Suggested Reference

Leptin Is Associated With Persistence of Hyperglycemia in Acute Pancreatitis

A Prospective Clinical Study

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Abstract: Adipokines have many homeostatic roles, including modulation of glucose metabolism, but their role in the pathophysiology of hyperglycemia associated with acute and critical illnesses in general, and acute pancreatitis (AP) in particular, is largely unknown. This study aimed to investigate the relationship between a panel of adipokines and hyperglycemia in the early course of AP, as well as the role of adipokines as predictors of AP severity.

Adiponectin, leptin, omentin, resistin, and visfatin were measured on a daily basis in the first 72 hours after hospital admission. A first set of analysis was performed to determine if adipokines stratify by severity, and a second set of analyses was undertaken based on persistence of early hyperglycemia. All of the analyses were adjusted for confounders.

A total of 32 patients with AP were included in this study. None of the studied adipokines was significantly associated with glucose level on admission. Leptin was significantly (P = 0.003) increased in patients with persistent hyperglycemia. Adiponectin was significantly associated with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score in patients with persistent hyperglycemia (P = 0.015), visfatin with APACHE II score in patients with persistent hyperglycemia (P = 0.014), and omentin with APACHE II score in all of the patients regardless of the presence or absence of hyperglycemia (P = 0.021).

Leptin is significantly associated with persistent hyperglycemia in the early course of AP. Omentin has a potential to become an accurate predictor of AP severity.

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 mmol/L. Patients with an admission glucose concentration of <4.0 or ≥20 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# EZH0MN1N1-29K, Visfatin; MBL Intl Corp, MA. Cat#JM-k9070-100). The results of the ELISA test for adiponectin and resistin were read by a Luminox 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 5-parameter logistic equation for adiponectin and resistin, a sigmoidal 5-parameter logistic equation for leptin and omentin (R² > 0.99 for each assay) and a regression curve formula in the form of the parameter-4 equation for visfatin. Assay sensitivity was 145.4 pg/mL, 0.135 ng/mL, 0.23 pg/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—Independence 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

<table>
<thead>
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<th>Glucose on Admission</th>
<th>Persistent Hyperglycemia</th>
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</thead>
<tbody>
<tr>
<td>Euglycemic</td>
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<tr>
<td>No. of patients</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Sex (male)</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>APACHE II score</td>
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<tr>
<td>Time from first symptoms to admission, hours</td>
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<tr>
<td>Glucose on admission</td>
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<tr>
<td>Etiology, Alcohol</td>
<td>0</td>
</tr>
<tr>
<td>Etiology, Unknown</td>
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</tr>
</tbody>
</table>

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

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

<table>
<thead>
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<th>Confounders</th>
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<th>Persistent Hyperglycemia</th>
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<tbody>
<tr>
<td></td>
<td>Leptin</td>
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<td>Age</td>
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<td></td>
<td>Interaction</td>
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<td>BMI</td>
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<td>Interaction</td>
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<td>APACHE II score</td>
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<td></td>
<td>Interaction</td>
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<td>Duration of symptoms</td>
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<tr>
<td></td>
<td>Interaction</td>
<td>0.782</td>
</tr>
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</table>

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.

Adipokines and Hyperglycemia in Acute Pancreatitis

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

With a mean 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 euglycaemia (n = 8, 3.3 ± 1.2), mild (n = 11, 2.7 ± 1.9), moderate (n = 6,
2.8 ± 1.0), and severe hyperglycemia (n = 2, 4.0 ± 1.0). This resulted in an unadjusted P value of 0.650, and with the inclusion of the aforementioned confounders resulted in an adjusted P value of 0.856. None of the confounders, both alone and as an interaction with glucose level, was associated with visfatin (Table 2).

**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 ± 24.4 μg/mL. The number of patients in each group and their mean adiponectin concentrations were: persistent hyperglycemia (n = 10, 63.2 ± 23.9), and without persistent hyperglycemia (n = 11, 50.4 ± 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 0.856. None of the confounders, both alone and as an interaction with glucose level, was associated with adiponectin and potential confounders, both alone and as an interaction with persistent hyperglycemia. Of these, significant associations were found between concentrations of adiponectin and potential confounders, both alone and as an interaction with persistent hyperglycemia. Of these, significant associations were found between 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 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 ± 29.4 ng/mL. The number of patients in each group and their mean omentin concentrations were: persistent hyperglycemia (n = 14, 65.7 ± 32.5) and without persistent hyperglycemia (n = 16, 59.0 ± 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 concentration of omentin 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).

**Resistin**

The mean resistin concentration in these patients was 15.9 ± 11.8 ng/mL. The number of patients in each group and their mean resistin concentrations were: persistent hyperglycemia (n = 14, 17.2 ± 13.5) and without persistent hyperglycemia (n = 16, 14.8 ± 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 ± 1.7 ng/mL. The number of patients in each group and their mean visfatin concentrations were: persistent hyperglycemia (n = 14, 3.5 ± 1.6) and without persistent hyperglycemia (n = 16, 3.6 ± 1.9). This resulted in an unadjusted P value of 0.930, and with the inclusion of the aforementioned confounders...
episode of early stress hyperglycemia, was associated with the presence of hyperglycemia early in the course of AP is a novel finding. 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 (both acute and chronic) in comparison with controls.33

FIGURE 3. Association between omentin and severity of acute pancreatitis. APACHE II = Acute Physiology and Chronic Health Evaluation II.

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 β 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

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proteins released by adipose tissue that may be altered in AP and will require investigation, including adipin, apelin, chemerin, retinol binding protein 4, and vispoin. 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 resitnin 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 insulin resistance), the data suggest that persistent hyperglycemia, especially associated with an elevated BMI, may contribute to the increased risk of new-onset diabetes after acute and critical illness. Other important findings from this study that warrant further investigation is the potential role of omentin as a predictor of AP severity.

REFERENCES


