SIWEK, Michal, BEUTLER, Jacek, BEUTLER, Katarzyna and LEWANDOWSKI, Jędrzej. The role of diabetes on the development of abdominal aortic aneurysms (AAA). Journal of Education, Health and Sport. 2024;65:62-72. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.65.004
https://apcz.umk.pl/JEHS/article/view/49837
https://zenodo.org/records/10963719

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.03.2024. Revised: 29.03.2024. Accepted: 10.04.2024. Published: 12.04.2024.

The role of diabetes on the development of abdominal aortic aneurysms (AAA)

1. **Michal Siwek [MS]**
   Poznan University of Medical Sciences, Poland
   https://orcid.org/0009-0002-0490-5512
   ms.michalsiwek@gmail.com

2. **Jacek Beutler [JB]**
   Poznan University of Medical Sciences, Poland
   https://orcid.org/0009-0009-9660-4207
   jacek.beutler@gmail.com

3. **Katarzyna Beutler [KB]**
   University Clinical Hospital of Poznan, Dluga 1/2, 61-848 Poznan
   https://orcid.org/0009-0000-4219-5676
   kasia.beutler@gmail.com

4. **Jedrzej Lewandowski [JL]**
   University Clinical Hospital of Poznan, Dluga 1/2, 61-848 Poznan
   https://orcid.org/0009-0006-0608-0154
   jedrzejlewandowski98@gmail.com

Abstract

An abdominal aortic aneurysm (AAA) is a pathological local dilatation of the abdominal aorta that may develop from a variety of causes. With a 80% mortality rate, it is mainly linked to male gender, age above 65 years, smoking, and a family history of AAA. Ultrasonography is an effective method for screening males who are 65 or older for AAA. Endovascular aneurysm repair (EVAR) procedure reduces 30-day operative mortality and hospital stay, becoming a global standard. Both open and endovascular surgery aim to cut off the aneurysm's circulation, preventing it from rupturing. Diabetes mellitus (DM) may provide protection against regrowth and the need for additional intervention after endovascular AAA repair, thereby limiting the enlargement and rupture of AAAs. Hyperglycemia thickens the aortic walls and reduces wall stress in diabetic patients' abdominal aortas. It stabilizes collagen structure and promotes the synthesis of collagen type IV. Anti-diabetic drugs like metformin, thiazolidinedione, and dipeptidyl peptidase 4 inhibitors (DPP-4i) have been shown in both animal and human studies to protect against aortic aneurysms. In a dose-response pattern, these antidiabetic drugs may lower the prevalence, incidence, and enlargement rate of AAA.

Keywords: abdominal aortic aneurysms; diabetes; antidiabetic drugs

Introduction

An abdominal aortic aneurysm (AAA), which is a pathological dilatation of abdominal aorta, can be caused by a variety of external and internal factors [1]. The main risk factors for aortic aneurysm include smoking, age over 65, male gender, and family history. The majority of risk factors for AAA are similar to those for other cardiovascular diseases, with the exception of diabetes mellitus. Since unruptured AAAs are usually asymptomatic, screening for AAA with ultrasonography has a positive effect, particularly in males who are 65 years old or older [2].

Hyperglycemia (or other DM-related variables like insulin resistance [IR]) and/or the impact of prescription DM medicines may have a direct or indirect effect on the formation and progression of AAAs. Recent research provides more evidence that antidiabetic medications, such as metformin or SGLT-2 inhibitors, may be responsible for the protective effect of DM in AAA. Diabetes mellitus (DM) not only prevents the enlargement and rupture of AAAs but also can protect against regrowth and the need for further intervention after endovascular AAA repair [3, 4].

Our review's objective was to compile the most recent data on preventive role of diabetes in individuals who also have a comorbid abdominal aortic aneurysm.

Epidemiology

The majority of AAA patients usually show no symptoms until the rupture of the aneurysm. However, in the event of an aneurysm rupture, the total fatality rate may exceed 80%. Because of the aging population, prevalence increases with each passing year [1]. In males, the prevalence rates of AAA range from 1.9% to 18.5%, whereas in females, they range from 0% to 4.2% [5].

Diagnostics and treatment

Ultrasound imaging is non-invasive, non-ionizing, and does not require the use of nephrotoxic contrast, it is a reliable method for visualizing the aorta in 99% of cases. All of the large AAA screening trials used ultrasonography, which contributed to the substantial body of research indicating that AAA screening using ultrasound was accurate, affordable and time-efficient [6].

According to a Cochrane collaborative comprehensive review, males between the ages of 65 and 79 who undergo ultrasonography screening appear to have a significantly lower risk of AAA mortality [7, 8].

Moreover, new research indicates that putting in place a screening system extends life expectancy and lowers treatment expenses at the same time. The World Health Organization has identified AAA screening as one of the cost-effective therapies. According to the guidelines set forth by the US Preventive Service Task Force (USPSTF), males who have smoked and are between the ages of 65 and 75 should have a AAA screening. [9, 10, 11]

If a scan reveals a 3.0-5.4 cm aneurysm, the patient must be assessed at a regional vascular service within 12 weeks. If the AAA is ≥5.5 cm, patient must undergo a medical assessment within 2 weeks. [4]

Endovascular aneurysm repair (EVAR) significantly reduces 30-day operative mortality and length of hospital stay compared to open surgical repair, therefore it has quickly become the standard treatment option worldwide over the last ten years. [1] The aim of the open and endovascular procedures is to cut off the aneurysm's circulation, thus removing the possibility of a rupture. Early complications following the procedure are not uncommon. These include endograft migration, endoleaks (continuous blood flow into the aneurysm sac following graft implantation), lower limb ischemia, renal failure, and access site issues (arterial rupture and dissection) [5].

Risk factors

An abdominal aortic aneurysm (AAA) is an irreversible dilatation of the abdominal aorta to a diameter exceeding 3.0 cm, or 1.5 times its typical anteroposterior diameter. Abdominal aortic aneurysms (AAA) are more common in men than in women, with an estimated 4% to 8% of men over 60 expected to be affected. [4, 12] The pathogenesis of AAA is complex and multifactorial and, although the etiology is unclear, it shares several risk factors associated with atherosclerotic disease, such as: age, smoking, male sex, genetic susceptibility, arterial hypertension, abdominal obesity, coronary heart disease and intermittent claudication. [13]

Smoking is the primary risk factor associated with the development of AAA. There is a lower incidence of AAA in countries where cigarette smoking has declined. According to al-Zahrani et al. there is a strong correlation between smoking and aortic diameter; smokers' aortic diameters are larger than non-smokers'. [9, 14]

The pathophysiology of AAA may involve lipoproteins, as suggested by two recent meta-analyses. Moreover, a population-based prospective cohort research has shown that HDL (high-density lipoprotein) cholesterol concentrations can be used to predict the pace of aneurysmal growth. To better understand the function HDL particles, play in aneurysmal disease, Martínez-López et al. investigated the effect of HDL particles on macrophage cholesterol efflux as well as the composition of HDL in patients with AAA. Patients with AAA had lower plasma HDL cholesterol and apoA-I concentrations than controls. [15, 16, 17]

The impact of diabetes

It has been demonstrated that diabetes mellitus (DM) increases the risk of certain comorbidities, which in turn increase the risk of abdominal aortic aneurysm (AAA).

Remarkably, data from epidemiologic studies has revealed a negative correlation between the two diseases. [18]

The majority of epidemiological research has reported DM's possible preventive effect on the prevalence and incidence of AAA, despite the fact that it is one of the major risk factors for CVD. The majority of studies point to DM's preventive role in AAA for non-post-operative data. A meta-analysis of prospective studies shows that the prevalence of AAA is lower in people with DM and that the progression of AAA is slower in people with DM who have small AAAs (aortic diameters between 3 and 5 cm). [19]

Additionally, data analysis from smaller research in specific groups and larger population prevalence studies showed a negative link between DM and AAA. Prospective investigations revealed that DM patients received a considerably decreased number of new AAA diagnoses. Based on pre-existing DM comorbidities, diabetic patients were divided into advanced and uncomplicated. It was found that people with advanced diabetes have a roughly 50% decreased risk of AAA rupture, suggesting that advanced diabetes offers a greater protection against AAA. [18, 20, 21]

Mechanism of the protective effect

Compared to patients without diabetes, diabetic patients' arteries are frequently harder and more calcified; nevertheless, this higher calcification of the vessel walls does not seem to account for the lower rate of aortic expansion in diabetic patients. [22] Because antidiabetic medication causes a gradual initial increase in AAA, diabetes can limit the rate of AAA growth and lower the body's overall level of inflammation. As a result, the mean AAA diameter in the diabetic group is smaller than in the nondiabetic group. [23]

The main testing ground for research on the protective role of DM in AAA has been animal models. To the best of our knowledge, the majority of these studies have made use of T1DM models. AAA generated by either elastase infusion in the abdominal aorta of C57BL/6 mice or by Angiotensin II (Ang II) infusion in apolipoprotein E knock-out (ApoE−/−) mice exhibits a protective effect in Streptozotocin-induced T1DM. Cell division autoantigen 1 (CDA1), which is elevated in diabetic mellitus (DM) and improves TGF-β signaling, including the vasculature, was shown by Dr. Zhonglin Chai's group. The authors of this work showed that CDA1 deletion in DM mice decreased TGF-β signaling and ECM buildup, which would reverse the protective effect of DM and subsequently aid in the formation of aneurysms. Crucially, TGF-β signaling activation inhibits AAA, whereas TGF-β inhibition hastens AAA

growth. Therefore, CDA1's protective effect on TGF-β signaling may account for it. [3, 24, 25, 26, 27]

Dysregulated prolyl hydroxylase domain (PHD) containing proteins may play a role in DM-mediated AAA suppression, according to a recent mouse study. According to the authors, dysregulated PHD activity led to greater aneurysmal angiogenesis, which in turn caused AAA attenuation in the context of DM. [3]

It has been demonstrated that hyperglycemia stabilizes the collagen network by thickening the aortic wall, which reduces wall stress in DM patients' abdominal aortas. In this sense, human diabetic arteries frequently exhibit collagen IV buildup, whereas the formation of AAA is linked to collagen IV shortage. Furthermore, in the VIVA cohort, circulating collagen IV degradation fragments were linked with the advancement of AAA. Additionally, Golledge et al. hypothesized that variations in monocyte-ECM interactions cause the progression of AAA to occur more slowly in diabetic patients. [3, 28, 29]

Hypoglycemic medications

Anti-diabetic drugs like metformin, thiazolidinedione, and dipeptidyl peptidase 4 inhibitors (DPP-4i) have been shown in both animal and human studies to protect against aortic aneurysms. In a dose-response pattern, these antidiabetic drugs may lower the prevalence, incidence, and enlargement rate of AAA. [18, 22, 30]

It has been demonstrated that metformin, even in normoglycemic mice, slows down the initiation and growth rate of AAA. According to research by Golledge et al., patients with diabetes who were administered metformin had considerably decreased death rates related to AAA repair and rupture when compared to patients without diabetes or those who were not prescribed metformin. However, compared to individuals without diabetes, diabetic patients who were not administered metformin did not exhibit a lower incidence of AAA events. This prompted the question of whether anti-diabetic medications are the source of the protective impact of diabetes mellitus. [18, 31, 32]

GLP-1RAs, like liraglutide and lixisenatide, prevent AAA development in animal models by preserving the extracellular matrix and exerting anti-inflammatory and antioxidant properties. Lixisenatide inhibits the production of reactive oxygen species (ROS) and oxidative DNA damage, which in turn delays the release of pro-inflammatory cytokines, macrophage filtration, and ultimately MMPs. [33, 34]

SGLT-2Is, such dapagliflozin and empagliflozin, have been shown to improve cardiovascular outcomes in individuals with heart failure. When empagliflozin was

administered in an Ang II-induced dissecting AAA mouse model, the maximal suprarenal aortic diameter significantly decreased. The disruption of elastin breakdown, neovascularization, and macrophage infiltration in the AAA formation process was further validated by an immunohistochemistry investigation using empagliflozin. [35]

Conclusions

The majority of DM disease characteristics are risk factors linked to CVD and most likely have a role in the development of AAA, even though other DM-related parameters (such as hyperglycemia-modulation of ECM) may protect against the formation and progression of AAA. It is becoming clear that the pharmaceutical treatments used for DM have an impact on the preventive effect against AAA. Current research on the subject demonstrates preventive benefits of antidiabetic medications (metformin, SGLT2-inhibitors, and incretin-based therapies, among others) on the occurrence and development of AAA. Numerous studies have been conducted in an attempt to clarify the mechanism underlying the protective effect of diabetes, which help us comprehend the genesis of AAA in general. For instance, it has been demonstrated that the advanced glycation linked to diabetes causes the collagen lattices in the aorta media to cross-link, which prevents proteolysis and suppresses the release of matrix metalloproteinases that are assumed to be involved in the formation of AAA. A growing number of studies attempting to clarify the peculiar link between the development of AAA and diabetes has already improved our understanding of AAA pathogenesis.

Disclosure

Author's contribution:

Conceptualization: MS

Methodology: JB

Software: KB, JB

Check: MS

Formal Analysis: MS

Investigation: JL, JB

Resources: JL, KB

Data Curation: JL

Writing-Rough Preparation: MS, KB

Writing-Review and Editing: MS, JB, JL

Visualization: KB

Supervision: MS

Project Administration: MS

All authors have read and agreed with the published version of the manuscript.

Funding Statement:

The Study Did Not Receive Special Funding.

Institutional Review Board Statement:

Not Applicable.

Informed Consent Statement:

Not Applicable.

Data Availability Statement:

Not Applicable.

Acknowledgments

Not Applicable.

Conflict of Interest Statement

The authors report no conflict of interest.

References

1. Gao JP, Guo W. Mechanisms of abdominal aortic aneurysm progression: A review. *Vasc Med*. 2022;27(1):88-96. doi:10.1177/1358863X211021170
2. Umebayashi R, Uchida HA, Wada J. Abdominal aortic aneurysm in aged population. *Aging (Albany NY)*. 2018;10(12):3650-3651. doi:10.18632/aging.101702
3. Picatoste B, Cerro-Pardo I, Blanco-Colio LM, Martín-Ventura JL. Protection of diabetes in aortic abdominal aneurysm: Are antidiabetics the real effectors?. *Front Cardiovasc Med*. 2023;10:1112430. Published 2023 Mar 23. doi:10.3389/fcvm.2023.1112430
4. Hellawell HN, Mostafa AMHAM, Kyriacou H, Sumal AS, Boyle JR. Abdominal aortic aneurysms part one: Epidemiology, presentation and preoperative considerations. *J Perioper Pract*. 2021;31(7-8):274-280. doi:10.1177/1750458920954014
5. Arellano-Gutiérrez G, Rodríguez-Andrade AY, Murillo-Barrios IE. Abdominal aortic aneurysm characteristics and outcomes: a single-center retrospective cross-sectional study. Características y resultados de aneurismas aórticos abdominales: estudio

transversal y retrospectivo de un solo centro. *Cir Cir*. 2023;91(6):730-735. doi:10.24875/CIRU.22000474

6. Benson RA, Meecham L, Fisher O, Loftus IM. Ultrasound screening for abdominal aortic aneurysm: current practice, challenges and controversies. *Br J Radiol*. 2018;91(1090):20170306. doi:10.1259/bjr.20170306
7. Rodríguez Donoso J, Martín Ramos E, Aparicio Velasco J, Fonte Eliozondo L, Muñoz Críspulo E, Ruiz Arribas C. Abdominal aortic aneurysm ultrasound screening in men with risk factors in Primary Care. *Aten Primaria*. 2022;54(3):102234. doi:10.1016/j.aprim.2021.102234
8. Cosford PA, Leng GC. Screening for abdominal aortic aneurysm. *Cochrane Database Syst Rev*. 2007;(2):CD002945. Published 2007 Apr 18. doi:10.1002/14651858.CD002945.pub2
9. Altobelli E, Rapacchietta L, Profeta VF, Fagnano R. Risk Factors for Abdominal Aortic Aneurysm in Population-Based Studies: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2018;15(12):2805. Published 2018 Dec 10. doi:10.3390/ijerph15122805
10. Ali MU, Fitzpatrick-Lewis D, Miller J, et al. Screening for abdominal aortic aneurysm in asymptomatic adults. *J Vasc Surg*. 2016;64(6):1855-1868. doi:10.1016/j.jvs.2016.05.101
11. Stather PW, Dattani N, Bown MJ, Earnshaw JJ, Lees TA. International variations in AAA screening. *Eur J Vasc Endovasc Surg*. 2013;45(3):231-234. doi:10.1016/j.ejvs.2012.12.013
12. Clancy K, Wong J, Spicher A. Abdominal Aortic Aneurysm: A Case Report and Literature Review. *Perm J*. 2019;23:18.218. doi:10.7812/TPP/18.218
13. Torres-Fonseca M, Galan M, Martinez-Lopez D, et al. Pathophisiology of abdominal aortic aneurysm: biomarkers and novel therapeutic targets. Fisiopatología del aneurisma de aorta abdominal: biomarcadores y nuevas dianas terapéuticas. *Clin Investig Arterioscler*. 2019;31(4):166-177. doi:10.1016/j.arteri.2018.10.002
14. al-Zahrani HA, Rawas M, Maimani A, Gasab M, Aba al Khail BA. Screening for abdominal aortic aneurysm in the Jeddah area, western Saudi Arabia. *Cardiovasc Surg*. 1996;4(1):87-92. doi:10.1016/0967-2109(96)83791-4
15. Davis FM, Daugherty A, Lu HS. Updates of Recent Aortic Aneurysm Research. *Arterioscler Thromb Vasc Biol*. 2019;39(3):e83-e90. doi:10.1161/ATVBAHA.119.312000

16. Martínez-López D, Cedó L, Metso J, et al. Impaired HDL (High-Density Lipoprotein)-Mediated Macrophage Cholesterol Efflux in Patients With Abdominal Aortic Aneurysm-Brief Report. *Arterioscler Thromb Vasc Biol*. 2018;38(11):2750-2754. doi:10.1161/ATVBAHA.118.311704
17. Burillo E, Lindholt JS, Molina-Sánchez P, et al. ApoA-I/HDL-C levels are inversely associated with abdominal aortic aneurysm progression. *Thromb Haemost*. 2015;113(6):1335-1346. doi:10.1160/TH14-10-0874
18. Huang Z, Su H, Zhang T, Li Y. Double-edged sword of diabetes mellitus for abdominal aortic aneurysm. *Front Endocrinol (Lausanne)*. 2022;13:1095608. Published 2022 Dec 16. doi:10.3389/fendo.2022.1095608
19. Picatoste B, Cerro-Pardo I, Blanco-Colio LM, Martín-Ventura JL. Protection of diabetes in aortic abdominal aneurysm: Are antidiabetics the real effectors?. *Front Cardiovasc Med*. 2023;10:1112430. Published 2023 Mar 23. doi:10.3389/fcvm.2023.1112430
20. Takagi H, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Negative Association of Diabetes With Thoracic Aortic Dissection and Aneurysm. *Angiology*. 2017;68(3):216-224. doi:10.1177/0003319716647626
21. Tsai CL, Lin CL, Wu YY, Shieh DC, Sung FC, Kao CH. Advanced complicated diabetes mellitus is associated with a reduced risk of thoracic and abdominal aortic aneurysm rupture: a population-based cohort study. *Diabetes Metab Res Rev*. 2015;31(2):190-197. doi:10.1002/dmrr.2585
22. Dattani N, Sayers RD, Bown MJ. Diabetes mellitus and abdominal aortic aneurysms: A review of the mechanisms underlying the negative relationship. *Diab Vasc Dis Res*. 2018;15(5):367-374. doi:10.1177/1479164118780799
23. Xu F, Wang W, Lei CX, Yang D, Chen YX, Zheng YH. Influencing Factors of Diabetes Mellitus on Abdominal Aortic Aneurysm Diameter and Biochemical Parameters. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2022;44(3):392-397. doi: 10.3881/j.issn.1000-503X.14706.
24. Raffort J, Lareyre F, Clément M, Hassen-Khodja R, Chinetti G, Mallat Z. Diabetes and aortic aneurysm: current state of the art. *Cardiovasc Res*. 2018;114(13):1702-1713. doi:10.1093/cvr/cvy174
25. Dua MM, Miyama N, Azuma J, et al. Hyperglycemia modulates plasminogen activator inhibitor-1 expression and aortic diameter in experimental aortic aneurysm disease. *Surgery*. 2010;148(2):429-435. doi:10.1016/j.surg.2010.05.014

26. Pham Y, Tu Y, Wu T, et al. Cell division autoantigen 1 plays a profibrotic role by modulating downstream signalling of TGF-beta in a murine diabetic model of atherosclerosis. *Diabetologia*. 2010;53(1):170-179. doi:10.1007/s00125-009-1555-9
27. Wang Y, Ait-Oufella H, Herbin O, et al. TGF-beta activity protects against inflammatory aortic aneurysm progression and complications in angiotensin II-infused mice. *J Clin Invest*. 2010;120(2):422-432. doi:10.1172/JCI38136
28. Golledge J, Karan M, Moran CS, et al. Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. *Eur Heart J*. 2008;29(5):665-672. doi:10.1093/eurheartj/ehm557
29. Steffensen LB, Stubbe J, Lindholt JS, et al. Basement membrane collagen IV deficiency promotes abdominal aortic aneurysm formation. *Sci Rep*. 2021;11(1):12903. Published 2021 Jun 18. doi:10.1038/s41598-021-92303-y
30. Golledge J, Moxon J, Pinchbeck J, et al. Association between metformin prescription and growth rates of abdominal aortic aneurysms. *Br J Surg*. 2017;104(11):1486-1493. doi:10.1002/bjs.10587
31. Golledge J, Morris DR, Pinchbeck J, et al. Editor's Choice - Metformin Prescription is Associated with a Reduction in the Combined Incidence of Surgical Repair and Rupture Related Mortality in Patients with Abdominal Aortic Aneurysm. *Eur J Vasc Endovasc Surg*. 2019;57(1):94-101. doi:10.1016/j.ejvs.2018.07.035
32. Su Z, Guo J, Gu Y. Pharmacotherapy in Clinical Trials for Abdominal Aortic Aneurysms: A Systematic Review and Meta-Analysis. *Clin Appl Thromb Hemost*. 2022;28:10760296221120423. doi:10.1177/10760296221120423
33. Yu J, Morimoto K, Bao W, Yu Z, Okita Y, Okada K. Glucagon-like peptide-1 prevented abdominal aortic aneurysm development in rats. *Surg Today*. 2016;46(9):1099-1107. doi:10.1007/s00595-015-1287-z
34. Raffort J, Chinetti G, Lareyre F. Glucagon-Like peptide-1: A new therapeutic target to treat abdominal aortic aneurysm?. *Biochimie*. 2018;152:149-154. doi:10.1016/j.biochi.2018.06.026
35. Ortega R, Collado A, Selles F, et al. SGLT-2 (Sodium-Glucose Cotransporter 2) Inhibition Reduces Ang II (Angiotensin II)-Induced Dissecting Abdominal Aortic Aneurysm in ApoE (Apolipoprotein E) Knockout Mice. *Arterioscler Thromb Vasc Biol*. 2019;39(8):1614-1628. doi:10.1161/ATVBAHA.119.312659