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LIFESTYLE CHANGES AND MEDICAL THERAPY IN SLOWING THE GROWTH OF SMALL ABDOMINAL AORTIC ANEURYSMS

PROMENE NAČINA ŽIVOTA I MEDIKAMENTNA TERAPIJA U USPORAVANJU RASTA MALIH ANEURIZMI ABDOMINALNE AORTE

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Summary

The goal of our review was to evaluate the impact of lifestyle changes and medical therapy in slowing the growth of small abdominal aortic aneurysms (AAA), as well as to introduce current ideas for future treatment. No viable evidence was found that medical therapy can slow the growth of small AAAs. The beneficial role of propranolol, angiotensin-converting enzyme inhibitors and doxycycline in reducing the growth rate of AAA was ruled out by randomized controlled studies, whereas the efficiency of statins, macrolides and anti-platelet therapy remains controversial. On the other hand, smoking cessation is the only established lifestyle change that was effective in impeding the AAA expansion. Also, there are a considerable number of novel therapeutic strategies related to the problem, which still need to be evaluated in clinical trials, including administration of Cyclosporine A, gene therapy and mesenchymal stem cell treatment.

Keywords: abdominal aortic aneurysm, medical therapy, lifestyle changes, growth.

Sažetak

Cilj našeg rada je bio da ispitamo uticaj promena načina života i medikamentne terapije na usporavanje rasta aneurizmi abdominalne aorte (AAA) i da ukažemo na aktuelne ideje za budući tretman. Nismo pronašli zadovoljavajuće dokaze da medikamentna terapije može da uspori rast malih AAA. Randomizovane kontrolisane studije su opovrgle povoljnu uloga propranolola, inhibitora angiotenzin-konvertujućeg enzima i doksiciklina u smanjenju rasta AAA, dok je efikasnost statina, makrolida i anti-trombocitnih lekova i dalje sporna. Sa druge strane, prestanak pušenja je jedina promena u načinu života koja se pokazala efikasnom u usporavanju rasta AAA. Takodje, značajnom broju novih terapeutskih strategija za usporavanje rasta AAA predstoje klinička ispitivanja, uključujući primenu ciklosporina A, genetsku terapiju i lokalnu primenu mezenhimalnih matičnih ćelija.

Ključne reči: aneurizma abdominalne aorte, medikamentna terapija, način života, rast.

Introduction

Abdominal aortic aneurysm (AAA) is a disease with vague or absent symptoms, which can have catastrophic consequences. Its prevalence in elderly population ranges from 4.0% to 7.2%, with a strong male preponderance (9, 12, 30). In a population-based study the overall mortality associated with AAA rupture was around 80%, with the majority of deaths occurring outside hospital (10). It is established that AAAs with a diameter ≥5.5 cm have a high incidence of rupture, and thus should be treated either with open surgery or with endovascular aneurysm repair (EVAR) (19, 35).

Due to the increasing number of screening programs, there is a growing population of patients aged 65-80 with a small AAA of 3.0 to 5.5 cm in diameter, which are considered safe for observation (11). As aneurysms grow over time, for instance, a 4.5 cm aneurysm would take 2.3 years on average to reach 5.5 cm in diameter, there is a need for non-invasive therapy that would suspend the growth of small AAAs (39).

There is an abundance of preclinical studies using different approaches to impede the aneurysmal growth in animal models (15, 47). In contrast, clinical studies on the subject are scant and their results vary considerably (4, 21, 26, 38). The goal of our review was to evaluate the impact of lifestyle changes and medical therapy in slowing the growth of small AAAs, and to introduce current ideas for future treatment.

The effectiveness of lifestyle changes

Smoking is the most important modifiable risk factor associated with development and expansion of AAA. A recent study including 567 patients from the Aneurysm Detection and Management (ADAM) trial showed that current smoking was a significant risk factor for expansion rate of AAA, aside from the elevated diastolic blood pressure (5). Also, smoking was the only risk factor The United Kingdom Small Aneurysmal Trial (UKSAT) linked with the increased growth rate of AAAs (8). Furthermore, in a systematic review by Lederle et al,

current smokers had a higher relative risk of abdominal aorta-related events than of coronary artery disease and cerebrovascular disease. Therefore, there is no doubt that the smoking cessation should be a standard course of action in patients with small AAAs. Several pharmaceutical agents were developed to help in this effort, varenicline being the most efficient one (20).

All the major guidelines recommend moderate physical activity for prevention and treatment of cardiovascular diseases (23, 46). Additionally, patients with prolonged sedentary lifestyle are more likely to develop AAA (49, 52). Several small studies have shown benefits of physical exercise therapy in terms of cardiopulmonary fitness of patients, but without any effects on AAA growth (28, 37, 44). There is an evident need for larger studies regarding this subject, however patient compliance could present as a major obstacle.

The impact of cardiovascular risk reducing drugs

Early reports gave incentive to evaluate the effect of beta blockers on aneurysmal expansion process (29). Wilmink et al. used data from two major cohorts in a case control study to find no significant evidence of beta blockers influence on AAA growth rate (50). In Propranolol Aneurysm Trial Investigators (PATI) study 548 patients with small AAAs were randomized to either propranolol or placebo control group (40). Even though patients receiving propranolol were less likely to undergo elective aneurysmal repair, there was no significant difference in growth rates of AAA between the groups. Patients with slow-growing AAAs and patients with previously prescribed beta blockers were not included in this trial. The only two randomized control trials (RCT) on the subject showed that propranolol was poorly tolerated in standard dosage, (31, 40) thus leaving the possibility of other beta blockers being more effective in reducing the AAA growth.

Two large retrospective studies concluded that even though angiotensin converting enzyme (ACE) inhibitors reduce the inflammation in the aneurysmatic tissue, they do not affect the aneurysmal growth rate (27, 45). On the other hand, in a prospective study of 1701 participants in UKSAT trial, the use of ACE inhibitors was linked with a significant increase in AAA growth rate (43). In addition, another large case control study found that ACE inhibitor use decreases aortic wall stiffness and increases collagen turnover, further suggesting the negative role of ACE inhibitors in aneurysmatic disease of abdominal aorta (50).

No association was found between other classes of antihypertensive drugs and expansion rate of AAA (5, 50).

Apart from their original effect of reducing cholesterol levels in blood, statins also decrease the activity of proteolytic enzymes in the aneurysmal tissue (51). To this day the role of statins in slowing the aneurysmal growth has been controversial (18). A meta-analysis by Twine et al. found insufficient evidence to confirm the restraining effect of statins on AAA growth (48). However, four high-quality studies from this review reported no significant difference in aneurysmal growth between the statin and the control group. Another more recent meta-analysis of 11 observational comparative studies showed that statin therapy was efficient in decreasing the growth rate of AAAs, especially those with the baseline diameter >3.6 cm. Nevertheless, there are still no RCTs on the subject to resolve the dilemma.

Anti-platelet therapy is associated with good outcomes in patients with cardiovascular disease (2). However, evidence on the influence of antiplatelet therapy on aneurysmal growth is limited. A case control study, conducted on 167 patients, reported that the growth rate of AAAs with a diameter of 4.0 to 4.9 mm is reduced in patients on anti-platelet therapy (32). On the other hand, analyses based on the data from large screening studies showed that there was no link between antiplatelet drugs and AAA growth rate (5, 43). It is still unclear if standard antithrombotic doses of aspirin are sufficient for any notable effects on AAA expansion.

The role of antibiotics

Tetracyclines are broad-spectrum antibiotics, which also inhibit the production of proteolytic enzymes and reduce the level of inflammation in human tissue (41). Several small RCTs provided promising results of short-term doxycycline treatment in slowing AAA growth (3, 36). In contrast, a later multicentre RCT reported that patients using doxycycline had an increased expansion rate of AAA over time, implying the negative effect of tetracycline therapy on patients with AAA (34).

Early reports, which suggested that chlamydial infection had a considerable role in formation of AAA, led to a hypothesis for macrolides efficacy in treatment of small AAAs (24, 25). Two small-sample RCTs associated roxithromicyn administration with a decrease in AAA growth. A large RCT, including 213 patients followed-up for a minimum of 18 months, showed no significant difference in AAA growth rates between patients on azithromycin therapy and the control group.

Future therapeutic strategies

Over the past decade a considerable progress has been made in understanding cellular mechanisms behind aortic aneurysm formation and its development. It has

been established that depletion of vascular smooth muscle cells and degradation of the extracellular matrix, both induced by inflammation, lead to the weakening of the aortic wall and its tendency to rupture (22). Thus began the search for therapeutic options to suspend and reverse these processes.

In their earliest two papers, Allair et al. demonstrated the role of transforming growth factor β (TGF-β) in stabilizing predeveloped aneurysms in an aortic xenograft model by seeding genetically-modified vascular smooth muscle cells (1, 33). In their further research they successfully used gene implementation therapy via adenovirus vectors to promote TGF-β activity in two animal models and human AAA explants (13). Their latest work proposed a short-course administration of Cyclosporin A to increase TGF-β levels in aortic tissue, thereby overcoming the disadvantages of gene and cell-implementation therapies (14). Additionally, they found that a 7-day course of Cyclosporin A had long-term effectiveness in experimental models, suggesting that TGF-B might be a self-promoting factor in abdominal aortic tissue.

A wide variety of genes has been associated with the formation of AAA, however most of these connections seem to be overestimated (7). On the other hand, there is an increasing interest in using non-coding RNAs for treatment of small AAAs, as their role in post-transcriptional processes becomes evident (16, 17).

Adventitial implantation of mesenchymal stem cells showed some success in impeding the process of AAA growth in animal models (6, 42). Although there are no human studies on this matter, focused delivery of stem cells to regenerate the medial tissue of the abdominal aorta is a promising option for the future.

Conclusion

Our review found no viable evidence that medical therapy can slow the growth of small AAAs. The beneficial role of propranolol, ACE inhibitors and doxycycline in reducing the growth rate of AAA was ruled out by RCTs, whereas the efficiency of statins, macrolides and anti-platelet therapy remains controversial. Smoking cessation is the only established lifestyle change that was undeniably effective in impeding the AAA expansion. There is a considerable number of novel therapeutic strategies related to the problem, which still need to be evaluated in clinical trials, including administration of Cyclosporine A, gene therapy and mesenchymal stem cell treatment.

References

1. Allaire E, Muscatelli-Groux B, Guinault AM, Pages C, Goussard A, Mandet C, et al. Vascular smooth muscle cell endovascular therapy stabilizes already developed aneurysms in a model of aortic injury elicited by inflammation and proteolysis. Annals of surgery. 2004;239(3):417-27.
2. Antithrombotic Trialists C, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849-60.
3. Baxter BT, Pearce WH, Waltke EA, Littooy FN, Hallett JW, Jr., Kent KC, et al. Prolonged administration of doxycycline in patients with small asymptomatic abdominal aortic aneurysms: report of a prospective (Phase II) multicenter study. J Vasc Surg. 2002;36(1):1-12.
4. Bergqvist D. Pharmacological interventions to attenuate the expansion of abdominal aortic aneurysm (AAA) - a systematic review. Eur J Vasc Endovasc Surg. 2011;41(5):663-7.
5. Bhak RH, Wininger M, Johnson GR, Lederle FA, Messina LM, Ballard DJ, et al. Factors associated with small abdominal aortic aneurysm expansion rate. JAMA surgery. 2015;150(1):44-50.
6. Blose KJ, Ennis TL, Arif B, Weinbaum JS, Curci JA, Vorp DA. Periadventitial adipose-derived stem cell treatment halts elastase-induced abdominal aortic aneurysm progression. Regenerative medicine. 2014;9(6):733-41.
7. Bradley DT, Badger SA, McFarland M, Hughes AE. Abdominal Aortic Aneurysm Genetic Associations: Mostly False? A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2016;51(1):64-75.
8. Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT, Participants UKSAT. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. Circulation. 2004;110(1):16-21.
9. Brunkwall J, Hauksson H, Bengtsson H, Bergqvist D, Takolander R, Bergentz SE. Solitary aneurysms of the iliac arterial system: an estimate of their frequency of occurrence. J Vasc Surg. 1989;10(4):381-4.
10. Choksy SA, Wilmink AB, Quick CR. Ruptured abdominal aortic aneurysm in the Huntingdon district: a 10-year experience. Annals of the Royal College of Surgeons of England. 1999;81(1):27-31.
11. Cosford PA, Leng GC. Screening for abdominal aortic aneurysm. The Cochrane database of systematic reviews. 2007(2):CD002945.
12. Crawford ES, Cohen ES. Aortic aneurysm: a multifocal disease. Presidential address. Archives of surgery. 1982;117(11):1393-400.
13. Dai J, Losy F, Guinault AM, Pages C, Anegon I, Desgranges P, et al. Overexpression of transforming growth factor-beta1 stabilizes already-formed aortic aneurysms: a first approach to induction of functional healing by endovascular gene therapy. Circulation. 2005;112(7):1008-15.
14. Dai J, Michineau S, Franck G, Desgranges P, Becquemin JP, Gervais M, et al. Long term stabilization of expanding aortic aneurysms by a short course of cyclosporine A through transforming growth factor-beta induction. PloS one. 2011;6(12):e28903.
15. Daugherty A, Cassis LA. Mouse models of abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 2004;24(3):429-34.
16. Davis FM, Rateri DL, Daugherty A. Abdominal aortic aneurysm: novel mechanisms and therapies. Curr Opin Cardiol. 2015;30(6):566-73.
17. Duggirala A, Delogu F, Angelini TG, Smith T, Caputo M, Rajakaruna C, et al. Non coding RNAs in aortic aneurysmal disease. Frontiers in genetics. 2015;6:125.
18. Dunne JA, Bailey MA, Griffin KJ, Sohrabi S, Coughlin PA, Scott DJ. Statins: the holy grail of Abdominal Aortic Aneurysm (AAA) growth attenuation? A systematic review of the literature. Current vascular pharmacology. 2014;12(1):168-72.
19. Filardo G, Powell JT, Martinez MA, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. The Cochrane database of systematic reviews. 2012;3:CD001835.
20. Garrison GD, Dugan SE. Varenicline: a first-line treatment option for smoking cessation. Clinical therapeutics. 2009;31(3):463-91.
21. Golledge J, Powell JT. Medical management of abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2007;34(3):267-73.
22. Guo DC, Papke CL, He R, Milewicz DM. Pathogenesis of thoracic and abdominal aortic aneurysms. Annals of the New York Academy of Sciences. 2006;1085:339-52.

23. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007;116(9):1081-93.
24. Ieven MM, Hoymans VY. Involvement of Chlamydia pneumoniae in atherosclerosis: more evidence for lack of evidence. Journal of clinical microbiology. 2005;43(1):19-24.
25. Karlsson L, Gnarpe J, Naas J, Olsson G, Lindholm J, Steen B, et al. Detection of viable Chlamydia pneumoniae in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2000;19(6):630-5.
26. Kokje VB, Hamming JF, Lindeman JH. Editor's Choice - Pharmaceutical Management of Small Abdominal Aortic Aneurysms: A Systematic Review of the Clinical Evidence. Eur J Vasc Endovasc Surg. 2015;50(6):702-13.
27. Kortekaas KE, Meijer CA, Hinnen JW, Dalman RL, Xu B, Hamming JF, et al. ACE inhibitors potently reduce vascular inflammation, results of an open proof-of-concept study in the abdominal aortic aneurysm. PloS one. 2014;9(12):e111952.
28. Kothmann E, Batterham AM, Owen SJ, Turley AJ, Cheesman M, Parry A, et al. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms: a pilot study. British journal of anaesthesia. 2009;103(4):505-10.
29. Leach SD, Toole AL, Stern H, DeNatale RW, Tilson MD. Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms. Archives of surgery. 1988;123(5):606-9.
30. Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Ann Intern Med. 1997;126(6):441-9.
31. Lindholt JS, Henneberg EW, Juul S, Fasting H. Impaired results of a randomised double blinded clinical trial of propranolol versus placebo on the expansion rate of small abdominal aortic aneurysms. International angiology : a journal of the International Union of Angiology. 1999;18(1):52-7.
32. Lindholt JS, Sorensen HT, Michel JB, Thomsen HF, Henneberg EW. Low-dose aspirin may prevent growth and later surgical repair of medium-sized abdominal aortic aneurysms. Vascular and endovascular surgery. 2008;42(4):329-34.
33. Losy F, Dai J, Pages C, Ginat M, Muscatelli-Groux B, Guinault AM, et al. Paracrine secretion of transforming growth factor-beta1 in aneurysm healing and stabilization with endovascular smooth muscle cell therapy. J Vasc Surg. 2003;37(6):1301-9.
34. Meijer CA, Stijnen T, Wasser MN, Hamming JF, van Bockel JH, Lindeman JH, et al. Doxycycline for stabilization of abdominal aortic aneurysms: a randomized trial. Ann Intern Med. 2013;159(12):815-23.
35. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.
36. Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. J Vasc Surg. 2001;34(4):606-10.
37. Myers J, McElrath M, Jaffe A, Smith K, Fonda H, Vu A, et al. A randomized trial of exercise training in abdominal aortic aneurysm disease. Medicine and science in sports and exercise. 2014;46(1):2-9.
38. Powell JT, Brady AR. Detection, management, and prospects for the medical treatment of small abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol. 2004;24(2):241-5.
39. Powell JT, Sweeting MJ, Brown LC, Gotensparre SM, Fowkes FG, Thompson SG. Systematic review and meta-analysis of growth rates of small abdominal aortic aneurysms. The British journal of surgery. 2011;98(5):609-18.
40. Propanolol Aneurysm Trial I. Propranolol for small abdominal aortic aneurysms: results of a randomized trial. J Vasc Surg. 2002;35(1):72-9.
41. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. Journal of the American Academy of Dermatology. 2006;54(2):258-65.
42. Sharma AK, Lu G, Jester A, Johnston WF, Zhao Y, Hajzus VA, et al. Experimental abdominal aortic aneurysm formation is mediated by IL-17 and attenuated by mesenchymal stem cell treatment. Circulation. 2012;126(11 Suppl 1):S38-45.
43. Sweeting MJ, Thompson SG, Brown LC, Greenhalgh RM, Powell JT. Use of angiotensin converting enzyme inhibitors is associated with increased growth rate of abdominal aortic aneurysms. J Vasc Surg. 2010;52(1):1-4.
44. Tew GA, Moss J, Crank H, Mitchell PA, Nawaz S. Endurance exercise training in patients with small abdominal aortic aneurysm: a randomized controlled pilot study. Archives of physical medicine and rehabilitation. 2012;93(12):2148-53.
45. Thompson AR, Cooper JA, Ashton HA, Hafez H. Growth rates of small abdominal aortic aneurysms correlate with clinical events. The British journal of surgery. 2010;97(1):37-44.
46. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation. 2003;107(24):3109-16.
47. Thompson RW, Curci JA, Ennis TL, Mao D, Pagano MB, Pham CT. Pathophysiology of abdominal aortic aneurysms: insights from the elastase-induced model in mice with different genetic backgrounds. Annals of the New York Academy of Sciences. 2006;1085:59-73.
48. Twine CP, Williams IM. Systematic review and meta-analysis of the effects of statin therapy on abdominal aortic aneurysms. The British journal of surgery. 2011;98(3):346-53.
49. Vollmar JF, Paes E, Pauschinger P, Henze E, Friesch A. Aortic aneurysms as late sequelae of above-knee amputation. Lancet. 1989;2(8667):834-5.
50. Wilmink AB, Vardulaki KA, Hubbard CS, Day NE, Ashton HA, Scott AP, et al. Are antihypertensive drugs associated with abdominal aortic aneurysms? J Vasc Surg. 2002;36(4):751-7.
51. Wilson WR, Evans J, Bell PR, Thompson MM. HMG-CoA reductase inhibitors (statins) decrease MMP-3 and MMP-9 concentrations in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg. 2005;30(3):259-62.
52. Yeung JJ, Kim HJ, Abbruzzese TA, Vignon-Clementel IE, Draney-Blomme MT, Yeung KK, et al. Aortoiliac hemodynamic and morphologic adaptation to chronic spinal cord injury. J Vasc Surg. 2006;44(6):1254-65.