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ORIGINAL RESEARCH

Relationship of Serum Bile Acids with Fat Deposition in the Pancreas, Liver, and Skeletal Muscle

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Introduction: Ectopic fat deposition is well appreciated as a key contributor to digestive and liver diseases. Bile acids have emerged as pleiotropic signalling molecules involved in numerous metabolic pathways. The aim was to study the associations of bile acids with ectopic fat deposition and lipid panel.

Methods: A single 3.0 Tesla magnetic resonance imaging scanner was employed to measure fat deposition in the pancreas, liver, and skeletal muscle in 76 adults. Blood samples were drawn to determine total bile acids and lipid panel. Linear regression analyses were run, taking into account age, sex, body mass index, and other covariates.

Results: The studied ectopic fat depots were not significantly associated with levels of total bile acids in serum. Total bile acids were significantly associated high-density lipoprotein cholesterol – consistently in both the unadjusted ($p = 0.018$) and all adjusted models ($p = 0.012$ in the most adjusted model). Low-density lipoprotein cholesterol, total cholesterol, and triglycerides were not significantly associated with total bile acids in both the unadjusted and all adjusted models.

Conclusion: Fat deposition in the pancreas, liver, and skeletal muscle is not associated with circulating levels of total bile acids. High-density lipoprotein cholesterol is the only component of lipid panel that is associated with total bile acids.

Keywords: bile acids, cholesterol, triglycerides, intra-pancreatic fat, skeletal muscle fat, intra-hepatic fat

Introduction

Gastrointestinal, pancreatic, and liver diseases have a considerable global burden, which is projected to further increase.[1–3] As complex, multi-faceted, and non-communicable diseases, their development often involves metabolic derangements and low-grade chronic inflammation.[4,5] Excess fat deposition in the pancreas, liver, and skeletal muscle are exemplar metabolic derangements that occur in individuals with pancreatic and liver diseases.[6–11] Further, ectopic deposition not infrequently plays an important role in the development of non-communicable diseases beyond the digestive system.[12–14]

Bile acids are amphipathic steroid molecules synthesised in the liver from cholesterol and excreted into bile.[15] Studies into the beneficial effects of bariatric surgery consistently showed the importance of bile acid signaling in resultant metabolic improvements.[16] There is growing appreciation that bile acids have the potential in the treatment of digestive and liver disorders, as signaling molecules acting through the Takeda G-protein receptor 5 and farnesoid X receptor.[17] This is in addition to their classic role as an emulsifier of lipids and fat-soluble vitamins in the gastrointestinal tract.[16] Given the detergent properties of bile acids, their overload can be harmful (eg, cholestatic liver disease) because of activation of pro-inflammatory and oxidative stress pathways.[17] High circulating levels of total bile acids were reported in people with fatty liver disease.[18] Changes in bile acids metabolism in people with excess deposition of fat in the pancreas or skeletal muscle have been sparsely investigated.[4,19]

The primary aim was to investigate the associations between total bile acids and fat deposition in the pancreas, liver, and skeletal muscle. The secondary aim was to study the associations between total bile acids and lipid panel.

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Methods

Study Design

The present cross-sectional study was part of the ARIES project.[20–23] Adults with a history of acute pancreatitis who gave informed consent to undergo follow-up with a view to identifying metabolic derangements after hospitalisation were eligible for the project. The exclusion criteria were detailed elsewhere.[24–26]

Measurement of Serum Bile Acids and Lipid Panel

The tertiary referral medical laboratory of Auckland City Hospital (Auckland, New Zealand) measured total bile acids and the lipid panel, which included total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides.[27] Serum bile acids were measured in serum (derived from venous blood samples collected in a fasted state) and reported in umol/L. LDL cholesterol was calculated using the 2020 Sampson formula.[28]

Measurement of Ectopic Fat

Abdominal magnetic resonance images at 3.0 Tesla were acquired specifically for the purpose of the ARIES project, using the same MAGNETOM Skyra scanner (Siemens, Erlangen, Germany) for all study participants. Two assessors post-processed the mages and measured intra-pancreatic fat deposition (IPFD) and skeletal muscle fat deposition (SMFD) independently. Intra-hepatic fat deposition (IHFD) was measured by a single assessor. IPFD represented the average of intra-organ fat in two slices with the best visualisation of the whole pancreas in a series of 5 mm slices.[29] A single axial slice at the lower endplate of L3 vertebra was used to measure intra-skeletal fat area of erector spinae muscles on T1-weighted images.[30] Single-voxel spectroscopy (with no correction for relaxation effects) was used to measure intra-hepatic fat deposition, as described elsewhere.[30,31]

Measurement of Covariates

Data on smoking status and alcohol consumption were collected at the time of magnetic resonance image acquisition in the form of an online questionnaire.[32–34] Weight and body mass index (BMI) were measured according to the standard protocol.[35] Glycated haemoglobin was measered at the tertiary referral medical laboratory of Auckland City Hospital and reported in mmol/mol.

Statistical Analysis

Data were analysed statistically with the use of SPSS (SPSS Inc., Chicago, IL, USA). Continuous and categorical variables were presented as median (and interquartile range) and frequency (and percentage), respectively. If the normality assumption was not met, data were log-transformed. Two tiers of linear regression analyses were conducted. The first analysis investigated the associations of serum bile acids with IPFD, IHFD, and SMFD. A total of 4 models were built as follows: model 1 was the unadjusted model; model 2 was adjusted for age, sex, and ethnicity; model 3 was adjusted for age, sex, ethnicity, and BMI; and model 4 was adjusted for age, sex, ethnicity, BMI, glycated haemoglobin, and triglycerides. The second analysis investigated the associations of serum bile acids with the components of lipid panel. The same statistical models were built, with the exception of model 4 – triglycerides were omitted to avoid collinearity. Serum bile acids were used as the dependent variable in all the above analyses. Findings were reported as β coefficients (ie, the degree of change in the dependent variable for every 1-unit of change in the independent variable), along with 95% confidence intervals and p values.

Results

Study Population

A total of 76 participants met the eligibility criteria. Their detailed characteristics are presented in Table 1. The mean (± SE) value of serum bile acids was 8.6 umol/L (±0.6 umol/L). The inter-assessor concordance of IPFD measurements was 0.968 (95% confidence intervals, 0.951–0.981) whereas the inter-assessor concordance of SMFD measurements was 0.984 (95% confidence intervals, 0.975–0.990) (Figure 1).

Table 1 Characteristics of Study Participants

Characteristic	n = 76
Age, years	57.5 (43.0–67.8)
Sex	
– Men	49 (64.5%)
– Women	27 (35.5%)
Ethnicity	
– European	35 (46.0%)
– Māori or Pacific Islanders	18 (23.7%)
– Asian	10 (13.2%)
– Other	13 (17.1%)
Body mass index, kg/m^2	28.3 (25.2–33.3)
Glycated haemoglobin, mmol/mol	38.0 (35.0–41.8)
Triglycerides, mmol/L	1.6 (1.1–2.5)
Heaviest alcohol consumption (g/wk)	195.0 (63.0–371.2)
Smoking status	
– Never	33 (43.4%)
– Former	27 (35.5%)
– Light (<20/d)	6 (7.9%)
– Moderate or heavy (≥20/d)	10 (13.2%)

Note: Data are presented as median and interquartile range or count frequency and percentage.

Relationship Between Serum Bile Acids and Ectopic Fat

The mean (± SE) percentages of ectopic fat depots in the study cohort were as follows: IPFD – 9.4% (± 0.2%), IHFD – 10.3% (± 1.2%), and SMFD – 15.5% (± 0.8%). There were no statistically significant associations between serum bile acids and IPFD, IHFD, and SMFD in both the unadjusted and adjusted models (Figure 2). Table 2 provides the detailed results.

Relationship Between Serum Bile Acids and Lipid Panel

The mean (± SE) levels of the components of the lipid panel were as follows: total cholesterol – 4.9 (± 0.16) mmol/L, HDL cholesterol – 1.3 (± 0.04) mmol/L, LDL cholesterol – 103.5 (± 4.7) mmol/L, and triglycerides – 2.5 (± 0.42) mmol/L. There was a statistically significant association between serum bile acids and HDL cholesterol in both the unadjusted ($p=0.018$) and all the adjusted models ($p=0.014$, $p=0.013$, and $p=0.012$ in models 2, 3, and 4, respectively). There were no statistically significant associations between serum bile acids and total cholesterol, LDL cholesterol, and triglycerides in both the unadjusted and adjusted models (Table 3).

Discussion

The present study was the first to investigate the relationship between bile acids in serum and three ectopic fat depots (IPFD, IHFD, and SMFD) in the same individuals. Measurements of IPFD and SMFD were completed by two independent assessors, with excellent concordance demonstrated. Moreover, several covariates were adjusted for in the statistical analyses, including age, sex, ethnicity, BMI, glycated haemoglobin, and triglycerides. The main finding was the absence of statistically significant associations between total bile acids and the three ectopic fat depots. At the same time, a statistically significant positive association was observed between total bile acids and HDL cholesterol, consistently across all the statistical models.

In humans, bile acids are predominantly synthesised from cholesterol (accounting for approximately a half of daily cholesterol turnover in humans), subsequently conjugated in the liver with glycine or taurine.[17] After being secreted into the duodenum, they are converted into secondary bile acids by intestinal bacteria, reabsorbed, and (mostly) recycled via the enterohepatic circulation.[36] As the transfer of HDL cholesterol to hepatocytes is physiologically a key determinant of

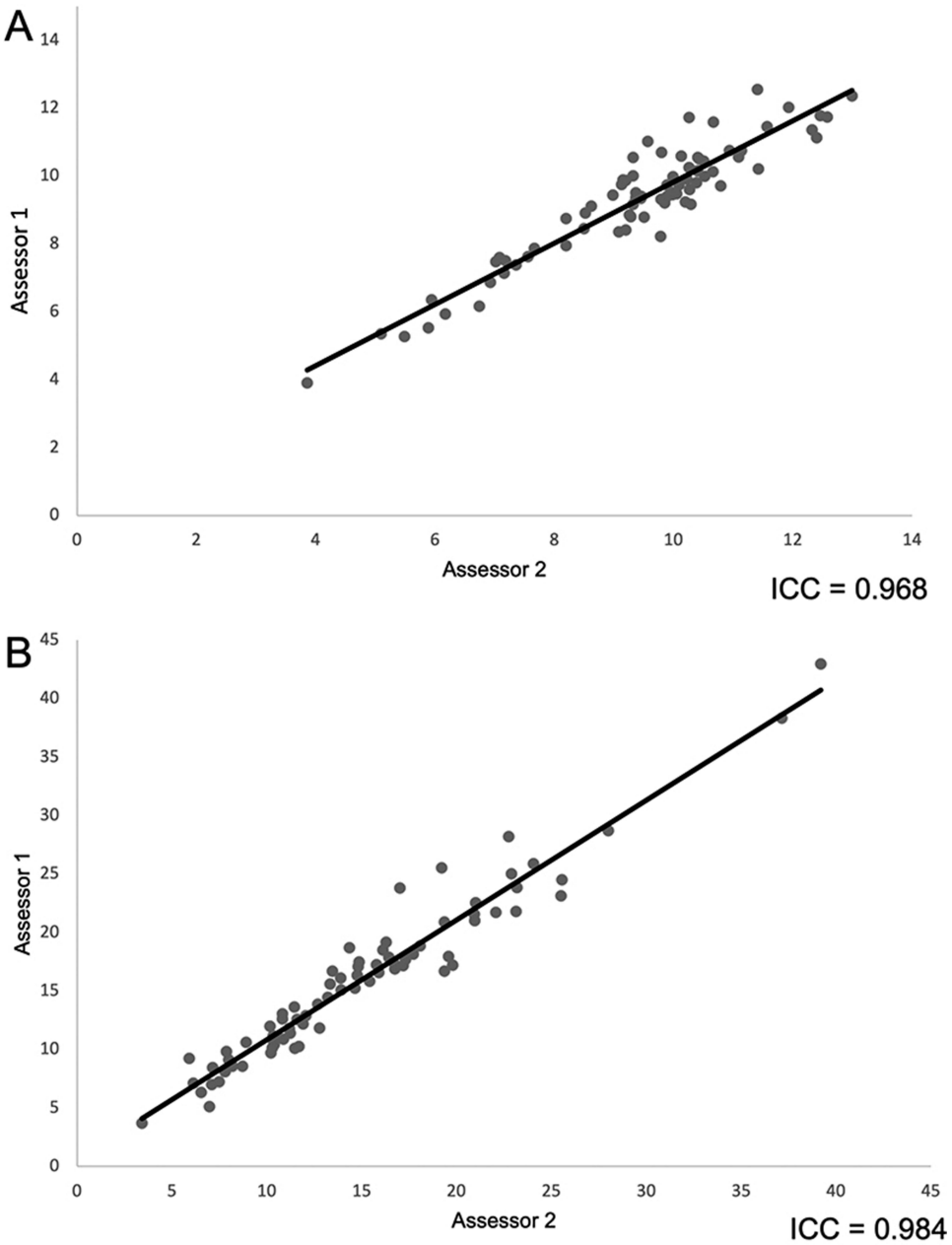

Figure 1 The concordance between two independent assessors in measuring intra-pancreatic fat deposition (**A**) and skeletal muscle fat deposition (**B**).
Abbreviation: ICC, intra-class correlation coefficient.

bile acids levels,[17,36] the presence of a significant positive association between HDL cholesterol and bile acids in the present study (observed consistently in both the unadjusted and all the adjusted models) demonstrated the internal validity of our findings. Given that decreased (not increased) levels of HDL cholesterol have clinical implications as a risk factor for cardiovascular disease, decreased levels of bile acids could be viewed as a harbinger of metabolic derangements. A 2017 COSMOS meta-analysis showed decreased HDL cholesterol strongly correlated with increased IPFD (weighted mean correlation −0.33).[19] A 2019 original COSMOS study demonstrated that the total cholesterol/HDL cholesterol ratio was significantly positively associated with IPFD, consistently across all statistical models.[27] Although no significant association between bile acids and IPFD was observed in the present study, it is conceivable that the relationship between them is intricate and involves mediation by HDL cholesterol (and possibly by gut microbiota and other mediators).

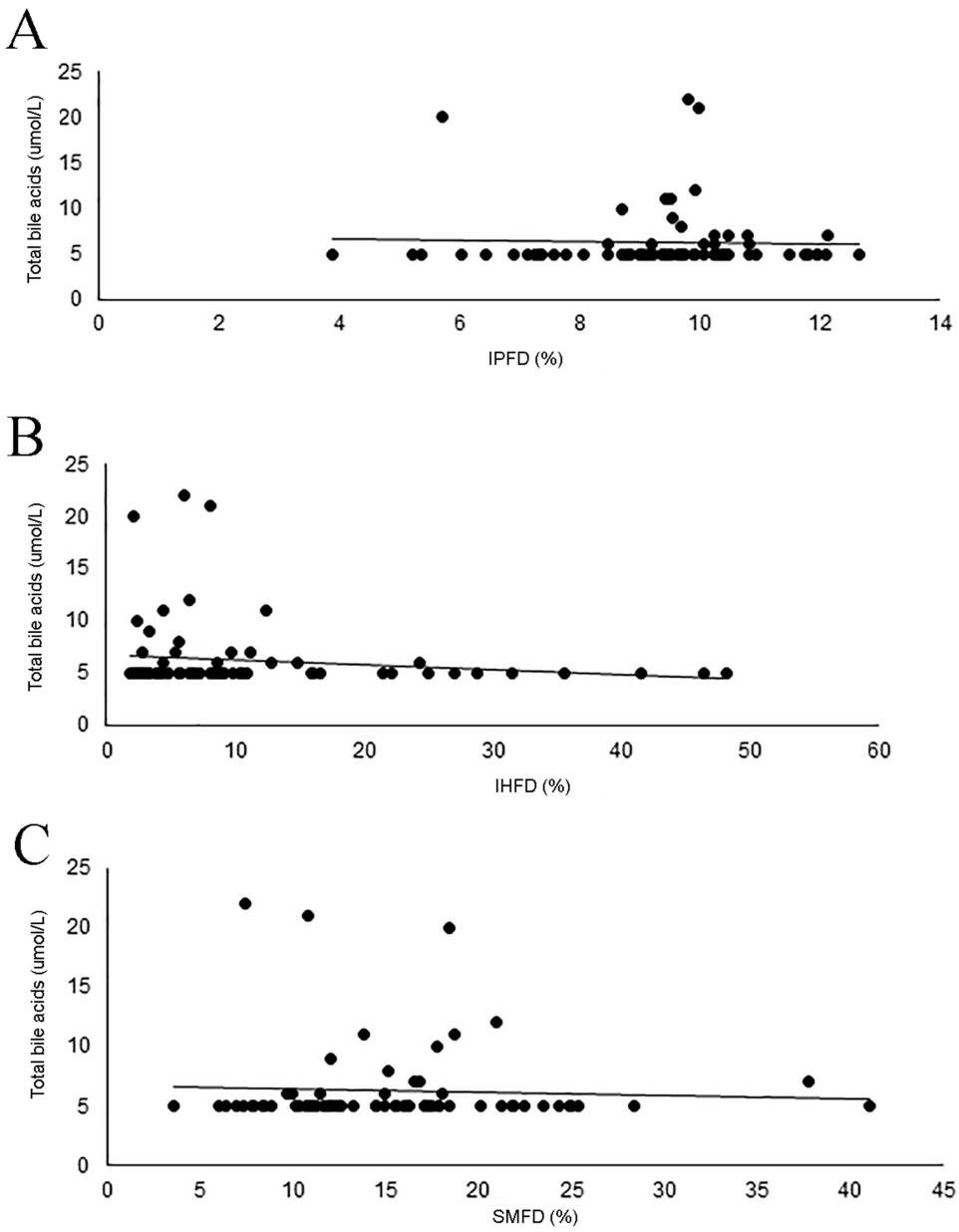

Figure 2 Associations between serum bile acids and fat deposition in the pancreas (**A**), liver (**B**), skeletal muscle (**C**).
Abbreviations: IPFD, intra-pancreatic fat deposition; IHFD, intra-hepatic fat deposition; SMFD, skeletal muscle fat deposition.

Another explanation for the lack of statistically significant association between bile acids and IPFD (as well as IHFD and SMFD) is centred on the fact that total, not individual, bile acids were investigated in the present study. As the total pool includes distinct individual compounds (primary bile acids produced via the acidic or neutral pathway with the involvement of more than dozen liver enzymes, conjugated primary bile acids, secondary bile acids, conjugated secondary bile acids) with unique and at times opposite effects,[36] a more nuanced analysis of individual bile acids and their derivatives may provide deeper insights into their relationship with ectopic fat depots.[5] Two recent untargeted metabolomics studies (both using liquid chromatography–mass spectrometry) are worth mentioning in this regard.[37,38] In one 2021 study,[37] taurodeoxycholate – a bile acid conjugate – was significantly associated with IPFD (but not IHFD). This was independent of total body fat and over covariates. In the other 2021 study,[38] sulfolithocholate – a major detoxified form of lithocholic bile acid – was significantly associated with IPFD (but not IHFD). Again, this was independent of total body fat and over covariates. Importantly, the above bile acids metabolites were not related to

Table 2 Relationship of Bile Acids with Ectopic Fat

Fat depot	Model 1				Model 2				Model 3				Model 4			
	β	95% CI		p value	β	95% CI		p value	β	95% CI		p value	β	95% CI		p value
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
IPFD (%)	0.024	−0.065	0.113	0.593	0.019	−0.064	0.103	0.646	0.031	−0.050	0.111	0.452	0.008	−0.077	0.092	0.854
IHFD (%)	0.012	−0.348	0.372	0.948	−0.039	−0.317	0.396	0.826	0.076	−0.275	0.427	0.666	−0.010	−0.371	0.351	0.956
SMFD (%)	0.020	−0.163	0.203	0.830	−0.008	−0.145	0.130	0.911	−0.017	−0.155	0.121	0.805	0.022	0.121	0.166	0.759

Notes: Model 1 = unadjusted analysis; model 2 = adjusted for age, sex, and ethnicity; model 3 = adjusted for age, sex, ethnicity, and body mass index; model 4 = adjusted for age, sex, ethnicity, body mass index, glycated haemoglobin, and triglycerides.

Abbreviations: β, β coefficient from linear regression analysis; CI, confidence interval; IPFD, intra-pancreatic fat deposition; IHFD, intra-hepatic fat deposition; SMFD, skeletal muscle fat deposition.

Table 3 Relationship of Bile Acids with the Components of Lipid Panel

Component	Model 1				Model 2				Model 3				Model 4			
	β	95% CI		p value	β	95% CI		p value	β	95% CI		p value	β	95% CI		p value
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Total cholesterol	0.269	−0.232	0.769	0.288	0.306	−0.216	0.827	0.246	0.310	−0.213	0.834	0.241	0.304	−0.237	0.844	0.266
HDL cholesterol	0.563	0.099	1.027	**0.018**	0.633	0.132	1.134	**0.014**	0.643	0.141	1.146	**0.013**	0.653	0.147	1.160	**0.012**
LDL cholesterol	0.238	−0.113	0.590	0.180	0.232	−0.141	0.606	0.218	0.223	−0.154	0.599	0.241	0.146	−0.250	0.541	0.464
Triglycerides	−0.071	−0.262	0.121	0.465	−0.070	−0.284	0.144	0.517	−0.069	−0.284	0.146	0.523	−0.069	−0.286	0.147	0.525

Notes: Model 1 = unadjusted analysis; model 2 = adjusted for age, sex, and ethnicity; model 3 = adjusted for age, sex, ethnicity, and body mass index; model 4 = adjusted for age, sex, ethnicity, body mass index, and glycated haemoglobin. Statistically significant p values (<0.05) are shown in bold.

Abbreviations: β, β coefficient from linear regression analysis; CI, confidence interval; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein.

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diabetes as either people with diabetes were excluded or fasting plasma glucose of study participants was statistically accounted for.[37,38] The above findings suggest that there are likely to be differences in metabolomic signatures between ectopic fat depots and it is likely that this includes individual bile acids and their derivatives.[4,5]

Limitations of this study include its cross-sectional design, as no causal inference can be made from it.[39–42] Longitudinal studies are now warranted to investigate temporal changes in bile acids and ectopic fat deposition in order to establish causality.[43,44] As the study was the first to investigate total bile acids in the context of IPFD and SMFD,[5] we were unable to estimate the required sample size prior to the commencement of the study. However, the presented findings will facilitate power calculation in future research. Also, the present study included people with a history of acute pancreatitis,[45,46] as the project focusing on this population had received funding.[47,48] Nevertheless, a complete clinical resolution was observed in all study participants at the time of magnetic resonance image acquisition.[20–23] The protocol to measure IHFD in the present study might have been suboptimal as we did not use T1 and T2 correction of water signal and lipid signal from single echo magnetic resonance spectroscopy data. Future studies may need to do this with individually measured relaxation times (especially, if individuals with pancreatic fibrosis or iron overload are included). Last, bile acids were measured in serum, which is known to represent only a fraction of bile acids in the body.[5] Moreover, the gut microbiota was not studied in the present study. The microbiota is known to transform bile acids (by means of deconjugation, dehydroxylation, epimerisation, and oxidation) and this may contribute to metabolic derangements.[49,50] More comprehensive studies are warranted to investigate the role of bile acids in the context of ectopic fat deposition and the influence of gut dysbiosis.

In conclusion, the present study demonstrated that reduced levels of HDL cholesterol are significantly associated with decreased circulating levels of total bile acids. This was independent of BMI, glycated haemoglobin, and other covariates. By contrast, other component of the lipid panel were not significantly associated with levels of total bile acids. Also, there were no significant associations of total bile acids with IPFD, IHFD, and SMFD (after accounting for BMI, glycated haemoglobin, and other covariates).

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the approved by the Health and Disability Ethics Committee (13/STH/182).

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Disclosure

The authors declare no conflict of interest.

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