

# Dietary management of gallstones: future possibilities

**Dr Angela Madden and Professor David Flum** suggest areas of further research to improve the management of gallstones

Gallstones are common and affect up to 20% of adults overall.<sup>1</sup> The prevalence is increasing with rising levels of obesity and aging populations.<sup>2</sup> Although many people with gallstones are asymptomatic and the overall mortality is low (0.6%), the associated morbidity and economic cost are high at approximately US\$6.2 billion (£4.6 billion) annually in the USA.<sup>2</sup>

## Prevention vs management

Gallstones are usually found in the gallbladder and occasionally lodged in bile ducts. The role of the gallbladder in digestion is to store bile until it is needed in the gut to emulsify dietary fat, and this role suggests potential interaction with diet.

However, the relationship between food intake and the gallbladder, bile and gallstones is complex. While it has been clinical dogma to encourage people with gallstones to avoid fatty food, it is likely that the relationship between food and the gallbladder involves more than just the digestion of fat. It's important to clarify the difference between dietary factors that are associated with the risk of developing of gallstones, i.e., prevention, and dietary factors that might influence the management of existing gallstones. There is strong evidence that factors associated with a higher risk of developing gallstone include excess energy intake leading to obesity<sup>3</sup> (probably mediated by high levels of cholesterol synthesis and secretion into bile and high levels of circulating insulin), high intakes of refined carbohydrate<sup>4</sup> and trans fatty acids,<sup>5</sup> high serum triglyceride<sup>6</sup> and low levels of physical activity.<sup>7</sup> Conversely, a lower risk of developing gallstones is associated with higher intakes of dietary fibre,<sup>4,8</sup> fish oil (n-3 fatty acid),<sup>9</sup> fruit and vegetables,<sup>10,11</sup> nuts,<sup>12</sup> coffee<sup>13</sup> and, in moderation, alcohol.<sup>6,14</sup> Current public health advice<sup>15,16</sup> encourages food intake that is compatible with reducing gallstone risk.

## Dietary fat

Evidence around the best diet to help manage symptoms associated with the gallbladder, such as biliary colic or episodes of cholecystitis, is less clear. The clinical recommendation to avoid fatty food<sup>17</sup> is neither evidence-based nor particularly specific, yet this practice continues. It is not clear whether this restriction intends to reduce pain by decreasing the extent or frequency of gallbladder contractions, i.e. as bile is ejected into the GI tract, or to reduce the risk of further stone development. There is little evidence for either.

## KEY POINTS

- 1 Traditional advice to people with gallstones has been to avoid fatty food but it is likely that the relationship between food and the gallbladder involves more than just the digestion of fat.
- 2 There is some evidence of a link between a Mediterranean eating pattern and prevention of gallstones although it is not clear whether these associations are causative. Timing of eating and physical activity levels are also worth extra study.
- 3 People with gallstones have said that diet as the most important issue for discussion in their condition. But good quality randomised controlled trials are needed to explore diet in this under-researched area which affects so many people.

## ABOUT THE WRITERS

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Dietary fat does lead to gallbladder contractions<sup>18</sup> but so do other food components, i.e. protein,<sup>19</sup> medium chain triglycerides<sup>20</sup> (which require less emulsification than other fats), elemental diets<sup>21</sup> and sham feeding.<sup>22</sup>

This contraction response is mediated via the gut hormone cholecystokinin<sup>23</sup> and a cephalic phase that is independent of intestinal stimulation.<sup>22</sup> As dietary fat is just one factor causing gallbladder contraction, restricting fat intake alone is unlikely to reduce pain. Indeed, extensive searches to date<sup>24</sup> have not identified reliable evidence to support this. There is, however, evidence that modest amounts of dietary fat, in line with current healthy eating guidelines, may be helpful by causing regular bile release and so decreasing the opportunity for biliary precipitation and the formation or enlargement of gallstones.<sup>25,26,27</sup>

### Mediterranean diet

While reducing dietary fat may not offer clear therapeutic benefit, a diet that reduces inflammation may be effective for patients with chronic cholecystitis because this is an inflammatory condition.<sup>28</sup> A Mediterranean diet has anti-oxidant and anti-inflammatory effects<sup>29,30</sup> and following this pattern of eating has documented health benefits associated with reducing risk of primary cardiovascular disease,<sup>31,32</sup> type 2 diabetes,<sup>33</sup> metabolic syndrome<sup>34</sup> and cancer.<sup>35</sup> Could these benefits extend to gallstones?

A Mediterranean diet can be assessed using different tools<sup>36</sup> but all agree that this pattern of eating includes a high intake of plant-based foods (vegetables, fruits, legumes, nuts, wholegrain cereals), olive oil, moderate amounts of dairy (yogurt, cheese), low or moderate amounts of fish and meat, moderate consumption of wine consumed with meals, limited refined sugar and an active lifestyle. Several of these items are compatible with the food described above that is associated with a lower risk of developing gallstones.

This pattern of eating provides a high fibre intake and is associated with a reduced transit time and changes to faecal bile acid metabolism<sup>37</sup> which, mediated via reduction of circulating insulin levels, has relevance to reduced risk of gallstone formation, i.e. prevention. However, in terms of managing existing gallstone disease, it may be the effects of dietary fibre, which is associated with reduced biliary sludge,<sup>38</sup> as well as the anti-inflammatory effects<sup>29,39</sup> of a Mediterranean pattern of eating that may reduce bile viscosity and relieve intermittent obstruction of an inflamed gallbladder.

These mechanistic links are important, but is there any clinical evidence of benefit between a Mediterranean diet and gallstones? Wirth et al<sup>39</sup> reported a prospective study of 43,635 men where those who followed a Mediterranean-style diet had a reduced risk of developing symptomatic gallstones (hazard ratio [95% confidence intervals] highest versus lowest quintile: 0.66 [0.57-0.77]). This indicates an association between a Mediterranean eating pattern and prevention of symptomatic gallstones. In another prospective study which included 1,033,955 person years of follow up in women, Barré et al<sup>40</sup> reported a reduced risk of undergoing cholecystectomy with a higher adherence to a Mediterranean diet (HR [95% CI] diet score 6-9 versus 0-3: 0.89 [0.80-0.99]). This indicates an association between a Mediterranean eating pattern and prevention of interventions for gallstones. Whether these associations are causative or not requires testing through an intervention study. To date, no randomised controlled trial has been published in this area but we believe there is evidence to justify undertaking this.

**“If the gallbladder is emptied in the early morning and regularly through the day, it potentially reduces the opportunity for lithogenic cholesterol-rich bile to precipitate”**

### Chrononutrition

Focus on food and nutrient intake in gallstone disease is important but there is evidence that the timing and frequency of intake, as well as the type and quantity of nutrients, may be important.

Gallstones composed of predominantly cholesterol form when bile is supersaturated with cholesterol. Cholesterol levels in bile are influenced by a number of factors including synthesis of endogenous cholesterol and bile salt concentration and these are influenced by diurnal variation with the highest cholesterol concentrations occurring at night.<sup>41</sup>

If the gallbladder is emptied in the early morning and regularly throughout the day, it potentially reduces the opportunity for lithogenic cholesterol-rich bile to precipitate out and so might reduce risk of gallstone formation. The timing and frequency of food intake, which leads to gallbladder contraction and thus ejection of bile, may have a role in helping this.

A cross-sectional study of 123 older adults found that ➤

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those with a ‘fasting or anorexic’ eating pattern had a significantly higher risk of biliary sludge than those who had a greater oral intake (odds ratio [95% CI], 5.25 [1.16,23.72]).<sup>42</sup> A larger cross-sectional study from Italy (n=29,584) reported that adults with a long overnight fasting time, >12 hours, had a significantly higher prevalence of gallstones than those with a shorter overnight fast<sup>9</sup> (relative risk [95% CI], 1.35 [1.01,1.80] in men; 1.28 [1.03,1.60] in women).

No robust clinical investigations of the effect of time of eating on gallstones have been identified but a small study from 1975 indicates bile cholesterol levels reduce in response to breakfast but not lunch.<sup>43</sup> Work by Williams described in 1987<sup>44</sup> described better rate of dissolution of gallstones (100%) with chenodeoxycholic acid and a dietary regime of regular meals and a shorter overnight fast than with chenodeoxycholic acid alone (70%) and, on follow up, a slower recurrence rate (33 versus 22 months). This limited evidence suggests that adjustment of time of food intake may have the potential to influence gallstone development and dissolution and merits further investigation by randomised controlled trial.

Physical activity

Although not a dietary strategy, it is worth considering the potential for physical activity to influence clinical outcomes in gallstone disease. There is clear epidemiological evidence that lower levels of physical

activity are associated with higher risk of gallstones.<sup>7</sup> A cohort study with 486,376 person years of follow up identified extended sitting time was also associated with higher risk of gallstones and this was independent of physical activity.<sup>45</sup> No clinical trials investigating the effects of increasing physical activity or reducing sedentary time in people with gallstones have been identified but this could form a useful strand, along with diet, in a lifestyle intervention.

Challenges of studies in gallstone disease

The lack of good quality evidence from randomised controlled trials, nihilism about the likelihood people will change their diet and uncertainty about the optimum diet and lifestyle for people with gallstones is challenging for both those experiencing the condition and the healthcare professionals working with them.

This evidence gap was identified by people with gallstones who contributed to the NICE clinical guidelines for gallstone disease<sup>46</sup> and they placed diet as the most important issue for discussion. Eight years on, little has changed. Good quality randomised controlled trials are needed to explore diet in this under-researched area which affects so many people. Such trials are expensive and difficult to undertake but this is not a reason for not attempting to do them. The ideas outlined above may have the potential to help and although this is currently uncertain, we believe they are worth investigating.

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