Garlic in cardiovascular disease – the last word?

Garlic has been used for its potential medicinal properties for centuries. It was cited 3,500 years ago by the Egyptians as useful in the treatment of heart disease, tumours, bites and worms.[1,2] Interest in its use, particularly in reducing cardiovascular disease, has increased markedly over the past two decades with the rise in use of complementary and alternative medicines. Animal studies have suggested that it may have useful potential in reducing the risk of coronary heart disease with hypolipidaemic, antihypertensive, antithrombotic and antiatherogenic properties.[3] But what about in man?

In the 1960s and 70s much research took place using raw garlic both in healthy volunteers and patients with ischaemic heart disease. Results suggested that regular ingestion of raw garlic may produce significant reductions in blood cholesterol and triglycerides. Large doses (7–28 cloves/day) were required to achieve a relatively modest effect and the potential 'garlic odour' has limited its use.[1] In addition, levels of active ingredients in raw garlic may vary up to 10 times depending on growth conditions and methods of preparation in the kitchen.[1]

Garlic preparations

Much effort has been expended in trying to produce 'standard' garlic preparations including the 'odour free' dehydrated tablets (e.g. Kwai® and Sapec®) and 'aged garlic extracts' (e.g. Kyloric®). The dehydrated tablets are 'standardised' according to their alliin content (usually 1.3%). This is enzymatically broken down by allinase to allicin, believed to be one of the most important active ingredients in garlic. Allicin is inherently unstable and is largely generated by enzymatic breakdown of alliin after ingestion. Allinase itself is also unstable at gastric pH and is quickly denatured.

Attempts have been made to reduce this effect by coating tablets to prevent premature dissolution, but liberation of alliin may still vary from otherwise identical standardised dehydrated garlic tablets produced by the same manufacturer but in different batches.[3] This potentially makes comparison of clinical trials difficult. When it is also considered that other garlic ingredients, which are non-standardised in the available preparations, may be just as important as allicin, it is easy to see why the debate regarding usefulness of garlic continues.

Clinical trials

Over 40 trials have looked at the potential benefits of garlic preparations, particularly standardised dehydrated preparations, on plasma lipids in a number of patient groups including those with hyperlipidaemia, known coronary heart disease (CHD), peripheral vascular disease and type 2 diabetes. Many of these trials have been criticised for having inappropriate methods of randomisation, short duration, insufficient statistical power and failing to undertake an intention-to-treat analysis. Nevertheless, two recent meta-analyses have been undertaken.[3,4] These suggest that garlic is superior to placebo in reducing cholesterol. The size of the effect is rather disappointing with a fall in total cholesterol of approximately 0.4 mmol/L and a fall in LDL cholesterol of 0.16 mmol/L after 8–12 weeks, an effect similar to that which can be achieved with diet alone[5] and far less than that with available pharmacological agents.[6] These effects may not be sustained in the longer term, although only a relatively small number of studies have continued beyond three months. No overall change was seen in HDL cholesterol and the reduction in triglycerides was also modest at 0.2 mmol/L. There appeared to be little difference between overall results using dehydrated garlic preparations (Kwai®, dose 600–1,200 mg/day) and other preparations, particularly aged garlic extract (Kyloric®, dose 1g–7.2 g), raw garlic (1–10 g) and garlic ether extract (1–10 g/day).

As well as the rather small effects on lipid lowering, garlic preparations may have other effects on lipid metabolism which are important in atherogenesis. *In vitro*, accumulation of cholesterol in cultured human aortic smooth muscle cells may be reduced if incubated with serum from patients with CHD taking garlic supplements compared with controls. The susceptibility to oxidation of LDL isolated from CHD patients may also be decreased in patients taking garlic. The importance of these effects *in vivo* is uncertain, as is the observed reduced ability of isolated LDL from garlic-treated CHD patients to stimulate proliferation of cultured smooth muscle cells.[7,8]

Assessment of the blood pressure-lowering effects of garlic preparations has often been considered as a secondary issue in trials looking at lipid-lowering effects, but there have been a number of small trials which have considered blood pressure-lowering effects as the primary end point in hyper-

tensive patients.[3,9] The overall effects of garlic preparations on blood pressure seem to be rather modest with a mean fall in systolic blood pressure of 7.7 mmHg and a mean fall in diastolic blood pressure of 5 mmHg relative to placebo when taking Kwai® tablets 600–900 mg for four weeks to 10 months. The magnitude of the blood pressure-lowering effect with garlic is similar to that achieved with non-pharmacological treatment of hypertension, but less than that which can be achieved with commonly used antihypertensives.[9] Whether such effects are maintained in the long term on garlic therapy is unknown.

The positive effects on platelet function seen in animal experiments have also been reproduced in man with modest but significant reductions in platelet aggregation with garlic compared with placebo in several studies.[3] A number of garlic constituents have been shown to inhibit multiple steps in the synthetic pathway from arachidonic acid to thromboxane in platelets.[10] It seems that this effect is highly dependent on the preparation of garlic ranging from no effect to strong inhibition of platelet aggregation. Attenuation of effect is particularly seen with cooking raw garlic but is also observed with different methods of preparation of commercial garlic extracts.[10]

Conclusion

Use of evidence-based garlic preparations, either in its raw form or as one of a number of commercially available products, seems to produce a number of effects which could potentially reduce the risk of atherogenesis. However, despite more than two decades of interest in this area, we are still not certain which constituents of garlic are most important, which of the available formulations might be best in reducing the risk of CHD and what the optimal treatment dose might be. Disappointingly, there have been no randomised trials of sufficient duration or containing large enough numbers to answer the important question of whether use of garlic produces positive outcomes in terms of morbidity and mortality.

Undoubtedly, patients will continue to spend significant sums of money purchasing garlic preparations believing such 'natural' remedies must be better than any single or multiple drug therapies physicians may suggest. It is possible that they do produce benefit in primary and secondary prevention of coronary heart disease but, to-date, the evidence does not exist. As therapeutic agents proven to be highly effective are significantly underused, the focus must remain on making sure that the right patients are using the right drug combinations and continually reiterating the importance of compliance.

Patient advice

What should we tell a patient who wants to take garlic? There may be benefits but the case remains unproven. Garlic in cardiovascular disease – the last word? Not yet.

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