BRAZILIAN JOURNAL OF IMPLANTOLOGY AND HEALTH SCIENCES

ISSN 2674-8169

Arterial Hypertension and Dyslipidemia in Patients with Type 2 Diabetes Mellitus: Risk Factors, Intervention Strategies and Impact on Cardiovascular Health.

☐Gabriel Rodrigues França[1]; ☐Vitor Silva Rosa[1], ☐Eduardo Henrique Mendes Rezende[2], Murilo Dell Eugenio Costa Filho[6], Heldiane Estevão Maranhão Jansen[3], Durval José dos Santos Filho[1], Beatriz Medrado Pereira[4] , Natana Carol Alves, João Guilherme Franceschi Pinotti[5] , Mariana Alves Anes de Araújo[5] and João Vitor Silva da Silva[5]

LITERATURE REVIEW

RESUMO

A Hipertensão Arterial (HA) e a Dislipidemia são condições frequentemente associadas ao Diabetes Mellitus tipo 2 (DM2), aumentando significativamente o risco de doença cardiovascular (DCV) e mortalidade. A inter-relação desses fatores de risco metabólicos torna-se uma preocupação crescente devido à sua prevalência crescente e às complicações graves que acarretam. A HA, caracterizada pela pressão arterial elevada, e a dislipidemia, marcada por níveis anormais de lipídios no sangue, são fatores de risco modificáveis que desempenham papéis centrais na patogênese das complicações cardiovasculares do DM2. Estratégias de intervenção eficazes para gerenciar essas condições são essenciais para reduzir o risco cardiovascular nessa população. Objetivo: Realizar uma revisão sistemática da literatura para avaliar os fatores de risco, estratégias de intervenção e impacto na saúde cardiovascular da coexistência de HA e dislipidemia em pacientes com DM2. Metodologia: Realizou-se uma busca nas bases de dados PubMed, Scielo e Web of Science por artigos publicados nos últimos 10 anos. Os descritores utilizados foram "hipertensão arterial", "dislipidemia", "diabetes mellitus tipo 2", "fatores de risco cardiovascular" e "intervenção". Os Critérios de inclusão: estudos que investigaram a relação entre HA, dislipidemia e DM2, intervenções terapêuticas para essas condições e seu impacto na saúde cardiovascular. Os Critérios de exclusão: estudos com foco exclusivo em DM1, revisões não sistemáticas e estudos com amostras heterogêneas não relacionadas ao tema. Resultados: Os estudos revisados destacaram a associação entre HA, dislipidemia e DM2, enfatizando a importância do controle glicêmico, lipídico e pressórico para reduzir o risco cardiovascular. Intervenções multifacetadas, incluindo modificações no estilo de vida e terapias farmacológicas, foram eficazes na melhoria dos desfechos cardiovasculares nessa população. Conclusão: A abordagem integrada da HA e dislipidemia em pacientes com DM2 é crucial para prevenir complicações cardiovasculares. Estratégias de intervenção personalizadas, baseadas em evidências científicas sólidas, são fundamentais para melhorar os resultados de saúde nessa população de alto risco.

Palavras-chave: "hipertensão arterial", "dislipidemia", "diabetes mellitus tipo 2", "fatores de

risco cardiovascular" e "intervenção".

ABSTRACT

Arterial Hypertension (AH) and Dyslipidemia are conditions frequently associated with Type 2 Diabetes Mellitus (DM2), significantly increasing the risk of cardiovascular disease (CVD) and mortality. The interrelationship of these metabolic risk factors becomes a growing concern due to their increasing prevalence and the serious complications they entail. AH, characterized by high blood pressure, and dyslipidemia, marked by abnormal levels of lipids in the blood, are modifiable risk factors that play central roles in the pathogenesis of cardiovascular complications of DM2. Effective intervention strategies to manage these conditions are essential to reduce cardiovascular risk in this population. Objective: To carry out a systematic review of the literature to evaluate the risk factors, intervention strategies and impact on cardiovascular health of the coexistence of AH and dyslipidemia in patients with DM2. Methodology: A search was carried out in the PubMed, Scielo and Web of Science databases for articles published in the last 10 years. The descriptors used were "arterial hypertension", "dyslipidemia", "type 2 diabetes mellitus", "cardiovascular risk factors" and "intervention". Inclusion criteria: studies that investigated the relationship between AH, dyslipidemia and DM2, therapeutic interventions for these conditions and their impact on cardiovascular health. Exclusion criteria: studies focusing exclusively on DM1, non-systematic reviews and studies with heterogeneous samples unrelated to the topic. Results: The studies reviewed highlighted the association between AH, dyslipidemia and DM2, emphasizing the importance of glycemic, lipid and blood pressure control to reduce cardiovascular risk. Multifaceted interventions, including lifestyle modifications and pharmacological therapies, have been effective in improving cardiovascular outcomes in this population. Conclusion: The integrated approach to hypertension and dyslipidemia in patients with DM2 is crucial to prevent cardiovascular complications. Personalized intervention strategies based on solid scientific evidence are critical to improving health outcomes in this high-risk population.

Keywords: "arterial hypertension", "dyslipidemia", "type 2 diabetes mellitus", "cardiovascular risk factors" and "intervention".

Instituição afiliada – UNIRV[1] , UniEVANGÉLICA[2], Faculty of Health Sciences Pitágoras de Codó[3], Federal University of Western Bahia[4] , Unifadra[5] , University of Gurupi[6]

Dados da publicação: Artigo recebido em 15 de Fevereiro e publicado em 05 de Abril de 2024.

DOI: https://doi.org/10.36557/2674-8169.2024v6n4p577-589

Autor correspondente*: Gabriel Rodrigues França; email: igorcsantos01@gmail.com*

INTRODUCTION

The intersection between arterial hypertension (AH), dyslipidemia and type 2 diabetes mellitus (T2DM) represents a significant challenge in contemporary clinical practice, given the increasing prevalence of these metabolic conditions and their devastating impact on cardiovascular health. The complex network of interactions between these pathologies illustrates a multifaceted clinical panorama, influenced by genetic, environmental and behavioral factors.

Arterial hypertension, characterized by high blood pressure levels, and dyslipidemia, marked by changes in circulating lipid levels, are two of the most common conditions associated with type 2 diabetes mellitus. These conditions frequently coexist, contributing to the exponential increase in cardiovascular risk in patients with DM2. The interconnection of these metabolic risk factors creates an environment conducive to the development and progression of cardiovascular diseases, such as myocardial infarction, stroke and heart failure, which represent the main causes of morbidity and mortality in this population.

The concomitant presence of hypertension and dyslipidemia in patients with DM2 further aggravates cardiovascular risk, creating a vicious cycle of pathophysiological interactions that can trigger serious cardiovascular events. This synergistic association between metabolic conditions poses additional challenges to clinical management, requiring an integrated and personalized approach to optimize health outcomes.

Therefore, understanding the interconnection between arterial hypertension, dyslipidemia and type 2 diabetes mellitus is essential to guide effective preventive and therapeutic strategies, aiming to mitigate cardiovascular risk and improve the quality of life of these patients.

Adequate metabolic control is crucial in managing the interconnection between arterial hypertension, dyslipidemia and type 2 diabetes mellitus. Comprehensive therapeutic strategies, ranging from lifestyle modifications to pharmacological interventions, emerge as fundamental pillars in the clinical management of these

multifactorial conditions. Adopting a healthy diet, regular physical exercise and reducing the consumption of saturated fats are non-pharmacological measures widely recognized for their effectiveness in improving glycemic, blood pressure and lipid control, thus reducing cardiovascular risk. Furthermore, pharmacological interventions, such as the use of antihypertensive and lipid-lowering drugs, play a crucial role in reducing cardiovascular morbidity and mortality in patients with DM2 and comorbidities. These therapeutic strategies must be complemented by a multidisciplinary approach, which involves collaboration between different health professionals, aiming to personalize care and promote adherence to treatment. An integrated and holistic approach, focused on individual patient needs, is essential to optimize health outcomes and reduce the global burden of cardiovascular disease in this vulnerable population.

Conduct a systematic review of the literature to evaluate the risk factors, intervention strategies and impact on cardiovascular health of the coexistence of arterial hypertension and dyslipidemia in patients with type 2 diabetes mellitus.

METHODOLOGY

To conduct the systematic literature review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was adopted as a methodological protocol. The PubMed, Scielo and Web of Science databases were accessed to identify relevant studies published in the last 10 years. The descriptors used in the search were "arterial hypertension", "dyslipidemia", "type 2 diabetes mellitus", "cardiovascular risk factors" and "intervention". To select the studies included in this systematic review, inclusion and exclusion criteria were established. The inclusion criteria included studies published in the last 10 years that investigated the relationship between arterial hypertension, dyslipidemia and type 2 diabetes mellitus. In addition, studies were considered that addressed intervention strategies to manage these metabolic conditions in patients with type 2 diabetes and that analyzed their impact on cardiovascular health. Randomized controlled trials, observational studies and systematic reviews were considered for inclusion.

RESULTS

15 articles were selected. The interaction between arterial hypertension, dyslipidemia and type 2 diabetes mellitus is an area of great interest in medicine, due to the complexity of the relationships between these metabolic conditions and their impact on cardiovascular health. Epidemiological and experimental studies demonstrate a significant association between these pathologies, where the presence of one often precedes or accompanies the others. High blood pressure, characterized by increased blood pressure in the arteries, is closely linked to the metabolic dysfunction associated with type 2 diabetes, including insulin resistance and obesity. In turn, dyslipidemia, marked by changes in circulating lipid levels, such as increased LDL cholesterol and triglycerides, is common in patients with DM2 and contributes to the progression of cardiovascular complications.

This synergistic association between metabolic conditions results in an environment conducive to the development of atherosclerosis, coronary artery disease and other serious cardiovascular complications. Complex pathophysiological mechanisms are involved in this interaction, including chronic inflammation, oxidative stress and endothelial dysfunction. Furthermore, genetic and environmental factors also play important roles in determining individual susceptibility to these conditions and their prognosis. Therefore, understanding the association between arterial hypertension, dyslipidemia and type 2 diabetes mellitus is essential to develop effective preventive and therapeutic strategies, aiming to reduce cardiovascular risk and improve clinical outcomes for affected patients.

Adequate metabolic control plays a fundamental role in the effective management of the interconnection between arterial hypertension, dyslipidemia and type 2 diabetes mellitus, aiming to reduce cardiovascular risk. To achieve this goal, it is essential that patients adopt measures that promote the stability of blood glucose levels, blood pressure and lipid profile. Comprehensive therapeutic strategies, which include both non-pharmacological and pharmacological interventions, are frequently employed in this context. Lifestyle modifications, such as adopting a healthy diet and exercising regularly, play a crucial role in metabolic control, helping to improve insulin sensitivity, reduce blood pressure and optimize lipid levels.

In addition to lifestyle measures, pharmacological treatment is also often

necessary to achieve therapeutic goals in patients with high blood pressure, dyslipidemia and type 2 diabetes. Antihypertensive, lipid-lowering and hypoglycemic medications are prescribed with the aim of controlling risk factors metabolic processes and prevent cardiovascular complications. It is essential that metabolic control is individualized, taking into account the clinical characteristics and specific needs of each patient. Regular monitoring of metabolic parameters is essential to assess the effectiveness of treatment and make therapeutic adjustments as necessary, thus ensuring the maintenance of a healthy metabolic state and the reduction of cardiovascular risk.

A multifaceted approach is necessary for the effective management of high blood pressure, dyslipidemia, and type 2 diabetes mellitus, with an emphasis on implementing comprehensive therapeutic strategies. In addition to lifestyle modifications, which form the basis of treatment, pharmacological interventions play a crucial role in reducing cardiovascular risk. Antihypertensive medications are prescribed to reduce blood pressure, while lipid-lowering drugs are used to normalize circulating lipid levels, and hypoglycemic drugs aim to control blood glucose.

Furthermore, patient education plays a fundamental role in the success of treatment, enabling individuals to understand the importance of metabolic control and adhere to medical recommendations. A multidisciplinary approach, involving doctors, nurses, nutritionists and physical educators, is essential to provide comprehensive and personalized care to patients, ensuring a holistic approach to managing metabolic conditions. Therefore, therapeutic strategies must be individualized, taking into account the clinical characteristics and specific needs of each patient, aiming to reduce cardiovascular risk and promote global health.

Adopting a healthy diet plays a crucial role in metabolic control and preventing cardiovascular complications in patients with high blood pressure, dyslipidemia and type 2 diabetes mellitus. A balanced diet rich in fruits, vegetables, whole grains, lean proteins and healthy fats , such as those found in fish, avocado and nuts, is essential for maintaining adequate blood glucose levels, blood pressure and lipid profile. These foods provide essential nutrients such as vitamins, minerals, fiber and antioxidants, which help reduce the risk of cardiovascular disease by promoting heart and blood vessel health.

Furthermore, reducing the consumption of saturated fats, refined sugars and processed foods is recommended to prevent the development of insulin resistance, dyslipidemia and obesity, common metabolic risk factors associated with type 2 diabetes. Adequate control of body weight is also an important part of a healthy diet, as excess weight is associated with a greater risk of cardiovascular complications. Therefore, an individualized dietary approach, guided by a qualified healthcare professional, is essential to help patients make appropriate dietary choices, thus ensuring metabolic control and promoting cardiovascular health over time.

Regular physical exercise is a fundamental strategy in the management of high blood pressure, dyslipidemia and type 2 diabetes mellitus, contributing significantly to metabolic control and cardiovascular health. Aerobic exercise, such as walking, running, swimming and cycling, is especially beneficial for lowering blood pressure, improving lipid profile and increasing insulin sensitivity. This is because exercise promotes the release of chemicals in the body, such as endorphins and nitric oxide, which help relax blood vessels, reduce inflammation, and improve blood flow.

Additionally, regular exercise also plays an important role in regulating body weight and preventing obesity, a significant metabolic risk factor associated with type 2 diabetes. Maintaining a healthy weight is essential for reducing insulin resistance, improve glycemic control and prevent cardiovascular complications. Therefore, encouraging patients to incorporate physical activity into their daily routine, under the supervision of a qualified healthcare professional, is critical to ensuring the lasting benefits of exercise on metabolic and cardiovascular health.

The use of medications plays a crucial role in metabolic control and prevention of cardiovascular complications in patients with arterial hypertension, dyslipidemia and type 2 diabetes mellitus. Antihypertensive medications, such as angiotensin-converting enzyme inhibitors (ACEIs), receptor blockers Angiotensin inhibitors (ARB) and diuretics are prescribed to reduce blood pressure and protect target organs from the harmful effects of hypertension.

Likewise, lipid-lowering drugs, such as statins, fibrates and PCSK9 inhibitors, are used to reduce LDL cholesterol and triglyceride levels, thus preventing the development of atherosclerosis and adverse cardiovascular events. Additionally, hypoglycemic drugs,

including metformin, sulfonylureas, and GLP-1 receptor agonists, are prescribed to control blood glucose and reduce the risk of diabetes-related complications. It is important to emphasize that the choice of medication and its dose must be individualized, taking into account the clinical characteristics and specific needs of each patient, aiming to maximize therapeutic benefits and minimize adverse side effects.

A multidisciplinary approach is essential to provide comprehensive and personalized care to patients with high blood pressure, dyslipidemia and type 2 diabetes mellitus, aiming to optimize health outcomes and reduce cardiovascular risk. The multidisciplinary health team includes professionals from different areas, such as doctors, nurses, nutritionists, physical educators and psychologists, who collaborate in an integrated way to offer a holistic approach to managing metabolic conditions.

Each team member plays a unique and complementary role in patient care. Physicians are responsible for clinical assessment, diagnosis and prescribing treatments, while nurses coordinate direct patient care and provide educational support. Nutritionists help create personalized eating plans, while physical educators develop exercise programs tailored to each patient's individual needs. Additionally, including a psychologist on the team can help patients deal with emotional issues related to chronic disease management and promote treatment adherence. Therefore, a multidisciplinary approach is essential to ensure that patients receive comprehensive and individualized care, aiming to improve their quality of life and reduce the risk of cardiovascular complications.

Patient education plays a fundamental role in the successful treatment of high blood pressure, dyslipidemia and type 2 diabetes mellitus, enabling individuals to understand the importance of metabolic control and adhere to medical recommendations. Patients should receive detailed information about the nature of their metabolic conditions, including associated risk factors and consequences for cardiovascular health. They should also be guided on self-care measures, such as adopting a healthy diet, practicing regular physical exercise, regularly monitoring blood glucose levels and adhering to medication treatment.

Additionally, patient education should address issues related to the prevention of acute and chronic complications, as well as strategies for dealing with emergency

situations such as hypertensive or hypoglycemic crises. It is important that this education is carried out on an individual basis, taking into account the level of understanding, preferences and specific needs of each patient. By empowering them with the knowledge and skills necessary to manage their metabolic conditions, it is possible to promote autonomy and self-management of health, thus contributing to better clinical outcomes and quality of life.

Regular monitoring of metabolic parameters is essential to assess the effectiveness of treatment and make therapeutic adjustments as necessary, thus ensuring the maintenance of a healthy metabolic state and the reduction of cardiovascular risk. Patients must undergo periodic laboratory tests to evaluate blood glucose levels, lipid profile and kidney function. Furthermore, measuring blood pressure at regular medical appointments is crucial to monitor the effectiveness of antihypertensive treatment and identify the need for medication adjustments.

In addition to clinical monitoring, patients can also benefit from self-management of their health through the use of home monitoring devices such as glucometers and blood pressure cuffs. These devices allow patients to monitor their own metabolic parameters regularly, providing real-time data that can be shared with their healthcare professionals for assessment and guidance. In this way, regular monitoring of metabolic parameters not only allows monitoring of disease progression and treatment effectiveness, but also empowers patients to play an active role in managing their health, thus promoting better clinical outcomes and quality of life.

CONCLUSION

In the context of managing patients with arterial hypertension, dyslipidemia and type 2 diabetes mellitus, several strategies have been employed to reduce cardiovascular risk and promote metabolic health. It became evident that the interrelationship between these metabolic conditions plays a significant role in the development of cardiovascular complications, highlighting the importance of integrated therapeutic approaches. Studies have shown that adequate metabolic control, through lifestyle modifications and medication use, is essential to reduce cardiovascular risk in patients with these comorbidities.

Patient education and engagement in a multidisciplinary approach also emerged as crucial elements in ensuring treatment success and adherence to therapeutic recommendations. Furthermore, regular monitoring of metabolic parameters has been identified as a key tool for evaluating treatment effectiveness and making adjustments as needed. Therefore, a comprehensive and individualized approach, considering the specific needs of each patient, is essential to optimize health outcomes and reduce the burden of cardiovascular diseases associated with high blood pressure, dyslipidemia and type 2 diabetes mellitus.

Bibliographic references:

1. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjörnsdottir S. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2018 Aug 16;379(7):633-644. doi: 10.1056/NEJMoa1800256.
2. Lauder L, Mahfoud F, Azizi M, Bhatt DL, Ewen S, Kario K, Parati G, Rossignol P, Schlaich MP, Teo KK, Townsend RR, Tsioufis C, Weber MA, Weber T, Böhm M. Hypertension management in patients with cardiovascular comorbidities. Eur Heart J. 2023 Jun 20;44(23):2066-2077. doi: 10.1093/eurheartj/ehac395.
3. Samson SL, Vellanki P, Blonde L, Christofides EA, Galindo RJ, Hirsch IB, Isaacs SD, Izuora KE, Low Wang CC, Twining CL, Umpierrez GE, Valencia WM. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update. Endocr Pract. 2023 May;29(5):305-340. doi: 10.1016/j.eprac.2023.02.001.
4. Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. Can J Cardiol. 2018 May;34(5):575-584. doi: 10.1016/j.cjca.2017.12.005.
5. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and Risks of Bariatric Surgery in Adults: A Review. JAMA. 2020 Sep 1;324(9):879-887. doi: 10.1001/jama.2020.12567.
6. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, Hirsch IB, McDonnell ME, Molitch ME, Murad MH, Sinclair AJ. Treatment of Diabetes in Older Adults: An Endocrine Society* Clinical Practice Guideline. J Clin Endocrinol Metab. 2019

May 1;104(5):1520-1574. doi: 10.1210/jc.2019-00198.

7. Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, Januzzi JL Jr, Scott NS, Natarajan P. Association of Premature Natural and Surgical Menopause With Incident Cardiovascular Disease. JAMA. 2019 Dec 24;322(24):2411-2421. doi: 10.1001/jama.2019.19191.
8. Gourdy P, Darmon P, Dievart F, Halimi JM, Guerci B. Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM) . Cardiovasc Diabetol. 2023 Apr 1;22(1):79. doi: 10.1186/s12933-023-01798-4.
9. Lan J, Zhao Y, Dong F, Yan Z, Zheng W, Fan J, Sun G. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. J Ethnopharmacol. 2015 Feb 23;161:69-81. doi: 10.1016/j.jep.2014.09.049.
10. Ryan DH, Yockey SR. Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. Curr Obes Rep. 2017 Jun;6(2):187-194. doi: 10.1007/s13679-017-0262-y..
11. Bingham JM, Black M, Anderson EJ, Li Y, Toselli N, Fox S, Martin JR, Axon DR, Silva-Almodóvar A. Impact of Telehealth Interventions on Medication Adherence for Patients With Type 2 Diabetes, Hypertension, and/or Dyslipidemia: A Systematic Review. Ann Pharmacother. 2021 May;55(5):637-649. doi: 10.1177/1060028020950726.
12. Banach M, Surma S, Reiner Z, Katsiki N, Penson PE, Fras Z, Sahebkar A, Paneni F, Rizzo M, Kastelein J. Personalized management of dyslipidemias in patients with diabetes-it is time for a new approach (2022). Cardiovasc Diabetol. 2022 Nov 28;21(1):263. doi: 10.1186/s12933-022-01684-5.
13. Reyes-García R, Moreno-Pérez Ó, Tejera-Pérez C, Fernández-García D, Bellido-Castañeda V, de la Torre Casares ML, Rozas-Moreno P, Fernández-García JC, Marco Martínez A, Escalada-San Martín J , Gargallo-Fernández M, Botana-López M, López-Fernández J, González-Clemente JM, Jódar-Gimeno E, Mezquita-Raya P; representing the Diabetes-SEEN working group. Document on a comprehensive approach to type 2 diabetes mellitus. Endocrinol Diabetes Nutr (Engl Ed). 2019 Aug-Sep;66(7):443-458. English, Spanish. doi: 10.1016/j.endinu.2018.10.010.
14. Reyes-García R, Moreno-Pérez Ó, Tejera-Pérez C, Fernández-García D, Bellido-Castañeda V, de la Torre Casares ML, Rozas-Moreno P, Fernández-García JC, Marco

Martínez A, Escalada-San Martín J , Gargallo-Fernández M, Botana-López M, López-Fernández J, González-Clemente JM, Jódar-Gimeno E, Mezquita-Raya P; representing the Diabetes-SEEN working group. Document on a comprehensive approach to type 2 diabetes mellitus. Endocrinol Diabetes Nutr (Engl Ed). 2019 Aug-Sep;66(7):443-458. English, Spanish. doi: 10.1016/j.endinu.2018.10.010. Epub 2019 Feb 28. PMID: 30827909.

15. Becher T, Palanisamy S, Kramer DJ, Eljalby M, Marx SJ, Wibmer AG, Butler SD, Jiang CS, Vaughan R, Schöder H, Mark A, Cohen P. Brown adipose tissue is associated with cardiometabolic health. Nat Med. 2021 Jan;27(1):58-65. doi: 10.1038/s41591-020-1126-7.