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Metformin and abdominal aortic aneurysm

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Recently published data from a number of sources appear to suggest that the oral hypoglycaemic agent metformin may prevent abdominal aortic aneurysm (AAA) development, attenuate growth and, perhaps even prevent rupture. Previous studies have hinted that hypoglycaemic agents might reduce AAA expansion.[1] The latest data, specific to metformin are compelling. Metformin is a biologically plausible drug since it has a wide range of effects on inflammation and metabolism. Although potentially exciting observations they remain preliminary and should be interpreted with some caution.

Although AAA and ruptured AAA appear to be declining (lifestyle and waning smoking habits), the widespread adoption of regional and national screening programmes continues to identify large numbers of men (and some women) with small AAA. In the UK this amounts to 3-4,000 new cases per year enrolled in to ultrasound surveillance as part of the national screening programme. The growth rates of these AAA and consequently the proportion reaching threshold for surgery haven't changed in the past 25 years.[2]

Methods to reduce AAA related mortality have recently focussed on screening and improving the outcomes from surgery. Multi-modal quality improvement programmes for surgery and refining new technology to increase the applicability and improve the durability of endovascular repair have been central in surgeons' minds. These are expensive approaches and significantly impact upon patients' quality of life.

Interventions that retard the growth of or reduce the risk of rupture represent could represent an additional opportunity to reduce AAA related mortality in screening programmes. This is particularly appealing since contemporary data appear to suggest that AAA diameter at rupture may be larger than previously thought (8.4cm in the IMPROVE Trial).[3] There are other potential advantages of an intervention that reduces aortic growth. AAA diameter appears to be an independent risk factor for subsequent cardiovascular and all-cause mortality.[4] It is tempting to hypothesise therefore that attenuating aortic growth may save lives and reduce cardiovascular events.

Unfortunately efforts to prevent AAA growth or rupture have largely proved futile. Smoking cessation appears to be effective. Therapies that have been encouraging in animal models and small-scale trials have included a variety of anti-hypertensives, antibiotics and even anti-allergic drugs. These have all proven ineffective in larger well-constructed randomised studies.

Observations that people with diabetes (5-6% of the adult population in Europe) are at lower risk of developing aneurysmal disease, progressing aneurysmal disease and rupture risk are well documented. Data from 17 population based studies were pooled and estimated that the odds of developing AAA in patients with diabetes are 0.80 (95% CI 0.70–0.90) compared to a non-diabetic population.[5] At first sight these observations appear counter-intuitive. Around 15% of people with AAA have diabetes (predominantly type 2). AAA have all the hallmarks of a systemic disease with many features in common with atherosclerosis and diabetes itself confers a two-fold excess risk of cardiovascular disease. There are a number of plausible biological explanations for this paradox that

have been confirmed in animal models. Among them are that hyperglycaemia has the effect of attenuating medial elastolysis, macrophage infiltration and neovascularisation.[6]

The observation in some RCTs of interventions for AAA growth suggest that diabetes is a very strong and independent negative predictor. In fact the effect size appears to be improbably large (>60% lower probability of aneurysm growth >5 mm) in some studies.[7] Competing risks may be an explanation for these observations. The competing risks include premature deaths in people with diabetes from other causes, especially cardiovascular disease. An alternative explanation may be that key lifestyle and pharmacological interventions associated with the onset of diabetes reduce the risk. These are frequently delivered at the onset of (or even before) diabetes and in some countries such as the UK as part of a pay for performance program in primary care. Most notably these interventions include drugs to prevent and manage the microvascular and macrovascular complications of diabetes including lipid lowering therapy, angiotensin receptor blockade and anti-platelet therapy. Importantly disease progression is monitored and adjusted frequently in people with diabetes.

For most people who develop type 2 diabetes the first line treatment is with lifestyle modification in combination with the oral hypoglycaemic agent metformin. Metformin is a biguanide and works by decreasing glucose production by the liver and increasing the insulin sensitivity of body tissues. Biologically, it has pleiotropic anti-inflammatory effects on the vasculature, a biologically plausible approach in AAA. [8]

Since none of the currently available cardiovascular medications have proven effective in controlling AAA growth eyes have turned to alternative explanations. Experimental studies have demonstrated that some of these hypoglycaemic drugs have biological plausibility. Rosiglitazone, one of the family of thiozalinedones (Peroxisome proliferator-activated receptor gamma agonist (PPAR-γ)) was found to reduce aneurysm expansion and prevent rupture in a mouse model.[9] Unfortunately, the side effect profile of these drugs meant they were never considered for in vivo studies.

Data from a case control study in Taiwan supported the association of both metformin and thiozalinedones / sulphonylureas with lower risk of development of AAA.[10] Moreover, those who had received the longest duration of metformin therapy were at lowest risk. In contrast alpha-glucosidase and DPP-4 inhibitors appeared to have no effect.

Golledge recently catalogued AAA growth rates in 3 separate Australasian cohorts.[11] In the 1357 (mean diameter 3.7cm) that were followed up with ultrasound over a mean of 3.6 years, the growth rates were significantly lower in those with diabetes taking metformin compared to those who were not taking metformin even after adjustment for other risk factors. Other diabetes medications did not appear to be associated with growth rates.

In a study of 58 patients with diabetes and AAA from Stanford, USA, the effect of 11 drug therapies on AAA was examined. Metformin was the only medication associated with a negative effect on AAA enlargement and this effect was robust to adjustment of known confounders. The same group performed analysed the effect of metformin in a murine model (elastase) of AAA. They found that non-diabetic mice given metformin were less likely to develop AAA (40% v 100% in the control group). There was preservation of medial elastin and smooth muscle cells in the metformin group with a reduction in immune cell (macrophage, T and B cells) accumulation and neovessel density. [12]

Metformin is an attractive drug that is now 60 years old. It has few drug interactions is cheap and well tolerated in people with and without diabetes. Gastrointestinal side effects occur in 10-20% of people but these effects appear to improve in most with appropriate dose titration. For many with diabetes the commencement of metformin is associated with an improvement in their overall symptoms and weight loss. There may be added benefits of a reduction in the incidence of cardiovascular events and cancer. It has been used for a variety of non-diabetes conditions including polycystic ovarian syndrome and is currently the subject of a number of RCTs in cardiovascular disease including heart failure.

The observational data on the effect of metformin on AAA development and expansion are interesting. They could be explained away by a number of confounders or competing risks as suggested by a recent Danish study that failed to demonstrate any effect of metformin on ruptured AAA rates.[13]

It is difficult to see how further observational studies will help answer the question of whether metformin will become a tool in the treatment of patients with AAA. The next logical step is an appropriately powered randomised clinical trial of metformin in patients with AAA.

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