Review

Paradoxical Associations of Diabetes and Obesity with Abdominal Aortic Aneurysm

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Abdominal aortic aneurysm (AAA), defined as a localized dilatation of abdominal aorta, is a significant cause of morbidity and mortality in aging populations. AAA is a life-threatening disease mainly because of the high fatality rates associated with aneurysm rupture. Early detection of AAAs will provide patients an opportunity to receive medical therapy and undergo elective repair before aneurysm rupture. Historically, AAA is considered a macrovascular atherosclerotic disease. Classic risk factors of atherosclerosis, such as advanced age, male gender, smoking, hyperlipidemia, and hypertension, have been associated with an increased risk of AAA formation and expansion. However, more recent laboratory and epidemiologic studies have challenged this conventional theory and indicate that the etiology of AAA is distinct from atherosclerosis per se. This review focused on the evidence on the seemingly paradoxical inverse and positive associations of diabetes and obesity, respectively, with AAA. AAA progresses more slowly in diabetics and diabetic patients are less likely to have a ruptured AAA at the time of repair, suggesting that diabetes or its medications may protect against the development and improve the prognosis of AAA. Meanwhile, obesity has been implicated in the pathogenesis of both diabetes and atherosclerosis, for which the key mechanisms include insulin resistance and release of adipokines. Data on the associations between measures of obesity and AAA are inconsistent. Insights into the relation between diabetes, obesity and AAA will help identify high-risk subpopulations for AAA screening and optimize prevention strategy for individual patients. An improved knowledge of the mechanisms underlying the link between diabetes, obesity and AAA also has important therapeutic implications.

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INTRODUCTION

Abdominal aortic aneurysm (AAA), defined as a localized dilatation of abdominal aorta, is a significant cause of morbidity and mortality in aging populations. The prevalence of AAA estimated from ultrasound screening in adults aged ≥ 65 years ranged from 1.7% to 12.9% among men [1-6] and from 0.6% to 1.7% among women [4,5,7] in western countries. AAA is a life-threatening disease mainly because of the high fatality rates associated with aneurysm rupture. Mortality of ruptured AAA is as high as 70% for patients reaching the hospital and 35% for those undergoing emergency surgery.[8,9] Early detection of AAAs will provide patients an opportunity to receive medical therapy and undergo elective repair before aneurysm rupture. Though typically silent for years, as many as 1 in 3 AAAs may eventually rupture if left undetected and untreated.[10] In the US, AAA is a top 15 leading cause of death among adults aged 60-89 years.[11] At least 14,000 deaths per year in the US are due to AAAs.[11] This number is likely an underestimation, because rupture is usually the first and only clinical manifestation of AAA;[12] an estimated 5% of the 200,000 people who died of sudden death each year may have AAA as the cause.[13] Thirty-day mortality after elective open repair for AAA ranges from 3.0%[14] to 8.4%;[15] short-term morbidity and mortality after endovascular repair is even lower.[16] Given these facts, AAA is a significant life-threatening disease that requires greater recognition and attention.

Historically, AAA is considered a macrovascular atherosclerotic disease. Classic risk factors of atherosclerosis, such as advanced age, male gender, smoking, hyperlipidemia, and hypertension, have been associated with an increased risk of AAA formation and expansion.[17] However, more recent laboratory and epidemiologic studies have challenged this conventional theory and indicate that the etiology of AAA is distinct from atherosclerosis per se. The United States Preventive Services Task Force (USPSTF) recommends AAA screening for men aged 65 to 75 years with a history of

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smoking based on the high prevalence of AAA in smokers.[18] However, these guidelines exclude other important high-risk subpopulations. More studies are critically needed to further improve AAA risk prediction. To our knowledge, only the Honolulu Heart Program,[19] Health Professionals Follow-up Study,[20] and Women's Health Initiative[21] have prospectively examined and reported results on risk factors for incident AAA in US adults. Most other US cohort studies either did not collect information on incident AAA, or have not explored AAA as an endpoint of interest.

ASSOCIATION BETWEEN DIABETES AND AAA

Diabetes and atherosclerotic disease share several important pathogenic mechanisms. Diabetic patients have significantly higher risk of atherosclerotic disease in many vascular beds (including renal vasculature, carotid artery, and coronary artery). In turn, it is reasonable to postulate diabetes a potential risk factor for AAA. However, a number of large-scale screening [1,6,22-27] and Clinical [20,21,28-31] studies reported that the prevalence of AAA was lower in participants with versus without diabetes. Majority of previous studies that have examined associations of diabetes [4,22,25,26,32,33] with AAA are cross-sectional, from which cause and effect cannot be inferred. Only a few prospective studies have examined the association between history of diabetes with incident AAA, the results are inconsistent. We are aware of 6 studies that examined the prospective associations of diabetes or impaired glucose tolerance (IGT) with incident AAA, of which one[21] reported a statistically significant inverse association for diabetes, two [20,30] found an inverse association for diabetes that were not statistically significant, and three [19,34,35] found no association for IGT or blood glucose. The inverse association of diabetes and AAA contradicts what is expected. One possible explanation is competing risk, i.e. AAA may be particularly lethal in diabetic patients, and thus fewer patients are observed with both conditions. However, hospital data have shown that diabetics were less likely to have a ruptured AAA at the time of repair.[36] AAA is also reported to progress more slowly in diabetics.[37-42] These findings suggest that the observed association may represent a true protective effect of diabetes, its medications, or both, on the development and growth of AAA. We recently conducted a prospective analysis among 25,554 male physicians in the Physicians' Health Study who were aged ≥ 50 years and reported no AAA at baseline. In this study, we documented 471 newly diagnosed AAA during a mean of 10.4 years' follow-up. Overall, baseline history of diabetes tended to be associated with a lower risk of diagnosed AAA (hazard ratio [HR]: 0.79, 95% CI: 0.57–1.11); this association appeared to vary by follow-up time (HR = 1.56 and 0.63 during ≤ and >2 years' follow-up, respectively). One plausible explanation is that lifestyle changes after diabetes diagnosis, such as smoking cessation, weight control and exercise, and medication treatment for diabetes may have favorable effects against AAA development and lead to a lower risk during longer-term follow-up.

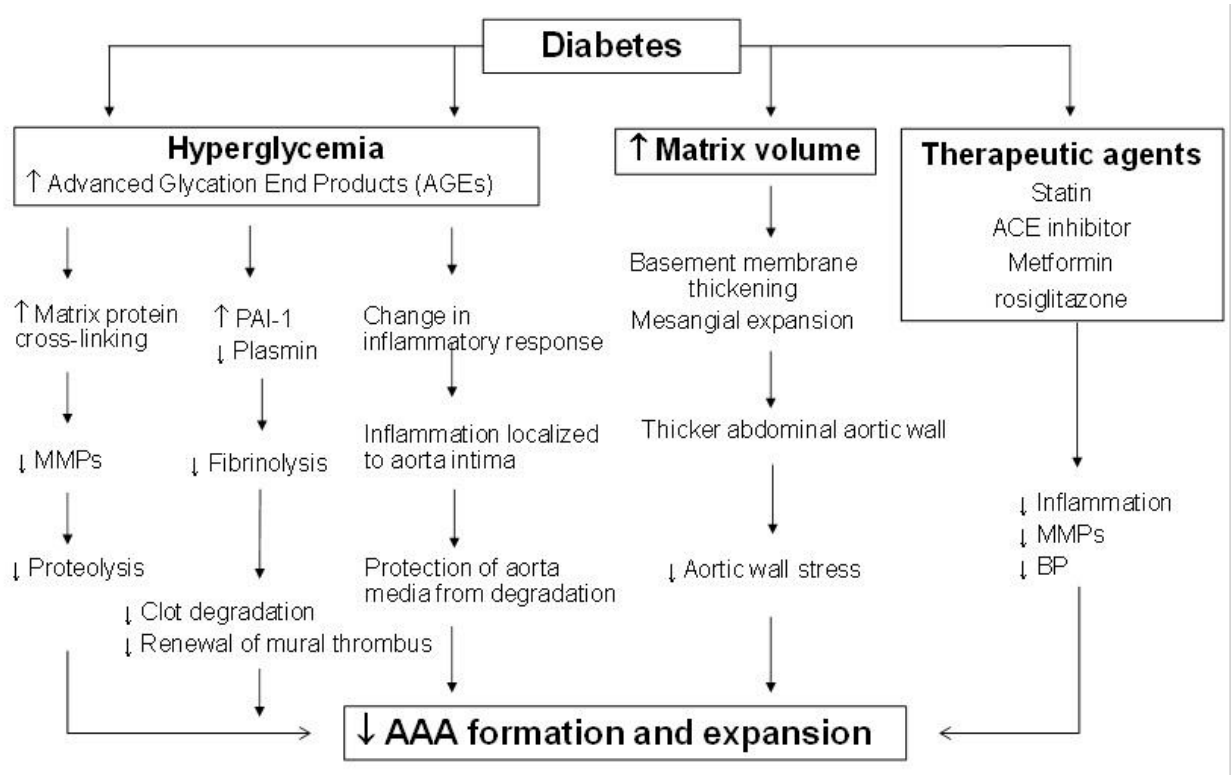

Figure 1. Potential effects of diabetes on pathogenesis of abdominal aortic aneurysms.

Laboratory studies have suggested that diabetes may modify the risk of AAA through multiple mechanisms **(Figure 1)**. The hyperglycemia-induced advanced glycation induces cross-linking of elastin and collagen in the extracellular matrix (ECM) within abdominal aorta wall.[43] This alteration in ECM composition inhibits secretion of metaloproteinases (MMPs) in local vascular bed and prevents excessive proteolysis, a process that plays key role in formation and progression of AAA.[39] Hyperglycemia also modulates expression of plasminogen activator inhibitor-1 (PAI-1) and subsequently suppresses activity of plasmin.[44] These changes in fibrinolytic system potentially reduce clot degradation and renewal of intraluminal thrombus in AAA, improving aneurysmal wall stability and slowing the rate of expansion.[45,46] Exposure to glycated and cross-linked collagen lattices also alter inflammation, another major factor that plays an important role in AAA.[47] In diabetic aorta, cellular response of inflammatory cells change, resulting in localization of inflammation to the intima and protecting the media from matrix degradation.[48] Moreover, a high aortic wall stress is fundamental to AAA development and progression.[49] Diabetics have a thicker abdominal aortic wall due to increased matrix volume[39,50] and therefore lower aortic wall stress.[51] Finally, several drugs used in diabetes management may benefit AAA, including statins,[52] angiotensin converting enzyme (ACE) inhibitors,[53] metformin,[54] and rosiglitazone.[55] However, experimental studies showed that hyperglycemia limited AAA enlargement in mouse models, and this effect was diminished by insulin therapy.[56] In clinical studies, an inverse association between fasting glucose and aortic diameter was found in non-diabetic participants.[6] These findings suggest that hyperglycemia, rather than its treatment, protects against AAA development and progression.

ASSOCIATION BETWEEN OBESITY AND AAA

Obesity, a major public health problem in the US[57] and worldwide,[58] is a known risk factor for many chronic diseases including diabetes and atherosclerosis. One primary mechanism by which obesity is implicated in both morbidities is insulin resistance. Findings of an inverse association between diabetes, characterized by insulin resistance, and AAA raise further interest in the association of obesity with AAA. Other pathogenic processes related to obesity, such as release of adipokines, add more complexity to the subject.[59] Data on the association between measures of obesity and AAA are limited and inconsistent. A recent meta-analysis of cross-sectional studies found that 3 in 5 that examined body mass index (BMI) and 2 in 3 that examined waist circumference reported a positive association with presence of AAA.[60] However, no causal relation can be inferred from these findings. There was no association between BMI and AAA growth based on limited data in 2 studies.[60] In contrast, another recent meta-analysis reported an inverse relation between BMI and growth rate of small AAA, with each kg/m^2 increase in BMI associated with a slower growth of AAA by 0.017 mm/y ($p = 0.039$) in an unadjusted model and 0.008 mm/y ($p = 0.35$) in an adjusted model.[42]

Majority of previous studies that have shown associations of obesity[25,27,59,61,62] with AAA are cross-sectional. Only a few prospective studies have examined the association between obesity and incident AAA, the results are inconsistent. Out of eight studies that examined the associations of obesity with incident AAA, two[20,34] reported a positive association for overall obesity (defined by BMI or body weight), six[19,21,30,35,63,64] found no association for BMI but in two of them[30,63] there was a positive association for abdominal obesity (defined by waist circumference or Sagittal abdominal diameter). These previous studies are generally limited in number of cases and method of case identification. In our recent prospective analysis in the Physicians' Health Study, with 471 newly diagnosed AAA during a mean of 10.4 years' follow-up, compared with men who had baseline BMI < 25 kg/m^2, the multivariable HR (95% CI) of newly diagnosed AAA was 1.30 (1.06-1.59) for BMI 25-<30 kg/m^2 and 1.69 (1.24–2.30) for BMI ≥ 30 kg/m^2. The risk of diagnosed AAA was significantly higher by 6% with each unit increase in baseline BMI. This association was consistent regardless of the other known AAA risk factors and preexisting vascular diseases. Though it remains possible that other lifestyle factors correlated with obesity may explain this association, finding in mouse models that weight loss limited AAA progression lends support to a direct effect of obesity on AAA.[65] Among several plausible pathogenic processes proposed to explain an association between obesity and AAA, the most compelling hypothesis is obesity-induced release of adipokines and aortic inflammation.[17,66] The abdominal aorta is surrounded by significant amounts of peri-vascular adipose tissue. These adipose tissues produce and release various adipokines such as adiponectin,[67] leptin,[68] and resistin,[69] that can modulate inflammation. In obesity, the release of pro-inflammatory adipokines by excessive peri-aortic adipose tissues will promote aortic inflammation, which leads to vessel weakening and dilatation.[70-72] Histological study has shown that peri-vascular adipose tissue is in close proximity to vascular walls and release adipokines in high concentrations to the peri-abdominal aortic zone.[73] Increased macrophage infiltration and inflammatory cytokine expression in peri-aortic adipose tissue had been found in mice with AAA.[74] In a case-control study of 35 AAA patients and 140 age- and sex-matched controls, high-sensitivity C-reactive protein (hsCRP) level was significantly associated with AAA (odds ratio [OR] per 1 mg/L: 1.1, 95% CI: 1.01-1.2).[75] In a population-based cohort study, serum concentrations of resistin (OR per 10 ng/mL: 1.53, 95% CI: 1.26-1.85) and adiponectin (OR per 5 μg/mL: 1.26, 95% CI: 1.07-1.50), but not leptin, were independently associated with the presence of AAA ≥ 30 mm, after controlling for other known risk factors.[59]

IMPLICATION FOR FUTURE RESEARCH

The seemingly paradoxical inverse and positive associations of diabetes and obesity, respectively, with AAA has important clinical and public health implications. Although AAA is more common in individuals with atherosclerosis such as coronary artery disease, ample evidence suggests that the pathogenesis of AAA is different from that of occlusive atherosclerotic disease.[76] Recent prospective evidence has also confirmed the

contrasting associations of obesity and diabetes with AAA. Insights into the relation between diabetes, obesity and AAA will help identify high-risk subpopulations for AAA screening and optimize prevention strategy for individual patients. An improved knowledge of the mechanisms underlying the link between diabetes, obesity and AAA also has important therapeutic implications. For example, if hyperglycemia in diabetes contributes to the lower risk of AAA, the intensive blood glucose-lowering therapy may actually increase the risk of AAA in diabetic patients. On the other hand, if obesity-induced inflammation is the reason for the association between obesity and AAA, the pro-inflammatory adipokines may be a target for therapeutic intervention. Given the high prevalence of diabetes and obesity and the high mortality associated with AAA rupture, the relation between these health conditions is an urgent, unsettled research area that warrants further investigation.

CONCLUSIONS

AAA is a significant cause of morbidity and mortality in aging populations. Multiple risk factors for atherosclerosis are also risk factors of AAA. Accumulating evidence from epidemiological studies, especially prospective cohorts, suggest that baseline obesity is associated with a higher risk of clinically diagnosed AAA while a history of diabetes might be associated with a lower risk of diagnosed AAA. The complex associations of diabetes and obesity with risk of AAA highlight a unique pathogenesis of AAA with important clinical and public health implications.

CONFLICT OF INTEREST

None.

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