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Lack of Association between Cholelithiasis and Significant Coronary Artery Disease: An Autopsy Study from Greece

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Cholelithiasis or Gallstone disease and coronary artery disease have been reported to share several common risk factors. The aim of this study was to examine if there is an association between coronary artery disease (CAD) and gallstone disease (GsD) through an autopsy study.
Methodology: A retrospective analysis of the records of consecutive autopsy cases performed at the Department of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens during the period from January 1, 2011, to December 31, 2015, was performed. The inclusion criteria were age between 35 and 65 years old. Our sample consisted of 1699 cases. Significant CAD was defined as stenosis of the lumen equal to or over 75% in any major coronary artery.

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Results: Significant CAD was found in 656 (38.6%) cases. Results showed that age, male sex, hypertension, smoking (*P* <0.001), presence of diabetes mellitus (DM)(*P* =0.005), hyperlipidemia (*P* =0.001), and illicit drug use (*P* =0.006) were statistically significant predictors of significant CAD presence. On the contrary, heavy alcohol use (*P* =0.069), GsD (*P* =0.838) and cholecystectomy (*P* =0.423) was not found to be related to significant CAD.
Conclusion: Our study did not show any statistically significant relationship between the presence of significant coronary artery stenosis and GsD. The same outcome was noticed when cholecystectomy was studied separately. Therefore, cholelithiasis and cholecystectomy cannot serve as possible predictors for CAD development. Future studies are needed to validate our findings that will lead to more beneficial prevention planning and monitoring of patients so as to maximize resources management and reduce healthcare costs.

Keywords: Gallstone disease; cholelithiasis; gallstones; coronary artery disease; coronary artery stenosis; autopsy study.

1. INTRODUCTION

CAD is a major health care and economic problem worldwide. Over the past four decades, CAD mortality rates have dropped in Western countries, however, it remains responsible for one-third of all deaths in people over the age of 35. In people with 2 or more major predisposing factors, the lifelong risk of developing CAD is 37.5% for men and 18.3% for women [1].

Cholelithiasis is also a frequent health problem. The formation of gallstones has been described to be more likely at a higher age and in females [2]. Around 20% of the European population is affected by the above condition [3]. Hospitalization rates in Greece for cholelithiasis and/or acute cholecystitis have been shown to increase with time, while fatality is reducing [4].

Gallstones are formed from the components of bile. The main structural elements involved in the formation of gallstones are cholesterol crystals, mucin, calcium bilirubinate, and proteins. More than 90% of gallstones are composed mainly of cholesterol (cholesterol gallstones), while the rest are composed of calcium bilirubinate and other calcium salts (pigmented gallstones) [2]. Cholesterol gallstone development is related to saturation of cholesterol in bile, cholesterol crystallization, and gallbladder stasis [5].

Given that CAD and cholelithiasis share some key predisposing factors such as diet, limited physical activity, obesity, diabetes, dyslipidemia [1,2], the question arises if there could be a link between these two pathological conditions and whether the growth of gallstones could function as a prognostic indicator for CAD and by extension for cardiovascular disease (CVD). Several studies have shown a significant association, without however proving a causal relation, whether others have not [6-18]. The correlation between cholecystectomy and CVD [11,13] and with CAD [8] respectively has also been addressed in previous studies.

The aim of the present study was to investigate whether there is an association between significant CAD and GsD as well as cholecystectomy in an autopsy study.

2. MATERIALS AND METHODS

A retrospective analysis of the records of consecutive autopsy cases performed at the Department of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens during the period from January 1, 2011, to December 31, 2015, was performed. The inclusion criteria were age between 35 and 65 years old. Data collection was conducted retrospectively by a separate doctor, while the forensic pathologists responsible for the autopsies were not aware of the aim of the study at the time of performing them. Our sample consisted of 1699 cases.

The recorded variables included a) demographic data of the deceased person (age, gender), b) presence of gallstones, cholecystectomy (where cholecystectomy was noted, a history of gallstone presence was assumed), c) coronary stenosis of the lumen as described below, d) smoking, heavy alcohol use, illicit drug use, and e) medical history of hyperlipidemia, DM, and arterial hypertension. Information about smoking, heavy alcohol use, illicit drug use, and the presence of hyperlipidemia, DM, and arterial hypertension was mainly assessed after communication with the relatives, as well as from the medical files and short history included in the Investigative Authority order.

Significant CAD was defined as stenosis of the lumen equal to or over 75% in any major coronary artery (right coronary artery, trunk, or anterior descending or circumflex branch of the left coronary artery).

The study was approved by the Ethics Committee of the National and Kapodistrian University of Athens (5843/19-02-2015) and the data were collected and processed anonymously.

The sample's demographic and clinical features were explored with descriptive statistics, calculating frequencies and percentages for categorical variables and mean and standard deviations for continuous variables. Comparisons regarding continuous variables were conducted using the Student's t-test. A binary logistic regression model was performed to ascertain the effects of age, sex, presence of DM, hypertension, hyperlipidemia, smoking, illicit drug use, heavy alcohol use, GsD and cholecystectomy on the likelihood of CAD presence. The variable GsD contained cases in which gallstones were found in the gallbladder and cholecystectomy cases. Statistical analyses were implemented using the statistical software SPSS Statistics 28.0 and significant were values with P <0.05.

3. RESULTS

The mean age of our sample (N =1699) was 52.74 ± 8.37 years old. No statistically significant difference between sexes' age was noticed (52.72 ± 8.34 and 52.81 ± 8.52 years for men and women, respectively). Significant CAD was found in 656 (38.6%) cases and were significantly older than cases with no CAD (55.15 ± 6.99 and 51.23 ± 8.81, respectively). The description of our sample's clinicodemographic data are presented in Table 1.

A binary logistic regression model was created using age, male sex, presence of DM, hypertension, hyperlipidemia, smoking, illicit drug use, heavy alcohol use, GsD and cholecystectomy as predictors and the presence of CAD as dependent variable. Results showed that age, male sex, hypertension and smoking were statistically significant predictors of the dependent variable (P <0.001). Moreover, the presence of DM (P =0.005), hyperlipidemia (P =0.001) and illicit drug use (P =0.006) were statistically significant predictors of CAD. On the contrary, neither heavy alcohol use, nor the presence of GsD or cholecystectomy were found to be related to CAD (P =0.069, P =0.838, P =0.423, respectively). Overall, the regression model was statistically significant (Chi square =220.810, P <0.001) and the results are presented at Table 2.

Table 1. Description of clinicodemographic data (N=1699)

Variables		Total N (%)	No CAD n = 1043 (%)	CAD n = 656 (%)
Age	35 – 44	322 (19%)	273 (16.1%)	49 (2.9%)
	45 – 54	581 (34.2%)	343 (20.2%)	238 (14%)
	55 – 65	796 (46.9%)	427 (25.1%)	369 (21.7%)
Sex	Male	1368 (80.5%)	782 (46%)	586 (34.5%)
	Female	331 (19.5%)	261 (15.4%)	70 (4.1%)
Diabetes Mellitus		179 (10.5%)	71 (4.2%)	108 (6.4%)
Hypertension		344 (20.2%)	147 (8.7%)	197 (11.6%)
Hyperlipidemia		131 (7.7%)	48 (2.8%)	83 (4.9%)
Smoking		981 (57.7%)	508 (38.1%)	473 (35.5%)
Illicit drug use		53 (3.1%)	45 (2.7%)	8 (0.5%)
Heavy alcohol use		163 (9.6%)	103 (6.1%)	60 (3.5%)
Cholecystectomy		85 (5%)	52 (3.1%)	33 (1.9%)
Gallstone disease (cases in which gallstones were found in the gallbladder and cholecystectomy cases)		136 (8%)	78 (4.6%)	58 (3.4%)

Table 2. Results of binary logistic regression using the existence of CAD as dependent variable and age, male sex, DM, hypertension, hyperlipidemia, smoking, illicit drug use, heavy alcohol use, gallstone disease and cholecystectomy as predictors (N=1699)

Predictors	Coefficient (β)	S.E.	Wald	*P*	exp(β) or O.R	95 % C.I. for O.R Lower	Upper
Age	.050	.008	38.274	< .001	1.051	1.035	1.068
Sex (male)	1.010	.170	35.446	< .001	2.747	1.969	3.830
DM	.541	.191	8.021	.005	1.718	1.181	2.499
Hypertension	.499	.146	11.652	< .001	1.647	1.237	2.193
Hyperlipidemia	.685	.213	10.326	.001	1.984	1.306	3.013
Smoking	1.080	.150	51.808	< .001	2.943	2.194	3.949
Illicit drug use	1.276	.466	7.507	.006	3.584	1.438	8.932
Heavy alcohol use	.355	.195	3.308	.069	1.426	.973	2.090
Gallstone disease	-.066	.324	.042	.838	.936	.496	1.765
Cholecystectomy	.329	.411	.642	.423	1.389	.621	3.107
Constant	- 6.704	.732	83.959	< .001			

4. DISCUSSION

Cholelithiasis and CVD are both prevalent health problems worldwide. The possible association between CVD and GsD has been debated in the literature for many years and it has been suggested to be due to shared risk factors with cholesterol playing an important role in the development of both diseases [19]. The precipitation of excess cholesterol in bile as solid crystals is required for cholesterol gallstone formation [20]. In CVD, including CAD, stroke, aortic atherosclerosis, and peripheral artery disease, the pathogenesis also involves the accumulation of cholesterol through a complex series of events leading to the formation of atheroma plaque [21].

Low plasma levels of insulin-like growth factor-1 (IGF-1) has also been suggested to play a role in gallstone formation and CAD [22]. Low IGF-1 level have shown to be connected with an alteration in postprandial gallbladder emptying leading to gallstone formation through prolonged nucleation of monohydrate cholesterol crystals in the supersaturated bile [23]. It has also been reported that IGF-1 has an atheroprotective effect with low levels causing apoptosis and vascular dysfunction, resulting in several cardiovascular pathologies [24,25].

Several studies implicate gut microbiota dysbiosis with the presence of cholesterol gallstones [26] and also as a factor for CVD [27,28]. Distorted bile acids secretion has been associated with bacterial overgrowth in the gut and with diet and antibiotic therapy affecting the balance of the microbiome-bile acid pool [29]. Elevated levels of CVD risk factors, including inflammation and dyslipidemia, may be a result of the abundance of gut microbiota [30,31]. Gut microbiota-related metabolites, like trimethylamine-N-oxide and L-carnitine from red meat intake, have been associated with an increased risk of CVD [28,32]. All the above observations have led to the conclusion that this bacterial pathway could be a target through which diet can influence both diseases. Finally, inflammation as well could be a link between these two conditions through oxidative stress in gallbladder mucosa and in the mechanism of atherosclerosis [33,34].

Several cross-sectional, cohort and prospective studies have reported a significant association between GsD and ischemic heart disease [6-9], GsD and carotid atherosclerosis [10,35], GsD and cardiovascular morbidity and mortality [11,13,14], and also GsD and stroke [12]. Other studies however showed no relationship between GsD and CVD [36-38], or the relationship was not consistent [39,40].

A 26-year follow-up of the Framingham Heart Study found that cholecystectomy (due to the presence of gallstones) was associated with CAD only in men [39], one study showed a stronger association between ischemic heart disease and GsD in women [9] and other studies reported no sex difference [11,13,14]. Moreover, a meta-analysis of eight studies [15] pointed out the fact that although the majority of studies reported a positive association, the relative risks reported by three articles were not statistically significant [13,39,41].

It is worth mentioning that heterogeneity has been observed between the above studies in population characteristics such as ethnicity, race, age, and gender. Differences were also seen in the determination, diagnosis, or definition of CVD, CAD and GsD [42]. In one study, CVD has been determined by ultrasonographic subjective measurements of carotid artery intima-media thickness [10], whereas in another CAD was defined as myocardial ischemia using the excise treadmill test based on the Bruce protocol [7], which presents low sensitivity and specificity for coronary heart disease and is not able to detect nonobstructive atherosclerotic lesions [43,44]. Coronary angiography has also been used as a reliable method of diagnosing CAD, where 50% stenosis of the lumen of any major coronary artery has been set as baseline for CAD [6].

Some studies defined GsD using the International Classification of Disease code (ICD) after medical files searching [11,12], whether in other studies GsD was defined as ultrasound-documented gallstones or evidence of cholecystectomy [6,7,10,13,35]. Regarding the ICD code, GsD is frequently omitted, which can lead to underestimation of the condition, and although ultrasound examination is an excellent tool to diagnose gallstones in clinical practice, its results depend on the operator [45]. Another method of defining GsD is the administration of questionnaires, however, the self-reported information on health conditions – including the presence of gallstones - may be an additional source for potential misclassification [8,9,14].

The treatment of symptomatic cholelithiasis is surgical by performing cholecystectomy. It has been argued that cholecystectomy might lead to an improvement in cardiovascular risk by increased cholesterol excretion through the gastrointestinal tract [46,47,48]. In the past, several studies found that cholecystectomy does not increase cardiovascular risk [11,13,15,16] and others showed no improvement in the increased cardiovascular risk [8,14] and one study suggested a protective effect, but with no conclusive results [46]. Interestingly González-Pérez et al. [36] showed that, when only cases undergoing cholecystectomy were considered, the observed association between GsD and CVD disappeared. Finally, Chavez-Tapia et al. [19] showed in their study that undergoing cholecystectomy increases prevalence of CVD risk factors. A higher risk for CVD after cholecystectomy could be explained by hepatic triglyceride concentrations increasing and thus a favored fat accumulation in the liver [49].

Khan et al. [37] conducted a 10-year prospective autopsy study between July 1988 to June 1998 in continuity with a study of the previous decade on gallstone prevalence [50]. Autopsies were performed in the Southeast Kent District Health Authority with 9.175 cases included in the study. Their autopsy study reported an association of GsD with diabetes and with increased body mass index, but not with CAD (P =0.6).

In consistence with the above-mentioned autopsy study, our results did not show any statistically significant association of significant CAD with GsD or with cholecystectomy, although associations with traditional risk factors for CAD (hypertension, hyperlipidemia, DM, smoking) that were studied was confirmed. It is worth mentioning that autopsy has been shown to present higher sensitivity for the detection of gallstones [51] and to be a valid measuring tool for gallstone prevalence [52].

Our results may differ from previous clinical studies for several reasons. Except for the above-mentioned differences in the recording of GsD, the measured outcome was significant CAD, which means stenosis of the lumen of any major artery disease equal to or over 75%. The age of the population studied was 35-65 years, a middle-aged population, in contrast with previous studies on either young East-Asians [38], or older populations [6]. Finally, environmental factors and the Mediterranean diet could have played a huge role in the outcome of our study [53-56]. An over 50year epidemiological study, seeking cultural contrasts, compared CVD rates related to diet differences and showed the lowest incidence and mortality rates from CAD in Greece and Japan in contrast to higher rates that were found in North America and northern Europe [56].

The strength of our study lies in the significant number of cases, in the objective way of collecting data through autopsies that also contains undiagnosed and asymptomatic GsD and it is characterized by a higher detection rate for small gallstones in contrast to ultrasonography [45,57]. Our study focuses on cases of significant narrowing of the coronary arteries compared to other studies that evaluate either a lower percentage of stenosis in any coronary artery [6], or only confirmed cases of myocardial infarction [14]. Moreover, in order to

control the possible effect of gallbladder removal on the final result, the predictive value of GsD and cholecystectomy in CAD presence were explored separately as independent variables in the logistic regression model. Traditional risk factors such as DM, hyperlipidemia, hypertension, and smoking were also controlled, and they were found to successfully predict CAD presence.

Unfortunately, some relevant clinical and lifestyle data were not available such as physical activity, dietary habits, and obesity, which is the main limitation of our study. Retrospective studies have also reported to be prone to bias since the study procedures (data collection, entry, and quality assurance) are not planned in advance. We believe, however, that selection bias was not an issue in the present study since data collection was conducted by a doctor who had not performed any of the above autopsies.

CAD and GsD are two major health problems. Strategies focused on preventing the progress and manifestation of both are of paramount importance and further research is needed in this direction. Knowledge, however, about their association (or not) is crucial so that effective and targeted prevention planning can be implemented.

5. CONCLUSION

Our study did not show any statistically significant relationship between the presence of significant coronary artery stenosis and GsD. The same outcome was noticed when cholecystectomy was studied separately. Therefore, cholelithiasis and cholecystectomy cannot serve as possible predictors for CAD development. Future studies are needed to validate our findings that will lead to more beneficial prevention planning and monitoring of patients so as to maximize resources management and reduce healthcare costs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study design was approved by the Ethics Committee of the School of Medicine of National and Kapodistrian University of Athens, Greece (5843/19-02-2015).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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