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Variations in Dietary Intake Between Newly Diagnosed Gallstone Patients and Controls

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Abstract: To compare dietary intake of newly diagnosed gallstone patients and controls, 56 gallstone patients and 101 randomly selected control subjects without gallstones were enrolled in the study. The presence of gallstones were determined by ultrasonography. Both patients and control subjects completed a questionnaire exploring their dietary intake. Aanthropometric measurements were collected. Blood samples were analyzed for glucose triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), Apolipoprotein A-I (Apo A-I) and Apolipoprotein B (Apo B). Oral contraceptive usage was significantly higher in gallstone patients than controls. Patients were significantly older than controls and had higher body mass index (BMI), however HDL-cholesterol levels were found significantly higher in controls. Dietary intake including energy, proteins, carbohydrates, refined sugar, sodium, calcium, and iron were significantly higher in patients. Dietary fiber and antioxidant vitamin (vitamin C) levels were significantly lower in patients. Dietary interventions that emphasize the prevention effect of some nutrients and the contributory effect of others might provide a method of avoiding the formation of gallstones.

Key words: Gallstones, BMI, contraceptives pills, dietary fiber, refined sugar, vitamin C

Introduction

Gallstone disease (cholelithiasis) has been identified as one of the diseases of civilization and modern affluent lifestyles of the developed nations (Caprini, 1979; Diehl *et al*., 1987). Although, a number of epidemiological studies have shown that the prevalence of gallstones is higher in affluent societies than in developing countries where the population still consumes a traditional diet (Brett and Barker, 1976; Burkitt and Tunstall, 1975; Heaton, 1979), and other research has been shown that gallbladder disease (GBD) prevalence can differ substantially between communities that differ in culture and in diet (Malhotra, 1968). The risk factors for the development of cholelithiasis include irreversible factors-female sex and advancing age, and reversible factors-obesity, repeated pregnancy, use of contraceptive pills, a family history of gallstones, smoking, diabetes mellitus, plasma lipids and dietary factors, chronic liver disease and possibly major abdominal surgery (Bennion and Grundy, 1978; Kosters *et al*., 2003). Further from literature it is clear that several factors, such as supersaturation of bile cholesterol, nucleation and growth of cholesterol crystals, gallbladder mucin, and altered gallbladder motility have been studied extensively.

Disease definition and ascertainment in studies on GBD are particularly problematic because as many as two-thirds of cases with gallstones are asymptomatic or silent (Heaton *et al*., 1991). Generally, asymptomatic cases can be identified only in screening studies, which use one of two primary techniques to detect the presence of gallstones: oral cholecystography and ultrasonography. Since cholecystectomy is the most common procedure for treating gallstones, individuals who have undergone cholecystectomy, or surgical removal of the gallbladder, are also commonly included as gallstone cases and presumably represent cases with symptomatic gallstones (Tseng *et al*., 1999).

Diet has long been a suspected risk factor for gallstones. One source of evidence for this is the presumed link between cholesterol and gallstones. In fact, cholesterol overfeeding is the primary means of inducing supersaturated bile and cholesterol gallstones in animal models. The observed relationship between obesity and GBD further implicates diet as an important risk factor (Maurer *et al*., 1990; Hanis *et al*., 1993; Kono *et al*., 1995). Observed trends in GBD over time also suggest a role for diet. Dietary changes, most notably a rise in caloric, lipid and animal protein intake (Sarles *et al*., 1978), may have contributed to the increase in GBD prevalence in European countries after World war II (Heaton, 1984). In Japan cholesterol gallstones were once rare but have become much more common in the past 30 years with the adoption of many North American eating habits (Nakayama and Miyake, 1970).

Saudi Arabia is the largest landmark in the Arabian Peninsula, with an estimated population of 21 millions increasing by more than 3% annually. Over the past few

decades it has undergone remarkable and rapid economic development, and has gone through significant changes in nutritional and lifestyle habits (Sebai, 1987; NCMDS, 1995). Mofti *et al.* (1987) reported an increasing incidence of gallstones in central region of Saudi Arabia. The incidence is still increasing constantly year after year according to hospital records. Reports from other regions of Saudi Arabia show a striking increase, several folds in magnitude, in occurrence of gallstones in Saudi population during the last two decades (Tamimi *et al.*, 1990).

This is a case-control study including controls and patients with new diagnosis of symptomatic and asymptomatic gallstones. Detailed dietary intakes were analyzed using a semiquantitative food-frequency questionnaire. Factors investigated in relation to gallstone included anthropometric measurements, blood biochemistry.

Materials and Methods

Source: The subjects (newly diagnosed gallstone patients) and controls included in this study were women attending Primary Health Care Clinics at King Khalid University Hospital (KKUH) Riyadh, Saudi Arabia, during the period from October, 2002 to November, 2003. KKUH is a 650 bed tertiary care facility in Riyadh, the capital of Saudi Arabia. All patients attending these clinics who were over the age of 30 years and who had been diagnosed during the study by ultrasonography as having gallstones were invited to participate in this study. Subjects were excluded if they had a major underlying illness (e.g., neoplasm) or an abnormal hepatic function test, diabetes mellitus or other endocrine disorders. Also excluded from the study those who were undergoing nutritional treatment in order to lose or gain weight, those who fail to provide the data required in the study tool. Patients who took medication likely to affect appetite e.g., anti-neoplasia drugs, steroids or anabolic drugs also were excluded. After the presentation of the study protocol, written consent of inclusion was obtained from interested subjects. Following the criteria of Yang *et al.*, (1992), the absence of gallstones in the control subjects was confirmed by ultrasonography prior to their entry into the study.

A total of 168 persons (60 patients and 108 controls) were invited to participate, of whom 56 patients and 101 controls were included in the study and the reminder were excluded. Study questionnaires were completed by participants during face-to-face interviews conducted by a dietitian who was experienced in this type of studies. Both patients and controls attended two separate appointments 1 month apart. No appointments were scheduled in weekends and no participant attended both of her appointments on the same day of the week.

Ultrasound examination: Ultrasonographic studies were performed following a 12-hour fast using a General Electric LOGIQ 9 trade mark scanner and a 3.5-MHZ sector transducer. Images of the gallbladder and biliary tree obtained in longitudinal and transverse sections. Gallstones were defined by the presence of strong, gravity-dependent intraluminal echoes which attenuated ultrasound transmission (acoustic shadowing).

Anthropometric survey: In the first appointment height and weight were measured, using a digital electronic weighing scale (Seca alpha; Rue Lavoisier 91430, Igmy, France; range: 0.1-150 kg) and a digital stadiometer (Harpender Pfifter 450; Badem, Carlstadt, NJ range 70-205 cm), respectively. BMI (kg/m^2) was calculated from the anthropometric data. Waist, hips and mid arm circumferences were determine, also the triceps skin folds thickness measured.

Blood Bio-chemical estimations: Blood samples were collected after an overnight fast to estimate fasting glucose, cholesterol, triglycerides, LDL-C, HDL-C, Apo A-I and Apo-B concentrations. Glucose, cholesterol, triglycerides, LDL-C and HDL-C concentrations were estimated manually by using BOEHRINGER MANNHEIM diagnostic kits. Apo-A and apo-B levels were determined by using BEHRING diagnostic kits.

Dietary survey: A 70-items semi-quantitative food frequency questionnaire was used to collect the nutrients intake data. The questionnaire is an updated and extended version of a previously validated 61-item version (Willett *et al.*, 1985). For each of the 70 food items listed, participants are asked to estimate their use of that food in terms of a standard portion size. Participants report the frequency of consumption of each food by selecting one of nine frequency categories. The questionnaire includes a write-in section for foods not listed and for the exact brand of margarine and type of fat used for frying, cooking, and baking.

The method of interviewing was carefully standardized so that the required information could be obtained and interpreted in a uniform way. After the questionnaire was completed, each food item was coded, and energy, protein, carbohydrate, fat and crude fiber intakes were determined as an average intake per day. Three major fatty acid groups: saturated fatty acid (SFA), mono-unsaturated fatty acid (MUFA) and poly-unsaturated fatty acid (PUFA) were calculated by multiplying the frequency of use of each food by the fatty acid composition for the portion size specified and then summing across all foods. Calculations included specific information on the usual types of fat or oil each individual used for frying, cooking, and baking. The food composition data were based primarily on US Department of Agriculture publications (National Research Council, 1989).

In order to validate overall energy intakes the overall

intakes were compared with estimated energy expenditure by calculating the ratio of intake/BMR with BMR (Basal Metabolic rate) estimated from the Schofield equations (Schofield *et al.*, 1985). The data analysis was performed using SPSS 10.0 for windows.

Results

After the exclusion of some of the participants (4 patients and 7 controls) who did not fulfill the inclusion criteria, the final study sample consisted of 56 gallstone patients and 101 controls. Sociodemographic data of cases and controls was analyzed using Chi-2 test. Gallstone patients used significantly more oral contraceptive pills and they were more literate and affluent compare to controls (Table 1).

Gallstone patients were significantly older (44.73 ± 8.53) and had higher BMI (28.68 ± 4.63 kg/m^2) than did control patients (38.42±9.85 and 26.74±4.92 kg/m^2) respectively. However, waist hip ratio, triceps skin folds thickness and mid arm circumference were found higher in cases as compared to controls but not statistically significant (Table 2).

Blood biochemistry measurements did not differ significantly between cases and controls with the exception of HDL-C, where cases had significantly lower mean value (1.03±0.41) than controls (1.22±0.40) (Table 3).

After analyzing the nutritive value of the food intake of the study participants both macro and micro nutrients consumption were compared between cases and controls (Table 4). Patients consumed significantly more energy than the controls. Gallstone patients had significantly higher BMR than the controls. Gallstone patients consumed significantly more protein, carbohydrate, sugar, sodium, calcium, iron and vitamin B_2 than control subjects. However, the gallstone patients consume significantly less dietary fiber, potassium and vitamin C as compared to controls. Furthermore, patients consumed, although not significant, less fat, cholesterol and saturated fat than control.

In Table 5 multiple logistic regression was used to explore the relationship of having a gallstone with various characteristics among adult Saudi females. Independent variables selected to be included in the models were based on the univariate comparisons. Factors associated with having gallstone among adult Saudi females were age, more oral contraceptive usage, high intake of table sugar, sodium and low intake of dietary fiber, and vitamin C.

Discussion

Present results showed that, gallstone patients used significantly more oral contraceptive pills than controls. Bennion *et al.* (1980) reported that, oral contraceptive usage increases biliary cholesterol secretion, thereby raising the level of cholesterol saturation of bile and predisposing to cholesterol precipitation and gallstone formation. In another study, Beck, (1975) reported that, estrogen administration produces changes in cholesterol and bile metabolism which favors gallstone formation.

The greater incidence of gallstones in older person (Jorgensen and Jensen, 1992) and in overweight or obese individuals (Gonzalez *et al.,* 1993; Ortega *et al.*, 1997; Misceiagna *et al.,* 1999) is frequently reported in the literature. This tendency was also reported in the present study.

Most studies that evaluated the relationship between lipids profile and GBD reported positive relationship between triglyceride concentration and GBD (Mohr *et al.,* 1991; Scragg *et al.,* 1984; Moran *et al.,* 2003); others did not find such a relationship (Cavallini *et al.,* 1987; Pettiti *et al.,* 1981). In this study no relationship was found in between triglyceride and total cholesterol with GBD. Results on association between GBD and HDL-C concentration were also inconsistent. We found significant association with HDL-C concentration, in agreement with other studies (Duque-L, 1999; Thijs, 1990). However, other says either no relation (Cavallini *et al.,* 1987; Mohr *et al.,* 1991) or inverse association (Pittiti *et al.,* 1981; Moran *et al.,* 2003).

Ecological comparisons offer indirect evidence the diet may be important factor in gallstone development. Early comparisons showed considerably higher prevalence of GBD in developed countries than in under developed countries (Heaton, 1984; Burkitt and Tunstall, 1975; Brett and Barker, 1976), and other research has shown that GBD prevalence can differ substantially between communities that differ in culture and in diet (Malhotra, 1968). However, the main dietary hypotheses proposed have focused on six dietary factors: energy intake, fatty acids, cholesterol, refined sugar and dietary fiber, calcium and alcohol.

Our results indicate that high intake of energy, proteins, carbohydrates, refined sugar and calcium may increase the risk of gallstone formation, whereas a high intake of dietary fiber, and vitamin C may protect against gallstone formation. With respect to energy intake, our results are similar to those obtained in the majority of studies that suggest the existence of a positive relationship between high energy intake and GBD (Trautwein, 1994; Ortega *et al.,* 1997; Lee, 1988).

Among the earliest report of an association between energy intake and GBD is one by Sarles *et al.* (1969), who found a 15% higher mean caloric intake in gallstone patient than in control. However, not all authors concur (Barbara *et al.,* 1987; Kato *et al.,* 1992). Discrepancies between results could be influenced by the greater obesity of gallstone patients, some of whom might be trying to loss weight at the time of study (Kato

Table 1: Sociodemographic variables of the study population

Variables	Gallstone patients 56	Control subjects 101	P
Education:			
Literate	36 (64%)	20 (36%)	
Illiterate	35 (35%)	66 (65%)	0.000
Monthly income:			
≤ 5000 SR	35 (62.5%)	87 (86.2%)	
> 5000 SR	21 (37.5%)	14 (13.8%)	0.001
Number of children:			
≤ 5 children	23 (41.1%)	48 (47.5%)	
> 5 children	33 (58.9%)	53 (52.5%)	0.436
Contraceptive usage:			
Yes	25 (44.6%)	26 (25.7%)	
No	31 (55.4%)	75 (74.3%)	0.015

Table 2: Anthropometric variables of the study population (mean ± S.D.)

Variables	Gallstone patients 56	Control subjects 101	P
Age (years)	44.73 ± 8.53	38.42 ± 9.85	0.000
Body mass index	28.69 ± 4.63	26.74 ± 4.92	0.016
Waist hip ratio	0.85 ± 0.06	0.84 ± 0.06	0.512
Triceps Skin folds thickness (mm)	27.11 ± 6.97	26.00 ± 7.20	0.344
Mid arm circumference (cm)	29.02 ± 4.31	27.6 ± 5.32	0.091

Table 3: Blood biochemistry variables of the study population (mean ± S.D.)

Variables	Gallstone patients 56	Control subjects 101	P
Fasting blood glucose (mmol/l)	5.87 ± 1.43	5.75 ± 1.46	0.629
Triglycerides (mmol/l)	1.19 ± 0.60	1.35 ± 0.67	0.130
Cholesterol (mmol/l)	4.40 ± 0.98	4.68 ± 0.94	0.085
LDL-Cholesterol (mmol/l)	3.03 ± 1.07	3.16 ± 0.84	0.374
HDL-Cholesterol (mmol/l)	1.03 ± 0.41	1.22 ± 0.40	0.005
Apolipoprotein A (mg/l)	2.15 ± 0.57	2.27 ± 0.53	0.184
Apolipoprotein B (mg/l)	0.98 ± 0.36	0.99 ± 0.29	0.833

et al., 1992). The underestimation of food intake is also a possibility, a problem that is more frequent amongst obese subjects (Ortega *et al.*, 1995; Kato *et al.*, 1992). Recently, Tseng *et al.* (1999) reported in a review that, no convincing evidence showed the association between the energy intake and gallstone formation.

In the present study gallstone patients consumed significantly more refined sugar and less dietary fiber compared to controls. The sugar could increase the likelihood of developing gallstones via an increased risk of obesity or an increase in insulin secretion and it tend to increase the cholesterol saturation of the bile and decrease the synthesis of bile acids (Lee, 1988; Moerman *et al.*, 1994). Insoluble fiber may protect against gallstone occurrence by reducing the generation of secondary bile acids such as deoxycholate (Marcus and Wheaton, 1986a; 1986b), which has been associated with increased cholesterol saturation of the bile (Hayes *et al.*, 1992; Low-Beer, 1985).

Although, in a cross-sectional study in Copenhagen, Jorgensen, (1989) found a non-significant trend of increased GBD prevalence with higher intake of refined sugar and a non-significant inverse trend for intake of dietary fiber. A similar pattern of increased risk for sugar intake and decreased risk for fiber intake was also seen in two of the larger case-control studies, one in Adelaide, Australia (Scragg *et al.*, 1984) and the other in Italy (Alessandrini *et al.*, 1982). Recently, Schwesinger *et al.* (1999) reported that, a dietary soluble fiber inhibits cholesterol stone formation by reducing the biliary cholesterol saturation indeed. Overall, results across studies and present study design suggest that some aspect of a diet that is high in fiber or low in simple sugars may protect against GBD.

Calcium has been hypothesized to protect against gallstones by binding secondary bile acids including deoxycholate in the small intestinal lumen, thus reducing the deoxycholate and cholesterol content of the bile. While, few studies showed no association between calcium intake and gallstone formations (Worthington *et al.*, 1997; Sichieri, *et al.*, 1991) and few of them showed inverse association between dietary calcium and gallstones (Ortega *et al.*, 1997; Moerman *et al.*, 1994). However, in the present study the gallstone patients

Table 4: Differences in nutrients intake between gallstone patients and controls (mean ± S.D.)

Variables	Gallstone patients 56	Control subjects 101	P
Energy (kcal)	2194 ± 241	2040 ± 15	0.000
Basal Metabolic Rate (BMR)	1449 ± 121	1377 ± 11	0.000
Energy to BMR Ratio	1.5 ± 0.20	1.48 ± 0.14	0.186
Protein (gm)	112.2 ± 21	100.0 ± 14.50	0.000
Carbohydrate (gm)	275.6 (41.40)	245.2 ± 49.70	0.000
Dietary Fiber (gm)	22.4 ± 3.70	23.5 ± 2.20	0.040
Table Sugar (gm)	128.0 ± 26.50	98.0 ± 22.00	0.000
Fat (gm)	79.9 ±14.70	80.2 ± 13.20	0.909
Cholesterol (mg)	391.6 ± 81.80	399.4 ± 90.50	0.594
Saturated Fat (gm)	29.5 ± 6.60	31.2 ± 6.50	0.121
Monounsaturated Fat (gm)	24.2 ± 4.50	24.3 ± 4.50	0.874
Polyunsaturated Fat (gm)	19.7 ± 5.50	18.4 ± 4.50	0.106
Potassium (mg)	3128 ± 565.1	3479 ± 480.7	0.000
Sodium (mg)	1877 ± 253.6	1575 ± 254.9	0.000
Calcium (mg)	615.2 ± 169.1	452.5 ± 73.1	0.000
Iron (mg)	19.6 ± 3.80	17.3 ± 3.10	0.000
Vitamin C (mg)	141.0 ± 34.00	156.0 ± 33.2	0.010
Vitamin B2 (Mg)	2.47 ± 0.64	1.89 ± 0.37	0.000
Vitamin B1 (Mg)	1.56 ± 0.32	1.47 ± 0.28	0.073
Vitamin A (µg)	2364 ± 713.5	2224 ± 390.0	0.112

Table 5: Factors associated with having gallstone among adult Saudi females

Factors	Odds Ratio*	P-value	95% C.I.**
Age‡	1.96	0.030	1.07, 3.57
Education	67	0.076	0.65, 1000
Monthly Income	2.77	0.603	0.05, 142
Contraceptive Usage‡	101	0.047	1.06, 9582
Body Mass Index	1.13	0.730	0.54, 2.37
HDL-Cholesterol	0.26	0.500	0.005, 12.72
Dietary Intake of:-			
Energy	1.03	0.094	0.99, 1.07
Protein	1.11	0.312	0.9, 1.33
Carbohydrate	1.13	0.070	0.99, 1.3
Fiber‡	0.28	0.029	0.09, 0.88
Table Sugar‡	1.25	0.021	1.03, 1.53
Sodium‡	1.02	0.018	1.003, 1.03
Potassium‡	0.98	0.011	0.98, 0.99
Calcium	1.03	0.062	0.99, 1.07
Iron	1.69	0.215	0.74, 4
Vitamin C‡	0.87	0.012	0.77, 0.97
Vitamin B1	1250	0.106	0.22, 1000
Vitamin B2	8.16	0.463	0.03, 2210

OR* = odds of gallstone patient having a factor compared to odds of control, all variables listed are adjusted for other variables in the table. C.I.** = confidence interval. ‡Significantly associated with gallstone.

consumed significantly higher dietary calcium than the controls.

The effect of vitamin C on plasma lipids in man has been analyzed in a number of intervention studies summarized in a review article (Hemila, 1992), showing a significant decrease in plasma cholesterol after vitamin C supplementation in subjects initially low in Vitamin C and high in plasma cholesterol. The review shows that, in some interventional and epidemiological studies, there has been a positive correlation between plasma vitamin C and plasma HDL-C, and a negative correlation between plasma vitamin C and plasma triglycerides. In the present study, results supported the correlation between vitamin C and HDL-C as they both significantly reduced in gallstone patients.

In conclusion, our study indicated that nutritional factors may play an important role in the etiology of gallstones and that most of these factors have been shown to play an important role in the etiology of other chronic diseases, such as type 2 diabetes, cardiovascular disease (Thornton *et al.*, 1983) and cancer (Kune, 1996). Thus, gallstone disease is one of a cluster of diseases that characterize affluent societies and that most likely share common pathophysiologic links and mechanisms. Preventive strategies aimed at improving nutrition and energy imbalance my have a powerful effect on a series of pathologic conditions that represent a major source of morbidity and mortality in our society.

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