Dietary factors in the aetiology of gall stones: a case control study

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SUMMARY Dietary intake was studied in 121 women with gall stones (identified in a prevalence survey using ultrasonography) and a similar number of age-matched controls in order to investigate nutritional factors in the aetiology of the condition. Despite the appreciably lower frequency of gall stones in vegetarians as compared with non-vegetarian women (11.5% and 24.6% respectively) nutrient intake did not differ between cases and controls. This may indicate the existence of a threshold effect where virtually all non-vegetarian women in affluent societies have a diet high in saturated fat, animal protein, and simple sugar to the extent that it is not possible to distinguish between cases and controls. In women with newly discovered gall stones, the prevalence of upper gastrointestinal symptoms was no different from that in the controls. Thus cholecystectomies carried out to relieve relatively low grade symptoms may not do so.

A number of epidemiological studies have shown that the prevalence of gall stones is higher in affluent societies than in developing countries where the population still consumes a traditional diet.¹⁻⁵ Dietary factors are believed to be at least partially responsible for these differences²⁻⁵ but hospital based case control studies have failed to show striking contrasts between the dietary intake of those with or without gall stones.^{6,7} We have recently shown an appreciably reduced frequency of gall stones amongst vegetarian women compared with women eating a more typical Western diet.⁸ We report here the results of a case control study of diet and gall stones carried out on women with and without gall stones identified in our population based study. Most of our subjects had not been previously diagnosed as having gall stones. We have, therefore, included in this study an investigation of the symptoms often attributed to this condition as their validity in the diagnosis of gall stones has been questioned.⁹⁻¹¹

Methods

PATIENTS

Ultrasound investigations were carried out on 652 non-vegetarian and 130 vegetarian women aged 40-70 years. One hundred and sixty non-vegetarians and 15 vegetarian women were found to have gall stones. Each was matched with a disease free control in the same five year age group. Two hundred and twenty eight of the 320 (71.2%) non-vegetarian cases and controls and 25 of the 30 (83.3%) vegetarians agreed to participate, resulting in 109 non-vegetarian and 12 vegetarian pairs. Thirty one cases had had a cholecystectomy. Gall stones had not been previously diagnosed in the remaining 88 cases.

All participants agreed to complete a four day fixed format dietary diary. The diary (which has been previously validated by comparison with other dietary instruments including a technique involving weighed food portions) (submitted for publication) included photographs of many food items to aid the estimation of portion size and general questions concerning dietary practices to provide a cross check with the reported intakes. Correlations between our four day and the seven day (weighed) dietary diary ranged from 0.68 for cholesterol to 0.86 to dietary fibre.

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Table 1 *Intake of total energy and various nutrients in women with and without gall stones*

Nutrient	Intake (mean SD)			p value
	Cases 109	Cases excluding post-cholecystectomy 78	Controls 109	
Total calories (Kcal)	1710 (471)	1694 (448)	1803 (412)	NS
Total protein (g)	62.9 (17.2)	61.9 (18.0)	67.2 (16.0)	NS
Protein (% energy)	15.1 (3.53)	14.9 (3.58)	15.2 (3.41)	NS
Animal protein (g)	23.1 (14.4)	22.0 (14.8)	25.0 (13.7)	NS
Animal product protein* (g)	19.9 (9.06)	19.9 (9.22)	20.6 (9.12)	NS
Non-animal protein (g)	19.9 (7.41)	20.0 (7.63)	21.6 (7.59)	NS
Total fat (g)	76.1 (28.6)	75.1 (26.2)	81.8 (24.6)	NS
Fat (% energy)	39.4 (6.89)	39.4 (6.68)	40.4 (5.42)	NS
Total carbohydrate (g)	191.2 (54.7)	188.6 (52.4)	200.5 (54.4)	NS
Carbohydrate (% energy)	42.5 (8.12)	42.3 (8.41)	41.7 (6.46)	NS
Refined sugars (g)	81.1 (30.4)	79.4 (30.9)	84.3 (30.9)	NS
Refined sugars (% energy)	18.4 (7.05)	18.1 (7.26)	17.6 (5.56)	NS
Fibre (g)	17.4 (7.38)	17.3 (7.83)	18.4 (7.24)	NS
Cholesterol (mg)	281.0 (152)	277 (149)	308.0 (152)	NS
Alcohol (g)	8.9 (15.4)	8.6 (13.8)	7.8 (10.3)	NS

*Animal product=dairy products, eggs, etc.

Within a month of completing the diary, each participant was interviewed by one of two trained interviewers in order to clarify any discrepancies in the diaries and to collect further clinical information including weight and height. A check list of upper gastrointestinal symptomatology was used to elicit the presence of any of the following symptoms: abdominal pain or discomfort, flatulence, nausea, vomiting, heartburn, acid regurgitation, water brash, and fatty intolerance. Body mass index was calculated according to Quetelet's index as: weight (kg)/height (m²).

The diet histories were analysed using a specially developed comprehensive computer database program. The dietary analyses of many foods typically eaten by vegetarians and other commercially available products had been added to the computerised version of the McCance and Widdowson Food Tables to provide the data base.¹² The statistical significances of the nutrient intakes were tested using PECAN, a program which carries out regression analysis of conditional likelihood functions in matched case control studies allowing comparison for single and grouped nutrients.¹³ Student's *t* test was used to compare group means.

Results

Cases were significantly more obese than controls (mean body mass index 25.2 and 23.4 respectively, *z*-score=3.42, *p*<0.001). Intake of total energy and various nutrients in women with and without gall stones is shown in Table 1. No significant differences were observed between cases and controls for any nutrients either looked at separately or as combined

variables (*z*-scores=-2.11 to 0.91 for all variables). Similarly there were no significant differences between cases and controls when postcholecystectomy cases were excluded (Table 1) or when considering women under and over the age of 50 years. Intakes of individual nutrients were normally distributed and distribution was similar in cases and controls as shown by the frequency histograms in the Figure. When considering nutrient intakes for non-vegetarians and vegetarians, however, striking differences emerged (Table 2).

Cases were significantly more likely to have experienced one or more episodes of epigastric or right upper quadrant pain (*z*-score=3.54, *p*<0.001),

Table 2 *Intake of total energy and various nutrients in non-vegetarians and vegetarians*

Nutrient	Intake (mean SD)		p value
	Non-vegetarian 218	Vegetarian 24	
Total calories (Kcal)	1774 (451)	1602 (349)	0.0001
Total protein (g)	67.0 (15.9)	48.0 (14.0)	0.0001
Protein (% energy)	15.5 (3.36)	12.2 (3.45)	0.0001
Animal protein (g)	26.7 (12.3)	0.5 (1.51)	0.0001
Animal product protein (g)	20.4 (8.88)	19.1 (10.9)	NS
Non-animal protein (g)	19.9 (6.60)	28.4 (10.7)	0.0001
Total fat (g)	80.2 (26.7)	67.7 (23.9)	0.0001
Fat (% energy)	40.1 (6.02)	37.3 (7.30)	0.0001
Total carbohydrate (g)	194.7 (55.6)	205.8 (44.3)	0.0001
Carbohydrate (% energy)	41.3 (6.82)	48.8 (8.46)	0.0001
Refined sugars (g)	81.6 (30.4)	91.9 (31.7)	0.0001
Refined sugars (% energy)	17.6 (6.05)	21.8 (7.67)	0.0001
Fibre (g)	17.0 (6.69)	26.0 (7.73)	0.0001
Cholesterol (mg)	309.0 (148)	170.0 (129)	0.0001
Alcohol (g)	8.7 (13.6)	5.3 (6.3)	0.0005

Figure Intake of individual nutrients – frequency histograms. Cases —. Controls ----.

Table 3 Prevalence of upper gastrointestinal symptoms for cases and controls: statistical summary of symptomatology for the case control study

	Cases excluding post cholecys- tectomy		Controls	p value excluding post choleli- thiasis	
	All cases %	%	%	p value all cases	
Abdominal pain	39.3	20.9	16.9	0.001	NS
Abdominal discomfort	54.7	43.0	29.7	0.001	NS
Flatulence	60.3	52.3	53.4	NS	NS
Nausea and vomiting	33.9	20.7	17.8	0.001	NS
Heartburn	45.2	43.0	39.0	NS	NS
Acid regurgitation	25.0	21.8	24.6	NS	NS
Waterbrash	9.6	8.0	9.3	NS	NS
Fatty intolerance	34.0	27.6	30.5	NS	NS
Cucumber indigestion	31.4	28.9	32.2	NS	NS

abdominal discomfort (z-score=3.51, $p<0.001$), or nausea and vomiting (z-score=2.71, $p<0.01$) than controls. If postcholecystectomy cases were excluded, however, no significant differences between cases and controls were apparent with regard to any of the commonly described upper gastrointestinal symptoms on the check list (Table 3).

Discussion

Obesity was confirmed as an important risk factor for gall stones confirming the findings of many previous studies.^{6,8,11,14} Despite the findings in our earlier prevalence study of a striking difference in frequency of gall stones between non-vegetarian (24.6%) and vegetarian (11.5%) women, however, this case control investigation was unable to show any differences in nutrient intake between women with and without gall stones. All methods of assessing dietary intake are fraught with difficulties but the method used here is at least as reliable as any other available method. It has been validated by comparison with a seven day weighed inventory (submitted for publication). The correlation coefficients for the nutrient intakes between the four day diary and the seven day weighed method are encouraging. Obese people probably underestimate their energy intake and consideration of percentage of total energy provided by various nutrients may be a more reliable measure than total intake. The fact that both cases and controls consumed an average daily calorie intake of less than 2000 Kcal supports the likelihood of underestimating intakes. When individual intakes were compared as a proportion of total daily intake, however, there were still no significant differences between cases and controls. This cannot completely take into account the difference in mean body mass

between the two groups but goes some way towards correcting for this potential source of bias. The suggestion that depletion of fibre and unprocessed starchy food from the diet and excessive intakes of sucrose and other highly processed carbohydrate foods are major aetiological factors in gall stone formation is derived principally from population comparisons^{2,3} although animal studies support this suggestion.¹⁵ A recent hospital based case control study has shown an increased consumption of refined sugars amongst cases but the difference between cases and controls was not marked.⁶ In the present study, which included nearly all cases of symptomatic and asymptomatic gall stones in a fairly large population, fibre consumption was slightly lower and percentage of total energy derived from simple sugar slightly higher in cases than controls, but these differences did not reach statistical significance when these two factors were considered separately or as a combined variable. If cholecystectomy cases were excluded, nutrient intakes for the cases were not significantly altered. Similarly, there were no significant differences when the results were analysed for women aged less than 50 years. This is in conflict with Scragg and colleagues⁶ who found increased total calorie intake in women of less than 50 with gall stones compared with controls. Unfortunately, the numbers of women aged less than 50 in our study were small (25) and the possibility of a positive risk associated with high calorie intake in young women cannot be excluded. The possibility that dietary habits may have altered in the time since gall stones developed must be considered but all participants were specifically questioned about major changes to their diets in the previous five years and few reported any significant alteration.

A possible explanation for failing to elicit dietary differences between cases and controls may be the existence of a threshold effect where virtually all non-vegetarian women in affluent societies eat excessive quantities of saturated fat, animal protein and refined sugar and too little dietary fibre and vegetable protein to allow these differences to be detected. The small number of vegetarians precluded an analysis of these participants alone. The vegetarian diet provides an interesting contrast with that of the non-vegetarians. Intakes of total energy, total protein, total fat and cholesterol are lower in vegetarians than non-vegetarians. Dietary fibre, total carbohydrate (including sugar) and vegetable protein intakes are significantly higher than in non-vegetarians and animal product protein intake is similar. This contrast together with the previously observed difference in gall stone prevalence between vegetarians and non-vegetarians provide supportive evidence for the role of some of these dietary factors in gall stone

formation. Similar difficulties have occurred when researchers have tried to look more closely at the blood pressure lowering effect of a vegetarian diet.¹⁶ Inability to show any protective effect of alcohol in the formation of gall stones puts the results at odds with several other studies.^{6, 17, 18} This may have been related to the inaccuracies of measuring alcohol intake using a dietary diary format. Interestingly, cases were shown to drink more alcohol per day (8.9 g) than controls (7.8 g) but the wide standard deviations ensured that this difference was not significant. Larger numbers may well have supported the findings from previous studies. It seems likely that a larger case control study of vegetarian women with or without gall stones in a developing country may be more helpful in detecting specific dietary factors.

The possibility of non-responders as a source of bias must be considered with a response rate of 69%. As all these non-responders participated in the first part of the study, however,⁸ each completed a food frequency postal questionnaire. These supplied sufficient information to compare diets but were not able to quantify nutrient intakes except for that of fibre. Non-responders matched responders for fibre intake and frequency intakes for the other variables were similar also. The two groups did not differ with respect to age and weight.

This study also provided an opportunity to examine the relevance of upper gastrointestinal symptoms in the diagnosis of gall stones. Classical teaching suggests that gall stones are commonly associated with specific, low grade symptoms of nausea and vomiting, abdominal fullness and discomfort and fat intolerance and eventually lead on to the full blown symptom complex of acute cholecystitis or biliary obstruction with right upper quadrant pain radiating around to the back and associated with nausea and vomiting. This study showed that the postcholecystectomy cases had experienced the classical symptoms of 'biliary colic' but they were no more likely to have experienced the supposedly low grade symptoms associated with gall stones. In women with newly discovered gall stones, the prevalence of upper gastrointestinal symptoms was not different from that in the controls. These results are in keeping with those of Price⁹ and Bainton¹⁰ and the Rome Group,¹¹ have important clinical implications in determining which patients might benefit from cholecystectomy. Cholecystectomies carried out to relieve low grade symptoms are unlikely to do so.¹⁹

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