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Original Article

Lipid metabolism in patients with chronic hyperglycemia after an episode of acute pancreatitis

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ABSTRACT

Background: The importance of dyslipidemia is well recognized in the context of both risk factor for acute pancreatitis and prognostic factor for its in-hospital outcomes. With a growing appreciation of post-pancreatitis diabetes mellitus, there is a need to catalogue changes in lipid metabolism after hospitalization due to an acute pancreatitis attack and their associations with glucose metabolism.
Objective: To investigate lipid metabolism in patients with impaired glucose homeostasis following acute pancreatitis.
Methods: There were two study groups: newly diagnosed chronic hyperglycemia or normoglycemia after acute pancreatitis. During the fasting state, venous blood samples were collected to analyse markers of lipid metabolism (triglycerides, glycerol, low density lipoprotein, high density lipoprotein, total cholesterol, free fatty acids, and apolipoprotein-B) and glucose metabolism (HbA1c, insulin, index of adipose tissue insulin resistance (Adipo-IR), and HOMA-IR). Binary logistic and linear regression analyses were conducted, and potential confounders were adjusted for in multivariate analyses.
Results: The study included 64 patients with normoglycemia and 19 - with chronic hyperglycemia. Glycerol was significantly associated with the development of chronic hyperglycemia in both unadjusted ($p = 0.02$) and adjusted ($p = 0.006$) models. Triglycerides were significantly associated with the development of chronic hyperglycemia in adjusted ($p = 0.019$) model. Other markers of lipid metabolism did not differ significantly between the two groups. None of the markers of lipid metabolism was significantly associated with Adipo-IR or HOMA-IR.
Conclusion: Overall, patients with chronic hyperglycemia after acute pancreatitis appear to have a lipid profile indicative of an up-regulation of lipolysis, which is not significantly affected by either general or adipose tissue-specific insulin resistance.

1. Introduction

Acute pancreatitis (AP) is the most common disease of the exocrine pancreas, developing in a considerable number of patients with disorders of lipid metabolism, and is a condition associated with a substantial number of cardiovascular comorbidities [1,2]. Also, significantly elevated triglycerides have been established as both a risk factor for AP and its prognostic factor [3–8]. Hypertriglyceridemia has long been regarded as the third most common aetiology of AP, accounting for up to 12% of all AP cases [9–11]. The relationship between hypertriglyceridemia and AP is receiving growing attention, with increased research into dyslipidemia during the course of AP [12,13]. In line with the earlier literature, a number of recent clinical studies have shown that elevated serum triglycerides levels during the course of AP are independently associated with acute kidney injury, acute respiratory distress syndrome, and a longer length of hospital stay [5,14–18]. More importantly, hypertriglyceridemia during the course of AP, regardless of the underlying aetiology of AP, has been associated with persistent organ failure [19] - a major determinant of mortality in AP [20,21].

Glucoregulatory disturbances after pancreatitis have typically been investigated in the context of chronic pancreatitis, where derangements in glucose metabolism and diabetes mellitus are considered a major late sequela [22,23]. By contrast, glucose metabolism after AP has received less attention. Although AP has classically been considered a self-limiting, reversible disease, there is an expanding body of evidence that demonstrates the significance of new glucoregulatory disturbances after AP. In

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particular, a recent comprehensive meta-analysis showed that new onset prediabetes or diabetes mellitus develops in nearly 40% of patients after AP, challenging the widely accepted view that hyperglycemia during AP is a transient phenomenon that completely resolves [24]. There is a growing appreciation of diabetes after disease of the exocrine pancreas, with the American Diabetes Association and World Health Organisation identifying it as a stand-alone entity given its unique clinical presentation, pathophysiology, and characteristics [24–27]. Despite the closely intertwined pathways regulating glucose and lipid metabolism, alongside the common occurrence of derangements in serum lipids observed during the course of AP, there is a lack of clinical studies investigating lipid metabolism following an attack of AP.

With respect to disturbances of lipid metabolism in AP, the first reports of an association between hyperlipidemia and AP date back to 19th century [28], when this was considered to be a rare finding during the course of AP. Later publications, however, indicated that dyslipidemia in patients with AP is a common occurrence, and has since been thoroughly investigated [10,11,18,19,29,30]. However, almost invariably, changes in lipid metabolism have been investigated during the course of AP, with a paucity of studies focusing on lipid metabolism after hospital discharge. In 1980s, Guzman et al. [31] was the first to report on elevated serum triglycerides levels following resolution of the acute disease, providing new evidence for a decreased clearance of triglycerides from the circulation following an ingested fat load. Durrington et al. [32] confirmed this observation, with findings of elevated serum triglycerides concentrations in 42% of their cohort of patients after an episode of pancreatitis. Strikingly, no further clinical study on lipid metabolism after AP was published in the ensuing 3 decades.

This study aimed to provide modern insights into the complex pattern of metabolism after AP, specifically by investigating the association between parameters of lipid and glucose metabolism.

2. Methods

2.1. Study protocol

This study was a cross-sectional follow up of patients with AP admitted to Auckland City Hospital (Auckland, New Zealand).

Individuals were considered eligible if they: (1) Had a diagnosis of AP based on international guidelines [33]; (2) Were at least 18 years of age; (3) Lived in Auckland at the time of the study; and (4) Provided informed consent. Eligible individuals were telephoned and invited to participate in the study. Certified phlebotomists conducted home visits for those patients unable to attend the hospital for data collection.

Individuals were not eligible to participate in the study if they had: (1) A current, or previous, diagnosis of chronic pancreatitis; (2) Post-endoscopic retrograde cholangiography pancreatitis; (3) An intra-operative diagnosis of pancreatitis; (4) A diagnosed malignancy; (5) Pre-existing prediabetes or type 2 diabetes mellitus (T2DM); or (6) Been pregnant.

Participants were categorized into two study groups in line with the American Diabetes Association guidelines [34] and based on glycated haemoglobin (HbA1c) levels, as this marker reflects blood glucose levels over a 12-week interval and is not affected by acute illnesses [35]. The groups were: (1) Normoglycemia after AP [NAP], defined as HbA1c $<$39 mmol/mol, and (2) chronic hyperglycemia after AP [CHAP], defined as HbA1c $\geq$39 mmol/mol.

The study protocol was approved by the Health and Disability Ethics Committee (13/STH/182) and the Auckland District Health Board (A+ 6139).

2.2. Laboratory assays

All study participants were required to fast for at least eight hours prior to blood collection. Blood for fasting blood glucose, HbA1c, insulin, high density lipoprotein (HDL), low density lipoprotein (LDL), and free fatty acids (FFA) was collected by a certified phlebotomist at LabPlus, the International Accreditation New Zealand accredited medical laboratory, at Auckland City Hospital.

Fasting blood glucose was measured using an enzymatic colourimetric assay (© 2015 F. Hoffmann-La Roche Ltd.). HbA1c was analysed using the boronate affinity chromatography assay (© 2015 Roche Products (New Zealand) Ltd and Roche Diagnostics NZ Ltd.). Insulin was measured using the Chemiluminescence sandwich immunoassay (© 2015 Roche Products (New Zealand) Ltd and Roche Diagnostics NZ Ltd.). LDL, HDL, FFA, adiponectin, and apolipoprotein-B were measured using commercially available enzyme-linked immunosorbent assay kits, according to the manufacturers' instructions. Rayto Microplate Reader (V-2100C, Santa Fe, Granada, Spain), with an absorbance of 405–630 nm, was used to obtain results. Glycerol and triglycerides were measured using the GM7 Micro-Stat (Analox Instruments Inc., Lunenberg, MA, USA). Fasting ketones were measured using a standard finger prick.

2.3. Calculations

Homeostasis model assessment of insulin resistance (HOMA-IR) calculation: glucose (mmol/L) and insulin (ρmol/L) values were entered into the validated HOMA2 calculator (HOMA2 v2.2.3 © β, Diabetes Trials Unit, University of Oxford) [36] to determine a measure of insulin resistance for all study participants.

Adipose tissue insulin resistance (Adipo-IR) calculation: insulin (ρmol/L) and FFA (μM) values were entered into the following equation to determine an extensively validated index of adipose tissue insulin resistance [37–39]:

$$\text{Adipo-IR} = \text{insulin} \times \text{FFA}$$

2.4. Definitions of confounding variables

Patient-related Variables

- Body Mass Index (BMI) (kg/m^2): height (cm) was measured using a stadiometer (Health o meter® Professional, 2013, © Pelstar, LLC, IL, USA), with study participants asked to remove shoes and head attire. For weight (kg) measurements, study participants were asked to remove shoes, jackets, belts and watches, along with emptying their pockets of any items before measurement.
- Body fat percentage (BFP): the BodyMetrix system was used to measure BFP (Bodymetrix™ system ©, 2010, Intelametrix, Livermore, CA, USA). Repeated measurements were taken from three sites for each study participant – chest, waist, and thigh were measured for male participants, while waist, hip, and tricep were measured for female participants, as according to the user manual.
- Smoking: classified as 'yes' or 'no', based on a questionnaire asking patients if they smoked cigarettes or tobacco products on a daily basis.

Pancreatitis-related Variables

- Duration (months): defined as the time from the first hospital admission due to AP to the time of recruitment into this study.

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