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Relationship of Fat Deposition in the Liver and Pancreas with Cholecystectomy

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Keywords

Fatty liver · Fatty pancreas · Hepatic fat · Intrapancreatic fat deposition · Obesity · Magnetic resonance imaging · Bile acids metabolism

Abstract

Introduction: Rates of cholecystectomy in the general population continue to rise despite little being known about its long-term metabolic implications. Existing studies have suggested that cholecystectomy may be linked to type 2 diabetes mellitus and metabolic syndrome, though there is yet to be quality investigation of its associations with important ectopic fat depots – hepatic fat and intrapancreatic fat. The aim of the present study was to investigate the relationship of cholecystectomy with both hepatic and intrapancreatic fat. ***Methods:*** The study involved 367 participants who underwent abdominal scanning, with hepatic and intrapancreatic fat quantified using gold-standard MRI-based methods. Linear regression analyses were adjusted for age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin, triglyceride, LDL-C, and HDL-C. ***Results:*** In the most adjusted model, cholecystectomy was significantly negatively associated with hepatic fat (β coefficient = –3.671; p = 0.019) but not intrapancreatic fat (β coefficient = 0.133; p = 0.586). In analyses stratified by BMI, this association with hepatic fat was significant in the obese group only (β coefficient = –7.163; p = 0.048). The association with intrapancreatic fat was not influenced by BMI. ***Conclusion:*** Cholecystectomy is significantly associated with lower hepatic fat in obese individuals. This affirms that people with indications for cholecystectomy should not be dissuaded from undergoing the procedure based on fears of harmful effects of increasing hepatic fat content.

Introduction

With more than 800,000 procedures performed annually in the USA alone [1], and increasing rates in recent years [2], cholecystectomy is one of the most common surgeries carried out in the general population [3, 4]. Considered to be a low-risk procedure with good prognosis, cholecystectomy has improved in safety within the last 30 years after the development and mainstreaming of laparoscopic techniques (which now account for the majority of cholecystectomies) [2, 3]. Potential early complications, such as bile duct injury and bleeding, are already acknowledged [5]; however, there may also be mechanisms by which

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cholecystectomy contributes to long-term metabolic complications [4]. Synthesized by hepatocytes and stored and secreted by the gallbladder, bile acids aid the digestive breakdown of fatty acids and absorption of lipid-soluble vitamins [6]. Signaling is an important function of bile acids: through activating the farnesoid X receptor – a ligand activated transcription factor – bile acids trigger the production of fibroblast growth factor 19, which has downstream insulin-like effects such as stimulation of glycogen synthesis, inhibition of fatty acid synthesis, and promotion of gallbladder relaxation [7–10]. Most fibroblast growth factor 19 is gallbladder-derived and its serum levels decrease after cholecystectomy [7]. Bile acids are also a ligand of the Takeda G-protein-coupled receptor 5 (TGR5), which is found on cholangiocyte and gallbladder epithelial cell membranes and has beneficial metabolic effects including increasing energy expenditure and improving glucose metabolism and insulin sensitivity [10, 11]. After cholecystectomy (and therefore without the contractile mechanisms of the gallbladder that regulate movement of bile), bile acids also circulate more quickly. This leads to an increase in exposure of the liver to bile acids and a more continuous concentration of bile acids within the duodenum, rather than the periodic fluctuations that occur in response to food intake when the healthy gallbladder is present [8, 10, 12]. The combination of the above mechanisms may therefore implicate the involvement of cholecystectomy in downstream disruptions of systemic metabolic homeostasis.

The role of the gallbladder as an endocrine organ has been investigated for more than a decade and current literature is conflicting. Recent studies have reported links of cholecystectomy with a range of metabolic disorders, including dyslipidemia, type 2 diabetes mellitus, hypertension, weight gain, and metabolic syndrome [10, 13–16]. In 2013, a US population-based study of 12,232 individuals found a significant association of cholecystectomy with non-alcoholic fatty liver disease (NAFLD) diagnosed by ultrasound [12]. A further study of 32,428 individuals similarly showed that cholecystectomy was significantly associated with fatty liver disease in unadjusted analysis; however, no significant association was observed after adjustment for covariates (including age, gender, body mass index [BMI], systolic and diastolic blood pressure, fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, albumin, and serum uric acid) [17]. Both studies were limited by methods of hepatic fat quantification, which was conducted through ultrasound – a method highly susceptible to inter-reader variability. Moreover, the latter study was a retrospective investigation only involving a single center and therefore a selection bias could not be ruled out. Another ultrasound-based prospective investigation of 4,307 participants found that, on unadjusted analysis, participants who underwent cholecystectomy had significantly higher odds of having metabolic syndrome and moderate to severe NAFLD; however, these associations were again no longer statistically significant on most-adjusted analyses for multiple potentially confounding factors (including age, sex, study cohort, education level, physical activity, energy intake, time since cholecystectomy being > 10 years, hypertension, diabetes, BMI, hepatic steatosis and presence of NAFLD for the metabolic syndrome analysis, and presence of metabolic syndrome for the NAFLD analysis) [18]. Using magnetic resonance imaging (MRI)-based methods for noninvasive quantification of hepatic fat, a 2017 prospective study found that cholecystectomy was significantly associated with increased hepatic fat 2 years after surgery; however, this study involved only a very small sample size [19]. Further, the liver and pancreas are often paired together as two metabolically active ectopic fat depots; however, to our knowledge, there has not been previous large MRI investigation into the relationship of cholecystectomy with intrapancreatic fat deposition (IPFD). With cholecystectomy being significantly associated with insulin resistance and insulin resistance also being significantly associated with IPFD [20, 21], it is plausible that cholecystectomy could have links with IPFD and other pathological processes in the pancreas of clinical interest. Using one of the largest sample sizes of participants to undergo manual MRI-based quantification of both hepatic fat and IPFD, gold-standard noninvasive quantification of these ectopic fat depots, and robust adjustment for relevant covariates (including age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin, triglyceride, LDL-C, and HDL-C) [22, 23], this study aimed to investigate the associations of cholecystectomy with hepatic fat and IPFD.

Methods

Study Cohort

This was a cross-sectional study of adult participants residing in Auckland (New Zealand), enrolled as part of four individual cohorts. Participants were excluded if within the last 6 months they had a history of acute inflammatory or infectious disorders that required medical care, had received special dietary advice, or participated in a weight loss program. Further exclusion criteria were history of pancreatic or bariatric surgery or radiologic or endoscopic procedure that involved the pancreas or liver, type 1 diabetes mellitus, chronic liver disease, chronic pancreatitis, malignancy, current pregnancy or breastfeeding, or contraindications of MRI such as end-stage renal failure, congestive heart failure, psychiatric disorders, or metal implants or implanted electronic devices including cardiac pacemakers.

Laboratory and Anthropometric Measurements

Participants fasted for 8–10 h prior to venous blood collection. Collected samples were then centrifuged at 4°C and analyzed separately for each of the four participant cohorts, using the same laboratory methods. Fasting plasma glucose was measured using hexokinase colorimetric assay. Fasting insulin, glucose-dependent insulinotropic polypeptide, amylin, and glucagon were measured using the MILLIPLEX MAP Human Metabolic Hormone Magnetic Bead Panel, based on Luminex xMAP technology (Merck KGaA, Hesse, Germany). Components of the lipid panel and liver enzymes were analyzed at a tertiary referral medical laboratory using standard methods. Blood lipids analyzed included triglyceride, HDL-C, and total cholesterol. Triglyceride was analyzed using the lipase/glycerol kinase method, HDL-C was analyzed using the detergent/cholesterol esterase/cholesterol oxidase/peroxidase method, and total cholesterol was analyzed using the esterase/cholesterol oxidase/peroxidase method. LDL-C (mg/dL) was calculated using the 2020 Sampson formula: total cholesterol/0.948 – HDL-C/0.971 – (triglyceride/8.56 + [triglyceride × non-HDL-C]/2140 – triglyceride^2/16100) – 9.44 [24]. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the formula: fasting glucose (mg/dL) × fasting insulin (μU/mL)/405, and homeostasis model assessment of β-cell dysfunction (HOMA-β) was calculated using the formula: 360 × fasting insulin (μU/mL)/(fasting glucose [mg/dL] – 63) [21, 25]. To calculate BMI, height and weight of participants were measured, with participants wearing light clothing only and no headwear or footwear, according to standard protocols.

Imaging Protocol

All MRI examinations were performed on a 3.0 Tesla whole-body unit (Siemens, Erlangen, Germany) at the Center for Advanced Magnetic Resonance Imaging at the University of Auckland. The same scanning protocol was used for all participants, as described elsewhere [21, 26]. In brief, participants lay in the supine position during scan acquisition and held their breath for 11 s at the end of expiration. An axial T1-weighted volumetric interpolated breath-hold Dixon sequence was used, with parameters including true form abdomen shim mode, field view 500 × 400 mm, slice thickness 5 mm, echo time 2.46 ms and 3.69 ms, repetition time 5.82 ms, flip angle 9°, pixel bandwidth 750 Hz, signal average 1, and matrix 512 × 410; partial Fourier and parallel imaging were used with total acceleration factor 2.8. Images created included in-phase, out-of-phase, fat-only, and water-only images, which were exported as DICOM files for further analysis of IPFD and assessment of presence of the gallbladder. Hepatic fat was quantified through magnetic resonance spectroscopy, during which a 20 mm × 20 mm × 20 mm voxel was placed in the right liver lobe (Fig. 1a, b), as described elsewhere [26, 27]. IPFD was quantified using a modified version of the “MR-opsy” technique (Fig. 1c, d) by two separate assessors, and their averaged data were used for statistical analysis [28]. History of cholecystectomy was determined based on structural findings on MRI, assessing presence or absence of the gallbladder.

Statistical Analyses

Statistical analyses were completed using IBM SPSS version 28.0.1.1 for Macintosh (IBM Corp., Armonk, NY, USA). Differences between the subgroup that had undergone cholecystectomy and the subgroup who had not were analyzed using Pearson’s chi-square tests (categorical variables) and independent-samples t tests (continuous variables). Associations between ectopic fat and cholecystectomy were investigated using linear regression analyses. The dependent variable was hepatic fat or IPFD and the independent variable was cholecystectomy. Five different statistical models were constructed: (1) unadjusted; (2) adjusted for age, sex, ethnicity; (3) adjusted for age, sex, ethnicity, BMI; (4) adjusted for age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin; (5) adjusted for age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin, triglyceride, LDL-C, HDL-C. Stratified analyses were undertaken according to the following BMI categories: lean, BMI <25 kg/m^2; overweight, BMI 25 to < 30 kg/m^2; obese, BMI ≥30 kg/m^2. Data were presented as unstandardized β coefficients, unstandardized standard errors, and p values, with two-sided $p < 0.05$ considered to be statistically significant.

Results

Characteristics of the Study Cohort

There were 367 participants included in this study. Of these, 208 participants were women (56.7%) and 159 were men (43.3%). The youngest participant was 18 years old whereas the oldest was 89 years old. The median BMI of the participants was 26.8 kg/m^2, above the cutoff for

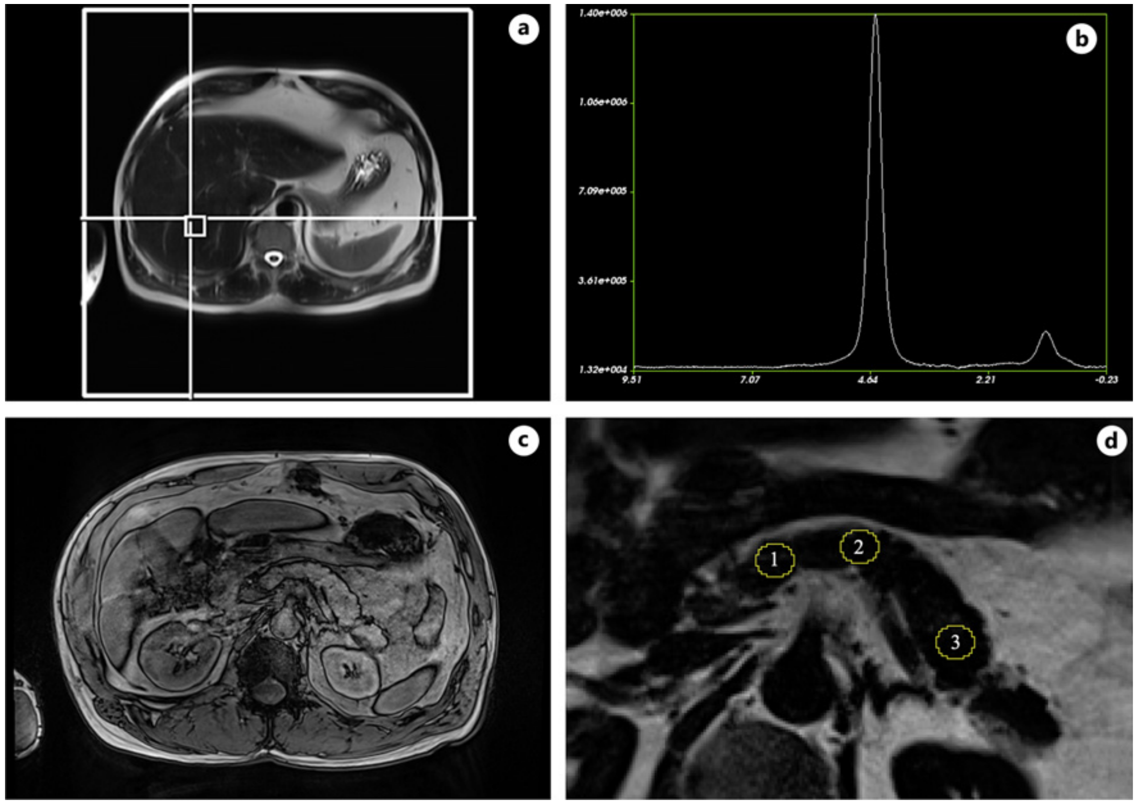

Fig. 1. Exemplar ectopic fat quantification. Spectroscopy voxel placed in the right lobe of the liver (**a**) and the corresponding spectroscopy data (**b**) showing how hepatic fat was quantified and the original out-of-phase slice of the pancreas (**c**) and magnified fat-only slice with the pancreas head (1), body (2), and tail (3) regions of interest placement (**d**) showing how IPFD was quantified.

overweight. There were 70 participants that had undergone cholecystectomy. Compared with the subgroup that had not undergone cholecystectomy, the subgroup that had undergone cholecystectomy included a larger proportion of European participants ($p < 0.001$), was older ($p < 0.001$), had a higher BMI ($p = 0.003$), and higher IPFD ($p = 0.003$). Other demographic and metabolic parameters of these participants did not differ significantly (Table 1). There were 111 participants in the lean BMI group, 168 participants in the overweight BMI group, and 87 participants in the obese BMI group. For the lean group, the median BMI was 23.2 kg/m^2 (IQR 21.5–24.1 kg/m^2), the median fasting plasma glucose was 91.8 mg/dL (IQR 82.8–99.0 mg/dL), 9.0% of the participants in the lean group had diabetes, and 22.5% had prediabetes. For the overweight group, the median BMI was 27.2 kg/m^2 (IQR 26.3–28.4 kg/m^2), the median fasting plasma glucose was 97.2 mg/dL (IQR 90.9–103.5 mg/dL), 8.9% of the participants in the overweight group had diabetes, and 35.7% had prediabetes. For the obese group, the median BMI was 34.0 kg/m^2 (IQR 32.0–36.5 kg/m^2), the median fasting plasma glucose was 99.0 mg/dL (IQR 92.7–110.7 mg/dL), 20.7% of the participants in the obese group had diabetes, and 36.8% had prediabetes.

Associations of Cholecystectomy with Hepatic Fat Deposition

In the overall cohort, there were no statistically significant associations of cholecystectomy with hepatic fat in the unadjusted model 1 ($\beta = -2.024$, $p = 0.198$) and model 2 adjusted for age, sex, ethnicity ($\beta = -2.174$, $p = 0.190$) analyses, but in model 3 additionally adjusted for BMI ($\beta = -3.831$, $p = 0.016$), model 4 additionally adjusted for fasting plasma glucose, fasting insulin ($\beta = -3.708$, $p = 0.020$), and model 5 additionally adjusted for triglyceride, LDL-C, HDL-C ($\beta = -3.671$, $p = 0.019$) analyses there were statistically significant, negative associations (Table 2). In the lean BMI group, there were no statistically significant associations of cholecystectomy with hepatic fat in model 1 ($\beta = 1.403$, $p = 0.552$), model 2

Table 1. Characteristics of the overall study cohort and subgroups according to cholecystectomy status

Characteristic	Overall cohort	Individuals without cholecystectomy	Individuals with cholecystectomy	*p* value
Women	208 (56.7%)	169 (56.9%)	39 (55.7%)	0.857
Ethnicity[a]				
Asian	178 (48.5%)	164 (55.2%)	14 (20.0%)	<**0.001**
European	121 (33.0%)	85 (28.6%)	36 (51.4%)	<**0.001**
Other	67 (18.3%)	47 (15.8%)	20 (28.6%)	**0.014**
Age, years	50.0 (36.0–60.0)	48.0 (35.5–59.0)	58.0 (45.8–66.3)	<**0.001**
BMI, kg/m^2	26.8 (24.3–29.7)	26.6 (24.1–29.2)	28.4 (25.4–33.1)	**0.003**
Fasting plasma glucose, mg/dL	95.4 (88.2–102.6)	95.4 (88.2–102.6)	95.4 (88.2–105.3)	0.217
Insulin, μU/mL	10.7 (7.0–16.3)	10.8 (7.0–16.3)	10.7 (6.6–15.2)	0.528
Triglyceride, mg/dL	106.3 (79.7–159.4)	106.3 (79.7–150.6)	124.0 (88.6–194.9)	0.735
LDL-C, mg/dL	110.3 (84.4–133.6)	110.4 (86.1–133.5)	104.9 (73.7–135.2)	0.182
HDL-C, mg/dL	50.3 (39.6–61.9)	50.3 (38.7–61.9)	50.3 (42.5–61.9)	0.747
IPFD, %	8.6 (7.0–10.1)	8.3 (6.9–10.0)	9.5 (8.1–10.4)	**0.003**
Hepatic fat, %	5.7 (3.1–12.0)	5.7 (3.0–12.2)	5.7 (3.7–8.9)	0.138
HOMA-IR	5.1 (3.1–8.7)	4.9 (3.0–7.9)	6.6 (4.1–11.4)	0.058
HOMA-β	228.4 (159.3–362.1)	225.2 (157.8–341.3)	260.3 (167.3–502.5)	0.133
ALT, U/L	20.2 (12.9–29.9)	17.2 (11.4–27.3)	24.3 (19.9–34.5)	0.119
AST, U/L	21.5 (17.1–26.7)	20.4 (16.2–25.5)	23.7 (19.0–32.4)	0.388
GGT, U/L	20.0 (14.4–34.5)	18.9 (14.0–30.4)	22.5 (15.5–49.8)	0.691
GIP, pg/mL	66.6 (35.3–111.2)	63.6 (35.3–97.9)	84.1 (33.7–171.6)	0.207
Amylin, pg/mL	30.5 (14.2–43.0)	30.9 (14.8–44.0)	29.0 (11.8–39.4)	0.600
Glucagon, pg/mL	53.2 (36.0–85.6)	55.8 (37.1–86.9)	48.8 (28.1–82.7)	0.343

Categorical variables are presented as *n* (%), and continuous variables are presented as median (interquartile range). Two-sided *p* values were calculated using Pearson's chi-square tests and independent-samples *t* tests for categorical and continuous variables, respectively. Statistically significant values ($p < 0.05$) are in bold. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; GIP, glucose dependent insulinotropic polypeptide; GLP, glucagon-like peptide; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell dysfunction; IPFD, intrapancreatic fat deposition; LDL-C: low-density lipoprotein cholesterol. [a]One participant had missing data on ethnicity.

(β = 1.416, *p* = 0.548), model 3 (β = 1.247, *p* = 0.600), model 4 (β = 1.551, *p* = 0.528), or model 5 (β = 1.623, *p* = 0.517) analyses. In the overweight BMI group, there were also no statistically significant associations of cholecystectomy with hepatic fat in model 1 (β = −2.402, *p* = 0.336), model 2 (β = −3.571, *p* = 0.169), model 3 (β = −4.611, *p* = 0.071), model 4 (β = −4.746, *p* = 0.068), or model 5 (β = −4.288, *p* = 0.094) analyses. In the obese BMI group, there were statistically significant negative associations of cholecystectomy with hepatic fat in model 1 (β = −8.288, *p* = 0.009), model 2 (β = −8.026, *p* = 0.024), model 3 (β = −8.129, *p* = 0.020), model 4 (β = −7.401, *p* = 0.043), and model 5 (β = −7.163, *p* = 0.048) analyses (Table 3). Figure 2 shows the distribution of IPFD and hepatic fat of participants with and without cholecystectomy, stratified by BMI group.

Associations of Cholecystectomy with IPFD

In the overall cohort, there was a statistically significant positive association of cholecystectomy with IPFD in model 1 analysis (β = 0.806, *p* = 0.007) but not in model 2 (β = 0.482, *p* = 0.091), model 3 (β = 0.076, *p* = 0.764),

Table 2. Associations of fat deposition in the liver and the pancreas with cholecystectomy

Model	Hepatic fat			IPFD		
	β	SE	*p* value	β	SE	*p* value
Model 1	−2.024	1.569	0.198	0.806	0.296	**0.007**
Model 2	−2.174	1.653	0.190	0.482	0.284	0.091
Model 3	−3.831	1.585	**0.016**	0.076	0.253	0.764
Model 4	−3.708	1.589	**0.020**	0.048	0.254	0.850
Model 5	−3.671	1.560	**0.019**	0.133	0.244	0.586

Data presented as unstandardized β coefficients, SEs, and *p* values (from multiple linear regression). Statistically significant values ($p < 0.05$) are in bold. Model 1: unadjusted; model 2: adjusted for age, sex, ethnicity; model 3: adjusted for age, sex, ethnicity, BMI; model 4: adjusted for age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin; model 5: adjusted for age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin, triglyceride, LDL-C, HDL-C. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IPFD, intrapancreatic fat deposition; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

model 4 (β = 0.048, p = 0.850), or model 5 (β = 0.133, p = 0.586) analyses (Table 2). In the lean BMI group, there were no statistically significant associations of cholecystectomy with IPFD in model 1 (β = 1.251, p = 0.052), model 2 (β = 1.006, p = 0.079), model 3 (β = 0.746, p = 0.168), model 4 (β = 0.395, p = 0.455), or model 5 (β = 0.654, p = 0.209) analyses. In the overweight BMI group, there were also no statistically significant associations of cholecystectomy with IPFD in model 1 (β = −0.051, p = 0.905), model 2 (β = −0.338, p = 0.409), model 3 (β = −0.486, p = 0.225), model 4 (β = −0.663, p = 0.104), or model 5 (β = −0.499, p = 0.211) analyses. In the obese BMI group, there were no statistically significant associations of cholecystectomy with IPFD on model 1 (β = 0.584, p = 0.138), model 2 (β = 0.175, p = 0.674), model 3 (β = 0.164, p = 0.684), model 4 (β = 0.118, p = 0.781), or model 5 (β = 0.016, p = 0.970) analyses (Table 3).

Discussion

In a large cohort of participants, using gold-standard MRI methods for quantifying ectopic fat and robust adjustment for nine covariates in five statistical models, the present study found that cholecystectomy was significantly negatively associated with hepatic fat. The participants in the two groups did not differ markedly in terms of important metabolic parameters. These results are not in line with the findings of other large studies that tended to find either no difference in hepatic fat or increased hepatic fat [12, 18, 19, 29]. However, most of these studies were ultrasound-based (except for the very small MRI-based 2017 study that only included middle-aged adults [19]), excluded individuals with obesity or diabetes, and did not perform adjustment for covariates. Ultrasound was the most common mode of hepatic fat quantification in existing studies as it is low cost, convenient, and widely available. However, it involves rather subjective measurement of hepatic fat and is highly user-dependent, therefore introducing substantial bias [29, 30]. The pooled sensitivity for ultrasound at detecting hepatic steatosis has been reported to be only 84.8% by a meta-analysis of 49 studies [31]. Ultrasound is particularly inaccurate at distinguishing mild levels of hepatic steatosis near the 5.6% threshold [32], which is a concern for general population studies, particularly in Western countries where mild forms of steatotic liver disease are common. MRI is currently the preferred method for accurate noninvasive quantification of both hepatic fat [33, 34] and IPFD [22, 28], as used in the present study. Existing studies of cholecystectomy and ectopic fat not only tended to use less accurate methods of quantification but also often failed to complete robust adjustment for covariates [19, 29]. This is a novel aspect of the present study as factors such as age [35], ethnicity [36], and BMI (as shown by our stratified analyses) may all have associations with hepatic fat and IPFD. The importance of covariate adjustment in research of cholecystectomy and ectopic fat is further highlighted by two studies that found cholecystectomy was significantly associated with NAFLD on unadjusted analyses, but after adjustment for covariates the associations were no longer significant [17, 18]. If we had not adjusted for covariates in the present study, the conclusions of the present investigation would have been drastically different in regard to both hepatic fat and IPFD (on unadjusted analyses, the associations were not significant and significant, respectively).

The significant association between cholecystectomy and lower hepatic fat found in the present study after adjustment for covariates may be due to a downstream mechanism of action of bile acids – through the TGR5 receptor (Fig. 3). The TGR5 receptor – which is a G-protein-coupled bile acid receptor found in the liver (barring hepatocytes), the small intestine, and the central nervous system [37] – has effects of improving insulin sensitivity and

Table 3. Associations of fat deposition in the liver and the pancreas with cholecystectomy, stratified by BMI group

BMI group/model	Hepatic fat			IPFD		
	β	SE	*p* value	β	SE	*p* value
Lean (n = 111, median BMI = 23.2 kg/m²)						
Model 1	1.403	2.349	0.552	1.251	0.636	0.052
Model 2	1.416	2.346	0.548	1.006	0.566	0.079
Model 3	1.247	2.373	0.600	0.746	0.537	0.168
Model 4	1.551	2.448	0.528	0.395	0.526	0.455
Model 5	1.623	2.492	0.517	0.654	0.517	0.209
Overweight (n = 168, median BMI = 27.2 kg/m²)						
Model 1	−2.402	2.486	0.336	−0.051	0.425	0.905
Model 2	−3.571	2.581	0.169	−0.338	0.408	0.409
Model 3	−4.611	2.531	0.071	−0.486	0.399	0.225
Model 4	−4.746	2.575	0.068	−0.663	0.405	0.104
Model 5	−4.288	2.540	0.094	−0.499	0.397	0.211
Obese (n = 87, median BMI = 34.0 kg/m²)						
Model 1	−8.288	3.084	**0.009**	0.584	0.390	0.138
Model 2	−8.026	3.487	**0.024**	0.175	0.414	0.674
Model 3	−8.129	3.420	**0.020**	0.164	0.403	0.684
Model 4	−7.401	3.587	**0.043**	0.118	0.422	0.781
Model 5	−7.163	3.549	**0.048**	0.016	0.420	0.970

Data presented as unstandardized β coefficients, SEs, and *p* values (from multiple linear regression). Statistically significant values ($p < 0.05$) are in bold. Model 1: unadjusted; model 2: adjusted for age, sex, ethnicity; model 3: adjusted for age, sex, ethnicity, BMI; model 4: adjusted for age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin; model 5: adjusted for age, sex, ethnicity, BMI, fasting plasma glucose, fasting insulin, triglyceride, LDL-C, HDL-C. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IPFD, intrapancreatic fat deposition; LDL-C, low-density lipoprotein cholesterol; SE, standard error.

glycemic control [11], mechanisms which when impaired are both linked to high hepatic fat [38]. After cholecystectomy, these processes may be further propagated by cholecystectomy-induced increased synthesis of bile acids [39], the continuous circulation of bile acids, and resultant increased exposure of hepatic tissues to bile acids. This may lead to lipid breakdown (through increased TGR5-induced mitochondrial respiration in hepatic and enteroendocrine cells), particularly in the liver [10, 40]. In healthy individuals, bile acid levels increase after meal ingestion as the gallbladder contracts and in turn downregulate their own synthesis [6, 41]. However, when there is continuous circulation of bile acids (as is the case after cholecystectomy), normal negative feedback mechanisms may be disrupted, hence further propagating the stimulation of TGR5 and subsequent downstream metabolic mechanisms that may result in lower hepatic fat. These findings also support the concept that therapeutics that target TGR5 may have beneficial effects in decreasing hepatic fat and/or treating conditions such as NAFLD and related metabolic disturbances. TGR5 has been demonstrated to be a potential target for multiple metabolic therapeutics [42, 43]. A 2009 animal model study reported that a TGR5 agonist and semi-synthetic bile acid derivative (specifically, INT-777) was effective in decreasing hepatic steatosis and body weight gain, promoting increased GLP-1 secretion and energy expenditure in mice with high-fat diet-induced diabesity [40]. A 2019 study also found that a TGR5 agonist (specifically, RDX8490) decreased hepatic fat and

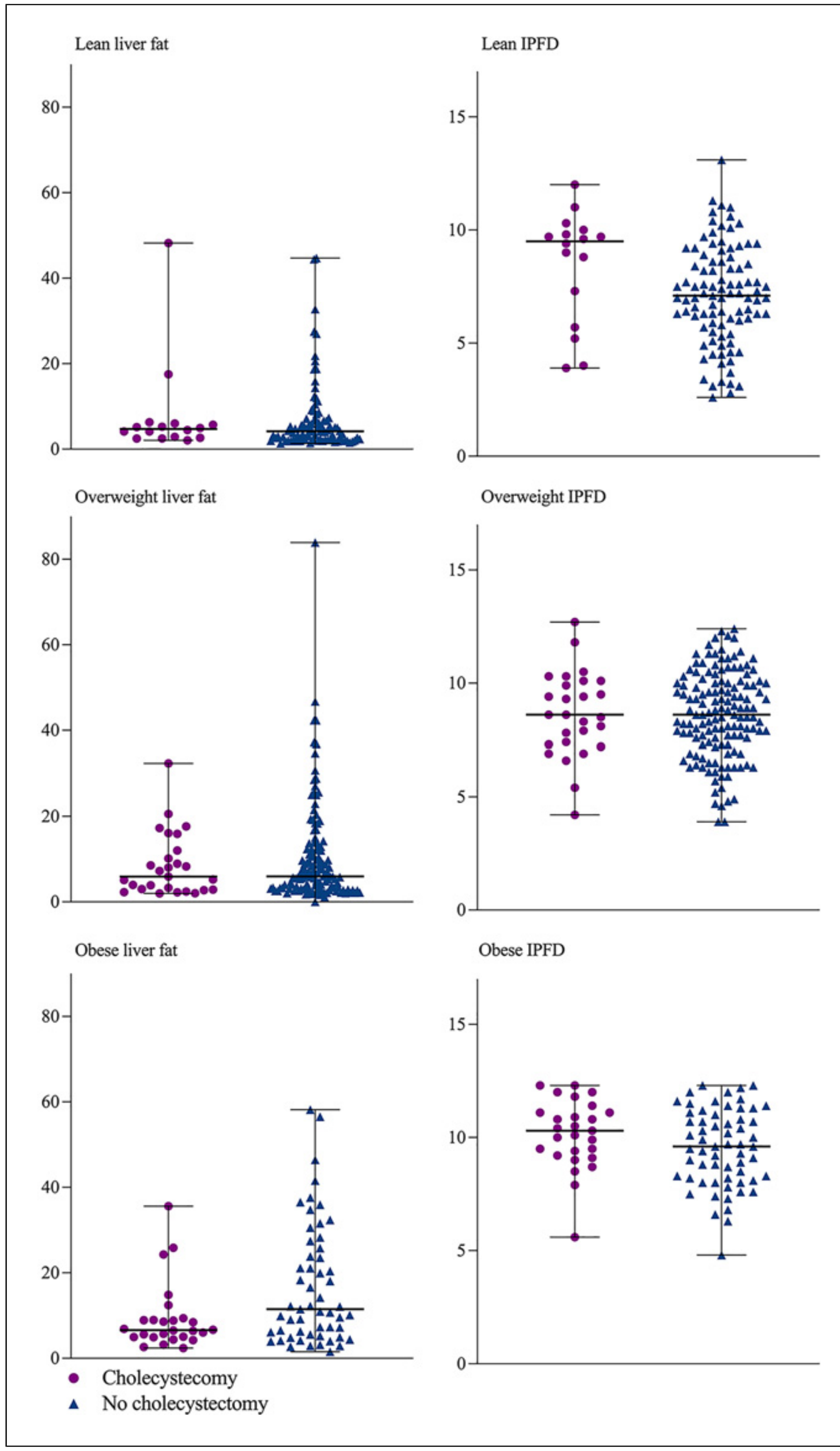

Fig. 2. Ectopic fat of participants with and without cholecystectomy, stratified by BMI groups. Scatter plots are from unadjusted analyses. IPFD, intrapancreatic fat deposition.

improved insulin sensitivity in mice fed a Western high-fat diet [44]. Since the TGR5 receptor itself was only discovered in 2002 [45], studies on its relevance as a pharmacological target remain few. Further translational studies are warranted to investigate these potential treatments with a view to developing TGR5-

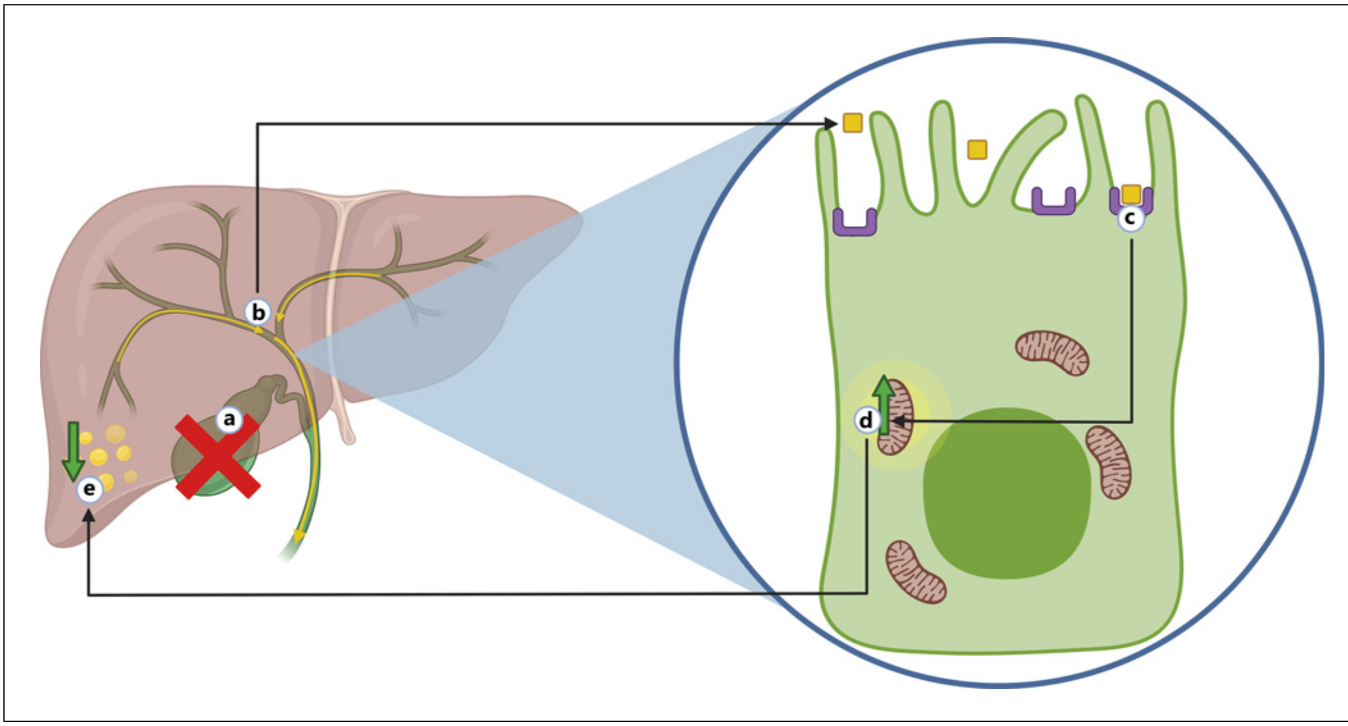

Fig. 3. Proposed mechanism by which cholecystectomy is linked to decreased hepatic fat. Cholecystectomy (**a**) leads to the continuous circulation of bile acids and increased exposure of the liver to bile acids (**b**); on certain liver cells (such as cholangiocytes) bile acids bind to TGR5 receptors (**c**), which increases mitochondrial respiration (**d**) and energy expenditure, leading to a decrease in liver fat (**e**) (figure created with BioRender.com).

targeted therapeutic interventions that decrease hepatic fat and hence can treat steatotic liver disease. It is worth noting that a comprehensive covariate adjustment was carried out in the present study (including accounting for both fasting plasma glucose and fasting insulin), which helps minimize the confounding effect of other downstream derangements in metabolism. Further, during calculation of LDL-C (which was included as a covariate in the most-adjusted model analyses), we used the Sampson equation. This 2020 formula has been shown to have higher accuracy than other more commonly used equations such as the Friedewald and Martin Hopkins formulas [46–48] and therefore strengthened the novelty of the present study.

On multivariable regression, we found significant associations of cholecystectomy with BMI, highlighting the importance of BMI as a confounding factor in associations between cholecystectomy and ectopic fat. This is crucial as many previous studies did not include BMI as a covariate. We also went one step further and conducted subgroup analyses stratified by BMI group, after which a significant association only persisted in the obese group. This may be due to different metabolic factors that are unique to individuals with obesity. Insulin resistance, hyperglycemia, and diabetes are common in people with obesity, so the metabolically beneficial effects of TGR5 stimulation could be especially marked in this group and contribute to the lower hepatic fat found by our study. This is supported by the characteristics of the obese group in the present study, which had a median fasting plasma glucose of 99.0 mg/dL. This is very close to the borderline for hyperglycemia and 57.5% of this group had either diabetes or prediabetes [49]. Since stimulation of TGR5 has been shown to decrease hepatic fat in obese mice fed high-fat diets [40], these may be models with features similar to the metabolic processes occurring in people with obesity. This further eludes to the effect of TGR5 increasing energy expenditure and decreasing fat stores with both being more pronounced in this group. Another explanation for our findings could be related to the increased risk of complications for people with obesity when undergoing surgical procedures such as cholecystectomy. Likely, due to low-grade systemic inflammation and associated comorbidities such as poor glucose control, people with obesity have higher rates of many perioperative complications [50–52]. Longer healing times or complications could result in decreased caloric intake during the recovery period and subsequent decrease in hepatic fat. Although we do not recommend cholecystectomy being provided to people with obesity for the purpose of reducing hepatic fat, the results of the present study could be factored into clinical decision-making and risk-benefit assessment of whether a patient with obesity should undergo cholecystectomy.

Another novel aspect of the present study is that it investigated the association between cholecystectomy and IPFD (using the gold-standard method for noninvasive IPFD quantification) and found a significant association on unadjusted analysis. However, after adjustment for covariates, no significant association was observed in any model. This indicates that cholecystectomy does not relate to IPFD and, in contrast with the significant association between cholecystectomy and hepatic fat, highlights the different metabolic relationships that the pancreas and liver have with the gallbladder. Unlike the liver, after cholecystectomy the pancreas is unlikely to undergo increased exposure to bile acids and, while bile acids can affect downstream triglyceride metabolism through the TGR5 receptor [40], they do not have direct physiologic action on the pancreas.

There are several limitations to this study that should be described. Since the present study was cross-sectional, we are unable to make conclusions about changes of ectopic fat before and after cholecystectomy at different periods of time or draw inferences about causation between cholecystectomy and lower hepatic fat. Associations between cholecystectomy and ectopic fat may be time-dependent as a case-control study found that the hepatic fat of patients who received cholecystectomy increased by 7%, 2 years after cholecystectomy, in comparison with baseline [19]. However, a 2013 study reported that, while cholecystectomy was significantly associated with NAFLD, the timing of the cholecystectomy was not [12]. Prospective longitudinal studies will be necessary to investigate temporal changes in ectopic fat and any causative associations between cholecystectomy and ectopic fat, especially over the years immediately following the procedure (as some individuals may gain weight during this period) [53]. Second, liver biopsy was not used for assessing hepatic fat content in the present study. Such an invasive procedure would not be feasible nor ethical in our study. Instead, we used MR-based quantification – the gold-standard method for noninvasive hepatic fat and IPFD quantification [54, 55] – that is an improvement on other major studies in this area that used ultrasound-based methods [12, 17]. Third, antidiabetic drugs are known to influence regression of hepatic fat [56]. However, we did not collect comprehensive data on whether the participants were taking antidiabetic medications and therefore could not conduct analyses that accounted for the potential effects of these medications [57, 58]. Future studies should consider doing so to more robustly characterize the association between cholecystectomy and ectopic fat [59, 60]. Fourth, there are many different indications for cholecystectomy, most of which have also been linked to metabolic disturbances that may involve hepatic fat or IPFD. A prospective study of 11,200 participants found that hepatic fat was an independent risk factor for cholelithiasis (the main indication for cholecystectomy), with multivariate analysis showing that women with NAFLD had an associated relative risk of cholelithiasis of 1.707 (p = 0.001) but this was not statistically significant in men (p = 0.961) [61]. Additional factors specific to the procedure may have also influenced results, such as whether it was an open or laparoscopic cholecystectomy, whether there were any complications, or whether individuals changed their dietary habits (e.g., portion sizes, meal timings, macronutrient composition) after the surgery [62, 63]. Further studies should investigate whether any of these factors or indications for cholecystectomy affect the studied associations. Last, regarding the distribution of patients undergoing cholecystectomy in New Zealand, a 2023 national cohort prospective study of 1,171 patients undergoing cholecystectomy from across the country identified that, of the patients included, 143 (12.3%) had BMIs within the normal range, 256 (22.1%) were overweight, 371 (32.0%) were obese, 142 (12.3%) had severe obesity, and 6 (0.5%) were underweight; the remainder were unknown or did not have available data [64]. This BMI distribution appears to differ slightly from that of the participants in the present study [65–70]. Future studies should align their sample more closely with the BMI distribution of people undergoing cholecystectomy in the general population, ensuring that a representative proportion of people with obesity are included.

In conclusion, the present study found a significant negative association of cholecystectomy with hepatic fat in adults with obesity. Also, it investigated the link between cholecystectomy and IPFD, finding no significant association. These highlight the different metabolic effects of cholecystectomy on the liver and pancreas as metabolically distinct ectopic fat depots. Considering the increasing frequency of cholecystectomy, and little acknowledgment in clinical practice of its potential long-term metabolic effects, longitudinal studies should be prioritized to investigate the effect of cholecystectomy on ectopic fat over time.

Statement of Ethics

This study involved four individual cohorts, each approved by the Health and Disability Ethics Committee (13/STH/182, 16/STH/23, 17/NTA/172, 18/NTB/1). The study was conducted in accordance with both the Declarations of Helsinki and Istanbul. Written informed consent was provided by all participants to participate in the study and undergo imaging of the abdomen.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Study concept: M.S.P.; participant recruitment: J.K., I.R.S.-B., and S.P.; imaging data acquisition: L.S.-H. and J.K.; statistical analysis and preparation of initial draft: L.S.H.; critically reviewing and revising the manuscript for intellectual content: J.K., I.R.S.-B., S.P., and M.S.P. M.S.P. is the guarantor of this work.

Data Availability Statement

The anonymized data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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