast reconstruction with subpectoral breast implants, and the use of a dermofatty flap to support and cover the breast implants in the lower breast pole. In this second mastectomy surgery, 2910 g was resected on the right side

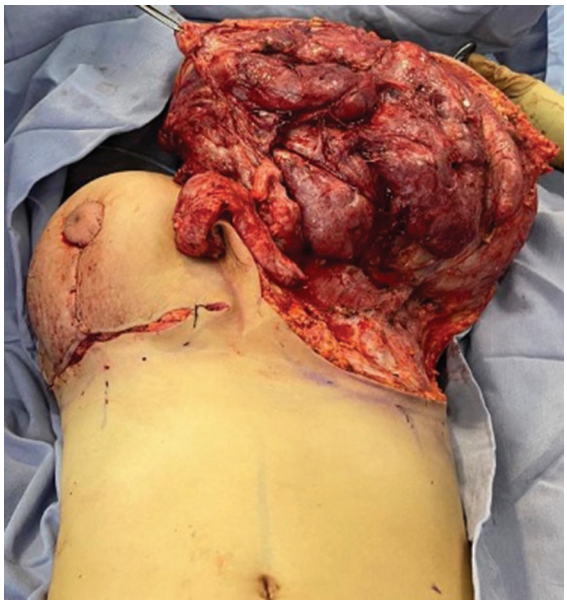

Figure 3. Surgical management with superomedial pedicle reduction mammoplasty. Left resection of 3261 g.

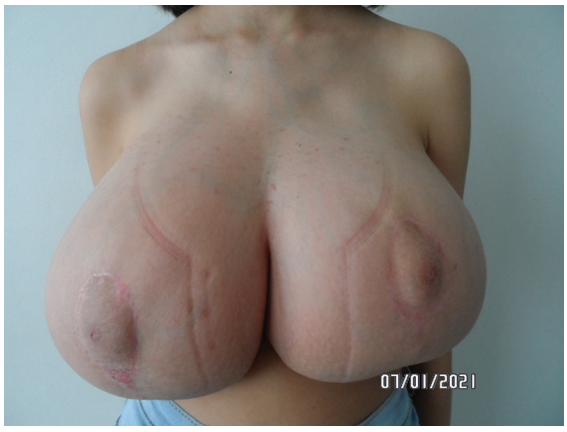

Figure 4. Recurrence 4 months after reduction mammoplasty.

and 2530 g on the left side, which is equivalent to a growth of 90% and 70% with respect to the initial pre-operative volume before the surgeries, despite having performed a first breast reduction (Fig. 4).

Discussion

GJ is also known as virginal breast hypertrophy, juvenile hypertrophy, or juvenile macromastia. Clinical manifestations include a sudden and continuous growth of breast tissue, usually accompanying the onset of puberty. There is usually a 6-month period of extreme growth, followed by a slower but sustained period[8,9].

The definition of gigantomastia varies depending on the author: excessive growth representing 3% or more of the patient's total weight or more than 1500 cc in volume[4,3]. It causes physical dysfunction, postural pain, deviation in the spine and dermal alterations, mainly hyperemia, orange peel and even necrosis. Dilation of subcutaneous veins and intertrigo can be observed in inframammary folds; with an impact on the psychosocial development of the patient, eating disorders, social distancing, inability to perform physical activity, esthetic non-conformity with body image distortion and alterations in habitual behavior may also occur[10,11].

JG is a diagnosis of exclusion and during the patient's approach, it is vitally important to rule out all differential diagnoses, which include: breast hypertrophy secondary to the use of medications, pseudo-gigantomastia associated with obesity, fibroepithelial tumors (breast fibroadenoma, phyllodes tumor), fibrocystic disease, endocrinopathies, hypertrophy associated with pregnancy, infection, tumors of benign origin (hemangiomas and lymphangiomas) and tumors of malignant origin (lymphoma, sarcoma). The definitive diagnosis is obtained with the anatomopathological study[2].

The most recommended treatment is surgical resection, as GJ is an absolute indication for a breast reduction or resection procedure in its entirety[12]. Other alternatives to consider are reduction with upper pedicle, lower pedicle, bipedicled, and free nipple grafts[13]. The other surgical option, used in a smaller proportion, as was the case in this case, is subcutaneous mastectomy, with reconstruction based on prostheses. Normally, it is reserved for cases with suspected malignancy and recurrences, as it is a management with less satisfactory esthetic results than reduction mammoplasty[7].

For patients such as the one presented here, the recurrence that reached 70-90% of the initial volume must be treated with radical surgery. In this case, subcutaneous mastectomy and reconstruction with bilateral breast implants, with the aim of minimizing residual breast tissue and obtaining a favorable result for health and esthetics. The surgical technique of subcutaneous mastectomy has the lowest recurrence rate and ensures a reliable and definitive final result. At present, the patient remains under follow-up, undergoing 2 years of evolution without recurrent breast growth, and very satisfied with her result (Fig. 5). If necessary, and especially when the patient reaches an older physical and mental age, subsequent breast surgeries for esthetic purposes may be considered.

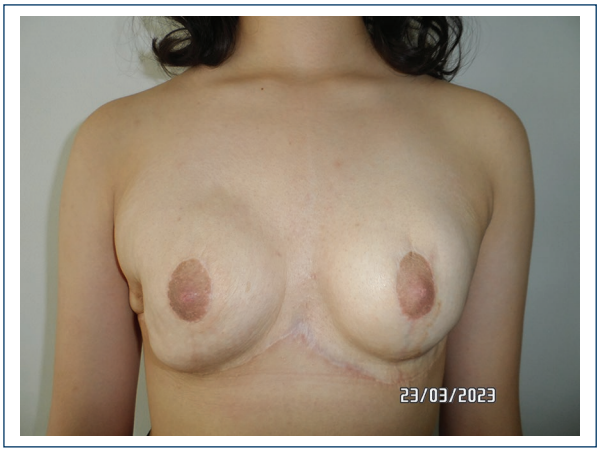

Figure 5. Posterior bilateral mastectomy.

Conclusion

Any case of JG merits multidisciplinary management, involving specialties such as endocrinology, psychology, pediatrics, and plastic and reconstructive surgery. To design a complete treatment plan, rule out possible etiologies, differential diagnoses, and obtain favorable results to improve the quality of life of our patients. Now, there are no evidence-based treatment guidelines, only case reports, due to the low incidence of the pathology. Further research is required to define etiopathogenesis, natural history, and response to medical and surgical treatment. However, both for the symptoms and for the patient's self-esteem and lifestyle, so far, the surgical approach with or without hormonal treatment is indicated.

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript.

References

1. De Silva NK, Brandt ML. Disorders of the breast in children and adolescents, part 1: disorders of growth and infections of the breast. J Pediatr Adolesc Gynecol. 2006;19:345-9.
2. Koves I, Zacharin M. Virginal breast hypertrophy of an 11-year-old girl. J Paediatr Child Health Division. 2006;43:315-7.
3. Bonilla OA. Hiperplasia virginal mamaria asociado a hiperplasia pseudoangiomatosa del estroma mamario difuso. Rev CES Med. 2015;30:122-8.
4. Figueroa S, Romero V. Hipertrofia virginal mamaria en niños y manejo quirúrgico. Rev Peruana Ginecol Obstet. 2012;58:127-32.
5. Jabaititi S, Fayyad L, Isleem U. Prednisolone-induced virginal mammary hypertrophy: case report. Int J Surg Case Rep. 2019;59:140-3.
6. Karaguzel G, Bilen S, Karacal N, Yildiz K, Livaoglu M. Virginal Breast Hypertrophy: different presentations of two cases and the role of Tamoxifen as an adjuvant therapy. J Pediatr Adolesc Gynecol 2015;29:e71-4.
7. Marcello G, Miro A, Dipasquale M. Gigantomastia juvenil. Hipertrofia virginal. Presentación de caso clínico. Rev Argent Cir Plást. 2016;22:114-8.
8. Menekse E, Onel S, Karateke F, Das K, Bali I, Sozen S, et al. Virginal breast hypertrophy and symptomatic treatment: a case report. J Breast Health. 2014;10:122-4.
9. Szymanska E, Moszczynska E, Polnik D, Jurkiewicz E. Virginal breast hypertrophy in a patient with Beckwith-Wiedemann syndrome. Clin Case Rep. 2017;6:484-9.
10. Egro FM, Davidson EH, Namnoum JD, Shestak KC. Congenital breast deformities. Plast Surg. 2023;5:509-19.
11. Wolfswinkel EM, Lemaine V, Weathers WM, Chike-Obi CJ, Xue AS, Heller L. Hyperplastic breast anomalies in the female adolescent breast. Semin Plast Surg. 2013;27:49-55.
12. Vyas S, Greenwood HI, Jankowski T, Freimanis RI. A case of acute onset gigantomastia in a 20-year-old woman. Clin Imaging. 2020;68:57-60.
13. Acea BN. Mamoplastía Vertical de Doble Rama. Cirugía Oncológica de la Mama. 4a ed. Netherlands: Elsevier; 2019. p. 213-40.