Abdominal Aortic Aneurysm Growth's Prediction

Subjects: Others
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Abdominal aortic aneurysm represents a distinct group of vascular lesions, in terms of surveillance and treatment. Amongst clinically applicable biomarkers, D-dimers, LDL-C, HDL-C, TC, ApoB, and HbA1c were found to bear the most significant association with AAA growth rates. In terms of the experimental biomarkers, PIIINP, osteopontin, tPA, osteopontin, haptoglobin polymorphisms, insulin-like growth factor I, thioredoxin, neutrophil extracellular traps (NETs), and genetic factors, as polymorphisms and microRNAs were positively correlated with increased AAA expansion rates.

abdominal aortic aneurysm biomarkers aneurysm growth

1. Introduction

Despite abdominal aortic aneurysm (AAA) being an asymptomatic entity, rupture complicates this silent pathology with a high mortality risk. Aneurysm identification on incidental imaging or screening programs at an early stage and small diameter allows for a close surveillance and repair [1]. However, not all aneurysms expand with the same rate and are not associated with the same risk of rupture, while diameter cannot always predict the physical evolution of an AAA [2][3][4]. A plethora of studies using imaging modalities and AAA anatomical characteristics tended to define models that could describe the expansion model of small or larger AAAs [5][6][7][8]. From ultrasonography to modern mathematical flow models, different methods have been used to identify these markers that could eliminate this group of patients needing closer re-evaluation and earlier management [9].

As different anatomical characteristics recorded on imaging modalities have been associated with aneurysm expansion, an analogous interest exists regarding the application of biomarkers that could identify AAA growth [10][11]. However, important discrepancies exist among the available studies [11]. A large spectrum of biomarkers is recorded in the current literature, from the commonly applied clinical circulating biomarkers to more specific sophisticated genetic models that could be used to evaluate AAA expansion rate [12]. The need to predict aneurysm evolution and if possible, to hamper sac expansion, is of high interest, as this approach would permit a closer surveillance screening and a more individualized therapeutic approach.

Along this line, a systematic review was conducted to present the existing evidence of different circulating biomarkers that may have a potential role on AAA growth prediction.

2. Development and Findings

AAA represent a category of vascular lesions with high morbidity and mortality, especially in the case of aneurysm rupture. Current guidelines suggest elective repair based mainly on aneurysmal diameter and/or other characteristics of the AAA [8][13]. Proposed screening strategies vastly stand on imaging techniques, including mainly DUS, adhering to the phenomenon of increased rupture risk in patients of specific demographic attributes and AAA diameter [14]. Studies have shown that patients with particular aneurysmal attributes would be acceptable surgical candidates, especially for endovascular interventions, even if AAA diameter has not achieved the diameter's threshold [15][16]. While AAA growth is observed through typical, time-set imaging follow-up, stratification of high-risk patients with expeditious AAA growth, through serum biomarkers, could be a valid approach for individualized imaging surveillance. These patients could benefit from a rather targeted surveillance approach as well as an early endovascular or open surgical repair.

The pathogenesis of AAAs advocates for an extensive list of serum circulating or histologically detected biomarker candidates. Each category bears an important role in the different phases of the natural history of AAA [17][18][19]. Biomarkers detected through histological evaluation of an AAA open surgical repair specimen do not conform with the concept of preoperative surveillance and disease progression and therefore cannot be used in clinical practice. However, serum circulating biomarkers appertaining to recognized pathophysiologic processes of AAA pathogenesis, including thrombosis, inflammation, extracellular matrix (ECM) degradation, lipid metabolism, as well as genetic predisposition, could potentially form the basis of a stratification screening or surveillance strategy for patients in need of more frequent follow-up.

As proposed by many studies, certain mediators or by-products of thrombosis and lipid metabolism have been linked to AAA growth. These biomarkers can be easily and cost-effectively implemented in everyday clinical practice [20][21][22][23][24]. D-dimers, a known fibrin degradation by-product, has been shown to be associated with AAA expansion, as higher levels have been correlated with increased growth rate. Correlation of other thrombosis-related biomarkers, including PAP complex [25][26], homocysteine [27], and TAT [24], has also been reported. Higher levels of HDL-C, a biomarker related to lipid metabolism, have been correlated with decreased AAA growth rates in a screening population [23]. Furthermore, increased levels of total cholesterol and apolipoprotein B, both markers easily quantified and major constituents of lipid metabolism, have been associated with increased growth rates of AAA [20]. On the other hand, given the potentially protective nature of diabetes mellitus in AAA, glycated hemoglobin (HbA1c) has been studied as a possible biomarker of inverse association with AAA expansion [28][29][30][31]. A lower growth rate was observed in patients with higher HbA1c levels; 1.8 mm/year decrease of rate in HbA1c 44–77 compared to 28–39 mmol/mol [32]. The recognized correlations of the abovementioned biomarkers, in addition to their cost-effectiveness and their wide-spread use in everyday clinical practice, renders them attractive candidates for future studies aiming to provide robust data on their relation to AAA expansion rates.

Concurrently, a plethora of less utilized biomarkers correlating to various stages of AAA progression have been studied, posturing as alluring secondary candidates. Firstly, extracellular matrix components and degradation enzymes have been associated with AAA growth rate. The well-defined role of elastin, biglycan, and type III collagen in the structural integrity of the aortic wall provided the basis for studies reporting data on the by-products of these proteins associated with AAA progress and increased sac expansion [20][33][34][35][36]. Inadvertently, extracellular matrix proteinases (MMP-2, MMP-9 [37], cathepsins B, D, L, and S [38]) responsible for ECM cleavage, and proteinases inhibitors (a1-antithrypsin [21], cystatin-B [39], cystatin-C [40]) play a significant role in the aortic wall remodeling occurring in AAA pathogenesis with several studies revealing either positive or inverse correlations with AAA growth rates. An abundance of modulators and mediators expressing the inflammatory and oxidative processes have also been studied with conflicting outcomes [41][42][43][44][45]. Synchronously, studies on promising novel biomarkers requiring genome sequencing analysis have been conducted, with propitious results. Specifically, genomic DNA analysis of genetic polymorphisms showed increased risk of aggressive-growth over slow-growth AAA [46][47][48][49][50]. Current data on these aforementioned biomarkers are promising, despite the fact that firm conclusions cannot be provided. Interestingly, calprotectin, a protein commonly associated with inflammatory cells (neutrophil granulocytes, monocytes, macrophages), has been related to AAA pathogenesis. These results provide further solid ground for future trials, aiming to assess the relation between the antimicrobial protein and AAA growth rate [51][52]. As the knowledge on AAA pathogenesis increases, novel studies may offer validated markers that could be used for the detection of this high-risk group of patients while pharmaceutical factors may provide a conservative management on AAA presence and expansion.

3. Limitations

The strength of the current review is limited by a series of factors. Firstly, the retrospective nature of the included studies confines its ability to reach pertinent results. Secondly, vast incoherencies among studies in terms of the types of biomarker assessed, studied population and cohorts, lack of control groups, follow-up intervals, and standardized methodological evaluations (imaging techniques, biomarkers quantification methods) impede the production of robust results, as well as the ability of quantitative analysis of the said results. Finally, most studies were judged as having “Moderate” risk of bias, mainly due to selection bias and inadequate confounder control.

4. Conclusions

Blood circulating biomarkers may offer a valid approach in the future for the detection of AAA expansion. The current literature provides a plethora of data with conflicting results and firm conclusions cannot be provided. In the presence of future robust data, specific serum biomarkers could potentially form the basis of an individualized surveillance strategy of patients presenting with increased AAA growth rates.

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