Serum Ascorbic Acid and Other Correlates of Gallbladder Disease Among US Adults

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ABSTRACT

Objectives. This study examined the correlates of clinical gallbladder disease among US adults and whether serum ascorbic acid levels are associated with a decreased prevalence of gallbladder disease.

Methods. Cross-sectional analyses of data from the Second National Health and Nutrition Examination Survey were conducted.

Results. A total of 384 women (8%) and 107 men (3%) reported a history of gallstone disease, and 347 women (7%) and 81 men (2%) reported a history of cholecystectomy. An inverted U-shaped relation was found between serum ascorbic acid level and clinical gallbladder disease among women but not among men.

Conclusions. Ascorbic acid, which affects the catabolism of cholesterol to bile acids and, in turn, the development of gallbladder disease in experimental animals, may reduce the risk of clinical gallbladder disease in humans. (*Am J Public Health.* 1998;88:1208–1212)

Introduction

As many as 20 million Americans are estimated to have gallstones,[1] most of which are composed partially or entirely of cholesterol.[2,3] The pathologic triad leading to cholesterol gallstone formation is made up of bile stasis, destabilization of bile, and supersaturation of bile with cholesterol.[4] When stasis of bile that is supersaturated with cholesterol undergoes destabilization, cholesterol gallstones are formed.[4]

One cause of biliary supersaturation is decreased cholesterol catabolism resulting from a low rate of cholesterol 7 α-hydroxylation, the rate-limiting step in the catabolism of cholesterol to bile acids.[4] In the guinea pig, an animal that, like humans, lacks the ability for ascorbic acid biosynthesis, the activity of cholesterol 7 α-hydroxylase is dependent on the hepatic concentration of ascorbic acid,[5] and ascorbic-acid-deficient guinea pigs frequently develop cholesterol gallstones.[6–9] Because of the evidence from animal studies and the observation that many risk factors for gallbladder disease are correlated with ascorbic acid status, it has been hypothesized that ascorbic acid may be a correlate of human gallbladder disease.[10] To ascertain whether ascorbic acid status is associated with clinical gallbladder disease in humans, we analyzed data from the Second National Health and Nutrition Examination Survey (NHANES II), which included serum ascorbic acid levels for more than 9000 American adults.

Methods

Subjects

NHANES II was a national probability survey of more than 20 000 Americans conducted between 1976 and 1980 that used a stratified, cluster sampling design.[11] Participants were interviewed and examined by study personnel at 2 visits.[11] Complete data from 9110 participants between the ages of 20 and 74 years were available for analysis.

Measurements

NHANES II questionnaire data included self-reported age, race, sex, years of education completed, level of leisure time physical activity, history of smoking and diabetes mellitus, level of alcohol intake, use of diuretic and cholesterol-lowering medications, and vitamin E supplement use. Nutrition data were collected via a food frequency questionnaire and 24-hour diet recall. We calculated body mass index (weight in kilograms divided by height in meters squared) from data recorded during the physical examination. The questionnaires, dietary methods, and examination procedures used in NHANES II have been described elsewhere.[11]

We ascertained whether participants had a history of clinical gallbladder disease via their responses to the following questions: "Has a doctor ever told you that you had gallstones?" and "Has your gallbladder been surgically removed?"[11] The question "Has a doctor ever told you that you had gallstones?" appeared twice in the questionnaire, and we used the initial question for these analyses because of the greater number of responses.

Serum ascorbic acid levels were measured at the Centers for Disease Control and Prevention by means of a standardized protocol.[12] Because there were a small number of extreme serum ascorbic acid values of questionable validity (ranging as high as 18.1 mg/dL), we excluded participants with levels in the top 0.5% of the sample (n = 54). Levels for the remaining 99.5% of the participants ranged from 0.1 to 2.7 mg/dL.

Measurements of low-density lipoprotein cholesterol were performed on only a subset of participants; we chose to include nonfasting total serum cholesterol levels, which have been shown to reflect fasting cholesterol levels accurately.[13] All lipid samples were measured at the George Washington

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Lipid Research Clinic Laboratory according to the Lipid Research Clinic Program protocol.[14]

Statistical Analyses

We examined the distribution of ascorbic acid concentrations and other variables using sample weights. We used logistic regression to examine associations of serum ascorbic acid level and other variables to prevalence of gallstones and cholecystectomy. To assess possible nonlinear associations, we examined the relation of serum ascorbic acid level to gallbladder disease using linear and quadratic terms. Level of education, level of physical activity, and alcohol consumption were analyzed as ordinal variables.

Analyses were performed with Stata software that included commands for examination of complex survey data.[15] For each predictor variable, we calculated an odds ratio and 95% confidence interval to estimate the relative prevalence of clinical gallbladder disease. We considered two-tailed P values of less than .05 statistically significant.

In analyses of the independent nonlinear association between serum ascorbic acid level and clinical gallbladder disease, the adjusted prevalence of gallstone disease and cholecystectomy was plotted as a function of serum ascorbic acid level. Logistic coefficients were used to compute individual predicted probabilities of gallbladder disease. Next, we computed the mean of these probabilities within each 0.1 mg/dL serum ascorbic acid level and then applied the lowess smoothing procedure[16] to produce plots of gallbladder disease prevalence vs serum ascorbic acid level.

Results

The baseline characteristics of the study participants are shown in Table 1. A total of 384 women (8%) and 107 men (3%) reported a history of gallstone disease. In addition, 347 women (7%) and 81 men (2%) reported undergoing gallbladder surgery. Women and men were similar in terms of age, race, body mass index, and serum cholesterol level. Fifteen percent of women reported use of oral contraceptives in the previous 6 months, and fewer than 1% of both women and men reported current use of lipid-lowering medications.

A number of variables were independent predictors of clinical gallbladder disease in women (Table 2). Increasing age, body mass index, and number of children, as well as White race, low levels of leisure time physical activity, smoking, and diabetes, were associated with an increased prevalence of gallstones (all Ps < .05). Women with higher intakes of dietary fat reported a slightly lower prevalence of gallstones (P = .02). Linear and quadratic terms indicated that both low and high levels of serum ascorbic acid were associated with a decreased prevalence of gallstones (Ps = .05 and .02, respectively) (see Figure 1). Number of children, physical activity, diabetes, and fat

TABLE 1—Characteristics of 9110 Participants 20 to 74 Years Old Enrolled in the Second National Health and Nutrition Examination Survey: 1976 Through 1980

Characteristic	Women (n = 4840)	Men (n = 4270)
Serum ascorbic acid level, mg/dL, mean ± SD	1.1 ± 0.5	0.9 ± 0.5
Age, y, mean ± SD	42 ± 15	42 ± 15
Body mass index, kg/m^2, mean ± SD	25 ± 6	25 ± 4
Dietary fat intake, g/d, mean ± SD	61 ± 34	101 ± 57
Energy intake, kcal/d, mean ± SD	1504 ± 647	2453 ± 1129
Serum cholesterol level, mg/dL, mean ± SD	214 ± 50	210 ± 45
High-density lipoprotein cholesterol level, mg/dL, mean ± SD	54 ± 15	45 ± 12
No. children, mean ± SD	2.3 ± 2.1	. . .
Postmenopausal, %	41	. . .
Ever pregnant, %	80	. . .
Diabetes mellitus, %	3	2
History of cigarette smoking, %	49	72
White race, %	88	89
Exercise level, %		
Frequent	31	40
Seldom	56	46
Never	13	14
Alcohol intake, drinks/wk, %		
None	42	24
1–6	52	57
>6	6	19
Diuretic use, %	12	5
Vitamin E supplement use, %	4	3

TABLE 2—Multivariate Relation of Serum Ascorbic Acid Level and Other Variables to Gallstone Disease and Cholecystectomy Among 4840 Women 20 to 74 Years Old Enrolled in the Second National Health and Nutrition Examination Survey: 1976 Through 1980

	Gallstones, Odds Ratio (95% CI)	Cholecystectomy, Odds Ratio (95% CI)
Serum ascorbic acid, mg/dL	2.34 (1.00, 5.51)	3.51 (1.17, 10.5)*
Squared serum ascorbic acid	0.67 (0.48, 0.93)*	0.60 (0.38, 0.93)*
Age, 5 y	1.15 (1.06, 1.26)**	1.17 (1.07, 1.28)**
Race (White vs other)	3.68 (2.20, 6.15)***	6.49 (3.10, 13.6)***
Body mass index, 5 kg/m^2	1.31 (1.15, 1.50)***	1.33 (1.17, 1.52)***
Oral contraceptive use, past 6 months	0.96 (0.51, 1.82)	0.73 (0.40, 1.33)
Pregnant (ever vs never)	1.26 (0.82, 1.94)	1.29 (0.80, 2.09)
No. of children	1.08 (1.03, 1.13)**	1.04 (0.99, 1.10)
Postmenopausal (yes vs no)	1.14 (0.67, 1.91)	1.20 (0.69, 2.09)
Level of physical activity[a]	0.81 (0.68, 0.96)*	0.85 (0.72, 1.01)
Level of alcohol consumption[a]	0.90 (0.69, 1.18)	0.74 (0.57, 0.96)*
History of smoking (yes vs no)	1.37 (1.07, 1.76)*	1.35 (1.05, 1.74)*
Diabetes (yes vs no)	1.64 (1.04, 2.59)*	1.26 (0.74, 2.12)
Dietary fat intake, 10 g	0.90 (0.83, 0.98)*	0.92 (0.84, 1.01)
Diuretic medication use (yes vs no)	0.83 (0.57, 1.20)	0.92 (0.65, 1.28)
Cholesterol-lowering medication use (yes vs no)	1.22 (0.38, 3.97)	1.38 (0.44, 4.29)

Note. Values were adjusted for level of education, energy intake, serum cholesterol level, high-density lipoprotein cholesterol level, vitamin E supplement use, and all variables noted here. CI = confidence interval.

[a]Analyzed as ordinal variable. Levels of leisure time physical activity were never, seldom, and frequent; levels of alcohol consumption were less than 1 drink per week, 1 to 6 drinks per week, and more than 6 drinks per week.

*P < .05; **P < .01; ***P < .001.

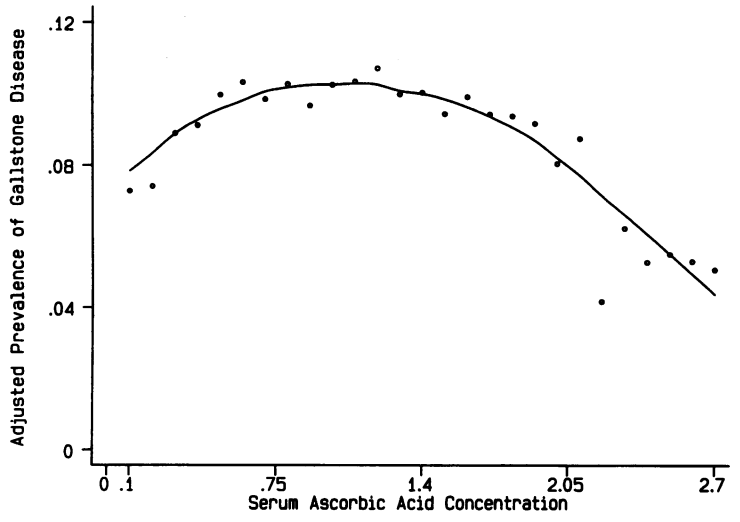

FIGURE 1—Relation between serum ascorbic acid concentration (mg/dL) and prevalence of gallstone disease among 4840 women enrolled in the Second National Health and Nutrition Examination Survey: 1976 through 1980 (adjusted for all variables noted in Table 2).

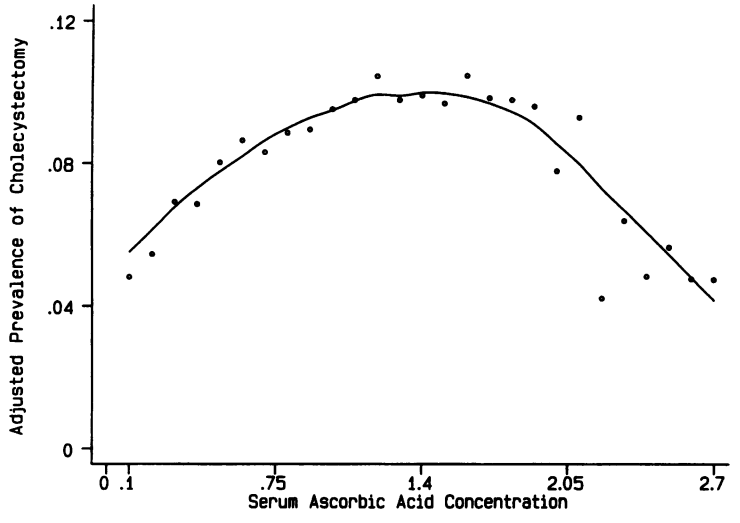

FIGURE 2—Relation between serum ascorbic acid concentration (mg/dL) and prevalence of cholecystectomy among 4840 women enrolled in the Second National Health and Nutrition Examination Survey: 1976 through 1980 (adjusted for all variables noted in Table 2).

intake, all of which were significant correlates of gallstones, were not significantly associated with prevalence of cholecystectomy. Alcohol consumption, which was not associated with prevalence of gallstones, was significantly associated with a decreased prevalence of cholecystectomy among women ($P = .03$). Serum ascorbic acid levels were significantly associated with cholecystectomy among women; linear and quadratic terms indicated that both low and high levels of serum ascorbic acid were associated with a decreased prevalence of cholecystectomy (both Ps = .03) (see Figure 2).

There were fewer correlates of clinical gallbladder disease among men than among women (Table 3). Increasing age and use of diuretic and cholesterol-lowering medications were independently associated with increased prevalence of gallstones. However, only age and body mass index were independently associated with prevalence of cholecystectomy among men. There was no significant linear or nonlinear association between serum ascorbic acid levels and prevalence of clinical gallbladder disease among men.

Other potential gallbladder disease correlates that were examined included level of education, energy intake, serum cholesterol and high-density lipoprotein cholesterol levels, and vitamin E supplement use. None of these factors were significantly associated with gallstones or cholecystectomy in either women or men. Because alcohol has been associated with lower ascorbic acid levels in some studies[17] and may decrease the activity of cholesterol 7 α-hydroxylase,[18,19] we examined whether alcohol consumption modified the association between serum ascorbic acid levels and prevalence of gallbladder disease among women. We found no evidence of such an interaction.

Discussion

We found an inverted U-shaped relation between serum ascorbic acid level and prevalence of clinical gallbladder disease among women; low levels and high levels of serum ascorbic acid were associated with the lowest prevalence of gallbladder disease. We observed no significant relation between serum ascorbic acid level and prevalence of clinical gallbladder disease among men.

We hypothesized that an inverse relation between serum ascorbic acid levels and gallbladder disease in humans would be observed.[10] In experimental animals, ascorbic acid affects the activity of cholesterol 7 α-hydroxylase, the enzyme that regulates the rate-limiting step in the catabolism ofcholesterol to bile acids.[20] Ascorbic acid supplementation in the guinea pig increases cholesterol 7 α-hydroxylase activity by as much as 15-fold relative to ascorbic acid–deficient guinea pigs,[21] and ascorbic acid–deficient guinea pigs develop cholesterol gallstones frequently.[7,8,22] In addition, hypersecretion of mucin, a glycoprotein that is secreted by the epithelium of the gallbladder, has been found to precede cholesterol destabilization and gallstone formation.[23,24] Hydroxyl and oxygen radicals stimulate the hypersecretion of mucin.[25] Because ascorbic acid is a potent antioxidant,[26] inhibition of oxidative changes within the gallbladder by ascorbic acid may lead to decreased mucoprotein production and gallstone formation.

Our results confirmed these hypotheses in part; among women, high serum ascorbic acid levels were independently associated with an approximately 50% lower prevalence of gallbladder disease. However, we also found that low serum ascorbic acid levels were associated with an approximately 30% decreased prevalence of gallbladder disease among women. Although the U-shaped association may be a chance finding, marked ascorbic acid deficiency is associated with decreased hepatic cholesterol synthesis and low blood cholesterol levels.[20] Thus, one possible explanation is that low serum ascorbic acid levels inhibit

TABLE 3—Multivariate Relation of Serum Ascorbic Acid Level and Other Variables to Gallstone Disease and Cholecystectomy Among 4270 Men 20 to 74 Years Old Enrolled in the Second National Health and Nutrition Examination Survey: 1976 Through 1980

	Gallstones, Odds Ratio (95% CI)	Cholecystectomy, Odds Ratio (95% CI)
Serum ascorbic acid, mg/dL	0.87 (0.51, 1.47)	0.99 (0.61, 1.62)
Age, 5 y	1.44 (1.32, 1.58)***	1.46 (1.31, 1.63)***
Race (White vs other)	1.23 (0.40, 3.81)	2.62 (0.44, 15.6)
Body mass index, 5 kg/m^2	1.12 (0.81, 1.54)	1.43 (1.02, 2.01)*
Level of physical activity[a]	1.06 (0.75, 1.49)	0.76 (0.50, 1.16)
Level of alcohol consumption[a]	0.80 (0.56, 1.13)	0.89 (0.62, 1.28)
History of smoking (yes vs no)	1.66 (0.95, 2.90)	1.36 (0.66, 2.78)
Diabetes (yes vs no)	1.00 (0.37, 2.66)	1.20 (0.57, 2.54)
Dietary fat intake, 10 g	1.00 (0.92, 1.08)	0.96 (0.90, 1.03)
Diuretic medication use (yes vs no)	1.97 (1.17, 3.32)*	1.65 (0.73, 3.71)
Cholesterol-lowering medication use (yes vs no)	7.69 (2.03, 29.1)**	4.36 (0.74, 25.8)

Note. Values were adjusted for level of education, energy intake, serum cholesterol level, high-density lipoprotein cholesterol level, vitamin E supplement use, and all variables noted here. CI = confidence interval.

[a]Analyzed as ordinal variable. Levels of leisure time physical activity were never, seldom, and frequent; levels of alcohol consumption were less than 1 drink per week, 1–6 drinks per week, and more than 6 drinks per week.

*$P < .05$; **$P < .01$; ***$P < .001$.

cholesterol synthesis, whereas high levels increase the catabolism of cholesterol to bile acids.

Among women, we found that the prevalence of gallstones and cholecystectomy increased with age, body mass index, and smoking and that White women had a threefold to sixfold increased prevalence of gallbladder disease relative to non-White women. Number of children, low levels of physical activity, diabetes, and low dietary fat intake were associated with an increased prevalence of gallstones, whereas a low level of alcohol consumption was associated with an increased prevalence of cholecystectomy. These results are generally consistent with the results of other investigators, although the relation of diet, diabetes, and smoking to gallbladder disease has not been observed consistently.[27,28] Several observational studies have reported no association between physical activity and gallbladder disease.[29–31] These studies, however, were smaller in scope than ours, and one study enrolled only men.[31]

Among men, only age was independently associated with an increased prevalence of gallstones and cholecystectomy. Use of diuretic and cholesterol-lowering medications was, however, associated with an increased prevalence of gallstones. Thiazide diuretic use and lipid-lowering medication use have been reported by some investigators to be associated with an increased risk for gallbladder disease.[27] Lipid-lowering medications available at the time of the survey included bile acid sequestrants, fibric acid derivatives, and niacin, all of which (and, notably, clofibrate) have been reported to increase the risk of gallbladder disease.[27]

Because NHANES II surveyed a large cross section of the US population and collected data using standardized procedures and protocols, our findings should be valid and generalizable. Furthermore, measurement of serum ascorbic acid levels in a large sample of the population allows a more precise and accurate assessment of ascorbic acid status as a correlate of clinical gallbladder disease than is the case with studies using dietary intake estimations only. It is unlikely that recall bias significantly affected our findings. Participants had their serum ascorbic acid levels measured and completed a comprehensive questionnaire that included information on many health outcomes. Our study, however, has limitations. We relied on self-reported history of gallstones and cholecystectomy, and, therefore, there may have been some outcome misclassification. We attempted to increase the validity of self-reported gallbladder disease by examining the correlates of cholecystectomy, an outcome less likely than history of gallstones to be misclassified. We are also unable to comment on the relation of serum ascorbic acid level and other gallbladder disease correlates to asymptomatic gallstones. Finally, because of the cross-sectional nature of the study, we cannot be certain that differences in serum ascorbic acid and other modifiable variables preceded gallbladder disease. Thus, inferences regarding causality should be made cautiously. For example, although dietary fat intake was associated with a lower prevalence of gallstones among women, this finding may reflect dietary changes that occurred as a consequence of gallbladder disease. It seems less likely, however, that women who received such a diagnosis would alter their diet in a way that would produce the U-shaped association observed in this study.

Although the results of our study must be interpreted cautiously, they suggest a role for ascorbic acid in the pathogenesis of gallbladder disease. If increased serum ascorbic acid levels are related causally to a reduction in gallbladder disease risk, ascorbic acid could be of potential public health importance for the prevention of gallbladder disease. Additional observational and clinical trial data are necessary to confirm these findings. □

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Trends in Food Label Use Associated With New Nutrition Labeling Regulations

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ABSTRACT

Objectives. This study compared use of food labels before and after implementation of new Food and Drug Administration regulations in 1994.

Methods. Data were obtained by random-digit-dial surveys of Washington State residents in 1993 (n = 1001) and 1996 (n = 1450).

Results. After implementation of the new regulations, usual label use increased significantly, by 8.5 percentage points in women and 11.3 percentage points in men. More respondents looked for information on fat content and fewer failed to use labels because they "take too much time" or "are too hard to understand."

Conclusions. Use of food labels and satisfaction with their content have increased, but 70% of adults still want labels to be easier to understand. (*Am J Public Health*. 1998;88:1212–1215)

Introduction

In 1990, the United States Congress passed the Nutrition Labeling and Education Act,[1] and new food labels were introduced in May 1994. New regulations now limit health claims, and new labels use standardized portion sizes and focus on nutrients associated with chronic diseases. It was hoped that these changes would help consumers make more healthful food choices.[2,3]

Most research evaluating food labels has found that labels before 1994 were difficult to use because formats were confusing and content claims (e.g., "lite") were inconsistent.[4–7] Since the new labels were designed to improve these characteristics, it is important to learn whether use and comprehension of labels has increased. Here we examine evidence that new food labels have increased consumers' use of nutrition information on packaged foods. We compare responses to 2 population-based surveys completed before and after introduction of the new labels to address 3 questions: (1) Has there been an increase in the proportion of persons reading and using nutrition labels? (2) Have there been changes in the information people most often use? and (3) Do people report fewer barriers to using nutrition labels?

Methods

Data were from the Washington State Cancer Risk Behavior Survey, a random-digit-dial survey of adults (18 years and older) to monitor attitudes and behavior related to cancer risk and prevention.[8] We used two cross-sectional surveys, the first completed between August 1992 and August 1993 (n = 1001) and the second between September 1995 and September 1996 (n = 1450), to characterize food label use before and after the introduction of the new label format. These are described below as the 1993 and 1996 surveys, respectively. Telephone numbers were purchased from GENESYS Sampling Systems.[9] To complete

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