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Interleukin-6 is associated with chronic hyperglycemia and insulin resistance in patients after acute pancreatitis

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ABSTRACT

Background: Diabetes is a pervasive disease, with a mounting prevalence and burden on health care systems. Under this collective term of diabetes falls diabetes after diseases of the exocrine pancreas, a condition which was previously under-recognised and often mislabeled as type 2 diabetes mellitus and is now increasingly acknowledged as a stand-alone entity. However, there is a paucity of clinical studies investigating the underlying pathophysiology of diabetes after acute pancreatitis, the most frequent disease of the pancreas. This study aimed to investigate the role of adipocytokines in glucose metabolism after acute pancreatitis.

Methods: This was a cross-sectional follow-up study of a patient cohort diagnosed with acute pancreatitis. Fasting venous blood samples were collected to analyse markers of glucose metabolism (fasting blood glucose, haemoglobin A1c, homeostasis model assessment (HOMA-IR) as a measure of insulin resistance) and adypocytokines (adiponectin, interleukin-6, leptin, monocyte chemoattractant protein-1, retinol binding protein-4, resistin, and tumor necrosis factor-α). Participants were categorized into two groups: normoglycemia after acute pancreatitis and chronic hyperglycemia after acute pancreatitis (CHAP). Binary logistic regression and linear regression analyses were used to investigate the association between each of the adipocytokines and markers of glucose metabolism. Potential confounders were adjusted for in multivariate analyses.

Results: A total of 83 patients with acute pancreatitis were included, of whom 19 developed CHAP. Interleukin-6 was significantly associated with CHAP in both unadjusted and adjusted models ($p = 0.030$ and $p = 0.018$, respectively). Further, it was also significantly associated with HOMA-IR in both unadjusted and adjusted models ($p = 0.029$ and $p = 0.037$, respectively). Other adipocytokines were not significantly associated with markers of glucose metabolism.

Conclusion: Interleukin-6 appears to be implicated in the development of chronic hyperglycemia and insulin resistance in patients after acute pancreatitis. It may become a potential target in the prevention and early treatment of diabetes after diseases of the exocrine pancreas.

1. Introduction

Diabetes is one of the most common chronic diseases worldwide. Whilst the prevalence of diabetes continues to climb, with an estimated 422 million adults affected worldwide in 2014, compared to the 108 million adults in 1980 [1], this debilitating disease imparts a significant economic burden on healthcare systems [2]. Diabetes after diseases of the exocrine pancreas, classified as a form of secondary diabetes mellitus, accounts for 5–10% of diabetes within the Western population [3–5]. This estimate, to date, has largely been based on studies focusing on the development of diabetes after chronic pancreatitis or pancreatic cancer, often not including the most frequent pancreatic disease - acute pancreatitis (AP) [6], and is therefore likely an underestimation. Findings from a recent comprehensive systematic review indicate that almost 40% of patients develop newly-diagnosed prediabetes or diabetes mellitus following an episode of AP, with the risk of diabetes mellitus doubling over a period of 5 years [7]. Although there is a

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growing appreciation for diabetes secondary to pancreatic disease as a stand-alone clinical entity, the pathogenesis of this complex endocrinopathy in general, and the underlying mechanisms of chronic hyperglycemia after AP in particular, remain poorly understood [3,4,7,8]. Diabetes secondary to pancreatic diseases is clinically distinct in its features from both type 1 and type 2 diabetes mellitus, with hepatic insulin resistance occurring alongside the additional burden of chronic hyperglycemia and enhanced peripheral insulin sensitivity [5,7]. Hence, a sound understanding of the mechanisms behind chronic hyperglycemia is required to better understand derangements of glucose metabolism after AP, improve clinical management, and identify potential novel targets for prevention and treatment.

Adipocytokines are a group of biologically active molecules derived from the adipose tissue, with an increasingly recognised role in glucose metabolism and inflammatory disease states [9–12]. Adipocytokines have been implicated in various glucoregulatory processes such as insulin sensitivity, insulin secretion, and inflammation [9–12]. While the role of adipocytokines in glucose metabolism has been abundantly explored in the context of type 1 and type 2 diabetes mellitus, studies investigating the role of adipocytokines in diabetes secondary to acute pancreatitis are lacking. Although studies to date have typically investigated adipocytokines as predictors of AP severity [9,13–18], a recent study highlighted a significant association between leptin and persistent hyperglycemia in AP [19]. Novel and emerging studies are now also investigating the changes in adipocytokines following nutritional interventions in AP, in particular tube feeding [20,21].

We hypothesised that adipocytokines play an important role in the development of abnormal glucose metabolism after AP. The aim of this study was to investigate the association between glucose metabolism and a comprehensive panel of adipocytokines in a cohort of patients after AP, without prior diagnosis of prediabetes or diabetes mellitus.

2. Methods

2.1. Study design

This was a cross-sectional follow up study of patients admitted to Auckland City Hospital (Auckland, New Zealand) with AP. The study protocol was approved by the Health and Disability Ethics Committee (13/STH/182) and the Auckland District Health Board Institution (A+ 6139).

2.2. Study population

Individuals were eligible if they had a diagnosis of AP based on recent guidelines [22]; were at least 18 years of age; lived in Auckland at the time of the study; and provided informed consent. Eligible individuals were then telephoned and invited to participate in this study. For those unable to attend appointments for data collection at the hospital, home visits by a certified phlebotomist were arranged.

Individuals were not considered eligible if they currently had or were previously diagnosed with chronic pancreatitis, post-endoscopic retrograde cholangiography pancreatitis, intra-operative diagnosis of pancreatitis, pregnancy during AP or afterwards, malignancy, and pre-existing prediabetes or diabetes mellitus.

2.3. Study groups

There were two study groups, determined based on the most recent American Diabetes Association definitions [23]: normoglycemic following AP (NAP) and chronic hyperglycemia following AP (CHAP). NAP was defined as haemoglobin A1c (HbA1c) <39 mmol/mol, while CHAP was defined as Hba1c ≥39 mmol/mol.

2.4. Laboratory assays

All study participants were required to fast for at least eight hours prior to blood collection. Blood tests for insulin, HbA1c and fasting blood glucose (FBG) were conducted at the International Accreditation New Zealand accredited medical laboratory, LabPlus, at Auckland City Hospital. Insulin was measured using the Chemiluminescence sandwich immunoassay (Roche Products (New Zealand) Ltd and Roche Diagnostics NZ Ltd.) HbA1c was analysed using the boronate affinity chromatography assay (Roche Products (New Zealand) Ltd and Roche Diagnostics NZ Ltd.). Fasting blood glucose was measured using an enzymatic colourimetric assay (F. Hoffmann-La Roche Ltd.).

Interleukin-6 (IL-6), Monocyte Chemoattractant Protein-1 (MCP-1), leptin, and Tumor Necrosis Factor-α (TNF-α) were determined using the MILLIPLEX® MAP Human metabolic magnetic bead panel based on the Luminex xMAP® (Luminex Corporation, Austin, Texas, USA). Results were quantified (ng/ml) based on fluorescent receptor signals recorded by the Luminex xPONENT® software (MILLIPLEX® Analyst 5.1). All assays were performed as indicated in the user's manuals. Adiponectin, Retinol Binding Protein 4 (RBP4), and resistin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit, and according to the supplier's instructions. Rayto Microplate Reader (V-2100C, Santa Fe, Granada, Spain), with an absorbance of 405–630 nm, was used to obtain the results.

Glucose (mmol/l) and insulin (pmol/l) values were entered into the validated HOMA2 calculator (HOMA2 v2.2.3, Diabetes Trials Unit, University of Oxford) [24] to determine insulin resistance for all patients.

2.5. Definition of confounders

Body mass index (BMI) (kg/m^2): was determined using a stadiometer. Study participants were asked to remove shoes and any head attire for height measurements (cm). Shoes, jackets, belts, and watches were removed and participants were asked to empty pockets of any items before weight measurements (kg).

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

Recurrence: individuals were considered to have recurrent AP if admitted with one or more episodes of confirmed AP since their first hospital admission with AP to the time of this study.

Severity: was determined based on recent international classifications [25].

Smoking: was recorded as ‘yes’ or ‘no’, as determined by a questionnaire which asked patients if they smoked cigarettes or tobacco products on a daily basis.

2.6. Statistical analyses

All statistical analyses were performed using SPSS 23.0 for Windows (IBM Corp). The Mann-Whitney *U* test and Chi-square test were used to determine differences in baseline characteristics between participants with CHAP and those with NAP, for continuous and categorical variables, respectively. Data were presented as median and interquartile ranges (IQR) or count frequencies.

Binary logistic regression, having met all assumptions, was used to investigate the association between each adipocytokine and

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