Diabetes mellitus and abdominal aortic aneurysm: Literature review and 10-year retrospective analysis

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Abstract:

Background: According to a number of epidemiological studies, diabetes mellitus (DM) is associated with a reduced risk of abdominal aortic aneurysm (AAA), but there is no evidence from prospective studies. We conducted a systematic review of prospective studies in search for a correlation between DM and AAA size, clinical presentation and outcome. The second part of our study is a retrospective analysis for a 10-year period involving AAA-patients, treated in National Heart Hospital.

Methods: We summarized several prospective studies that report the relative risk of the natural history of AAA and its association with DM. In the retrospective part of our study we assessed the following characteristics: age, risk factors, pharmacological treatment of DM, type of clinical presentation and surgical repair, early complications and outcome.

Results: The retrospective analysis comprises the period between 2008-2018. A total of 387 patients are included, of which 8.3% are women and 91.7% - male. The mean age for the women is 70.8 years, and for the men 67.9 years The total number of patients with DM was 50 (12.9%). Of these, 10 patients had ruptured AAA, 10 patients were with symptomatic clinical presentation and 30 patients underwent elective repair. The mean diameter of the AAA in men without or with DM is 63.1 mm. and 61.3 mm., and for women - 57.6 mm. and 56.8 mm. respectively. We observed a lower complication rate in non-diabetic population- 2.6%. As anticipated the complications were higher in diabetic patients-14.3%.

Conclusion: Our results revealed that patients with DM have smaller AAAs compared with non-diabetic population, but they experience more early surgical complications. Nevertheless, whether the use of pharmacological agents for treatment of DM explain these results should be discussed in further studies. They should focus on development of new therapeutic agents aimed at slowing or even preventing the progression of abdominal aortic aneurysm.

INTRODUCTION

The epidemiology of abdominal aortic aneurysm (AAA) is easier to understand through analyzing data from screening and biology studies. AAA often occurs when genetically predisposed individuals are exposed to additional risk factors such as smoking and advanced age. Epidemiological evidence suggests that patients with diabetes mellitus (DM) have a lower incidence of AAA. Unfortunately, the exact mechanisms of this negative association are unclear. There is limited information on the clinical outcome of patients with or without medical treatment of diabetes and concomitant aneurysms.[1]

The most widespread definition of AAA is based on the diameter of the abdominal aorta: an abdominal aortic diameter of 3.0 cm or more, which is usually more than 2 standard deviations above the mean diameter for men, is considered to be aneurysmal. This definition, based on external ultrasound diameters, had a sensitivity of 67% and a specificity of 97% in predicting the need for AAA repair within 10 years. A lower threshold might be more appropriate in women and some Asian populations. Diameter measurements vary according to the imaging modality. Therefore, all studies should specify the site and plane of measurement of aortic diameter. [2]

There are a few suggested reporting standards for AAA.

- AAA in men of European origin can be defined as an abdominal aortic diameter of 3.0 cm in either anteroposterior or transverse planes.
- AAA also can be defined when the maximum diameter is 50% greater than the suprarenal diameter.

We summarized several prospective studies that report the relative risk of the natural history of AAA and its association with DM. In the retrospective part of our study we assessed the following characteristics: age, risk factors, pharmacological treatment of DM, type of clinical presentation and surgical repair, early complications and outcome. All included patients were hospitalized and underwent an elective or emergency AAA repair.

MATERIALS AND METHODS

Statistical analysis was performed with SPSS v.13.0 for Windows. A descriptive analysis, Pearson Chi-square test, Fisher's

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exact test, Independent Samples T-test and nonparametric K independent samples test (Mann-Whitney U-test) were used. A p-value <0.05 was considered significant.

RESULTS

The retrospective analysis comprises the period between 2008 -2018. A total of 387 patients with AAA were included. They were stratified by known risk factors for AAA- arterial hypertension, smoking, dyslipidemia, gender and age. Gender distribution is as follows: 8.3% female and 91.7% male. The mean age for women is 70.8 years, and for men 67.9 years. 362 patients (93.5%) suffer from concomitant arterial hypertension (AH). 164 patients (42.4%) have dyslipidemia. 274 (70.8%) were current smokers, 65 patients (16.8%) had no smoking history and for 48 patients (12.4%) there was no collected data about tobacco use. The total number of patients with diabetes was 50 (12.9%). Among the male population 37 patients (10.4%) were treated with oral anti-diabetic drugs, 6 patients (1.7%) with insulin and 2 patients (0.6%) were on mixed therapy. Among the female population 4 patients (12.5%) were on oral anti-diabetic drugs, 1 patient (3.1%) was on insulin, no patients on mixed therapy. (There is no adequate data about the type of diabetes, but it could be suspected that the majority of patients have Type-2 Diabetes (T2D)). 35 patients from the whole diabetic population were medicated with metformin, 3 were on a diet and 3 were medicated with sulfonylurea drugs (SUD).

DM (+)	Oral antidiabetic drug	Insulin therapy	Mixed therapy
male	37p. (10.4%)	6p. (1.7%)	2p. (0.6%)
female	4p. (12.5%)	1p. (3.1%)	0p.

We evaluated the known risk factors for AAA in both diabetic and non-diabetic populations. The table represents the history of known risk factors such as arterial hypertension, dyslipidemia and smoking history and the presence or not of DM.

	Arterial Hypertension	Dyslipidemia	Smoking history
DM (+)	49p. (13.5%)	24p. (14.6%)	39p. (14.3%)
DM (-)	313p. (86.5%)	140p. (85.4%)	235p. (85.7%)
P-value	0.13	0.23	0.55

*p.=patients'

We appraised the link between DM and one or more than one risk factor. AH and smoking combined seem to be the two major risk factors associated with development of AAA in both diabetic and non-diabetic population.

	One risk factor	Two risk factors	Three risk factors
DM (+)=50p.	5p. (10%)	24p. (48%)	21p. (42%)
DM (-)= 337p.	150p. (44.5%)	173p. (51.3%)	112p. (33.2%)

*p.=patients'; p=0.55

We evaluated the mean AAA diameter in both diabetic and non-diabetic populations. The mean diameter in the non-diabetic population was 63.6mm, while in the diabetics was significantly smaller- 61.6mm. When separating the population by gender, we found that the diameter of AAA in men with diabetes was 61.3mm, in women with diabetes was 56.8mm, in men without diabetes was 63.1mm and in women without diabetes- 57.6mm. (p=0.04). Our results showed statistically significant diminished diameters in diabetic group.

	Whole population	Male	Female
DM (-)	63.6mm	63.1mm	57.6mm
DM (+)	61.6mm	61.3mm	56.8mm

The following tables represent the type of AAA presentation and surgical treatment in both diabetic and non-diabetic groups, distributed by gender.

Male	Symptomatic AAA	Ruptured AAA	Elective repair
DM (+)= 45p.	10p. (22.2%)	8p. (17.8%)	27p. (60%)
DM (-)= 310p.	42p. (13.5%)	67p. (21.6%)	201p. (64.7%)

*p.=patients'; p=0.29

Female	Symptomatic AAA	Ruptured AAA	Elective repair
DM (+)= 5p.	0p.	2p. (40%)	3p. (60%)
DM (-)= 27p.	4p. (14.8%)	7p. (26%)	16p. (59%)

*p.=patients'; p=0.59

To make a clearer statistical analysis we selected two cohorts of patients - 50 diabetics and 50 non-diabetics. The patients without diabetes were selected sequentially. All the patients were selected to correspond to appropriate criteria – similar age and concomitant arterial hypertension. T-test analysis showed that the mean diameter of the AAA in non-diabetics was 63.6mm and 61.1mm in the diabetic patients (p=0.04) Our data shows a significant difference in the mean diameter of AAA dependent on concomitant history of diabetes.

Group Statistics	DM	N	Mean diameter of AAA	Std. Deviation	Std. Error Mean
	(-)	50	63.6mm	8,428232	1,191932
	(+)	50	61.1mm	15,51222	2,193759

Endovascular and surgical treatments, including aneurysm exclusion and vascular prosthesis implantation are standard procedures, but prevention of complications is important. We summarise those among the study population.The most common complications include wound infection and graft thrombosis. The table shows generally low rates in regards to every type of complication listed after both open and endovascular repair. Early death rate was 10 patients, among which 6 patients presented with rupture of AAA.

Type of complication	Wound infection	Ureter injury	Graft thrombosis	endoleak	Wound bleeding	Pseudoaneurysm of distal anastomosis	Stenosis of distal anastomosis	Amputation	Ileus	Death
+DM	4.1%	0.26%	2.3%	0.8%	1.3%	1.5%	0.5%	0.8%	0.5%	2.3%
- DM	0.8%	-	0.5%	0.26%	-	0.26%	-	0.5%	-	0.26%

DISCUSSION

AAAs remain one of the most important preventable, life-threatening diseases. Recent studies suggest an average annual death rate of 2.8 per 100 000 due to AAA. This marks a 12% increase in the last 20 years. AAA is a multifactorial disease with both genetic and environmental factors involved. Population screening suggests several common cardiovascular risk factors for AAA, including smoking, family history and gender. Smoking is the strongest risk factor for AAA, with an odds ratio of >3 for the association and higher in women. It has been estimated that 75% of all AAA cases in the population are mainly attributable to smoking. [2]. Unique twin registry studies from Sweden and Denmark suggest that the heritability may be as high as 70%. Of all risk factors tobacco usage was observed to be the strongest one in our study,linking to 70% of smokers suffering from AAA.

AAA prevalence and incidence rates have decreased over the last 20 years, which has been attributed partially to the decline in smoking. Prevalence is negligible before the age of 55-60 years and thereafter increases steadily with age. Population screening studies offer the best evidence regarding the contemporary prevalence of AAA. The current prevalence in 65 year old men is 1.7% in the Swedish Screening Programme with an additional 0.5% with an already known AAA and 1.3% in the UK National Screening Programme and 3.3% in a Danish screening program targeting men aged 65-74 years. In contrast, a programme in the USA which only offers screening to smokers reports a prevalence of over 5%. Most studies show that the prevalence is up to fourfold less in women than men. Our results fully support the expected distribution of AAA mostly in men- 91.7% of all patients. The mean age of the subjects in our study is 70.8 years for women and 67.9% for men. A recent systematic review of publications between 2000 and 2015 indicates that the pooled prevalence of AAA in women over 60 years was 0.7% [2]

Diabetes is a highly prevalent chronic disease which affects the whole body metabolism. DM corresponds to a heterogeneous disease characterized by a chronic hyperglycemia and is generally classified in several categories - mainly type 1 (T1D) and type 2 diabetes (T2D). The risk of developing AAA in a person with diabetes, especially T2D, is about half that in a person without diabetes.[2] Paradoxically, despite the fact that diabetes is a strong risk factor for cardiovascular diseases, multiple epidemiological studies and meta-analyses have suggested an inverse relationship between DM and AAA. The underlying mechanism of how DM influences the pathology of the aorta is not well understood. Alternatively, aortic aneurysm disease may be limited by medications for DM in addition to the disease itself. Recent studies indicate that metformin, one of the most frequently prescribed oral antidiabetic drugs, was associated with a statistically decreased risk of aortic aneurysm disease and a potential to limit the enlargement of AAA. Metformin is a standard medication for the treatment of insulin-resistant (type 2) diabetes. Besides its broad influence on metabolism, metformin was suggested to inhibit aortic smooth muscle cell proliferation and matrix metalloproteinase-2 expression in biological experiments, which might induce a pleiotropic effect on cardiovascular protection. However, the relationship between metformin prescription and aortic aneurysm is still nubilous[3]. Unfortunately, based on the retrospectively collected data in our study, we could not prove statistically significant correlation between the size of AAA and type of antidiabetic therapy.

Natural history of small AAA.

The natural history of small AAA consists of progressive growth in the majority of patients. The RESCAN study, an individual patient meta-analysis of >15,000 patients with AAA, 3.0-5.5 cm in diameter, indicated that: (1) there was no difference in aneurysm growth rates between men and women, both on average grew 2.2 mm/ year, (2) smoking increased aneurysm growth rates by 0.35 mm/year (about 16%), and (3) diabetes was associated with decreased aneurysm growth rates by 0.51 mm/year (approximately 25% reduction). Within the diameter range studied, there was an exponential increase in average growth rates from 1.3 mm/year for 3.0 cm aneurysms to 3.6 mm/year for 5.0 cm aneurysms. Aneurysm growth rates do not appear to have changed over the past 25 years.[2]

Several reports have shown that diabetic patients develop smaller AAA, as demonstrated by significantly lower aortic diameters compared to non-diabetic subjects. These results correspond to our evidence that only 12.9% of all patients with AAA have DM. In practice, the decision to treat AAA takes into consideration the risk of rupture. As large aortic diameter and high growth rate represent major risk factors of rupture, it is not surprising that a negative association between DM and aneurysm rupture was identified. While DM appears as a protective factor of AAA formation and expansion, the prognosis and outcome after AAA treatment also differs between diabetics and non-diabetic patients. [7]

It is noteworthy that in the wide majority of epidemiological studies on AAA, DM was defined as a known history of the disease according to the patient's declaration and to medical records. Moreover, most of the studies did not distinguish between T1D and T2D diabetic patients. Given the distinct characteristics of pathophysiological patterns between these two forms of DM, it is possible that their effects and relationships with AAA differ.[7]

Although various studies have been published regarding how diabetes affects the abdominal aortic wall, the results can be broadly grouped into four main biological pathways af-

fecting: (1) extracellular matrix (ECM) volume, (2) ECM glycation and advanced glycation end-product (AGE) formation, (3) inflammation and oxidative stress and (4) intraluminal thrombus (ILT) biology. Significant research also suggests that the medications used to treat DM may play a bigger role than the disease itself in explaining this relationship.[8]

Recent meta-analysis of adjusted relative risk estimates from 13 studies including data on >3 800 000 participants confirmed that DM is inversely associated with the presence of AAA, and this supports the hypothesis that DM may be negatively associated with AAA growth. A meta-analysis of 6268 IPD from 10 studies (of the available 18 studies) demonstrated that DM patients had growth rates that were on average 0.51 (standard error [SE], 0.10) mm/year slower than those of non-DM patients after adjustment for all demographics, medical history, and drug history. [15]

The observational studies on the effect of metformin on the enlargement of AAA are revealing, but they could be interfered by a series of confounding factors, such as race, diabetes and other oral antidiabetic medications. Therefore, a randomized clinical trial with greater scope is required. The basic characteristics of the population, the methodologies and the follow-up durations could always contribute to the between-study heterogeneity.[3]

The development of better predictive tools for individual rupture risk including bio-markers, functional imaging, and morphology based indicators should be the subject of long-term research projects. Another ambitious research initiative focuses on medical treatment to slow AAA growth. A number of projects in the early stages of animal models are ongoing. A potential candidate drug for imminent clinical trials is metformin. The impact of cardiovascular secondary preventive medical treatment in AAA patients and refinement of pre-operative assessment should be studied in close collaboration with other societies and GL groups. The size threshold for AAA repair in women and specific ethnic groups is an area of uncertainty requiring further research and high quality long-term follow up cohort data may be the basis for better substantiated future recommendations.[2]

Limitations

Retrospective studies included the possibility of missed information. Interpretation of our results was complicated by the heterogeneity among the patients. Due to inability to track growth in AAA diameter over time, the major limitation of our study is having only one reliable piece of data – the size of AAA recorded during the hospitalization, we did not have data from follow-up of the diameter of AAA and the time of the diagnosis. Because of the small number of patients in our retrospective analysis it is with fair methodological quality and unclear risk of bias and no strong epidemiologic data that can currently support the suggested inverse association between diabetes and AAA. Furthermore the precise mechanism remains yet to be determined.

In order to demonstrate the protective role of DM in development of AAA is valuable to compare AAA patients with similar age and risk factors with patients without AAA. Such comparison would be of interest but because of the retrospective nature of our study this was not possible.

CONCLUSION AND PERSPECTIVES:

Our data shows a significant difference in the mean diameter of AAA dependent on concomitant history of diabetes. As expected the diabetic population in our study experience more early surgical complications. Arguably, a larger subset of diabetic patients is needed to draw any robust conclusions.

Our study analyses the relationship between the occurrence of one or more risk factors and DM. This relationship, however, requires further exploration.

Epidemiologic and experimental studies demonstrated a negative association between DM and aortic aneurysm formation and expansion. In addition to DM itself, antidiabetic drugs interfere with the pathophysiological mechanisms of aneurysm and may contribute partly to the protective effect observed in diabetic patients.

REFERENCES

1 Rango P De, Farchioni L, Fiorucci B, Lenti M. Diabetes and Abdominal Aortic Aneurysms. *Eur J Vasc Endovasc Surg*. 2013;47(3):243-261.

2 Wanhainen A, Verzini F, Herzeele I Van, et al. European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. *Eur J Vasc Endovasc Surg*. 2019;(2018).

3 Yu X, Jiang D, Wang J, et al. Metformin prescription and aortic aneurysm: Systematic review and meta-analysis. *Heart*. 2019:1-7. doi:10.1136/heartjnl-2018-314639

4 Sidloff D, Stather P, Dattani N, Bown M, Thompson J, Sayers R. The online version of this article, along with updated information and services, is located on the World Wide Web at: 2014:747-753.

5 Tang W, Yao L, Roetker NS, et al. Lifetime Risk and Risk Factors for Abdominal Aortic Aneurysm in a 24-Year Prospective Study: The ARIC Study (Atherosclerosis Risk in Communities). *Arterioscler Thromb Vasc Biol*. 2016;36(12):2468-2477.

6 Kubota Y, Folsom AR, Mph JSP, Wagenknecht LE, Tang W. Annals of Epidemiology Diabetes-related factors and abdominal aortic aneurysm events : the Atherosclerotic Risk in Communities Study. *Ann Epidemiol*. 2017:3-8.

7 Raffort J, Lareyre F, Clément M, Hassen-khodja R. Diabetes and aortic aneurysm : current state of the art. (July 2018).

8 Dattani N, Sayers RD, Bown MJ. Diabetes mellitus and abdominal aortic aneurysms: A review of the mechanisms underlying the negative relationship. *Diabetes Vasc Dis Res*. 2018;15(5):367-374.

9 Jones SC, Saunders HJ, Qi W, Pollock CA. Intermittent high glucose enhances cell growth and collagen synthesis in cultured human tubulointerstitial cells. *Diabetologia*. 1999;42(9):1113-1119.

10 Shi Q, Rafii S, Wu Hong-De M, et al. Evidence for circulating bone marrow-derived endothelial cells. *Blood*. 1998;92(2):362-367.

11 Death AK, Fisher EJ, Mcgrath KCY, Yue DK. High glucose alters matrix metalloproteinase expression in two key v ascular cells : potential impact on atherosclerosis in diabetes. 2006;168(2003):263-269.

12 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.

13 Hurks R, Vink A, Hoefer IE, et al. Atherosclerotic risk factors and atherosclerotic postoperative events are associated with low inflammation in abdominal aortic aneurysms. *Atherosclerosis*. 2014;235(2):632-641.

14 Cifarelli V, Luppi P, Tse HM, He J, Piganelli J, Trucco M. Human proinsulin C-peptide reduces high glucose-induced proliferation and NF-κB activation in vascular smooth muscle cells. *Atherosclerosis*. 2008;201(2):248-257.

15 Takagi H, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Diabetes and Abdominal Aortic Aneurysm Growth. Angiology. 2016 Jul;67(6):513-25.

16 Hsu CY, Su YW, Chen YT, Tsai SH, Chang CC, Li SY. Association between use of oral - antidiabetic drugs and the risk of aortic aneurysm : a nested case – control analysis. *Cardiovasc Diabetol*. 2016:1-8.

17 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.