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Aortic Aneurysm and Diabetes

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Aortic Aneurysm and Diabetes

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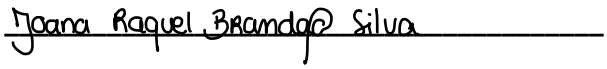

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Dedicatória

Aos meus pais e familiares que me apoiaram ao longo de todas as etapas desta jornada.
Aos professores pelas capacidades e ensinamentos transmitidos.
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"Não sou nada.

Nunca serei nada.

Não posso querer ser nada.

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Fernando Pessoa

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Resumo

Introdução

Os aneurismas da aorta correspondem a uma expansão localizada e permanente da aorta, resultantes de uma fragilidade na parede da mesma, superior a 50% quando comparados com segmentos normais de indivíduos da mesma idade e sexo.

Correspondem à segunda patologia mais comum da aorta, logo atrás da aterosclerose. Constituem a 15ª causa de morte em pessoas com mais de 55 anos e a 19ª causa de morte global.

Contudo, nos doentes com diabetes que possuem um risco elevado de patologia vascular, devido à hiperglicemia e consequentes alterações, alguns estudos têm demonstrado, que este grupo poderá apresentar um menor risco de desenvolver um aneurisma da aorta abdominal e torácica.

Objetivos

A presente revisão da literatura apresenta como objetivo recolher o conhecimento científico atual acerca dos diversos domínios da relação dos aneurismas da aorta com a diabetes.

Metodologia

A pesquisa foi realizada através da base de dados "PubMed" de acordo com os seguintes termos MeSH: ("aortic aneurysm" E "diabetes mellitus") OU ("aortic aneurysm" E "hyperglycemia") OU ("aortic aneurysm" E "blood glucose") OU ("aortic aneurysm E "hypoglycemic agents") OU ("aortic aneurysm" E "insulin"). Foram selecionados artigos publicados entre janeiro 2012 e fevereiro 2022, escritos em inglês, português e espanhol. Os critérios de exclusão foram: título e resumo em desacordo com o conteúdo, estudos com experimentação animal ou irrelevantes para o objetivo de estudo. No total foram incluídos 45 artigos.

Desenvolvimento

A diabetes mellitus é um fator de risco comprovado para doenças cardiovasculares devido aos seus efeitos negativos na microcirculação e nas artérias de médio calibre. Os investigadores descobriram que a DM apresentava uma relação inversa com a frequência, incidência e taxa de crescimento anual dos aneurismas da aorta. De acordo com Raffort *et al*., pode ser devido aos efeitos diretos da DM nas paredes da aorta, como a neoangiogénese, inflamação,

desenvolvimento de trombo intraluminal, alterações na fibrinólise, remodelação da matriz extracelular, glicolisação e homeostase vascular.

Conclusões

Nos últimos anos, várias meta-análises foram publicadas e confirmaram a hipótese de Lederle de 1997 de uma possível relação inversa entre a diabetes e o aneurisma da aorta. A comunidade científica tem tentado aumentar o conhecimento face à doença tentando compreender de que forma mais concreta e precisa esta relação se estabelece. Vários estudos foram realizados para determinar os efeitos exatos da diabetes no aneurisma aórtico. A incidência, crescimento aneurismático e eventos adversos foram estudados. A diabetes foi benéfica tanto para os aneurismas da aorta abdominal como torácica em cada um dos parâmetros avaliados.

Palavras-Chave

"Aortic Aneurysm, Abdominal"; "Aortic Aneurysm, Thoracic"; "Diabetes Mellitus"; "Hypoglycemic Agents".

Abstract

Background

Aortic aneurysms are a localized and permanent expansion of the aorta, caused by aortic wall weakness, higher than 50% when compared to sex and age of normal aorta segments. AA can be classified according to the portion of the affected aorta, namely thoracic aortic aneurysm, abdominal aortic aneurysm, or both.

AAs are the second most common aortic pathology after atherosclerosis and are the 15th leading cause of death in people over 55 years old and the 19th leading cause of death overall.

However, in diabetic patients who have a higher risk for vascular diseases, due to persistent hyperglycemia, some studies have shown that this group of patients can have a lower risk of AAA and TAA.

Objectives

The present literature review´s main goal is to consolidate the most up-to-date scientific information regarding the association between aortic aneurysms and diabetes.

Methods

Research was carried out through "PubMed" with the following MeSH terms: ("aortic aneurysm" AND "diabetes mellitus") OR ("aortic aneurysm" AND "hyperglycemia") OR ("aortic aneurysm" AND "blood glucose") OR ("aortic aneurysm AND "hypoglycemic agents") OR ("aortic aneurysm" AND "insulin"). Articles published between January 2012 to February 2022, written in English, Portuguese or Spanish were included. The Exclusion criteria were: title and abstract do not match the content, studies with animal experimentation, or irrelevant to the topic. In total, 45 articles were included.

Development

Diabetes mellitus is a verified risk factor for cardiovascular diseases due to its negative effects on microcirculation and medium-sized arteries. Researchers discovered that DM had an inverse relationship with aortic aneurysms´ frequency, incidence, and annual growth rate. According to Raffort *et al.*, it might be due to the direct effects of DM on aorta walls, such as mural neoangiogenesis, inflammation, intraluminal thrombus development, extracellular matrix remodeling, glycation, and vascular smooth muscle homeostasis.

Conclusions

Several meta-analyses published in recent years have confirmed Lederle's 1997 hypothesis of an inverse connection between diabetes and aortic aneurysm. Many researchers have attempted to increase information and establish the characteristics of this relationship in a more precise, concise, and transparent manner. Studies have been conducted to determine the exact effects of DM on aneurysms. The incidence, severity, and occurrence of aneurysmal sac expansion and adverse events were studied. DM was advantageous for both AAA and TAA in each of the points.

Keywords

"Aortic Aneurysm, Abdominal"; "Aortic Aneurysm, Thoracic"; "Diabetes Mellitus"; "Hypoglycemic Agents".

Abbreviations

AA – aortic aneurysms
AAA – abdominal aortic aneurysms
ADA - American Diabetes Association
AGE - advanced glycation end products
ApoE–/– - apolipoprotein E-deficient
ARIC - atherosclerosis Risk in Communities Study
CCL19 - C-C motif chemokine 19
CCL23 - C-C motif chemokine 23
CEL - carboxyethyllysine
CI - confidence interval
CML - carboxymethyllysine
CVD - cardiovascular diseases
DIAMANTE - DIAbetes Meta-ANalysis of Trans-Ethnic association studies
DM – Diabetes Mellitus
DM2 – type 2 Diabetes Mellitus
DPP- 4 - dipeptidyl peptidase-4
ECM – extracellular matrix
HbA1C - glycated hemoglobin A1c
HR - hazard ratio
I^2 - I-square
MD - mean difference
MetS - metabolic syndrome
miRs - micro-RNA
MMP - matrix metalloproteinase
MMP-2 - metalloproteinases type 2
MMP-9 - metalloproteinases type 9
NHIRD - Taiwan National Health Insurance Research Database
NOG - normoglycemic
OAD - oral antidiabetic drugs
OR - odds ratio
PAI – 1 - plasminogen activator inhibitor type 1 levels
PPE - porcine pancreatic elastase
RNA - ribonucleic acid
SMC - smooth muscle cells
SNPs - single nucleotide polymorphisms
T1DM – type 1 diabetes mellitus
T2DM – type 2 diabetes mellitus
TAA – thoracic aortic aneurysms
TAD - thoracic aortic dissection
TZD - thiazolidinediones
vs. – versus
VSMC - vascular smooth muscle cell

WMD - weighted mean difference

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Aortic Aneurysm

Aortic aneurysms (AA) are a localized and permanent expansion of the aorta, caused by aortic wall weakness, higher than 50% to the localized diameter when compared to sex and age of normal aorta segments. [(1)] A distinction should be made between true and false aneurysms, as a true aneurysm involves all aorta layers, and a false aneurysm (or pseudoaneurysm) is a periaortic hematoma that forms between the tunica media and the tunica adventitia, maintaining contact with the aortic lumen. [(2)].

Most often, AA are an incidental finding on ultrasonography, when imaging studies are undertaken for another reason, with an asymptomatic course. However, they are also associated with high mortality rates, presenting tragic consequences such as rupture, which accounts for 50-80% of all AA-associated deaths.[(3)]

AA are the second most common aortic pathology behind atherosclerosis [(4)] and are the 15th leading cause of death in people over 55 years old and the 19th leading cause of death overall. [(2)]. In 2015, aortic aneurysms caused 168 200 deaths worldwide and 2.9 million disability-adjusted life years. In Western populations, the new abdominal aortic aneurysms (AAA) rate is 0.4-0.67 %, but it is ten times lower in Asian people. [(5)]

Over the past decades, the global mortality associated with aortic disease, including aortic aneurysms as well as acute dissection of the aorta, has been rising, probably associated with the increase in life expectancy.

According to the portion of affected aorta, AA can be classified in thoracic aortic aneurysms (TAA) or AAA. TAA can include the aortic root, ascending aorta, arch, or descending aorta. [(6)]

However, the most frequent location is in the infrarenal abdominal segment. [(7)] As mentioned, either TAA or AAA can present without symptoms. The TAA cardinal symptoms may be linked to the site and nearby structures. A pulsatile abdominal mass and unusual abdominal pain are common in AAA. [(2)]

The risk factors for AAA and TAA are different. According to the Management of Abdominal Aortic Aneurysms Clinical Practice Guidelines of the European Society for Vascular Surgery, [(8)] the major risk factors for AAA include advanced age, male sex, smoking, and family history of AAA, especially in male first-degree relatives. There are other aspects like a history of other vascular aneurysms, atherosclerosis, cerebrovascular disease, hypertension, and coronary artery disease. [(9)]

In the descending segment of TAA, the most prevalent risk factor is atherosclerosis. On the other hand, in the ascending segment, TAAs are commonly associated with connective tissue diseases, such as Marfan syndrome or the presence of a bicuspid aortic valve. Other causes have been described such as mechanical injury, inflammatory conditions (giant cell arteritis, Takayasu's arteritis, Bechet's disease), corticosteroids or immunosuppression, and exposure to fluoroquinolones. In fact, some microorganisms have been associated with AAA development (Neisseria *spp*., gram-negative bacilli, fungi, Streptococcus *spp.*, Staphylococcus aureus, Salmonella *spp.*, Escherichia coli). [2]

The structure, biochemical composition, origin, and biology of the smooth muscle cells of the thoracic and abdominal aorta are different and even the aneurysms of both, despite sharing mechanisms, have other characteristics. [2]

The process involved in the pathophysiology of AAA is complex. It consists of the alteration and loss of vascular smooth muscle cells associated with infiltration by inflammatory cells, alteration of the extracellular matrix, and the formation of thrombi within the lumen. TAA presents an inflammatory component and apoptosis of vascular smooth muscle cells less relevant when compared to the pathogenesis involved in the formation of AAA. [10]

TAA, on the other hand, are more common at younger ages and are strongly influenced by familial factors. According to genetic studies, 20% of TAA have a positive family history. [2]

Despite the years of research to understand the disease mechanism, the only curative treatment available nowadays consists of endovascular repair or open surgery. [2, 11]

Diabetes Mellitus

According to American Diabetes Association (ADA) [12], diabetes is a group of metabolic disorders. It is marked by hyperglycemia caused by problems with insulin secretion, insulin action, or both. Diabetes' persistent hyperglycemia is linked to long-term damage, dysfunction, and failure of various organs, such as the eyes, kidneys, nerves, heart, and blood vessels.

Several different pathologic mechanisms cause diabetes. These can range from autoimmune death of pancreatic b-cells, resulting in insulin insufficiency, to anomalies that cause insulin resistance. It causes glucose, lipid, and protein metabolism abnormalities due to insulin's ineffective action on target tissues. Inadequate insulin secretion and/or decreased tissue responses cause insulin deficiency along the complicated hormone action pathways at one or more locations. Insulin secretion and insulin action anomalies sometimes coexist in the same patient, making it difficult to determine which abnormality is the primary cause of hyperglycemia. Depending on the severity of the underlying illness process, the degree of hyperglycemia may change over time. Even with strict blood sugar control, persons with diabetes mellitus (DM) may have deadly consequences. [12]

Even though people with diabetes mellitus have a higher risk of various cardiovascular diseases [5], some epidemiological studies have shown that diabetic patients have a lower risk of AAA. The degree of hyperglycemia can influence the aortic wall biologic alterations and fibrinolytic features. [13] Nevertheless, the link between diabetes and AAA formation and expansion is still uncertain. [14]

The aim of this study was to consolidate the most up-to-date scientific information on the many aspects of the association between aortic aneurysms and diabetes.

Methods

The research was carried out through “PubMed” with the following MeSH terms: (“aortic aneurysm” AND “diabetes mellitus”) OR (“aortic aneurysm” AND “hyperglycemia”) OR (“aortic aneurysm” AND “blood glucose”) OR (“aortic aneurysm AND “hypoglycemic agents”) OR (“aortic aneurysm” AND “insulin”). Articles published between January 2012 to February 2022, written in English, Portuguese or Spanish were included. The Exclusion criteria were: title and abstract that do not match the content, studies with animal experimentation, or irrelevant to the topic. In total, 45 articles were included.

After removing duplicates, all titles and abstracts were screened for relevance. The full text of relevant studies was then evaluated to apply the inclusion/exclusion criteria.

To be included in this review, the studies had to report at least one of the following topics:

- articles reporting the association between AA (AAA or TAA or both) and DM.

- articles explaining the relationship and mechanism between AA (AAA or TAA or both) and DM.

- articles explaining the relationship and mechanism between AA (AAA or TAA or both) and the use of pharmacologic agents for diabetes.

A total of 226 records were identified.

After the exclusion of duplicates, 189 were screened for relevance. Of these, 121 were irrelevant on a review of the titles and abstracts, and 68 were assessed for full-text eligibility. One article with animal experimentation was included due to its clinical relevance. In total, 45 articles were included.

Figure 1 show the flow of the literature selection by applying the systematic search and selection strategies to identify eligible reports.

Diabetes' physiological implications on aortic aneurysm

Diabetes mellitus is a verified risk factor for cardiovascular diseases (CVD) due to its negative effects on microcirculation and medium-sized arteries [3] Researchers discovered that DM had an inverse relationship with aortic aneurysms´ frequency, incidence, and annual growth rate. [5, 14-18] There are multiple reasons for these findings, but a precise mechanism has not yet been described.

According to Raffort *et al.* [19], it may be due to the direct effects of DM on aorta walls, such as mural neoangiogenesis, inflammation, intraluminal thrombus development, extracellular matrix (ECM) remodeling, glycation, and vascular smooth muscle homeostasis.

Takagi *et al.* [17] showed that the glycemic-related processes involved in AAA and TAA are similar.

Some potential pathophysiological pathways are described to explain this correlation and in table I we summarize the effects of diabetes on aortic aneurysms.

In aortic aneurysm, the aortic wall has lesser levels of collagen and elastin, due to higher proteolytic activity. Additionally, there is an increased activity of enzymes such as metalloproteinases type 2 and 9 (MMP-2 and MMP-9), responsible for protein matrix degradation, [20] contributing to the controlling of the volume and structure of the ECM. [5, 20, 21]

- *Aortic wall stiffness*

One of the reasons explaining the potential benefit of diabetes in the aneurysm may be due to the higher aortic wall stiffness. Diabetes is characterized by an accumulation of vascular matrix (decreased extracellular matrix proteolysis) and decreased aortic wall remodeling [14, 21] and hyperglycemia has been shown to promote ECM production and decrease breakdown, resulting in a thicker intima-media layer of the aorta wall. [9]

Additionally, hyperglycemia promotes collagen production [20, 22, 23], resulting in increased aorta wall thickness and a drop in MMP levels. This protective action is mediated mainly through reduced MMP2 and MMP9. [20, 21] The diminution of MMP activity can develop a thicker aortic wall and slow matrix loss. [20, 23]

There is a progressive rise in volume as ECM breakdown decreases and ECM synthesis increases. [21] This may limit aortic distention, [9] according to LaPlace's law. [23]

The increased rigidity of the aorta wall in patients with DM could be due to an increase in vinculin. This focal adhesion protein connects the extracellular matrix to the actin cytoskeleton. [20, 22]

These mechanisms can lower wall stress and hence protect against aortic aneurysm development. [5] Increased stiffness could potentially result in aortic wall stabilization, which would make it more resistant to expansion. [17]

- *Advanced glycation end products*

Advanced glycation end products (AGE) correspond to proteins or lipids that become glycated as a result of exposure to sugars. AGE can be non-cross-linking AGE such as carboxymethyllysine (CML) and carboxyethyllysine (CEL) or cross-linking AGE like pentosidine. [24]

Hyperglycemia is linked to increased AGE, resulting from glycation of ECM, [23] making the vascular matrix resistant to proteolysis. [24] AGE may slow down the breakdown of the extracellular matrix, [9] preserving vessel wall architecture and regulating cathepsin and MMP production. [21]

In fact, the AGE in the extracellular matrix promote the artery wall's elastin and collagen to bind together, generating covalent cross-links within the ECM, [23] facilitating smooth muscle cells (SMC) proliferation [1, 20].

These changes contribute to a higher aorta wall strength and resistance, lowering the chance of aneurysm formation. [17, 20, 22, 25]

Koole *et al.* [24] analyzed samples from diabetic AAA patients (n=30), matched with nondiabetic patients (n=30). There were no variations between non-diabetic and diabetic elastin or collagen content when AAA samples were graded histologically.

In their study, aorta wall biopsies from patients with AAA diabetic and non-diabetic and patients without reported aneurysm diabetic and non-diabetic were compared, to see if AGE can protect diabetic individuals from developing AAA. The concentration of 3 AGE were compared. Pentosidine concentrations were increased in diabetic patients with AAA. They were negatively connected with aortic diameter ($r = 0.43$, $p = 0.02$), and glycation of AAA tissue was associated with a significant reduction in MMP proteolysis. No significant changes were seen for CEL or CML. The authors concluded that cross-linking AGE like pentosidine, but not non-cross-linking AGE can protect the collagen network and enhances its proteolysis resistance. This may protect diabetics against the advancement of AAA.

- *Neovascularization and inflammatory changes*

Hyperglycemia is linked to less adventitial neovascularization and inflammatory cell infiltration into the medial layer of the aorta reducing VSMC death and ECM deterioration, slowing AA progression. [17, 21]

Additionally, Milutinovic *et al.* [26] examined inflammatory and immune cell infiltration in ascending aortic aneurysms, respectively to the tunica intima, media, and adventitia. The authors compared aortic aneurysms in non-hypertensive type 2 diabetes mellitus (DM2) patients and hypertensive non-diabetic patients, finding remarkably less inflammatory infiltration in all three layers of the vessel wall. Specifically, tunica intima has fewer B cells and M1 macrophages, tunica media with lower b cells, plasma cells, and M1 macrophages, and finally tunica adventitia has fewer plasma cells. The number of M2 macrophages, Th, and Tk cells did not differ between the two groups. Also, in the tunica adventitia, diabetics exhibited much more collagen fibers.

Moreover, the CC cytokine family can be related to aneurysm development, namely C-C motif chemokine 19 (CCL19). However, it has been inadequately studied thus far. To evaluate if CCL19 or other CC cytokines had any implication on AAA, the inflammatory plasma profile of 10 diabetic patients with AAA and ten non-diabetic individuals with AAA was examined in a pilot investigation, performed by Lareyre *et al.* [27] They were all men and had similar clinical features. Diabetic patients have considerably lower CCL19 expression than nondiabetic patients. Nonetheless, multiple investigations have pointed to its function in the development of atherosclerosis and cardiovascular disease. These findings may indicate that decreasing inflammatory cell infiltration could have a protective effect on AAA by enhancing aortic wall integrity. CCL19 also increased the expression of matrix metalloproteinase (MMP), which means that lower levels of CCL19 are directly connected to lower levels of MMP, already described to have an important role in AAA pathogenesis.

Also, C-C motif chemokine 23 (CCL23) was significantly decreased in diabetic patients with AAA. Higher levels of CCL23 were found in atherosclerotic patients´ plasma. CCL23 can induce MMP-2 expression and has chemotactic actions on immune cells like monocytes and dendritic cells. CCL23 has been shown to play a role in neoangiogenesis by stimulating endothelial cell proliferation, differentiation, and migration in several investigations.

Overall, lower CCL23 plasma expression in diabetic patients may contribute to a protective impact against AAA development by restricting immune cell infiltration and neoangiogenesis in the aneurysmal wall and reducing extracellular matrix degradation.

- *Hyperinsulinism and fibrinolytic system*

Hyperinsulinism may cause a rise in fibrinogen and plasminogen activator inhibitor type 1 levels (PAI-1). The latter suppresses the fibrinolytic system primarily by preventing the conversion of plasminogen to plasmin. [20] Plasmin, which catalyzes the conversion of pro-MMP-2 and pro-MMP-9 to their active forms MMP-2 and MMP-9, is another regulator of MMP expression. [1, 21].

As a result of increased PAI-1 levels caused by hyperinsulinemia in diabetic individuals, the aortic wall could be stabilized, avoiding aneurysm formation by lowering MMP levels. [20]

It is also important to refer that type 2 diabetes mellitus T2DM patients' fibrin clots were denser, less porous, and hence less vulnerable to fibrinolysis [21], which may reduce the rate of expansion typically favored by matrix metalloproteinases and fibrinolytic mediators. [28]

- *Oral Hypoglycemic Drugs*

The claimed preventive impact of DM in the formation of AA has been believed to be owned by the changes in the pathophysiological pathways described above. Nonetheless, the most used oral anti-diabetic medicines have been described to impact this relationship, in research.

Climent *et al.* [20] in a review pointed the paper of metformin, thiazolidinediones (TZD) or dipeptidyl peptidase-4 (DPP-4) inhibitors on diminution of inflammation and proteolytic activity. Such mechanisms can reduce the aneurysm development and growth as previously described.

DPP-4 inhibitors can also lower the macrophage infiltration and, consequently the inflammatory response. [29]

Pafili *et al.* [1] also mentioned that metformin could reduce the aortic smooth muscle cell proliferation and MMP-2 activity.

Metformin may reduce local inflammatory cell deposition and hemodynamic alterations since AAA is frequently accompanied by aortic atherosclerotic changes within the arterial lumen. [3]

Unosson *et al*. [20] analyzed plasma samples from 240 AAA patients to understand the reported link between metformin and AAA. They discovered that chemokine expression was significantly lower in those taking metformin, suggesting it may downregulate serum chemokines. However, the connection between chemokine level and aneurysm growth rate was unclear.

On the other hand, Wang *et al.* [30] collected peripheral blood from patients previously diagnosed with AAA. There weren´t changes in cytokine signaling, CD4+ phenotypic expression, or circulating antigens/antibodies that could explain the benefit of metformin.

Metformin prescription is linked to alterations in the expression of ECM proteins such as alpha1 type IV collagen, alpha2 type XVIII collagen, gamma1, and beta2 laminin, according to Raffort *et al*. [31] These findings could help to explain why metformin protects against AAA growth and rupture. [31]

Metformin suppresses the effect of leptin on SMC proliferation and MMP-2 levels, resulting in decreased MMP levels and wall SMC proliferation, according to in vitro studies, inhibiting the genesis of aneurysms in the human aortic artery. [20]

These findings suggest that metformin has a complex effect on the pathophysiological events that lead to AAA formation and progression. Due to the low prevalence of AAA among diabetes patients, there is still a lack of solid evidence to indicate that metformin directly affects the aortic walls. [32]

Because thoracic aortic aneurysms are more likely to be genetically inherited than AAA, these subject warrant additional investigation, and future research should focus on subgroups of aortic aneurysms. [33]

- *Genetic implications*

Besides the pathophysiological reasons mentioned above, in a pilot study, Lareyre *et al.* [34] compared diabetic and non-diabetic AAA patients' micro-RNA (miRs) expression for the first time. MicroRNAs are small non-coding ribonucleic acid (RNA) molecules that regulate post-transcriptional gene expression and silence RNA. Three miRs (miR-144-3p, 20a-5p, and 188-3p) were shown to be considerably upregulated in diabetes patients' peripheral blood mononuclear cells, and miR-144-3p and miR-548k expression was also enhanced in aneurysmal tissue.

In contrast, miR-20a-5p expression was more significant in serum.

They potentially offer new therapeutic targets, even if their significance in AAA development and advancement is unknown.

On the other hand, using publicly available summary data from an extensive genetic consortium, Morris *et al*. [35] developed a genetic risk score for diabetes and assessed its connection with AAA in six large genomewide association studies in a two-stage Mendelian randomization approach.

This genetic risk score involving single nucleotide polymorphisms (SNPs) from the DIAbetes Meta-ANalysis of Trans-Ethnic association studies (DIAMANTE) consortium study was found to be

strongly linked to type 2 diabetes. This study reveals that genetic diabetic propensity has no bearing on the chance of getting AAA. Furthermore, the genetic tendency for diabetes does not have an impact on preventing AAA development.

Diabetes and Aortic Aneurysm

Diabetes mellitus has been linked to a lower incidence of abdominal aortic and thoracic aortic aneurysms in studies. Tsai *et al.* [13] looked at these relationships in an Asian population using Taiwanese national insurance data. The type 2 diabetes group included 160 391 patients, while the non-DM comparative cohort included 646 710 people. The DM2 group had a 15 % lower total pooled incidence rate of thoracic and abdominal aortic aneurysm than the non-DM cohort (3.85 vs 4.51 per 10 000 person-years), with an adjusted hazard ratio (HR) of 0.64 [95 % confidence interval (CI) 0.56–0.74] in the multivariable Cox model.

Additionally, Ning *et al.* [9] investigated incident AAA in 13,116 individuals (1990–1992) according to baseline glycemic status (diabetes, prediabetes, normal glycemia) and the time-varying exposure of duration post-incident diabetes in 11,675 participants (1987–1989). Diabetes (vs. normal glycemia) at baseline was independently linked with lower AAA risk (489 cases) for 20 years (HR: 0.71 [95 % CI 0.51–0.99), particularly after ten years (HR: 0.58 [0.38 – 0.87]). Prediabetes did not show an independent relationship. The unfavorable relationship was stronger with a longer diabetes duration (p for trend = 0.045), with a 30–50 % decreased risk eight years after diagnosis. When compared to non-diabetes, the cross-sectional study revealed reduced aorta diameters with longer diabetes duration (e.g., 0.76 mm [1.24, 0.28] in diabetes with 8–12 years), although prediabetes continuously exhibited nominally higher diameter.

Diabetes, particularly long-term diabetes, but not prediabetes, was linked to a decreased risk of AAA and a smaller aortic diameter likewise the study described above.

Data imply that long-term clinical hyperglycemia is significant in lowering AAA risk and that a smaller aorta diameter is a structural reason underpinning this seemingly contradictory connection.

In this way, several meta-analyses were performed, and summary findings can be found in table II.

De Rango *et al*. [14], in a systematic review and meta-analysis including 64 articles that provided information on the association between diabetes and AAA, showed that diabetes individuals have a lower prevalence of AAA and, when monitored prospectively, have a reduced chance of getting new AAA or growing their existing AAA than non-diabetics.

Furthermore, according to pooled adjusted data from North American and European studies, Xiong *et al*. [15] demonstrated that the risk of AAA was 38 % and 55 % lower in people with diabetes than in those without diabetes. In addition, prevalence studies have revealed that diabetic people may have a reduced AAA prevalence, and prospective incidence studies suggest that diabetic patients have a lower risk of AAA formation than nondiabetic patients. [14]

Moreover, Aune *et al.* [5] evidenced that the relative chance of developing an abdominal aortic aneurysm is reduced by 42% in people with diabetes mellitus. There was general evidence of lower growth rates of small AAA in patients with diabetes compared with non-diabetics. [14] These were congruent to Takagi *et al.* systematic literature search and a meta-analysis. [16] Data suggests that diabetes and AAA formation, prevalence, and enlargement are inversely related.

Takagi *et al*. [36] conducted a thorough literature search and meta-analytic evaluation to describe the relationship between diabetes and abdominal aortic aneurysm rupture. Their findings imply a negative relationship between diabetes and AAA rupture, as well as presence and growth, which was confirmed in sensitivity analyses.

Reported association between DM and TAA

D´ Cruz *et al.* showed a negative relationship between DM and TAA. TAAs have been linked to a decreased prevalence of diabetes in ten studies. (OR, 0.77; 95% CI, 0.61 0.98; P for effect 1⁄4 .03; P for heterogeneity 1⁄4 .03;)[18]. Five population cohort studies and five case-control studies with 1,006,360 patients were included in the study. The results show that the subgroup analyses differ, with the population cohort studies subgroup describing a statistically significant negative association and the case-control studies subgroup describing a statistically insignificant negative association between the two clinical entities. This can happen by the inherent biases in the original studies.

These results were similar to a previous meta-analysis performed by Takagi *et al.* [17], where the correlation between DM and thoracic aortic dissection (TAD) and/or TAA was explored. Lower prevalence of TAD/TAA was associated with DM than controls (OR, 0.43; 95% CI, 0.31-0.59; P for effect < .00001; P for heterogeneity < .00001;), according to an analysis of all 11 studies.

Diabetes and Aortic Aneurysm growth

Three hundred and sixty aneurysm patients with minor AAA (4.1-5.4 cm) were enrolled in a trial by De Rango *et al.* [28] comparing early endovascular repair versus surveillance and delayed repair. Data were analyzed to assess the relation between diabetes and the risk of all-cause mortality, complications, and growth of aneurysms. The median growth rate for both diabetes and nondiabetic groups was 0.044 mm in the first year; however, there was a trend for a higher median growth rate in the nondiabetic group in the second year (0.07 mm vs. 0.008 mm). [28]

Indeed, diabetes was the strongest and only independent negative predictor of aneurysm expansion of less than 5 mm (HR, 0.37; 95 % CI, 0.15-0.91; P.0033).

Another study has confirmed that diabetes has a protective effect on AAA growth rate, attenuating the growth rate by roughly 65 %. [37] Tsai *et al*. have shown the same growth relation for AAA or TAA. (13)

Kristensen *et al.* [38] performed a prospective cohort study to see if glycemia levels are linked to aneurysm growth, demonstrating an inverse relationship between the expansion rate of abdominal aortic aneurysms and glycated hemoglobin A1c (HbA1c) levels, which were inversely related to the aneurysmal growth rate. Adding that long-term high blood sugar slows aneurysmal growth in people with and without diabetes. [9, 38] It's also essential to refer there was no association between HBA1c value and aneurysmal size or stiffness existed. [38] This can be complemented by a multivariate study [39] at age 65, showing that aortic diameter and AAA prevalence did not differ between men with newly diagnosed diabetes and those without diabetes. As a result, any preventive effects of DM2 on AAA development are likely to occur later in the disease's course. [9, 38, 39] In fact, as atherosclerosis advances, the influence of DM on the aorta wall may change. [40]

Metabolic Syndrome and Aortic Aneurysm

Metabolic syndrome (MetS) is a collection of metabolic disorders closely related to the risks of cardiovascular illnesses. In many people, MetS is a precursor to diabetes.

Nonetheless, MetS were linked to an elevated risk of AAA, due to the number of non-glucose MetS components enhancing the risk of AAA. [41] Data from patients (n=354) diagnosed with AAA between march 2011 and february 2020 was used to conduct a retrospective cohort analysis. By comparing clinical features and AAA characteristics between MetS and no-MetS groups, the impact of MetS on the risk of developing AAA was investigated. The effects of DM and no-DM

components on the expansion of AAA were evaluated independently among MetS components. According to logistic regression analysis, the size of AAA was substantially more significant in the non-DM group (n=294) than in the DM group (n=60).

As a result, the study showed that DM might be inversely related to AAA growth. On the other hand, DM had no impact on the rate of AAA rupture or survival.

When DM was removed from MetS components, MetS was proportionally associated with AAA size and rupture rate and inversely with AAA survival rate. [42]

The Atherosclerosis Risk in Communities Study (ARIC) a population-based prospective study, analyzed 13,763 patients to see if diabetes-related factors have an inverse relationship with the likelihood of an abdominal aortic aneurysm (AAA). Compared to regular participants, those with MetS had a higher risk of AAA, and those with more non-glucose MetS components had a higher risk of AAA. In contrast, regardless of the number of MetS components, people with DM had a lower or equal chance of AAA than those without DM. [43]

Furthermore, Wang *et al*. [41] discovered that baseline obesity was related to a greater risk of clinically diagnosed AAA in this prospective sample of United States male physicians with a mean follow-up of 10.4 years. On the other hand, there is some evidence that a history of diabetes is linked to a decreased risk of diagnosed AAA after two years of follow-up.

Diabetes and Aortic Aneurysm Risk of Rupture

Besides de paradoxical protective effect of diabetes on the development and progression of aneurysms that has been shown, the link to rupture is also an object for analysis.

Tsai *et al.* [13], in a retrospective cohort study using the Taiwan National Health Insurance Research Database (NHIRD), showed that patients with advanced DM2 were substantially linked with reduced thoracic aortic aneurysm rupture and abdominal aortic aneurysm rupture. Reduced abdominal aortic aneurysm without rupture was linked to uncomplicated type 2 diabetes. Furthermore, with research of 5395 cases with ruptured abdominal aortic aneurysm, Kristensen *et al*. [44] demonstrated that given the presence of a AAA, diabetes was not proven to protect against rupture.

Furthermore, Theivacumar *et al*. [45] found that diabetic patients with aortic aneurysms are much less likely to present with rupture or die from aortic aneurysms than nondiabetic patients

with aortic aneurysms, either AAA or TAA. Alternatively, the hypothesis that DM prevents the aneurysm´s rupture is suggested, but there is no sufficient evidence to prove it.

Aortic Aneurysm and Oral Antidiabetic Drugs

AA and Metformin use

Treatments for diabetes mellitus may reduce aortic aneurysm disease in addition to the disease itself. Global practice guidelines recommend metformin as the first-line treatment for type 2 Diabetes Mellitus. It decreases hepatic glucose production and enhances insulin sensitivity. According to recent research, metformin has been linked to a lower risk of aortic aneurysm illness and may restrict the expansion of abdominal aortic aneurysms. [32]

Metformin has been shown in scientific experiments to reduce aortic smooth muscle cell proliferation and matrix metalloproteinase 2 production, suggesting that it may have a pleiotropic effect on cardiovascular protection in addition to glycemic control. [32, 33, 46]

According to Fujimura *et al*. [47], metformin dramatically reduced AAA progression while preserving medial elastin and smooth muscle. It inhibited aortic mural macrophage and CD8+ T cell infiltration without affecting blood glucose levels.

To further understand the link between metformin prescription and aortic aneurysm, Yu *et al*. [46] enlisted the participation of 29587 volunteers in a systematic review and meta-analysis. Overall, metformin use may be linked to a lower risk of aortic aneurysm, and metformin therapy may be able to prevent AAA from enlarging significantly. Effectively, metformin could substantially limit the expansion of AAA (weighted mean difference (WMD): −0.83mm/year, 95%CI −1.38 to −0.28). Nevertheless, it is essential to refer to there is variation in research. The length of follow-up and radiographic measurement techniques vary amongst studies, contributing to heterogeneity.

After this systematic review, [46] two extensive cohort studies have been published [32, 48], adding to the evidence.

In a retrospective cohort of male patients with 43,073 diabetes not on metformin, 24,361 diabetics on metformin, and 56,006 non-diabetics, Sutton *et al.* [48] have shown that non-diabetics had a higher rate of AAA surgery than the individuals with diabetes who have not been exposed to metformin. Nevertheless, this group had a higher surgery rate than those exposed to metformin. Those findings may add that the negative link between diabetes and abdominal aortic aneurysm (AAA) may be due to metformin rather than diabetes itself. Individuals with diabetes can be taking metformin without concern of increasing their risk of AAA rupture. [49]

Yuan *et al*. [3] attempted to review the effect of metformin in the development of AAA. Metformin was shown to slow the aneurysm's yearly development rate (mean difference (MD) -0.67 cm [95% (CI) -1.20 ~ -0.15 cm]) and minimize the risk of fatal AAA events, such as aneurysm rupture or death (OR 0.61 [95% CI 0.41-0.92]). Independent of research populations, geographies, imaging methods, or follow-up years, a negative relationship between yearly growth rate and

metformin prescription was found. Patients with diabetes who used metformin had a lower risk of aortic aneurysm than those who didn't, according to a nested case-control study. [33]

According to observational studies [50-52], metformin medication appears to be linked to a meaningful reduction in growth. AAA growth was considerably reduced in metformin-treated patients (0.9 +/- 0.4 mm/year) compared to non-treated patients [50] (1.8 +/- 0.4 mm/year; WMD 0.8 mm/year, 95% CI 0.5 e 1.1; p.001; I^2 14 89 %), which were similar to decreased growth rate found by Yu *et al.* (46) when compared to 0,67 cm reported by Yuan *et al.* [3] In fact, this potential beneficial paper of metformin is also verified in a sub-analysis within people with diabetes (WMD 0.7 mm/year, 95 % CI 0.3 e 1.0). The clinically relevant events were statistically considerably lower when comparing participants prescribed metformin to those who did not take metformin. This was in line with the previous data. [3]

Thanigaimani *et al.* [50] also suggested the necessity for randomized controlled trials to assess metformin's effectiveness. This is the most comprehensive meta-analysis of the relationship between metformin and AAA growth to date, with quality assessments of papers, several sensitivity analyses, and an examination of the effect on clinically relevant events. The relatively small number of research, particularly about AAA occurrences, is a weakness. In addition, the definition of AAA events and the people included in them differed. Apart from metformin, all patients were given various additional drugs. As a result, it's impossible to rule out the possibility that the impact attributed to metformin was caused by another aspect of diabetes, such as other antidiabetic drugs or hyperglycemia's extracellular matrix cross-linking effects. Confounders likely are to blame for the links between metformin, slower AAA growth, and fewer AAA events.

AA and other Oral Antidiabetic Drugs

Hsu *et al.* [33] used a database taken from Taiwan's National Health Insurance Research Database to conduct a nested case-control study with 4468 cases and matched controls, where they investigated the correlation between exposure to oral antidiabetic drugs (OAD) including metformin, sulfonylureas, TZD, alpha-glucosidase inhibitors, meglitinide, DPP-4 inhibitors, and the development of aortic aneurysm (TAA and AAA).

Metformin, sulfonylurea, and TZD use were all linked to a decreased incidence of AA, with adjusted OR of 0.72 (95 % CI 0.64–0.80), 0.82 (95 % CI 0.74–0.92), and 0.82 (95 % CI 0.69–0.98, respectively.

Itoga *et al.* [51] also showed that patients under sulfonylureas´ treatment were linked to a slower progression of AAA.

As far as AAA events, Golledge *et al*. have shown that metformin is the only one associated with a lower risk of rupture. Patients with diabetes who did not use metformin had no reduction in AAA events. [53] Nevertheless, there was no reported link between alpha-glucosidase inhibitors (adjusted OR 0.95; 95 % CI 0.81–1.11) or DPP-4 inhibitors (adjusted OR 0.85; 95 % CI 0.68–1.07) and the development of AA. [33]

There are some reasons to explain the findings concerning DPP-4 inhibitors, such as the length of DPP-4 inhibitor exposure possibly being insufficient. In Taiwan, the first DPP-4 inhibitor was licensed in 2009. The data collection ended in 2013. As a result, the patients had only been on DPP-4 inhibitors for less than four years. It's expected that a more extended follow-up period is required. Second, the case number could be insufficient to establish a relation. [33]

Other medications, such as sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, meglitinide, and DPP-4 inhibitors, have demonstrated their potential role.

However, there is still a lack of knowledge regarding these oral antidiabetic drugs and how they can aid individuals with an aneurysm. On the other side, there is a lack of data comparing the benefits of the two and determining which one has the more important use.

Nonetheless, prospective studies are needed to understand the exact link with insulin and to determine the molecular composition of this binding.

AA and Insulin Therapy

Although insulin is frequently used as a treatment, particularly in patients with type 1 diabetes, little research has been done on its effects on development, growth, and rupture risk. Although some groups received insulin therapy, the result was mixed with other medicines, making it impossible to establish the causal association. It's also understandable that, because hyperinsulinemia is responsible for some of the biochemical causes of diabetes's favorable effects, insulin injection reverses them.

In fact, Miyama *et al*. [54] with an intra-aortic porcine pancreatic elastase (PPE) infusion in C57BL/6 mice or systemic injection of angiotensin II in apolipoprotein E-deficient (ApoE–/–) mice developed aortic aneurysms in hyperglycemic (DM) and normoglycemic (NOG) mice, respectively. Insulin therapy was started following aneurysm induction in another DM cohort. Serial transabdominal ultrasonography measurements were used to track the course of aneurysmal aortic enlargement. Insulin treatment expands the diameter of AAA. Serum glucose levels fell from 465 +/- 26 mg/dL before insulin to 120 +/- 69 mg/dL two weeks later (P .0001). Despite decreasing serum glucose levels, there was no significant difference in body weight between the start of insulin therapy. AAA diameter was inversely related to serum glucose levels in a dose-response pattern in all three groups (PPE, n= 6; PPE-DM, n=6; PPE-DM insulin, n=6), with higher aneurysm enlargement in PPE-DM insulin mice compared to PPE-DM animals. PPE-DM mice had less aortic mural neovascularization, macrophage infiltration, and elastolysis compared to the other two groups.

Discussion

This review consolidates the most up-to-date scientific information regarding the association between aortic aneurysms and diabetes.

Aneurysms correspond to a disease with a high impact due to the severe consequences that result from it. Currently, there isn´t an effective preventive treatment. This demonstrates the relevance that the study of the pathology requires, to reduce its adverse effects and the feared risk of rupture.

Nonetheless, diabetes mellitus, a disease widely known with multiple adverse outcomes, associated, is associated with increased cardiovascular risk. It would be predictable to correspond to a risk factor for the development of aneurysmal pathology like atherosclerosis. However, recent investigations point out that this analogy does not correspond to the reality. It can even point to diabetes as a protective factor in several aspects.

In order to better understand this link, several studies and bibliographic reviews were elaborated in order to understand the biochemical reasons that could explain such findings. Although there is no specific mechanism indicated, at the moment, there are several hypotheses and changes resulting from the aortic wall that may be the starting point for explaining these data.

We can group these changes by to the effects of hyperglycemia, hyperinsulinemia, and oral antidiabetic agents. Increased wall stiffness, ECM glycation, decreased neovascularization, and inflammation promotes stability of the aortic wall, decreasing both the risk of an aneurysm forming and for those with aneurysmal pathology, the risk of aneurysmal sac growth or rupture is also diminished. In addition, hyperinsulinemia causes changes in the fibrinolytic system that consequently lead to the maintenance of wall integrity and a decrease in fibrinolysis.

Additionally, one of the proposals made was that in addition to the disease, the pharmacological therapies could help to explain the link between AA and DM.

Nevertheless, with a decrease in blood glucose, the biochemical changes would cease to occur or be less prevalent. However, metformin, TZD and DDP-4 inhibitors have been shown to reduce local inflammation and cell deposition.

Effectively, the genetic role has already been questioned, but still without a definitive answer. It is only known that there may be an upregulation of miRs in diabetic patients, but there

is no evidence that the genetic predisposition to diabetes can influence the predisposition to aneurysm formation.

Several meta-analyses published in recent years have confirmed Lederle's [55] 1997 hypothesis of an inverse connection between diabetes and aortic aneurysm. Many researchers have attempted to increase information and establish the characteristics of this relationship in a more precise, concise, and transparent manner. Studies have been conducted to determine the exact effects of DM on aneurysms. The incidence, severity, and occurrence of aneurysmal sac expansion and adverse events were studied. DM was advantageous for both AAA and TAA in each of the points.

In the last 10 years, 5 extensive meta-analyses studied the correlation between AAA and DM and 2 on TAA and DM. The conclusions were like each other, showing diabetes can be negatively related to abdominal and thoracic aneurysms in an apparently unexpected manner. The research performed to understand the link to AAA is far more extensive than for TAA, indicating that the TAA requires more investigation.

One of the advantages of studying the relationship between aortic aneurysms and diabetes is to improve the treatment and management of the disease. In most diabetic individuals, due to slower aneurysm extension, with 4 cm to 5 cm AAA, the conservative strategy appears to be preferred to others with higher cardiovascular mortality and increased severe adverse event rates associated with the repair. [28]

The pathophysiology of aneurysms in humans is complex and multifaceted, involving genetic and environmental factors. The condition is varied, and various factors, including the patients' comorbidities and therapies, might influence it. Determining the best medication administration regimen can be tricky. Therefore pharmacokinetic techniques could be helpful in determining whether metformin impacts. [31]

Metformin is the most widely given medication for people with type 2 diabetes. In recent years, various studies have shown that metformin may have other possible roles outside glucose-lowering, such as anticancer, antiaging, cardiovascular protection, neuroprotection, or as a therapy for the polycystic ovarian syndrome. [56] The link to the hypoglycemic drugs is significant because some of them, like metformin, can be a potential medical choice for asymptomatic patients.

Limitations of this work are i) most studies were observational studies. However, as De Rango *et al*. [14] suggested, most of the current data on diabetes and AAA comes from research with poor methodological quality or a high risk of bias. At the same time, the actual mechanism is still unknown. ii) the definition of DM used in several studies was not consistent or well established, allowing for fluctuations in glycemic parameters assessed in various analyses; iii) and there's no certainty that patients with diabetes died of causes other than rupture. [45]

This review emphasizes the necessity of knowing the link between diabetes and abdominal and thoracic aortic aneurysms and the consequences of exploring this association to better the outcomes that the pathology can present today.

Conclusion

According to current research, diabetes mellitus is inversely related to AAA and TAA prevalence, enlargement, and adverse consequences such as rupture.

The actual mechanism of this beneficial relationship is unknown.

Numerous pathophysiological explanations linked to hyperglycemia, hyperinsulinemia, and antidiabetic drugs have been suggested, but the exact cause has yet to be determined. More research is needed to understand better this link, which could lead to key therapeutic options in the future.

For more definitive conclusions, more clinical-based research is required especially on the direct impact of diabetes on aortic wall changes and the exact role of pharmacologic therapeutic options, such as antidiabetic drugs. The adverse effects of diabetes mellitus on the risk of many other chronic diseases, such as coronary heart disease, stroke, heart failure, atrial fibrillation, several cancers, digestive diseases, kidney stones, infections, respiratory diseases, neurological disorders, and all-cause mortality, greatly outweigh the benefits related to aortic aneurysm. Because of these various problems of diabetes mellitus, international efforts to reduce the incidence of diabetes mellitus should continue.

Attachments

Table I *- Summary of effects of Diabetes on Aortic Aneurysm.*

Authors	Topic discussion	Conclusions
De Rango *et al.* [14] Dattani *et al.* [21] Ning *et al.* [9] Patel *et al.* [23] Climent et al. [20] Takagi *et al*.[22] Aune *et al.* [5] Takagi *et al*. [17]	**Increased aortic wall stiffness**	- Accumulation of vascular matrix by decreased extracellular matrix proteolysis and decreased aortic wall remodeling. - Increased vinculin with bigger connection to the extracellular matrix to the actin cytoskeleton. - Hyperglycemia promotes collagen production, resulting in increased aorta wall thickness and a drop in MMP levels.
Koole *et al.* [24] Patel *et al*. [23] Ning *et al.* [9] Dattani *et al.* [21] Pafili *et al.* [1] Climent et al. [20] Takagi *et al*. [17] Takagi *et al*.[22] Avdic *et al.* [25]	**Advanced glycation end products**	- Glycation of ECM is linked to increased AGEs. - AGEs slow down the breakdown of ECM by regulating cathepsin and MMP production. - AGEs promote the artery wall's elastin and collagen to bind together, generating covalent cross-links facilitating SMC proliferation.
Takagi *et al*. [17] Dattani *et al.* [21] Milutinović *et al.* [26] Lareyre et al. [27]	**Neovascularization and inflammatory changes**	- Less adventitial neovascularization and inflammatory cell infiltration into the medial layer of the aorta reducing VSMC death and ECM deterioration.
Pafili *et al.* [1] Climent et al. [20] Dattani *et al.* [21] De Rango et al. [28]	**Hyperinsulinism and fibrinolytic system**	- Increase fibrinogen and PAI-1 levels with suppression of fibrinolytic system. This decreases active forms of MMP-2 and MMP-9. - Fibrin clots denser, less porous, and consequently less vulnerable to fibrinolysis.
Pafili *et al.* [1] Yuan *et al.*[3] Climent *et al.* [20] Raffort *et al.* [29] Wang *et al.* [30] Raffort *et al.* [31] Unusson *et al.* [32] Hsu *et al*.[33]	**Oral Hypoglycemic Drugs**	- Metformin, TZD or DPP-4 inhibitors may reduce local inflammatory cell deposition.
Lareyre *et al*. [34]	**Genetic implications**	- Upregulation of miRs in diabetic patients. - Diabetic propensity has no impact on preventing AAA development.

Table II *- Summary table of meta-analyses included in the review.*

Author	Topic discussion	Articles included	Conclusions
Xiong *et al.* [15]	**Association between diabetes and AAA prevalence**	49 articles	- Diabetes was negatively associated with AAA regardless of study type, geography and time period of data collection.
De Rango *et al.*[14]	**Clinical outcomes of an inverse relationship between AAA and DM**	Quantitative synthesis (n=54) Qualitative synthesis (n=64)	- Clinical outcomes were worst in patients with diabetes and AAA. - Patients with DM have less prevalence of AAA. - Patients with DM have a small growth rate when compared with non–DM.
Takagi *et al.* [16]	**Association between diabetes and AAA growth**	19 articles	- DM was found to be associated with slower AAA growth rates.
Aune *et al.* [5]	**Analysis of DM and risk of AAA development**	16 articles	- DM was found to be associated with lower AAA formation.
Takagi *et al.* [36]	**Association between diabetes and AAA rupture**	11 articles	- DM was negatively associated with presence, growth and rupture of AAA.
Takagi *et al.*[17]	**Association of DM with the presence of TAA**	11 articles	- DM is negatively associated with the presence of TAA.
D´Cruz *et al.* [18]	**Relationship between DM and TAA**	10 articles	- TAA is significantly inversed associated with DM.

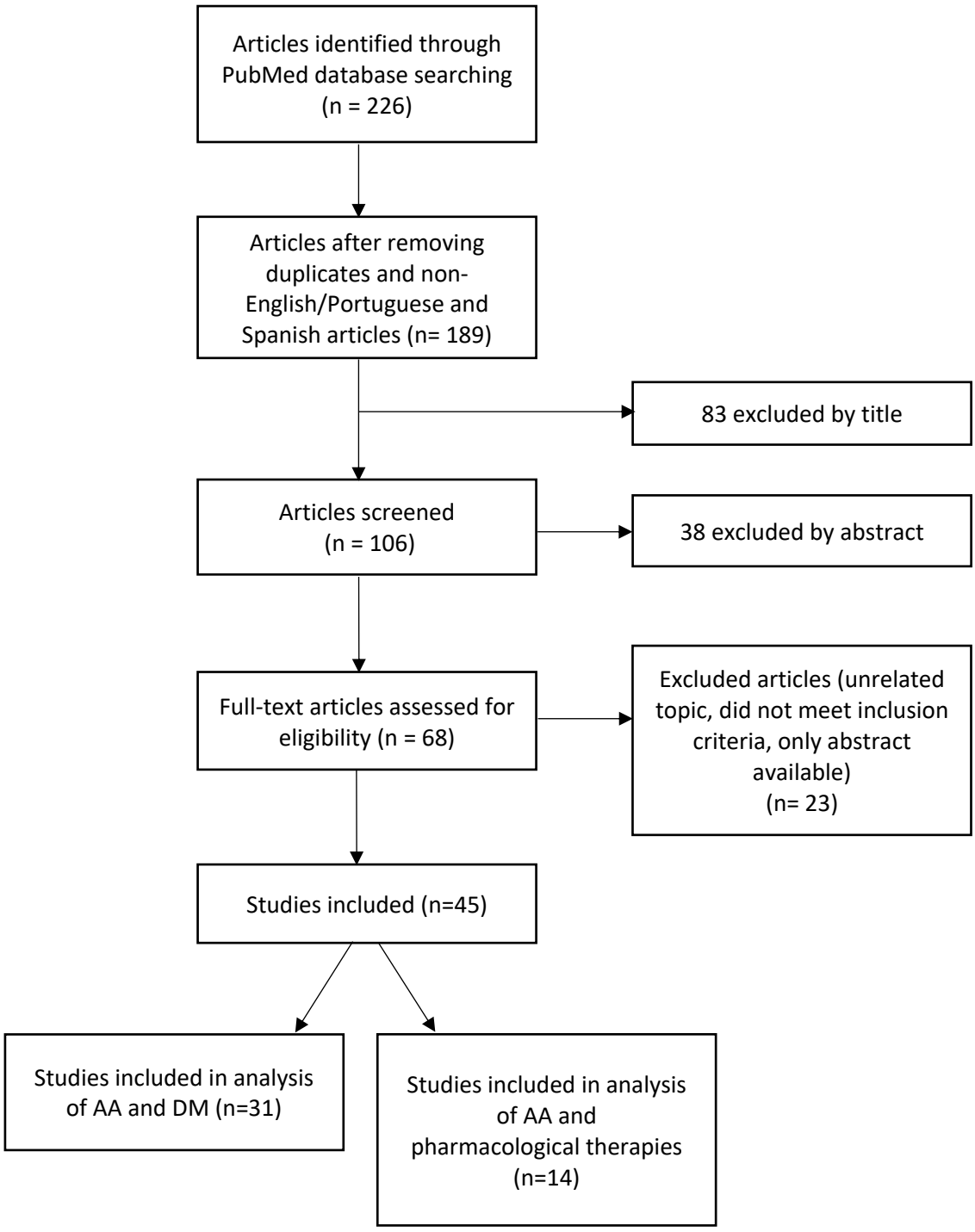

Figure 1 Flow diagram of the literature search and trial selection process according to PRISMA.

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