RESEARCH LETTER

Cholecystectomy is associated with dysglycaemia: Cross-sectional and prospective analyses

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Abstract

Cholecystectomy has been reported to be associated with increased risk of diabetes in cross-sectional studies. In the current study, we performed both cross-sectional and prospective analyses to examine the association between cholecystectomy and dysglycaemia in Chinese community-dwelling adults. A total of 1612 participants (n = 1564 without cholecystectomy and n = 48 with cholecystectomy) were evaluated for glycaemic status (according to the World Health Organization (WHO) 1999 criteria) and then followed up over ~3.2 years. Percent changes (Δ) in fasting blood glucose and HbA1c from baseline at the follow-up visit were calculated to define glycaemic control as stable (−10% ≤ Δ < 10%), improved (Δ < −10%), or worsened (Δ ≥ 10%). The baseline cross-sectional analyses indicated that cholecystectomy was associated with an increased risk of both prediabetes and diabetes, while the prospective analysis indicated that cholecystectomy was also associated with a greater risk of deterioration in glycaemic control (ΔFPG ≥10% and ΔHbA1c ≥10%) ($P < 0.05$ for each, both before and after adjusting for potential confounding covariates). These observations suggest that individuals in the Chinese community-dwelling population who have undergone cholecystectomy are at increased risk of dysglycaemia. Further studies are warranted to both delineate the underlying mechanisms and to clarify whether more intense surveillance for future development of diabetes is needed in this group.

KEYWORDS
cohort study, glycaemic control, observational study

1 | INTRODUCTION

There is increasing recognition that bile, rather than simply assisting fat digestion in the small intestine, plays a pivotal role in the regulation of glucose metabolism.[1-3] In healthy individuals, intrajejunal administration of the physiological bile acid (BA) taurocholic acid markedly reduces the glycaemic response to small intestinal glucose infusion.[2] In rodent models of type 2 diabetes (T2D), diversion of bile from the proximal to the distal region of the gut recapitulates the metabolic benefits of bariatric surgery.[4,5] By contrast, non-diabetic individuals who have undergone cholecystectomy exhibit prolonged elevation in postprandial glycaemia.[6] While it is clear that T2D is associated with an increased risk of gallbladder diseases, the outcomes of several cross-sectional studies suggest that cholecystectomy is associated with an increased risk of T2D.[7-9] We have performed both cross-sectional and prospective analyses to examine the association between cholecystectomy and dysglycaemia in Chinese community-dwelling adults.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 1707 Chinese community-dwelling adults from the Study on Evaluation of iNnovative Screening tools and determInation of

TABLE 1 Characteristics of study participants with and without cholecystectomy

	Total (n = 1612)	Without cholecystectomy (n = 1564)	With cholecystectomy (n = 48)	P
Years since cholecystectomy		NA	11.2 ± 7.1	
Female, n (%)	1031 (64.0)	995 (63.6)	36 (75.0)	0.11
Age, years	52.3 ± 9.1	52.1 ± 9.2	56.1 ± 6.3	<0.001
Current smoking, n (%)	264 (16.4)	260 (16.6)	4 (8.3)	0.13
Current drinking, n (%)	397 (24.6)	386 (24.7)	11 (22.9)	0.78
BMI, kg/m^2	25.3 ± 3.5	25.3 ± 3.5	25.7 ± 3.2	0.47
Waist circumference, cm	85.3 ± 9.4	85.2 ± 9.4	86.2 ± 8.9	0.49
SBP, mmHg	132.9 ± 18.9	132.8 ± 18.9	137.2 ± 18.5	0.12
DBP, mmHg	81.2 ± 11.4	81.2 ± 11.4	81.2 ± 12.0	0.97
FPG, mmol/L	5.9 ± 1.1	5.9 ± 1.1	6.2 ± 1.1	0.06
2hPG, mmol/L[a]	7.4 ± 2.5	7.4 ± 2.4	8.2 ± 2.7	0.03
HbA1c, % (mmol/mol)	5.5 ± 0.8 (36.6 ± 8.4)	5.5 ± 0.8 (36.6 ± 8.4)	5.6 ± 0.8 (37.3 ± 8.9)	0.5
TyG	8.8 ± 0.7	8.8 ± 0.7	8.7 ± 0.7	0.74
SPISE	6.7 ± 1.8	6.7 ± 1.8	6.5 ± 1.9	0.39
TC, mmol/L	4.9 ± 0.9	4.9 ± 0.9	4.9 ± 0.9	0.68
TG, mmol/L	1.3 (0.9, 1.9)	1.3 (0.9, 1.9)	1.4 (0.9, 2.1)	0.67
HDL, mmol/L	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	0.93
LDL, mmol/L	2.7 ± 0.7	2.7 ± 0.7	2.7 ± 0.6	0.67
BUN, mmol/L	5.3 ± 1.4	5.3 ± 1.4	5.5 ± 1.5	0.28
Cr, umol/L	64.7 ± 15.7	64.7 ± 15.7	65.6 ± 15.3	0.69
Glycaemic status, n (%)				<0.001
Normoglycaemia	899 (55.8)	887 (56.7)	12 (25.0)	<0.001
Prediabetes	544 (33.7)	520 (33.2)	24 (50.0)	0.02
Diabetes	169 (10.5)	157 (10.0)	12 (25.0)	0.001
Glucose-lowering therapies				
Baseline, n (%)	52 (3.2)	49 (3.1)	3 (6.3)	0.20
Follow-up, n (%)	54 (3.3)	52 (3.3)	2 (4.2)	0.67

Data are presented as means ± SD or median (25th percentile, 75th percentile) or number (%).
Unpaired Student's *t*-test or Mann–Whitney *U*-test for continuous data and chi-squared test or Fisher's exact test for categorical data were used to compare parameters between two groups.
Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SPISE, single-point insulin sensitivity estimator; TC, total cholesterol; TG, triglycerides; TyG, triglyceride-glucose index; 2hPG, 2-hour plasma glucose.
[a]2hPG was not measured in 54 participants at baseline due to previously confirmed diagnosis of diabetes (n = 49 in the subgroup without cholecystectomy, and n = 5 in the subgroup with cholecystectomy).

optimal diagnostic cut-off points for type 2 diabetes in Chinese multi-Ethnic (SENSIBLE) and SENSIBLE-Addition cohorts were surveyed to assess history of cholecystectomy, and followed up approximately 3.2 years later.[10,11] Participants were excluded if they had previous gastrointestinal surgery (except for appendectomy) other than cholecystectomy (n = 73), cholecystectomy during the follow-up period (n = 20), or onset of diabetes prior to cholecystectomy (n = 2). Accordingly, 1612 participants were included in the final analysis. The study protocol was approved by the Human Research Ethics Committee of Zhongda Hospital, Southeast University, Nanjing, China. All participants provided written informed consent prior to their enrolment in the study.

2.2 | Measurements

At both baseline and follow-up visits, demographic data, medical history, and smoking and alcohol consumption were recorded. Waist circumference, body mass index (BMI), systolic blood pressure and diastolic blood pressure were measured. Fasting venous blood was collected for measurements of fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), blood urea nitrogen and serum creatinine. Plasma glucose at 2 hours after a 75-g oral glucose drink (2hPG) was also measured in participants without known diabetes.

Glycaemic status was defined according to the World Health Organization 1999 criteria, consistent with the Chinese Diabetes Society guidelines. Insulin resistance and sensitivity were assessed by the TG-glucose index (TyG) and single-point insulin sensitivity estimator (SPISE), as previously.[3] The percent changes (Δ) in FPG, HbA1c, TyG and SPISE from baseline to follow-up were calculated, to define glycaemic control as stable ($-10\% \leq \Delta < 10\%$), improved ($\Delta < -10\%$), or worsened ($\Delta \geq 10\%$); the magnitude of $\Delta \geq 10\%$ in HbA1c is predictive of an increased risk of cardiovascular events in T2D.[12] Because 2hPG was not measured in participants with confirmed diagnosis of diabetes at baseline and follow-up visits, which led to disproportional missing data between participants with and without cholecystectomy, Δ 2hPG could not be evaluated.

2.3 | Statistical analysis

Continuous data were presented as means ± SD or median (25th-75th percentile), and categorical data as numbers (percentages). Differences between participants with and without cholecystectomy were tested by unpaired Student's *t*-test or Mann–Whitney *U*-test for continuous data, and the chi-squared test or Fisher's exact test for categorical data, where appropriate. Multinomial logistic regression analyses were used to explore the association of cholecystectomy with presence of prediabetes and diabetes at baseline, with and without adjustment for covariates (including age, gender, BMI, current smoking status [yes or no], current alcohol consumption status [yes or no], hypertension [yes or no], TG, HDL and LDL levels), and to compare the percent changes in glycaemic indices (ΔFPG, ΔHbA1c, ΔTyG and ΔSPISE) between participants with and without cholecystectomy

TABLE 2 Changes in glycaemic indices from baseline to follow-up visit

	Without cholecystectomy (n = 1564)	With cholecystectomy (n = 48)	P1	P2
Δ FPG subgroup			0.001	
$\Delta < -10\%$, n (%)	436 (27.9)	11 (22.9)	0.45	0.65
$-10\% \leq \Delta < 10\%$, n (%)	990 (63.3)	25 (52.1)	0.11	Reference
$\Delta \geq 10\%$, n (%)	138 (8.8)	12 (25.0)	<0.001	0.02
Δ HbA1c subgroup			0.002	
$\Delta < -10\%$, n (%)	63 (4.0)	1 (2.1)	0.76	0.49
$-10\% \leq \Delta < 10\%$, n (%)	1133 (72.4)	25 (52.1)	0.002	Reference
$\Delta \geq 10\%$, n (%)	368 (23.5)	22 (45.8)	<0.001	0.002
Δ TyG subgroup			0.22	
$\Delta < -10\%$, n (%)	63 (4.0)	4 (8.3)	0.27	0.39
$-10\% \leq \Delta < 10\%$, n (%)	1433 (91.6)	43 (89.6)	0.81	Reference
$\Delta \geq 10\%$, n (%)	68 (4.3)	1 (2.1)	0.72	0.49
Δ SPISE subgroup			0.02	
$\Delta < -10\%$, n (%)	368 (23.5)	7 (14.6)	0.15	0.58
$-10\% \leq \Delta < 10\%$, n (%)	809 (51.7)	21 (43.8)	0.28	Reference
$\Delta \geq 10\%$, n (%)	387 (24.7)	20 (41.7)	0.01	0.06

P1: Chi-squared test or Fisher's exact test was used to compare the changes in glycaemic indices between the two groups.
P2: Multinomial logistic regression analyses were used to compare the changes in glycaemic indices between the two groups after adjusting for age, gender, change in body weight over the follow-up, and baseline body mass index and glycaemic status.
Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SPISE, single-point insulin sensitivity estimator; TyG, triglyceride-glucose index.

during the follow-up period, after adjusting for covariates (including age, gender, change in body weight over follow-up, and baseline BMI and glycaemic status). A sensitivity analysis was performed by excluding participants receiving glucose-lowering agents. Statistical analysis was performed using SPSS software (version 25.0, IBM). *P* values < 0.05 were taken to indicate statistical significance.

3 | RESULTS

The characteristics of participants with (n = 48) and without (n = 1564) prior cholecystectomy at baseline are summarized in Table 1. Those with cholecystectomy were slightly older and had a higher prevalence of prediabetes (50.0% vs. 33.2%) and diabetes (25.0% vs. 10.0%) compared to those without cholecystectomy (*P* < 0.05 each). Accordingly, cholecystectomy was associated with an increased risk of both prediabetes (odds ratio [OR] 3.4, 95% confidence interval [CI] 1.7-6.9; *P* = 0.001) and diabetes (OR 5.7, 95% CI 2.5-12.8; *P* < 0.001), which remained evident after adjusting for covariates (OR 2.9, 95% CI 1.4-6.2, *P* = 0.003 for prediabetes; OR 5.0, 95% CI 2.1-11.9, *P* < 0.001 for diabetes).

At approximately 3.2-year follow-up (range: 3.1-3.6 years), a further seven participants (19.4%) in the cholecystectomy group and 239 participants (17.0%) in the non-cholecystectomy group developed diabetes. The proportions with ΔFPG ≥10% (25.0% vs. 8.8%; *P* < 0.001), ΔHbA1c ≥10% (45.8% vs. 23.5%; *P* < 0.001) and ΔSPISE ≥10% (41.7% vs. 24.7%; *P* = 0.01) were higher in participants with previous cholecystectomy. After adjusting for age, sex, change in body weight over the follow-up, and baseline BMI and glycaemic status, cholecystectomy was associated with an increased risk of ΔFPG ≥10% (OR 2.5, 95% CI 1.2-5.4; *P* = 0.02) and ΔHbA1c ≥10% (OR 2.6, 95% CI 1.4-4.8; *P* = 0.002 [Table 2]). The sensitivity analysis showed that the association between cholecystectomy and ΔHbA1c ≥ 10% remained significant after excluding individuals taking glucose-lowering medication(s) (data not shown).

4 | DISCUSSION

Our study examined the association of cholecystectomy with dysglycaemia in Chinese community-dwelling adults at both baseline and over approximately 3.2 years of follow-up. The baseline cross-sectional analyses indicated that history of cholecystectomy was associated with an increased risk of both prediabetes and diabetes, while the prospective analysis indicated that cholecystectomy was also associated with a greater risk of deterioration in glycaemic control. These observations provide strong support for the concept that BA signalling is important in glucose metabolism.

The strong link between cholecystectomy and dysglycaemia dictates the need for further studies to explore potential underlying mechanisms. BAs are natural ligands of the nuclear farnesoid X receptor and the membrane Takeda G protein receptor 5, activation of which is known to influence glucose metabolism.[1] There is recent evidence that the serum BA response to an oral glucose load is predictive of glucose tolerance in non-diabetic individuals, and is markedly impaired in Han Chinese adults with T2D,[3] suggesting that after cholecystectomy the lack of physiological pulses of postprandial BA release may be important.

We recognize that the number of participants with cholecystectomy in our study was relatively small, since participants were sampled from a community-dwelling population, in which participants tended to be more "healthy" than hospital-based cohorts. Future studies of larger sample size are indicated to validate our observations. In addition, information on dietary habits was not collected in our study; it would not be surprising that the cholecystectomized participants had reduced dietary fat intake due to fat intolerance, although this would be expected to favour a reduced risk of dysglycaemia.

In conclusion, individuals in the Chinese community-dwelling population who have undergone cholecystectomy are at increased risk of dysglycaemia. Further studies are warranted to both delineate the underlying mechanisms and clarify whether more intense surveillance for future development of diabetes is needed in this group.

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