

Original

Stress hyperglycaemia in critically ill patients; Potential role of incretin hormones; a preliminary study

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Abstract

Background: Stress hyperglycaemia is common in the intensive care unit (ICU) setting and has been related to a worst outcome.

Objective: The objective was to characterize the association of glucoregulatory hormones, mainly incretins, with the levels of glycaemia, and its relationship with outcome in ICU patients.

Methods: We prospectively studied 60 patients. Stress hyperglycaemia was diagnosed when glycaemia was > 115 mg/dL. At ICU admission we determined glycaemia, insulin, glucagon, cortisol, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) plasma levels. Groups were compared using Kruskal-Wallis test. The association between glycaemia levels and glucoregulatory hormones was evaluated using linear regression.

Results: Forty-five patients (75%) had hyperglycaemia. We observed no differences in glucoregulatory hormones levels between normo- and hyper- glycaemia groups. Glycaemia levels were not significantly correlated with insulin, glucagon, cortisol or GIP levels, but were correlated with GLP-1 (p = 0.04). GLP-1 was also correlated with cortisol (p = 0.01), but failed to show a significant correlation with insulin, glucagon or GIP levels. Lower levels of plasma GLP-1 were found in patients with stress hyperglycaemia requiring vasoactive support (p = 0.02).

Conclusions: Glycaemia levels were correlated with GLP-1 levels in ICU patients. GLP-1 levels were also associated with cortisol. Patients with stress hyperglycaemia who required vasoactive support had lower incretin levels compared with those patients with stress hyperglycaemia who were hemodynamically stables. (ClinicalTrials.gov Identifier: NCT01087372).

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HIPERGLUCEMIA DE ESTRÉS EN EL PACIENTE CRÍTICO; PAPEL POTENCIAL DE LAS INCRETINAS; ESTUDIO PRELIMINAR

Resumen

Antecedentes: La hiperglucemia de estrés es habitual en el contexto de la Unidad de cuidados intensivos (UCI) y se ha relacionado con un peor pronóstico.

Objetivo: el objetivo fue caracterizar la asociación de hormonas glucorreguladoras, principalmente las incretinas, con las glucemias y su relación con el pronóstico de los pacientes de UCI.

Métodos: Estudiamos de forma prospectiva a 60 pacientes. La hiperglucemia de estrés se diagnosticaba cuando la glucemia era > 115 mg/dl. En el ingreso en la UCI, determinamos la glucemia y las concentraciones plasmáticas de insulina, glucagón, cortisol, polipéptido insulinotropo dependiente de glucosa (GIP) y péptido-1 de tipo glucagón (GLP-1). Se compararon los grupos mediante la prueba de Kruskal-Wallis. La asociación entre las glucemias y las hormonas contrarreguladoras se evaluó mediante regresión linear.

Resultados: 45 pacientes (75%) tenían hiperglucemia. No observamos diferencias en las concentraciones de hormonas glucorreguladoras entre los grupos de normo e hiperglucemia. Las glucemias no se correlacionaron de forma significativa con las concentraciones de insulina, glucagón, cortisol o GIP, pero sí con el GLP-1 (p=0,04). El GLP-1 también se correlacionó con el cortisol (p=0,01), pero no consiguió mostrar una correlación significativa con las concentraciones de insulina, glucagón o GIP. Se encontraron menores concentraciones plasmáticas de GLP-1 en los pacientes con hiperglucemia de estrés que requerían soporte vasoactivo (p=0,02).

Conclusiones: las glucemias se correlacionaron con las concentraciones de GLP-1 en los pacientes en UCI. Las concentraciones de GLP-1 también se asociaron con el cortisol. Los pacientes con hiperglucemia de estrés que necesitaron soporte vasoactivo tenían menores concentraciones de incretina en comparación con aquellos con hiperglucemia de estrés con estabilidad hemodinámica (ClinicalTrials.gov Identifier: NCT01087372).

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Palabras clave: Hiperglucemia de estrés. Incretinas. Polipéptido insulinotropo dependiente de glucosa. Péptido-1 de tipo glucagón. Pacientes críticos.

Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II score.

BMI: Body mass index.

GIP: Glucose-dependent insulinotropic polypeptide.

GLP-1: Glucagon-like peptide-1. HIV: Human immunodeficiency virus. HOMA: Homeostatic Model Assessment.

ICU: Intensive care unit. IIT: Intensive insulin therapy.

LOS: Length of stay. SD: Standard deviation. TBI: Traumatic brain injury.

Introduction

Stress hyperglycaemia is a common problem in critically ill patients^{1,2} independently of the acute condition they suffer and has been related to a worst outcome^{1,5} in the intensive care unit (ICU) setting. Treatment of this condition constitutes a relevant scientific topic, since the landmark studies by Van den Berghe et al.⁶ showed a reduced mortality in surgical patients treated with intensive insulin therapy (IIT), where as medical patients treated with IIT, obtained a less marked benefit in terms of survival with this therapy.⁷ As consequence of these trials, treatment with IIT became a standard of care in the ICU population

However, recent multicenter trials have shown opposite results and in addition, raised concerns about the feasibility and indications for IIT.⁸⁻¹² Specifically, safety was compromised by the increased incidence of hypoglycaemic episodes and significant glycaemic levels variability associated to insulin therapy, which was also associated to a worst outcome.^{13,14}

Incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are insulinotropic glucagonostatic gastrointestinal hormones that lower glucose in a stable glycaemia-dependent manner, and therefore, minimize the risk of hypoglycaemia. 15,16 Their concentrations rapidly increase after food intake. 15 An experimental model recently developed in rats, suggested a potential role of GLP-1 in the treatment of hyperglycaemia in the context of acute critical illness.17 Although preliminary studies with small sample size have shown a potential benefit role of treatments with incretins analogs (especially GLP-1) in hyperglycaemia in different populations of ICU patients, 18-23 we still do not have a clear understanding of the role of incretins in critically ill patients and its correlation with other glucoregulatory hormones. We speculate that endogenous incretins levels should be decreased in the stressed ICU patient and could play a role in the development of stress hyperglycaemia in this setting.

Objective

The aim of this study was to characterize the association of the glucoregulatory hormones (with especial focus on incretins levels) with the levels of glycaemia and its relationship with outcome in critically ill patients.

Methods

This study was conducted at the ICU of our tertiary university hospital (Hospital Universitari Son Dureta Palma de Mallorca, Spain) from January 2010 to April 2010. The Ethics Committee of the Balearic Islands approved the study on December 21st, 2009. In all cases, written informed consent for inclusion in the study was obtained from the patient or closest relative.

Patients

This was a prospective and observational study. We prospectively studied all patients consecutively admitted to the medical-surgical ICU of our institution who fulfilled the following inclusion criteria and none of the exclusion criteria.

Inclusion criteria: Age > 18 years, emergent ICU admission, having obtained written informed consent from patients or relatives.

Exclusion criteria: Previously known type I or type II diabetes, patients who received insulin or oral antidiabetic agents before ICU admission, malignancies, scheduled surgery, patients receiving enteral or parenteral nutrition, inability to obtain informed consent.

In all cases, patients were managed according to international guidelines depending on the admission diagnosis.

Data collection. Predefined subgroups

The following clinical and demographic data of interest were prospectively recorded: age, gender, ICU admission diagnosis, cardiac rate, mean arterial pressure, the Acute Physiologic and Chronic Health Evaluation (APACHE) II score, Glasgow coma scale score, use of vasoactive agents, use of mechanical ventilation, paO2 to FiO2 ratio, body mass index, ICU length of stay and ICU mortality.

The values of the glucoregulatory hormones were evaluated in patients with hyperglycaemia and in a control group, constituted by patients with glycaemia levels equal or less than 115 mg/dL. In addition, based on the controversy existing on the optimal glycaemia thresholds and the potential role of IIT in the treatment of stress hyperglycaemia in different populations of critically ill patients, we analyzed the following predefined subgroups: 1) Surgical (trauma, surgery and

 Table I

 Baseline clinical characteristics of the 60 patients distributed by normo- or hyperglycaemia. Dara are presented as mean ± SD or number and percentage as appropriate

	Glycaemia ≤ 115 mg/dL n: 15	Glycaemia > 115 mg/dL n: 45	p value
Gender female, n (%)	3 (20.0)	9 (20.0)	1.0
Age, years	37 ± 17	43 ± 18	0.26
BMI	24.9 ± 4.5	24.7 ± 3.0	0.90
APACHE II	14.2 ± 4.4	14.0 ± 6.0	0.48
Past history, n (%)			
Hypertension	3 (20.0)	6 (13.3)	0.68
Dyslipidemia	1 (6.7)	3 (6.7)	1.0
Heart disease	1 (6.7)	3 (6.7)	1.0
Lung disease	0(0.0)	2 (4.4)	1.0
Liver disease	0(0.0)	3 (6.7)	0.57
Kidney disease	0	0	
HIV infection	0 (0.0)	3 (6.7)	0.57
Alcohol abuse	1 (6.7)	3 (6.7)	1.0
Tobacco	2 (13.3)	4 (8.9)	0.63
Main Diagnosis, n (%)		0.34	
TBI	8 (53.3)	18 (40)	
Trauma (non-TBI)	1 (6.7)	8 (17.8)	
Sepsis	4 (26.7)	5 (11.1)	
Cerebrovascular disease	1 (6.7)	7 (15.6)	
Outcome			
ICU LOS, days	7.7 ± 6.8	12.8 ± 12.0	0.25
Mortality, n (%)	1 (6.7)	6 (13.3)	0.67

BMI: Body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II score; HIV: Human immunodeficiency virus; TBI: Traumatic brain injury; ICU: Intensive care unit; LOS: Length of stay.

burns) vs. non-surgical patients. 2) Neurological (brain injury, cerebrovascular disease, subarachnoid hemorrhage and meningitis) vs. non-neurological patients. 3) Patients who required vasoactive support vs. hemodynamically stable patients without vasoactive support.

Samples and analysis

Samples were obtained from an arterial line at ICU admission, after cardiopulmonary stabilization was achieved and before initiating enteral or parenteral nutrition and/or treatment with insulin. Blood was collected in 10-mL serum tubes and for plasma analysis into chilled ethylenediaminetetraacetic acid tubes. Both serum and plasma were separated by centrifugation (3,500 rpm for 10 minutes at 4°C). Samples were frozen at -80°C until analyzed. Serum glycaemia was determined by enzymatic calorimetric assay GOD-PAP in Hitachi Modular Analyzer (Roche diagnostics GmbH, Mannheim, Germany). Normal values for nonstressed volunteers: 70-100 mg/dL. Serum insulin was measured by a commercial chemiluminiscent assay in Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics, NY, USA). Reference values: Insulin 2-29 µUI/mL. Serum Cortisol was determined by chemiluminiscent assay in Advia Centaur analyzer (Siemens Medical Solutions Diagnostics, NY, USA). Reference values: 4.3-25 μ g/dL. Plasma glucagon was determined by enzyme linked inmunosorbent assay (ELISA) using commercially available kits (DRG International Inc, USA), in a DSX System. Reference values: 59-177 pg/mL. Serum GIP (pg/mL) and plasma GLP-1 (ng/mL) were measured using ELISA (DRG International Inc, USA), in a DSX System. Using the previous data, we also evaluated the insulin resistance using the Homeostatic Model Assessment (HOMA) index, which was calculated as the product of the fasting plasma insulin level (μ U/mL) and the fasting plasma glucose level (mg/dl), divided by 405.

Statistical analysis

Variables are expressed in mean and standard deviation (SD) for continuous variables and numbers and percentages for categorical variables as appropriate. Differences were compared between groups using the independent Student's *t* test or Mann-Whitney U test (for continuous variables) or Chi-square or Fisher exact test (for categorical variables) when appropriate. Differences were compared between the different subgroups studied using Kruskal-Wallis test. The association between glycaemia levels and glucoregulatory hormones in the whole population and in the predefined subgroups was evaluated using linear regression.

Table IIGlucoregulatory hormones levels at ICU admission. Data are presented as mean ± SD

	Glycaemia ≤ 115 mg/dL n: 15	Glycaemia > 115 mg/dL n: 45	p value
Glycaemia	100 ± 15	160 ± 59	< 0.001
Insulin	5.0 ± 4.8	8.0 ± 5.6	0.07
HOMA	1.2 ± 1.3	3.1 ± 2.5	0.001
Glucagon	219 ± 86	223 ± 122	0.90
Cortisol	18.5 ± 11.1	22.4 ± 13.7	0.33
GIP	25.5 ± 23.8	36.1 ± 45.5	0.91
GLP-1	0.52 ± 0.12	0.58 ± 0.27	0.24

ICU: Intensive care unit; HOMA: Homeostatic Model Assessment index; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

A *p* value less than 0.05 was considered significant. Data were analyzed using specific software: SPSS statistical package version 17.0 (SPSS Inc, Chicago).

Results

Baseline clinical characteristics of the 60 patients studied are summarized according to normo- or hyperglycaemia (table I). Forty-five patients (75%) had hyperglycaemia at ICU admission. The main clinical parameters at the time of sampling were: time from ICU admission 116 ± 92 minutes, heart rate 85 ± 23 bpm, mean arterial pressure 87 ± 17 mmHg, mean PaO2 to FiO2 ratio 320 ± 153 , mean Glasgow coma scale score 10 ± 4 . Ten patients (16.7%) received norepinephrine and 46 patients (76.7%) were mechanically ventilated at the time of assessment. Severity of illness was similar in normo- and hyper- glycaemic patients (table I), as well as in the subgroups analysis: surgical vs. non-surgical patients (p = 0.35), neurological vs. non-neurological patients (p = 0.78) and patients requiring vasoactive support vs. hemodynamically stables (p = 0.24).

We did not observe significant differences in mean values of the glucoregulatory hormones between normo- and hyper- glycaemia groups (table II). Interestingly, insulin plasma levels were $5.0 \pm 4.8 \,\mu\text{UI/mL}$ in the normoglycaemic group whereas insulin levels elevated to $8.0 \pm 5.6 \,\mu\text{UI/mL}$ in the hyperglycaemic group (non-significative p = 0.07). The levels of plasma glucagon were similar in both groups. HOMA index was lower in the normoglycaemia group, as expected (table II). Analysis of mean values of glucoregulatory hormones according to predefined subgroups, surgical vs. non-surgical, neurological vs. nonneurological and patients with vasoactive support vs. hemodynamically stable are shown in tables III, IV and V respectively. We found lower levels of incretin hormones (especially GLP-1) in the group of patients with hyperglycaemia who required vasoactive support compared with those patients with stress hyperglycaemia who were hemodynamically stables (table V).

Glycaemia levels were not significantly correlated with insulin, glucagon, cortisol or GIP levels, but were correlated with GLP-1 (fig. 1). Along with this correlation with glycaemia levels, GLP-1 was also correlated with cortisol, but failed to show a significant correlation with insulin, glucagon or GIP levels (fig. 2).

Mean values of the following glucoregulatory hormones were not found to be correlated with mortality:

Table III

Glucoregulatory hormones levels at ICU admission distributed by surgical and non-surgical patients.

Data are presented as mean \pm SD

	Surgical		Non-surgical		
	$G \le 115 mg/dL$ $n: 9$	G > 115 mg/dL n: 32	$G \le 115 mg/dL$ $n: 6$	G > 115 mg/dL n: 13	p value
Glycaemia	99 ± 18	158 ± 59	102 ± 9	164 ± 59	< 0.001
Insulin	4.9 ± 4.3	7.7 ± 5.9	5.0 ± 5.9	8.6 ± 5.1	0.20
Glucagon	177 ± 43	202 ± 96	283 ± 99	275 ± 164	0.14
Cortisol	15.1 ± 8.6	19.8 ± 12.0	23.6 ± 13.1	28.4 ± 16.6	0.20
GIP	19.4 ± 12.5	36.2 ± 41.6	34.8 ± 34.2	35.8 ± 55.8	0.88
GLP-1	0.56 ± 0.09	0.59 ± 0.23	0.46 ± 0.14	0.57 ± 0.35	0.48

ICU: Intensive care unit; G: Glycaemia; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

Table IV Glucoregulatory hormones levels at ICU admission distributed by neurological vs non-neurological patients. Data are presented as mean \pm SD

	Neurological		Non-neurological		
	$G \le 115 mg/dL$ $n: 10$	G > 115 mg/dL n: 28	$G \le 115 mg/dL$ $n: 5$	G > 115 mg/dL n: 17	p value
Glycaemia	99 ± 17	144 ± 23	103 ± 8	186 ± 86	< 0.001
Insulin	4.8 ± 4.4	8.6 ± 6.3	5.2 ± 6.1	7.1 ± 4.5	0.20
Glucagon	196 ± 69	199 ± 96	264 ± 106	263 ± 151	0.33
Cortisol	13.9 ± 7.6	22.0 ± 12.9	27.7 ± 11.8	23.1 ± 16.1	0.17
GIP	16.8 ± 9.6	41.9 ± 49.4	43.1 ± 34.8	26.5 ± 37.6	0.57
GLP-1	0.54 ± 0.09	0.56 ± 0.17	0.48 ± 0.18	0.61 ± 0.38	0.76

ICU: Intensive care unit; G: Glycaemia; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

Table V Glucoregulatory hormones levels at ICU admission in patients treated with vasoactive support vs hemodinamically stables. Data are presented as mean \pm SD

	Vasoactive support		Hemodinamically stables without vasoactive support		
	$G \le 115 mg/dL$ $n: 2$	G > 115 mg/dL n: 8	$G \le 115 mg/dL$ $n: 13$	G > 115 mg/dL n: 37	p value
Glycaemia	100 ± 8	163 ± 39	100 ± 16	159 ± 62	< 0.001
Insulin	3.2 ± 1.9	8.0 ± 5.7	5.2 ± 5.1	8.0 ± 5.7	0.25
Glucagon	336 ± 24	206 ± 145	201 ± 77	227 ± 119	0.25
Cortisol	31.2 ± 15.3	20.0 ± 14.4	16.6 ± 9.6	23.0 ± 14.0	0.29
GIP	31.7 ± 32.4	10.4 ± 6.4	24.6 ± 23.8	41.7 ± 48.4	0.16
GLP-1	0.52 ± 0.05	0.36 ± 0.19 *	0.52 ± 0.13	0.63 ± 0.26 *	0.02

*p value < 0.05.

ICU: Intensive care unit; G: Glycaemia; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

glycaemia (p = 0.53), insulin (p = 0.87), glucagon (p = 0.11), cortisol (p = 0.85), GIP (p = 0.70), HOMA index (p = 0.69) and GLP-1 (p = 0.05).

Discussion

The main findings of our study were that glycaemia levels were correlated with GLP-1 levels. GLP-1 was also associated with cortisol. Patients with stress hyperglycaemia who required vasoactive support had lower endogenous incretins levels compared with those patients with stress hyperglycaemia who were hemodynamically stables.

Stress hyperglycaemia is a common feature in critically ill patients, which is considered a marker of worst prognosis in this population.¹⁻⁵ Whether treatment of this condition by means of IIT improves prognosis remains unclear, according to published studies⁶⁻¹³ which raised concerns about safety due to an increased number of hypoglycaemic episodes and increased glycaemia variability.^{13,14}

A novel approach to stress hyperglycaemia is based in the use of incretins analogs. ¹⁵⁻²³ Specifically, GLP-1

increases insulin secretion to normal levels only in hyperglycemia states, suppresses glucagon, and therefore, lowers glucose in a stable manner in the setting of hyperglycaemia, avoiding episodes of hypoglycaemia^{15,16} and might have beneficial effects on cardiac function. 18,20,21 These characteristics makes GLP-1 an ideal agent to be considered in the treatment of stress hyperglycemia in critically ill patients.¹⁶ However, some questions are still unclear, such as what dose should we use, which is the best route of administration, and which groups of critically ill patients might benefit the most from this therapy.16 Little is known about the levels of endogenous incretins in critically ill patients, and its potential contribution to the development of stress hyperglycaemia, which is multifactorial and not fully understood.24 Different factors have been related with the development of stress hyperglycaemia in critically ill patients:24 some of them exogenous such as treatment with steroids, vasopressors, parenteral and enteral nutrition; others affecting patient predisposition, such as pancreatic reserve and insulin resistance, and some related to severity and nature of underlying illness, such as use of catecholamines, inflammatory

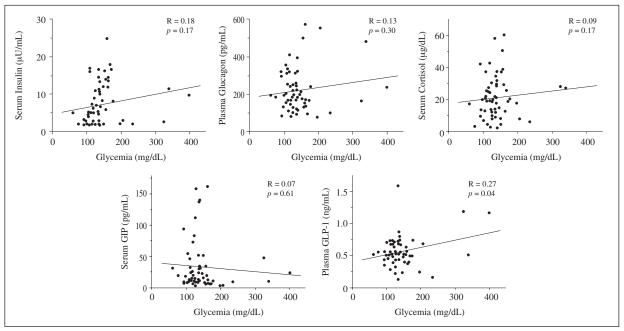


Fig. 1.—Correlation between glycaemia levels and the glucoregulatory hormones studied.

cytokines, lipotoxicity and hypothalamic-pituitaryadrenal axis activation.

We hypothesized that patients with stress hyperglycaemia should present decreased levels of glucoregulatory hormones. Therefore, in this study we evaluated the levels of glucoregulatory hormones (with special focus on incretins levels) at ICU admission.

In our fasting ICU patients we found that the only glucoregulatory hormone which presented a significant association with glycaemia was GLP-1. In addition, GLP-1 showed a moderate correlation with cortisol levels. Interestingly GLP-1 and GIP were lower in patients with hyperglycaemia who required vasoactive support compared with those patients with stress hyperglycaemia who were hemodynamically stables (table V). Analyzing together these results, one could speculate that an interaction between the hypothalamic-pituitary-adrenal and enteroendocrine systems exists. However, in those patients requiring vasoactive support, the activation of the enteroendocrine axis seems to be disturbed, leading to lower incretins levels. A possible explanation to these findings is based on a detrimental effect of cathecolamines in incretins levels, a fact that would not affect the potential clinical implications of the study. The fact that all groups had similar severity of illness evaluated by the APACHE II score supports this affirmation.

Our results suggest that the failure of the enteroendocrine axis might play a role in the development of stress hyperglycaemia, and therefore, treatment with GLP-1 analogs may constitute a promising tool in the treatment of this condition in the ICU patients. The fact that in the hyperglycaemic group of ICU patients the presence of higher levels of plasma insulin were insufficient to maintain euglycaemia, underlines a

potential role of GLP-1 analogs, (stimulating insulin secretion and specifically reducing glucagon levels) helping to control hyperglycaemia in these patients. According to our results, this treatment could potentially benefit the most, those ICU patients requiring vasoactive support. However, certain points should be taken into account and can influence our results: GLP-1 has a short half-live and the main stimuli for its secretion are the food intake and the presence of nutrients in the gastrointestinal tract.²⁵ Our patients were in a fasting status to exclude potential confounders. The time the patients were in a fasting status was unknown. which constitutes a potential drawback in our study. However, in all cases, the patients were admitted through the emergency department, so a minimum fasting period of 90 minutes could be ensured. As previously stated, different mechanisms which are not completely understood can be involved in the development of stress hyperglycaemia.24

Our study presents some limitations: the most important one is that we analyzed the glucoregulatory hormones at one single point, so we can not evaluate the time-course of these hormones. However, we decided to perform the analysis in this fashion in fasting patients to rule out potential confounding factors, such as treatment with oral antidiabetic agents, insulin or with exogenous factors involved in the development of stress hyperglycaemia, for example, treatment with glucocorticoids or enteral and parenteral nutrition. In addition, our sample is relatively small to find significant differences in some of the subgroups of patients studied, and therefore, the risk of type I and type II errors in the statistical analysis increases.

In summary, our study showed that glycaemia levels were correlated with GLP-1 levels. GLP-1 levels

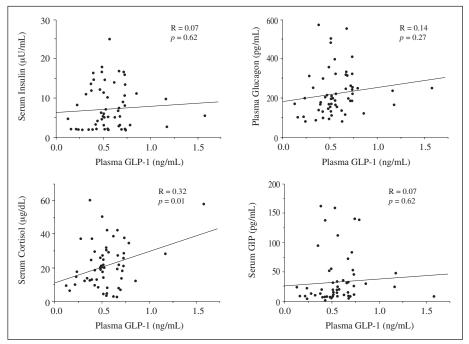


Fig. 2.—Correlation between GLP-1 levels and the other glucoregulatory hormones.

were also associated with cortisol suggesting an interaction between the hypothalamic-pituitary-adrenal and enteroendocrine systems, which seems to be especially disturbed in the patients requiring vasoactive support, who presented lower incretin levels compared with those patients with stress hyperglycaemia who were hemodynamically stables. A randomized controlled study evaluating the role of GLP-1 analogs in the management of stress hyperglycemia in critically ill patients is warranted, with special focus on patients requiring vasoactive support and in the dynamic evolution in patients receiving enteral and parenteral nutrition, which were not included in this study.

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