

Role of Ghrelin and Leptin in Predicting the Severity of Acute Pancreatitis

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Abstract Ghrelin and leptin are the hormones that influence endocrine and exocrine functions of the pancreas and regulate feeding behaviors and energy metabolism. The aim of this study was to investigate the levels of ghrelin and leptin in pancreatitis of different severities and the relation of these hormones with blood glucose level and proinflammatory cytokines. The study was performed on 90 Wistar Albino rats. Three experimental groups composed of 30 rats were established: control group, 0.9% NaCl solution was injected intraperitoneally (i.p); acute edematous pancreatitis (AEP) group, 1 μ g/100 g cerulein was injected i.p. five times, at 1-hr intervals; and acute necrotizing pancreatitis (ANP) group, 500 mg/100 g L-arginine was injected i.p. Ten animals in each group were sacrificed under anesthesia 12, 24 and 48 hr after the last injection. After blood withdrawal, the pancreas was totally excised. The levels of blood sugar, lipase, serum tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), ghrelin, and leptin were investigated and histopathologic examination was performed. Following pancreatitis induction, serum ghrelin levels increased at 24 hr and reached the peak level at 48 hr. Its level in the AEP group was higher than in the ANP group. Serum leptin levels in the AEP and ANP groups increased after 12 hr and stayed at high levels

until 48 hr compared with the control group. Similarly to ghrelin and leptin, blood glucose levels increased in both pancreatitis groups, but the increase was more prominent in the ANP group, with levels >200 mg/ml at 48 hr. The levels of TNF- α and IL-1 β in the AEP and ANP groups reached the peak level at 24 hr and then decreased to a level close to that of the control group at 48 hr. We conclude that serum leptin and ghrelin levels increase in the first 48 hr of AEP and ANP. As the serum ghrelin levels in ANP are higher than in AEP, it can be used as a marker to show the severity of pancreatitis. While TNF- α and IL-1 β can be used as a prognostic factor in the first 24 hr, ghrelin and leptin can be used subsequently.

Keywords Ghrelin · Leptin · Acute pancreatitis

Introduction

Acute pancreatitis (AP) is a severe disease with significant morbidity and mortality for which there is no specific treatment beyond supportive therapy. An amplified cytokine response plays an important pathophysiological role in the development of complications, especially in the progression of limited local pancreatic inflammation into a potentially dangerous systemic inflammatory reaction termed multiple organ dysfunction syndrome [1]. The spectrum of AP ranges from mild inflammation to severe necrotizing inflammation with systemic manifestations. Several scoring systems have been presented to determine the severity of pancreatic injury [2, 3]. The early detection of potentially severe AP is imperative because accurate and timely selection of those patients who will require intensive care may improve mortality. For this reason, cytokines, immune response markers, proenzymes, and enzyme complexes have been the subject

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of several studies for determining the severity of disease [4]. In this study, we aimed to find out the relation between the levels of ghrelin and leptin in edematous, necrotizing pancreatitis and the prognostic factors.

Ghrelin is a 28-amino acid polypeptide originally isolated from rat stomach [5] and it has been localized in endocrine X/A-like cells in the gastric mucosa [6] and ϵ -islet cells in the pancreas [7–9]. Ghrelin is considered to bind to the growth hormone secretagogue receptor (GHS-R) and then affects GH release, gastrointestinal function, feeding behavior, and energy metabolism [10–14]. In fetal pancreas, ghrelin is expressed in a prominent endocrine cell population [7, 9]. In adult pancreas, the number of ghrelin-immunoreactive cells is reduced and these cells are localized at the periphery of human and rat pancreatic islets. Pancreatic exocrine secretion has been found to be inhibited by ghrelin in rat acinar cells [15]. Recent studies have indicated that ghrelin may have a direct action on β cell function. However, both inhibitory [16, 17] and stimulatory [8, 18, 19] actions have been reported in vitro.

Leptin, which is a 16-kDa protein encoded by the obese gene, is an adipocyte-derived hormone that acts centrally in the hypothalamus to regulate body weight and peripheral energy expenditure [20]. The presence of leptin and expression of its receptors have been detected in other tissues like the stomach [21], liver [22], and pancreas [23]. Leptin receptors have been detected on pancreatic AR42J cells and their gene expression has been documented in pancreatic acini, suggesting that this protein could take part in the regulation of pancreatic exocrine secretion [24]. On the other hand, the presence of leptin receptors on pancreatic β cells suggests that leptin could be involved in the regulation of pancreatic endocrine function as well [25, 26].

Considering the information mentioned above, it is accepted that both ghrelin and leptin can influence endocrine and exocrine functions of the pancreas. In AP, in which endocrine and exocrine functions of the pancreas are disturbed, the levels of these hormones can change and these changes can be used as a prognostic factor. The aim of this study was to investigate (a) the changes of these two hormones in the first 48 hr of pancreatitis in different severities, (b) the relationship between the changes of these hormones and blood glucose levels, and (c) the relation of proinflammatory cytokines (tumor necrosis factor [TNF]- α and interleukin [IL]-1 β) with hormone levels.

Materials and methods

Animals and experimental design

The study was performed on male Wistar Albino rats weighting 240–280 g and was conducted following the experimental

protocol approved by the Committee for Research and Animal Ethics of Gazi University. Animals were housed in cages at a normal room temperature under a 12-hr light-dark cycle. Food and water were available ad libitum. All rats were allowed at least 1 week of adaptation to the laboratory before the experimental procedure was begun. Rats were fasted for 16 hr before injections, while access to water was maintained until euthanasia. Rats were anesthetized with an intramuscular injection of 40 mg/kg ketamine (Ketalar; Parke Davis, Eczacıbasi, Istanbul, Turkey) and xylazine (Rompum; Bayer AG, Leverkusen, Germany).

Three experimental groups were established: in the control group ($n=30$), animals were injected with a 0.9% NaCl solution intraperitoneally (i.p.); in the acute edematous pancreatitis (AEP) group ($n=30$), AEP was induced by five intraperitoneal injections of cerulein at a dose of 1 μ g/100 g/injection, at 1-hr intervals (Sigma-Aldrich Chemical, Steinheim, Germany); and in the acute necrotizing pancreatitis (ANP) group ($n=30$), ANP was induced by one i.p. injection of 500 mg/100 g L-arginine (Merck, Darmstadt, Germany). Four milliliters of serum physiologic was injected subcutaneously in the flank region of all rats after the last i.p. injection. All rats were permitted to take water and food after the experiment. Food intake was ceased 2 hr before sacrifice. Ten animals in each group were sacrificed under anesthesia 12, 24, and 48 hr after the last injection. A midline incision was made and blood samples were taken at the abdominal aorta. After blood withdrawal, the pancreas was carefully dissected out from its attachment to the stomach and was totally excised. All rats were killed by hemorrhage. Blood samples were kept at -80°C for biochemical analyses, which were run in duplicate.

Blood sugar and lipase assay

Serum blood sugar and lipase were determined using a Beckman Coulter LX-20 System analyzer (Beckman, Fullerton, CA, USA) and Beckman kits, according to the supplier's specification.

Serum tumor necrosis factor- α and interleukin-1 β assay

To determine the levels of TNF- α and IL-1 β , a commercial solid phase sandwich enzyme-linked immunosorbent assay (ELISA) from Biosource International (Camarillo, CA, USA) was used. TNF- α and IL-1- β levels were determined from a standard curve for recombinant TNF- α and IL-1 β , and concentrations are expressed as picograms per milliliter. The ELISA detection limit for TNF- α and IL-1 β was 3 pg/ml.

Serum ghrelin and leptin assay

Ghrelin concentration in the serum was determined using a commercially available ELISA kit from Phoenix Pharmaceuticals (Belmont, CA, USA). Serum leptin concentrations were determined using a commercially available kit from Linco Research (USA). Serum ghrelin and leptin concentrations are expressed as nanograms per milliliter.

Histological examination

Samples of pancreatic tissue excised from the body portion for morphological examination were fixed in 10% formalin, then embedded in paraffin, and sections were stained with hemotoxylin and eosin. The slides were examined by two experienced pathologists without knowledge of the chemicals given. Histological grading of edema was done using a scale ranging from 0 to 3 (0 = no edema, 1 = interlobular edema, 2 = interlobular and moderate intralobular edema, 3 = interlobular edema and severe intralobular edema). Leukocytic infiltration was also graded from 0 to 3 (0 = absent, 1 = scarce perivascular infiltration, 2 = moderate perivascular and scarce diffuse infiltration, 3 = abundant diffuse infiltration). Grading of vacuolization was based on the appropriate percentage of acinar cells involved: 0 = absent, 1 = less than 25%, 2 = 25–50%, and 3 = more than 50% of acinar cells [27].

Statistical analysis

Results are expressed as the mean \pm SE. Comparisons within groups were made using the Mann-Whitney *U* test. One-way ANOVA and Scheffe's post hoc test were carried out for multiple comparisons. $P < 0.05$ was considered statistically significant. Statistics were analyzed using the SPSS program, version 11.5.

Results

During the experiment two rats in the ANP group died. New rats replaced these two.

Histopathologic examination

Edema, inflammation, vacuolization, and necrosis in the ANP group at 12, 24, and 48 hr were significantly higher than in the control group ($P < 0.001$). Also, edema at 12 and 24 hr ($P = 0.01$) and necrosis at 48 hr ($P < 0.05$) were higher in the ANP group compared to the AEP group. All parameters except necrosis in the AEP group were higher than in the control group. Edema, vacuolization, and necrosis at 48 hr were more significant than at 12 hr in the AEP group ($P < 0.05$). In the ANP group, all histologic parameters except necrosis were higher at 48 hr than at 12 hr ($P < 0.05$).

Serum lipase levels

Serum lipase levels at 12, 24, and 48 hr in both the AEP and the ANP groups were significantly higher than in the control group ($P < 0.001$). Lipase at 24 and 48 hr in the ANP group was higher than in the AEP group ($P = 0.006$ and $P < 0.001$, respectively) (Table 1).

Blood sugar levels

Serum glucose levels at 12, 24, and 48 hr in the ANP group were higher than in the control group ($P < 0.001$). The blood glucose level in the ANP group at 48 hr was >200 mg/dl. Although the blood glucose level in the AEP group was higher than in the control group, the difference was not statistically significant ($P > 0.05$). Blood glucose levels of the ANP and AEP groups showed no significant difference ($P > 0.05$; Table 1).

Table 1 Serum sugar, lipase, TNF- α , and IL-1 β levels (mean \pm SE) in all groups

	12 hr			24 hr			48 hr		
	Control	AEP	ANP	Control	AEP	ANP	Control	AEP	ANP
Lipase (I U/L)	108 \pm 17	259 \pm 57 ^a	241 \pm 16 ^a	113 \pm 8	388 \pm 22 ^a	461 \pm 22 ^{a,b}	115 \pm 18	378 \pm 66 ^a	465 \pm 20 ^{a,b}
Blood sugar (mg/ml)	88 \pm 12	142 \pm 32 ^a	178 \pm 54 ^a	93 \pm 23	143 \pm 53 ^a	202 \pm 27 ^a	136 \pm 34	186 \pm 18 ^a	220 \pm 22 ^a
TNF- α (pg/ml)	13 \pm 3	41 \pm 7 ^a	64 \pm 20 ^{a,b}	16 \pm 9	53 \pm 13 ^a	80 \pm 14 ^{a,b}	17 \pm 5	29 \pm 6	35 \pm 13
IL-1 β (pg/ml)	18 \pm 5	39 \pm 5 ^a	58 \pm 19 ^{a,b}	29 \pm 8	53 \pm 10 ^a	73 \pm 18 ^{a,b}	19 \pm 5	31 \pm 9	34 \pm 6

^a $P < 0.05$ vs. the control group.

^b $P < 0.05$ vs. the AEP group.

Serum TNF- α levels

Serum TNF- α levels measured in both the AEP and the ANP groups at 12 and 24 hr were significantly higher than in the control group ($P = 0.001$ and $P < 0.001$, respectively). Serum TNF- α levels at 12 and 24 hr in the ANP group were significantly higher than in the AEP group ($P = 0.013$ and $P = 0.001$). On the other hand TNF- α levels at 48 hr in the AEP and ANP groups were decreased close to those in the control group (Table 1).

Serum IL-1 β levels

Serum IL-1 β level in the ANP group at 12 and 24 hr was significantly higher than in the controls ($P = 0.001$ and $P < 0.001$, respectively) and the AEP group ($P = 0.038$ and $P = 0.049$, respectively). Also, IL-1 β levels at 12 and 24 hr in the AEP group were higher than in the control group ($P = 0.028$ and $P = 0.04$, respectively). Serum IL-1 β levels in the ANP and the AEP groups reached the peak level at 24 hr but decreased to the control-group level at 48 hr (Table 1).

Serum ghrelin levels

There was no significant difference among the three groups in serum ghrelin levels at 12 hr ($P > 0.05$). Although serum ghrelin levels in the ANP and the AEP groups at 24 hr were significantly higher than in the control group ($P = 0.003$), no differences were seen between them ($P > 0.05$). Serum ghrelin levels in the ANP group at 24 and 48 hr were higher than the level at 12 hr ($P < 0.05$ and $P < 0.001$, respectively). Serum ghrelin level at 48 hr in the ANP group was higher

than in the control and the AEP group. Considering that the histopathologic findings of pancreatitis last longer than 48 hr, serum ghrelin levels increased more and continued to increase significantly after 24 hr (Fig. 1).

Serum leptin levels

Serum leptin levels at 24 and 48 hr in both the AEP ($P = 0.027$ and $P < 0.001$, respectively) and the ANP ($P = 0.027$ and $P < 0.001$, respectively) groups were significantly higher than in the control group. At 12 hr, serum leptin levels in the ANP group were significantly higher than in the control group ($P < 0.001$). There was no significant difference in serum leptin levels at 48 hr in either the AEP or the ANP group. In the AEP group the serum leptin level at 48 hr was higher than the level at 12 hr, but in the ANP group there was no difference between the 48- and the 12-hr level ($P > 0.05$). Serum leptin levels showed an increasing line after 12 hr compared to the control group (Fig. 2).

Discussion

In this study, we investigated the serum levels of ghrelin and leptin in experimental models of AP of differing severities. This is an original study, being the first to determine the serum ghrelin levels in AP. Serum ghrelin levels started to increase 24 hr after i.p administration of L-arginine and cerulein and reached the peak level at 48 hr. Serum ghrelin levels in the ANP group were higher than those in the AEP group. Similarly, serum leptin levels in both pancreatitis groups started to increase after 12 hr and stayed at a higher

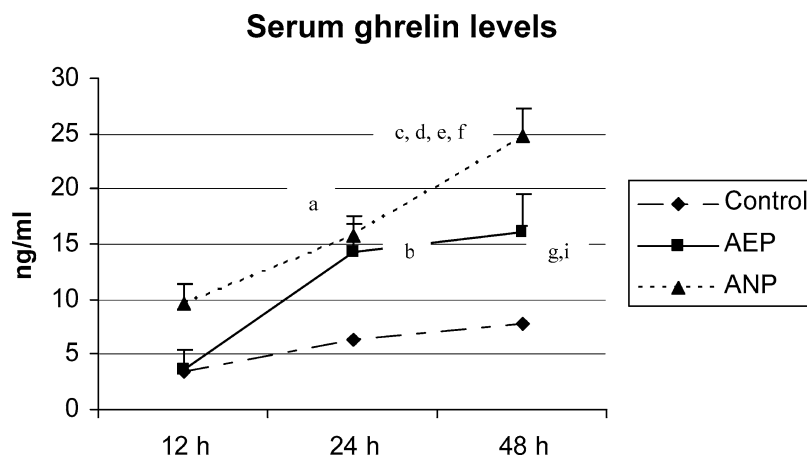
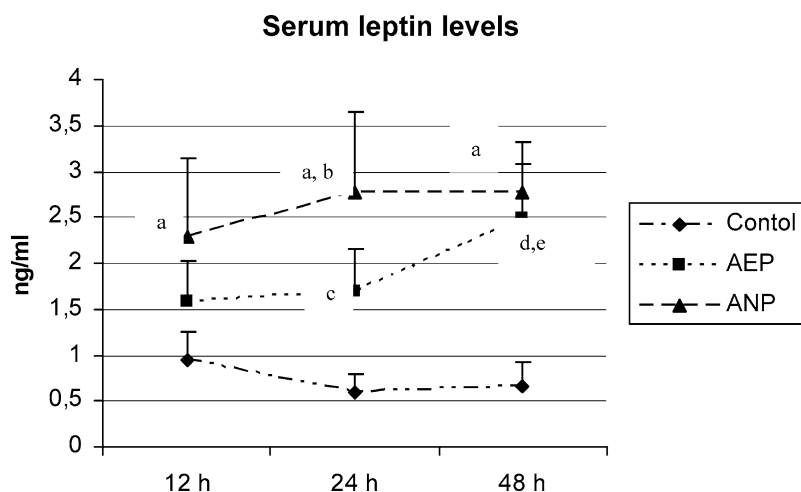


Fig. 1 Serum ghrelin levels at 24 and 48 hr in both the AEP and the ANP groups were significantly higher than in the control group. At 48 hr the serum ghrelin level in the ANP group was significantly higher than in the AEP group. ^a $P = 0.003$ vs. the control group; ^b $P = 0.023$

vs. the control group; ^c $P < 0.001$ vs. the control group; ^d $P = 0.07$ vs. the AEP group; ^e $P = 0.001$ vs. 12 hr in the ANP group; ^f $P = 0.001$ vs. 24 hr in the ANP group; ^g $P = 0.014$ vs. the control group; ⁱ $P < 0.001$ vs. 12 hr in the AEP group

Fig. 2 Serum leptin levels at 24 and 48 hr in both the AEP and the ANP groups were significantly higher than in the control group. At 12 hr the serum leptin level in the ANP group was significantly higher than in the control group. ^a $P < 0.001$ vs. the control group; ^b $P = 0.027$ vs. the AEP group; ^c $P = 0.022$ vs. the control group; ^d $P < 0.001$ vs. the control group; ^e $P < 0.05$ vs. 12 and 24 hr in the AEP group



level compared to the control group. Parallel to the increase in serum ghrelin and leptin levels at 48 hr, blood glucose levels in both pancreatitis groups increased in the same period; but the blood glucose level increased to >200 mg/ml in the ANP group, which is a worse prognostic factor [3]. In recent studies, several cytokines such TNF- α , which was investigated as a prognostic factor [4], and IL-1 β , which has an important role in the pathophysiology of AP [1, 4], has been studied several times before. In our study, it was seen that following i.p administration of cerulein and L-arginine, IL-1 β and TNF- α levels reached peak levels at 24 hr and decreased to the control-group level at 24 hr.

The biological effects of leptin are exerted via specific leptin receptors which have been detected in gastric mucosa, small intestine, and liver, as well as in pancreatic β cells and pancreatic acini and afferent nerves [21–23]. A recent study showed that leptin receptors have been detected on pancreatic AR42J cells and their gene expression has been documented in pancreatic acini, suggesting that this protein could take part in the regulation of pancreatic exocrine secretion [24]. Based on the information that leptin has a regulatory effect on endocrine and exocrine functions of the pancreas, levels of leptin in AP have been the subject of several studies. Yavuz *et al.* [27] showed that 24 hr and 7 days after the induction of edematous pancreatitis with i.p cerulein, serum leptin levels were higher than in the control group, but there was no difference between the levels on day 1 and day 7. Similarly Konturek *et al.* [28] showed high serum leptin levels in patients with AP compared with the control group. In our study serum leptin levels increased after 12 hr in the ANP group and after 24 hr in the AEP group and reached the peak level at 48 hr in both groups compared with the control group.

AP is associated with induction of a systemic inflammatory response, which is responsible for its morbidity and mortality [1–3]. With increasing neutrophil migration to the

pancreas, a variety of inflammatory cytokines is realized, including IL-1, IL-6, IL-8, platelet activating factors, and TNF- α . There is considerable evidence that pro-inflammatory cytokines (TNF- α and IL-1 β) play a central role in AP and may mediate the systemic complications of AP [1, 2]. Pro-inflammatory cytokine production correlates with disease severity [1, 2]. Konturek *et al.* [28] showed that leptin given in the experimental model of AP has a modulating effect on inflammation by increasing the levels of TNF- α and the anti-inflammatory cytokine IL-4. And also, Warzecha *et al.* [29] showed a decline in IL-1 β level following the administration of leptin in experimental ischemic AP. Dembinski *et al.* [30] demonstrated that pancreatic treatment with ghrelin diminished pro-inflammatory IL-1 β release. Leptin and ghrelin generated in the pancreas during AP could act by reducing the increments of proinflammatory cytokines, such as TNF- α and IL-1 β . In our study TNF- α and IL-1 β levels increased 24 hr after the induction of pancreatitis in both pancreatitis groups, especially in the ANP group, and decreased to the level of the control group at 48 hr. As the serum leptin and ghrelin levels at 24 and 48 hr were significantly higher than in the control group, they are probably responsible for the decrease in pro-inflammatory cytokine levels. Especially, this effect may be more prominent in the AEP group because of the higher ghrelin levels compared with the ANP group.

As a result, serum leptin and ghrelin levels are increasing at 48 hr of experimental AP. Serum ghrelin levels can be used in follow-up of the severity of pancreatitis. Endogenous leptin and ghrelin may be responsible for the hyperglycemia and the moderation of pro-inflammatory cytokines in AP. While TNF- α and IL-1 β are valuable as prognostic factors in the first 24 hr, the levels of ghrelin and leptin can be used for this purpose in later periods. The long-term effects of these two polypeptides on AP can be determined by more studies.

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