Leptin Is Associated With Persistence of Hyperglycemia in Acute Pancreatitis

A Prospective Clinical Study

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INTRODUCTION

Emerging evidence suggests that in-hospital hyperglycemia in acute and critical illness may be a useful marker for identifying those patients at higher risk of future development of diabetes mellitus.\textsuperscript{1–4} In critically ill patients, in-hospital hyperglycemia is associated with up to a 5-fold increased risk of new onset diabetes after hospital discharge with emergence of diabetes in up to half of these patients within the first year after hospital discharge.\textsuperscript{4} Acute pancreatitis (AP), an acute inflammatory disease of the pancreas and classic example of acute and critical illnesses, is a known cause of diabetes.\textsuperscript{5} In addition, recent research has shown that the pathogenesis of diabetes after AP may be more complex than being simply due to mechanical destruction of the islets of Langerhans by pancreatic necrosis.\textsuperscript{5,7}

Adipokines, a family of adipose-derived hormones, are biologically active mediators that have several important roles, including modulation of glucose metabolism.\textsuperscript{8–11} Adipokines have been shown to be involved in various metabolic processes such as insulin sensitivity, insulin secretion, appetite control, fat distribution, energy expenditure, inflammation, regulation of adipogenesis, and chemotraction of immune cells into adipose tissue.\textsuperscript{8,11} In addition, they have a potential role in the pathophysiology of hyperglycemia associated with AP. While adipokines have been previously studied in the setting of AP, this has invariably been in the context of disease severity prediction.\textsuperscript{10,12–15} To date, there have been no studies examining the relationship between adipokines and hyperglycemia early in the course of AP.

First, the aim of this study was to investigate the relationship between several adipokines (adiponectin, leptin, omentin, resistin, and visfatin) and early hyperglycemia associated with AP, drawing conclusions about its time course and the effect of specific confounders such as sex, personal history of diabetes, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, body mass index (BMI), age, and duration of symptoms to hospital admission. Second, this study aimed to consider adipokines as predictors of severity of AP through APACHE II score in patients with and without persistent hyperglycemia.

METHODS

Patient Recruitment

Consecutive adult patients (aged ≥18) with a confirmed diagnosis of AP admitted to Auckland City Hospital over a 12-month study period were considered for inclusion. Diagnosis of AP was determined by ≥2 of the following: total amylase and/or pancreatic amylase (3× the upper limit of normal), pain typical of AP, and characteristic findings of AP on computed tomography and/or ultrasound. Patients were excluded if they had any of...
the following: chronic pancreatitis, postendoscopic retrograde cholangiopancreatography pancreatitis, intraoperative diagnosis, pregnancy, or malignancy. Informed written consent was gained from all patients prior to their inclusion in the study, and the project was approved by the local ethics committee.

**Data Collection**

Baseline data were prospectively collected from all eligible patients, including age, sex, BMI, APACHE II score, personal history of diabetes mellitus, fasting glucose concentration (daily; during the first 72 hours after hospital admission), and time from first symptoms to hospital admission. None of the patients without diabetes on admission received insulin or oral antglycemic agents during the study period. Venous blood was taken for adipokine assays at 24, 48, and 72 hours after admission. Patients were required to fast for ≥8 hours prior to their fasting blood glucose being measured.

**Study Groups**

Two separate analyses were undertaken based on the patients' venous glucose level in order to examine the relationship between adipokines and glucose on admission, and the persistence of early hyperglycemia in the first 72 hours of admission.

**Glucose on Admission Analysis**

Admission glycaemia was stratified by severity as follows: euglycemia 4 to 6 mmol/L, mild hyperglycemia 6.1 to 7.7 mmol/L, moderate hyperglycemia 7.8 to 11.0 mmol/L, and severe hyperglycemia 11.1 to 20.0 mmol/L. Patients with an admission glucose level of <4.0 or >20.0 mmol/L were excluded on the basis that such values warranted urgent medical attention.

**Persistent Hyperglycemia Analysis**

Persistent hyperglycemia was defined as fasting blood glucose >6.1 mmol/L on ≥2 consecutive 24-hour periods during the first 72 hours after hospital admission.

**Adipokine Assays**

Plasma adipokine concentrations were measured at 24, 48, and 72 hours after hospital admission. The "glucose on admission" analysis used the 24-hour time point concentration, whereas the "persistent hyperglycemia" analysis used the highest concentration measurement out of the 48- and 72-hour assessment times. If only the 48- or 72-hour assessment time was available then that value was used.

Adipokine levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit, according to the supplier's instructions (Adiponectin, resistin; Millipore Inc, MA. Cat#H-ADK1-61K-A Leptin; Millipore Inc. Cat# EZHL-80SK, Omentin; Millipore Inc. Cat#EZ0H0NTN1-29K, Visfatin; MBL Intl Corp, MA. Cat#JM-k4907-100). The results of the ELISA test for adiponectin and resistin were read by a Luminex 100 IS microplate reader (Luminex Corporation, Austin, TX), leptin and omentin were read by a plate reader (Perkin Elmer, Enspire, 2300 Multilabel Reader, MA) at 450 and 590 nm, and visfatin on the same reader at 450 nm. Readings were interpreted using interpolation of a 2-parameter logistic equation for adiponectin and resistin, a sigmoidal 5-parameter logistic equation for leptin and omentin ($R^2$ >0.99 for each assay) and a regression curve formula in the form of a parameter-4 equation for visfatin. Assay sensitivity was 145.4 pg/mL, 0.135 ng/mL, 0.23 ng/mL, 6.7 pg/mL, 30 pg/mL with the range of measured concentrations being 12.3 to 93.6 μg/mL, 0.27 to 29.5 ng/mL, 10.7 to 156.3 ng/mL, 1.5 to 60.4 ng/mL, 0.2 to 6.8 ng/mL for adiponectin, leptin, omentin, resistin, and visfatin, respectively.

**Statistical Analysis**

Statistical analysis was performed using Microsoft Excel (Windows) and SPSS 21 for Windows (IBM Corp). All data was presented as mean ± standard deviation. ANOVA (analysis of variance) and ANCOVA (analysis of covariance) tests were used to determine differences between the groups. ANCOVA analysis was used to reduce within group variance and also to adjust for confounders. The 2 key assumptions of ANCOVA—indepedence of the covariate and groups, and homogeneity of regression slopes—were confirmed for all but the resistin "glucose on admission", resistin "persistent hyperglycemia," and leptin "glucose on admission" analyses. The additional variables—sex, history of diabetes, APACHE II score, BMI, age, and duration of symptoms, were all entered in the model. In addition, the interaction between these factors and study groups was investigated. For all tests $P$ values <0.05 were considered statistically significant.

**RESULTS**

**Patient Characteristics**

A total of 32 patients (mean age 53.6 ± 19.6 years), 17 men and 15 women, with AP were included in this study. For the glucose on admission analysis, patients were distributed through the following groups: euglycemia (n = 8), mild (n = 12), moderate (n = 8), and severe hyperglycemia (n = 3). Patient characteristics are shown in Table 1. There were no significant differences between the groups for age, BMI, sex, APACHE II score, time from onset of symptoms, and etiology.

For the persistent hyperglycemia analysis, 15 patients had persistent hyperglycemia, whereas 17 patients did not. Patient characteristics are shown in Table 1. There were no significant differences between the 2 groups for age, BMI, APACHE II score, time from onset of symptoms, and etiology; however, men had persistent hyperglycemia more frequently than women ($P = 0.036$).

**Association Between Adipokines and Glucose on Admission**

Adipokine concentrations were available for patients on admission as follows: adiponectin (n = 13), leptin (n = 24), omentin (n = 25), resistin (n = 18), and visfatin (n = 27).

**Adiponectin**

The mean total adiponectin concentration in these patients was 39.6 ± 22.7 μg/mL. The number of patients in each group and their mean adiponectin concentrations were euglycemia (n = 3, 43.2 ± 39.2), mild (n = 6, 43.3 ± 17.9), moderate (n = 3, 37.7 ± 21.9), and severe hyperglycemia (n = 1, 17.9). This resulted in an unadjusted $P$-value of 0.824. Due to the limited sample size, it was not possible to calculate an adjusted $P$ value.

**Leptin**

The mean leptin concentration in these patients was 6.4 ± 7.7 ng/mL. The number of patients in each group and their mean leptin concentrations were euglycemia (n = 8, 3.1 ± 2.1), mild (n = 8, 11.8 ± 11.2), moderate (n = 6, 4.0 ± 4.1), and severe
TABLE 1. Baseline Characteristics

|                      | Glucose on Admission | Persistent Hyperglycemia |
|----------------------|----------------------|--------------------------|
|                      | Euglycemic | Mild | Moderate | Severe | P          | Yes | No | P          |
| No. of patients      | 8          | 12   | 8        | 3      | 0.204     | 15  | 17 | 0.815     |
| Age                  | 47.9 ± 18.6 | 50.7 ± 20.4 | 55.5 ± 19.1 | 75.0 ± 8.7 | 0.204 |
| Sex (male)           | 6          | 6    | 3        | 2      | 0.498     | 12  | 5  | 0.036     |
| BMI, kg/m²           | 24.1 ± 3.3 | 25.9 ± 4.7 | 28.3 ± 4.7 | 26.8 ± 0.5 | 0.265 |
| APACHE II score      | 2.5 ± 2.8  | 6.6 ± 5.0   | 6.0 ± 5.4    | 12.3 ± 1.5 | 0.230 |
| Time from first symptoms to admission, hours | 28.6 ± 18.7 | 11.0 ± 10.3 | 17.1 ± 14.8 | 46.0 ± 43.4 | 0.240 |
| Glucose on admission | 5.3 ± 0.4  | 6.9 ± 0.5   | 9.2 ± 1.2    | 14.1 ± 3.0 | <0.001 |
| Etiology, Biliary     | 4          | 6    | 5        | 3      | 0.483     | 7   | 11 | 0.252     |
| Etiology, Alcohol     | 0          | 4    | 3        | 0      | 0.121     | 6   | 2  | 0.076     |
| Etiology, Unknown     | 4          | 2    | 0        | 0      | 0.053     | 2   | 4  | 0.392     |

Data presented as mean ± standard deviation. APACHE II = Acute Physiology and Chronic Health Evaluation II, BMI = body mass index.

hyperglycemia (n = 2, 5.6 ± 3.7). This resulted in an unadjusted P value of 0.103, and with the inclusion of the aforementioned confounders resulted in an adjusted P value of 0.273. None of the confounders, both alone and as an interaction with glucose level, was associated with leptin (Table 2).

Omentin

The mean omentin concentration in these patients was 74.8 ± 35.1 ng/mL. The number of patients in each group and their mean omentin concentrations were euglycemia (n = 7, 66.7 ± 19.7), mild (n = 10, 77.1 ± 39.0), moderate (n = 6, 67.0 ± 34.8), and severe hyperglycemia (n = 2, 114.4 ± 28.0). This resulted in an unadjusted P value of 0.372, and with the inclusion of the aforementioned confounders resulted in an adjusted P value of 0.564. None of the confounders, both alone and as an interaction with glucose level, was associated with omentin (Table 2).

Resistin

The mean resistin concentration in these patients was 13.1 ± 12.5 ng/mL. The number of patients in each group and their mean resistin concentrations were euglycemia (n = 8, 15.1 ± 18.8), mild (n = 2, 13.3 ± 10.8), moderate (n = 6, 9.5 ± 6.6), and severe hyperglycemia (n = 2, 14.6 ± 9.0). This resulted in an unadjusted P value of 0.880, and with the inclusion of the aforementioned confounders resulted in an adjusted P value of 0.451. None of the confounders, both alone and as an interaction with glucose level, was associated with resistin (Table 2).

Visfatin

The mean visfatin concentration in these patients was 3.0 ± 1.4 ng/mL. The number of patients in each group and their mean visfatin concentrations were euglycemia (n = 8, 3.3 ± 1.2), mild (n = 11, 2.7 ± 1.9), moderate (n = 6, 28.0).

TABLE 2. Relationship Between the Studied Adipokines and Potential Confounders in Patients With Hyperglycemia on Admission and Persistent Hyperglycemia

| Confounders              | Glucose on Admission | Persistent Hyperglycemia |
|--------------------------|----------------------|--------------------------|
|                         | Leptin | Omentin | Resistin | Visfatin | Adiponectin | Leptin | Omentin | Resistin | Visfatin |
| Age                      | Alone   | 0.164  | 0.836    | 0.314    | 0.519       | 0.901   | 0.767   | 0.284    | 0.705    | 0.312   |
|                         | Interaction | 0.122  | 0.796    | 0.08     | 0.507       | 0.541   | 0.018   | 0.869    | 0.809    | 0.096   |
| BMI                      | Alone   | 0.092  | 0.328    | 0.444    | 0.223       | 0.741   | 0.002   | 0.156    | 0.755    | 0.077   |
|                         | Interaction | 0.248  | 0.569    | 0.15     | 0.868       | 0.119   | 0.007   | 0.209    | 0.703    | 0.086   |
| Sex                      | Alone   | 0.407  | 0.996    | 0.106    | 0.458       | 0.138   | 0.872   | 0.457    | 0.063    | 0.48    |
|                         | Interaction | 0.658  | 0.899    | 0.702    | 0.864       | 0.313   | 0.59    | 0.723    | 0.338    | 0.023   |
| APACHE II score          | Alone   | 0.769  | 0.795    | 0.946    | 0.897       | 0.231   | 0.449   | 0.021    | 0.211    | 0.636   |
|                         | Interaction | 0.416  | 0.661    | 0.332    | 0.665       | 0.015   | 0.094   | 0.842    | 0.188    | 0.014   |
| Personal history of diabetes | Alone   | 0.158  | 0.987    | 0.3      | 0.893       | 0.475   | 0.53    | 0.541    | 0.793    | 0.337   |
|                         | Interaction | N/E   | N/E      | N/E      | N/E         | 0.012   | 0.113   | 0.341    | 0.971    | 0.531   |
| Duration of symptoms    | Alone   | 0.735  | 0.74     | 0.606    | 0.903       | 0.455   | 0.486   | 0.337    | 0.891    | 0.432   |
|                         | Interaction | 0.782  | 0.662    | 0.716    | 0.619       | 0.112   | 0.973   | 0.465    | 0.796    | 0.500   |

Adiponectin P values for glucose on admission analysis were not estimable due to lack of data.

Interaction refers to a combined effect of the particular covariate and the adipokine in predicting hyperglycemia.

APACHE II = Acute Physiology and Chronic Health Evaluation II, BMI = body mass index, N/E = not estimable.
Association between Adipokines and Persistent Hyperglycemia

Adipokine concentrations were available for patients at the 48- and 72-hour time points as follows: adiponectin \((n = 21)\), leptin \((n = 23)\), omentin \((n = 30)\), resistin \((n = 30)\), and visfatin \((n = 30)\).

Adiponectin
The mean total adiponectin concentration in these patients was \(56.5 \pm 24.4 \mu g/mL\). The number of patients in each group and their mean adiponectin concentrations were: persistent hyperglycemia \((n = 10, 63.2 \pm 23.9)\), and without persistent hyperglycemia \((n = 11, 50.4 \pm 24.2)\). This resulted in an unadjusted \(P\) value of 0.237, and with the inclusion of the aforementioned confounders resulted in an adjusted \(P\) value of 0.060. Table 2 demonstrates the association between concentration of adiponectin and potential confounders, both alone and as an interaction with persistent hyperglycemia. Of these, significant associations were found between concentrations of adiponectin and history of diabetes in patients with persistent hyperglycemia.

Leptin
The mean leptin concentration in these patients was \(6.3 \pm 6.0 \text{ng/mL}\). The number of patients in each group and their mean leptin concentrations were persistent hyperglycemia \((n = 9, 9.3 \pm 8.5)\) and without persistent hyperglycemia \((n = 14, 4.4 \pm 2.7)\). This resulted in an unadjusted \(P\) value of 0.055, and with the inclusion of the aforementioned confounders resulted in an adjusted \(P\) value of 0.003. Table 2 demonstrates the association between concentration of leptin and potential confounders, both alone and as an interaction with persistent hyperglycemia. Of these, significant associations were found between concentration of leptin and age, in patients with persistent hyperglycemia, and between concentration of leptin and BMI (Figure 2), both in all patients with AP and in those patients with persistent hyperglycemia.

Omentin
The mean omentin concentration in these patients was \(62.7 \pm 29.4 \text{ng/mL}\). The number of patients in each group and their mean omentin concentrations were: persistent hyperglycemia \((n = 14, 65.7 \pm 32.5)\) and without persistent hyperglycemia \((n = 16, 59.0 \pm 27.0)\). This resulted in an unadjusted \(P\) value of 0.540, and with the inclusion of the aforementioned confounders resulted in an adjusted \(P\) value of 0.298. Table 2 demonstrates the association between the concentration of omentin and potential confounders, both alone and as an interaction with persistent hyperglycemia. Of these, significant associations were found between concentration of omentin and APACHE II score in all patients with AP (Figure 3).

Resistin
The mean resistin concentration in these patients was \(15.9 \pm 11.8 \text{ng/mL}\). The number of patients in each group and their mean resistin concentrations were: persistent hyperglycemia \((n = 14, 17.2 \pm 13.5)\) and without persistent hyperglycemia \((n = 16, 14.8 \pm 10.3)\). This resulted in an unadjusted \(P\) value of 0.593, and with the inclusion of the aforementioned confounders resulted in an adjusted \(P\) value of 0.247. None of the confounders, both alone and as an interaction with glucose level, was associated with resistin (Table 2).

Visfatin
The mean visfatin concentration in these patients was \(3.5 \pm 1.7 \text{ng/mL}\). The number of patients in each group and their mean visfatin concentrations were: persistent hyperglycemia \((n = 14, 3.5 \pm 1.6)\) and without persistent hyperglycemia \((n = 16, 3.6 \pm 1.9)\). This resulted in an unadjusted \(P\) value of 0.930, and with the inclusion of the aforementioned confounders
resulted in an adjusted \( P \) value of 0.112. Table 2 demonstrates the association between the concentration of visfatin and potential confounders, both alone and as an interaction with persistent hyperglycemia. Of these, significant associations were found between the concentration of visfatin and sex, and between the concentration of visfatin and APACHE II score, both in patients with persistent hyperglycemia.

**DISCUSSION**

This is the first study to investigate the association between a panel of adipokines and early hyperglycemia in patients with AP. There were no significant associations between admission hyperglycemia and the 5 adipokines studied, in both univariate and multivariate analyses. But in patients with AP and early persistent hyperglycemia, there was a significantly higher concentration of leptin compared with those patients without persistent hyperglycemia. Further, the mean concentrations of adiponectin, omentin, and visfatin were significantly associated with APACHE II score, either in all of the patients with AP (omentin) or only among those with persistent hyperglycemia.

The significant association between leptin and persistent hyperglycemia early in the course of AP is a novel finding. Leptin, a protein hormone secreted predominantly by the white adipose tissue,\(^{18}\) is known for its important role in regulating bodyweight. But recent evidence suggests that it also modulates peripheral insulin sensitivity and suppresses insulin secretion from pancreatic \( \beta \) cells.\(^{19-23}\) Leptin is independently and positively associated with features of the metabolic syndrome including increased body weight (directly proportional to body fat mass), insulin resistance, blood pressure, and inflammation.\(^{20,21,24,25}\) Intravenous administration of glucose has been demonstrated to raise leptin levels in a dose-dependent manner,\(^{19,22}\) suggesting that the elevated leptin levels observed in this study are an effect of hyperglycemia rather than a cause. Given that only persistent hyperglycemia, but not a single episode of early stress hyperglycemia, was associated with hyperleptinemia and taking into account that adjusting for duration of symptoms did not affect the estimates, this study provides the first evidence that secretion of leptin is influenced by the duration of hyperglycemia.

Further, leptin was found to be significantly associated with BMI both alone and as an interaction with glycemic status. While the significance of association between BMI and leptin levels has been shown in a number of disease settings,\(^{24-26}\) this is the first study in AP patients which shows that persistence of hyperglycemia accounts for >70% of the variation in the level of leptin in relation to patient’s BMI (Figure 2). Taken together with the known action of leptin-suppressing insulin secretion and increasing insulin resistance, these findings suggest that leptin may be an important mediator of the effect of early hyperglycemia on the risk of new onset diabetes mellitus after acute and critical illnesses.\(^{1-5}\)

This study also provides new insights into the role of adipokines in relation to the severity of AP (as determined by APACHE II score). Adiponectin has previously been identified as a predictor for AP severity.\(^{10,12,27}\) The new finding here is that adiponectin is positively correlated with the severity of AP in patients with persistent hyperglycemia and inversely correlated in those patients without hyperglycemia (Figure 1). Adiponectin has been acknowledged as an anti-inflammatory adipokine; however, its role in human physiology is not completely understood. It has been previously shown to increase in inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease but also has insulin sensitizing properties.\(^{28,29}\) Further, while visfatin was previously found to be associated with severity of AP,\(^{10,12,20}\) in this study, it was found to be negatively correlated with APACHE II score in patients with persistent hyperglycemia and positively correlated with APACHE II score in patients without it. In both cases, however, the correlation was too weak (\( r < 0.1 \)) and further studies are required. Another important finding in this study is the significant association between omentin and APACHE II score in all the patients with AP, regardless of their glycemic status (Figure 3). Omentin is an adipokine predominately secreted by the visceral, but not subcutaneous, fat.\(^{31,32}\) A recent experimental study found that serum omentin levels are increased in pancreatitis (both acute and chronic) in comparison with controls.\(^{33}\) Taken together, these findings support an important role of visceral fat in AP\(^{34,35}\) and suggest that omentin should be investigated as a predictor of AP severity. A number of previous studies also suggested that leptin may be a predictor of severity of AP.\(^{36-38}\) This study however has not shown a similar pattern (alone: \( P = 0.449 \); interaction with persistence of hyperglycemia: \( P = 0.094 \)).\(^{12,38,39}\)

This study has several limitations that need to be acknowledged. First, the study sample size was relatively small and hence the findings need to be replicated in a larger study. Conversely, findings that have previously been identified as significant may not have had the power to be significantly detected in this study. Nevertheless, interesting and potentially important associations were found between leptin and hyperglycemia and between the severity of AP and adiponectin, omentin, and visfatin. In addition, a number of samples were not included due to them being below the limit of detection of the particular adipokine assay or the coefficient of variation being too high between duplicate samples. Second, no long-term follow-up was conducted with these patients to see whether these adipokines predicted occurrence of new-onset diabetes. Third, although this is the largest panel of adipokines to be investigated early in AP, there are a number of other
proteins released by adipose tissue that may be altered in AP and will require investigation, including adipin, apelin, chemerin, retinol binding protein 4, and vaspin. Fourth, there was an unexplained predominance of men among the patients with persistent hyperglycemia, but sex was adjusted for in multivariate analyses, yielding no significant association. Last, the assumptions for ANOVA and ANCOVA are that data meet the requirements of normality and homogeneity of variances. Most adipokines in both sets of analyses met the assumptions of normal distribution and the homogeneity of variance, with the exception of the resistin data for “on admission” analyses, the resistin data for “persistent hyperglycemia” analyses, and the leptin data for on “on admission” analyses. Given that no significant findings had been found in those analyses, we believe the use of more conservative nonparametric tests would not have significantly changed the findings.

In conclusion, this study has found, for the first time, that there is a significant association between leptin and persistent hyperglycemia early in the course of AP. Given the known actions of leptin (decreased insulin secretion and increased hyperglycemia early in the course of AP), it is possible that leptin may be contributing to the development of persistent hyperglycemia in patients with AP. Further research is needed to confirm this finding and to understand the potential role of leptin in the pathogenesis of persistent hyperglycemia in AP.

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