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Dysfunctional pancreatic β-cells of critical stress play a more prominent role in the development of stress diabetes in critically burned Korean subjects

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Abstract

The purposes of this study are to identify the predictive parameters for the development of stress-induced hyperglycemia and to investigate the glucose metabolic homeostasis in critically burned Korean subjects. We conducted a prospective cross-sectional study of adult patients with glucose management targeting fasting and postprandial blood glucose levels less than 140 and 200 mg/dL, respectively, in patients with unrecognized diabetes. Clinical and laboratory stress parameters and insulin secretory and sensitivity parameters were assessed. Stimulated C-peptide and 24-hour urinary free cortisol predicted new-onset stress diabetes requiring insulin therapy. The subjects requiring insulin therapy were leaner and more insulin sensitive than insulin-free subjects, without significance. Glycated hemoglobin, stimulated C-peptide, homeostasis model assessment of insulin resistance, and age had a significant influence on the mean daily dose of insulin. Our present data showed that Korean subjects with dysfunctional pancreatic β-cells of critical stress are prone to become stress diabetic and require more insulin to control the hyperglycemia.

1. Introduction

One of the typical metabolic characteristics of critical illness is the stress-induced hyperglycemia, known as *stress diabetes* [1]. The metabolic milieu after acute severe burns in adults is caused by the increase in both excessive releases of counterregulatory hormones and overproduction of inflammatory cytokines, and results in significant insulin resistance and hepatic glycogenesis [2,3]. It is known that the acute burn stress-induced hyperglycemia appears to occur in 2 stages. The first phase, named the *ebb phase*, occurs immediately after injury through 2 or 3 days post–burn injury during which their metabolic rates and insulin secretion were decreased, which is followed by the second *flow* phase around the fifth day postinjury and continues up to 9 months during which increased insulin resistance, muscle catabolism, and hyperglycemia persist [4-6]. Another origin of hyperglycemia in this situation could be the unrecognized impairment of glucose tolerance, including occult frank diabetes.

Although severe insulin resistance develops in the flow phase, not all severely burned subjects express states of hyperglycemia requiring glucose-lowering therapy with insulin. In addition, the deterioration of glucose levels in subjects with burn injuries has been characterized; but the metabolic characteristics in Korean patients with severe burn injuries are not well elucidated, and the clinical and laboratory parameters predicting the development of burn

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stress diabetes also remain unclear. We thus tried to identify the predictive parameters for the development of stress-induced hyperglycemia and to investigate the parameters for glucose metabolic homeostasis and aggravation of stress diabetes in severely burned Korean subjects without a history of disease.

2. Subjects and methods

2.1. Subjects and burn care design

This was a prospective, cross-sectional study of adult patients (≥18 years of age) conducted in the burn intensive care unit (ICU) at the Burns Center of Hangang Sacred Heart Hospital from October 2008 to June 2009. Patients were excluded for the following reasons: a history of hepatic or renal disorders, cardiac failure or malignancy, diabetes mellitus, preexisting metabolic disorders, or glucocorticoid therapy.

After obtaining approval from the local ethical committee, written informed consent was obtained from a first-degree relative of each severely burned patient admitted to the burn ICU. The Abbreviated Burn Severity Index (ABSI) [7] and Acute Physiology And Chronic Health Evaluation (APACHE) II scores [8] of all patients were assessed by an experienced physician at the time of hospital admission. The diagnosis and severity classification of inhalation injuries were made based on a history of a fire and bronchoscopy within 24 hours after admission [9]. Briefly, 8 bronchoscopic points (airway edema, blistering, carbonaceous material, soot, hemorrhage, inflammation, ulceration, and necrosis of mucosa) were used in the bronchoscopic scoring system. We treated all patients admitted to the burn ICU with a standard feeding protocol using the Modified Harris-Benedict formula of Long et al [10] for nutritional support. Briefly, all subjects received parenteral nutrition for 24 hours after admission and then had a prepyloric feeding tube installed. Caloric goals were estimated by indirect calorimetry (Sensor-Medics 2900Z, SensorMedics, Yorba Linda, CA) measurements of resting energy expenditure and nitrogen balance. In addition, blood and plasma products, albumin, antibiotics, and analgesics were also administered when clinically indicated. The excision of the eschar was performed as soon as possible after the end of the early phase of fluid therapy, and the wounds were covered with allograft skin grafts.

2.2. Glycemic management protocol

The glycemic management protocol (Table 1) was incorporated. The target goal of the protocol is to maintain less stringent target fasting and postprandial blood glucose (BG) levels less than 140 and 200 mg/dL, respectively. Initially, we measured capillary BG levels with point-of-care testing Precision PCx glucose meters (Abbott Laboratories, Irving, TX) at 6:30 AM, 10:00 AM, 4:00 PM, and 9:00 PM, but less frequently at 6:30 AM and 4:00 PM if fasting (<110 mg/dL) and postprandial (<160 mg/dL) glucose values were stable for 3 consecutive days.

Table 1
Glucose management protocol

	Initial LAA	Dose down LAA	Dose up LAA	SAA
<70 mg/dL		Stop LAA		
<80 mg/dL		0.3 U/kg		
<90 mg/dL		0.2 U/kg		
<110 mg/dL		0.1 U/kg		
<140 mg/dL	0.0 U/kg			
140-169 mg/dL	0.3 U/kg		0.1 U/kg	
170-199 mg/dL	0.4 U/kg		0.2 U/kg	
200-249 mg/dL	0.6 U/kg		0.3 U/kg	4 U
250-299 mg/dL	0.8 U/kg		0.4 U/kg	6 U
300-349 mg/dL	1.0 U/kg			8 U
350-399 mg/dL	1.2 U/kg			10 U

SAA indicates short-acting analogue.

Basal and/or fasting BG is controlled with a single dose of the long-acting analogue (LAA) glargine (Lantus; Sanofi-Aventis Pharmaceuticals, Paris, France), and postprandial BGs are controlled with short-acting analogue lispro (Humalog; Eli Lilly, Fegersheim, France). Insulin administration begins with LAA on admission day 2. Long-acting analogue is started if the fasting BG value exceeds 140 mg/dL, and titrations of LAA are made based on 3 successive 6:30 AM BG.

Major hypoglycemic events were defined as events compatible with following characteristics: (*a*) BG measurement less than 50 mg/dL and (*b*) reversal of signs and symptoms after intravenous glucose administration.

2.3. Glucose control markers and β-cell function and insulin sensitivity

Glycated albumin (GA) and glycated hemoglobin (A_{1c}) were measured as surrogate markers for average BG on the first and 21st days of post–burn injury. Glycated hemoglobin was determined by high-performance liquid chromatography using a Tosoh G7 (Tosoh Bioscience, Inc, Tokyo, Japan). The overnight fasting serum biochemistry, insulin, and a glucagon stimulation test (8:00 AM) were also taken on the fourth and 21st days of post–burn injury. Serum insulin and C-peptide (Immunotech, Marseille, France) levels were measured in duplicate with an immunoradiometric assay method.

Pancreatic β-cell function was obtained by homeostasis model assessment (HOMA) using HOMA of pancreatic β-cell function (HOMA-β) = fasting insulin × 3.33/(fasting glucose − 3.5) [11]. Additional β-cell secretory function or insulin reserve was determined by 1-mg glucagon (Daihan Pharmaceuticals, Seoul, Korea) stimulation testing that measured basal C-peptide (bCP) at 0 minute and stimulated C-peptide (sCP) at 6 minutes; C-peptide increment (ΔC-peptide = sCP − bCP) and incline of C-peptide increment (ΔC-peptide/bCP) [12].

Insulin sensitivity was assessed using HOMA of insulin resistance (HOMA-IR) [11], which was calculated from fasting glucose and insulin levels, using HOMA-IR = fasting insulin/(22.5 × $e^{-\ln \text{ fasting glucose}}$). Another insulin sensitivity index was defined with the quantitative insulin sensitivity check index (QUICKI) using the following formula: 1/[$\log_{10}$ (fasting glucose) + $\log_{10}$ (fasting insulin)] [13].

2.4. Levels of total serum cortisol and 24-hour urinary free cortisol

On post–burn injury day 4, serum cortisol (RADIM, Rome, Italy) and plasma corticotropin (BRAHMS, Hennigsdorf, Germany) concentrations were analyzed using a commercially available radioimmunoassay kit with a coated-tube technique. Twenty-four–hour urinary free (u-free) cortisol levels were measured on the fourth and 14th days of post–burn injury by radioimmunoassay (RADIM).

2.4.1. Statistical analyses

Results are presented as mean ± SD or as medians. Levene test was used to test the data for equality of variances. Analysis of variance (ANOVA) with post hoc Bonferroni multiple comparison test was used to assess differences between groups, and *t* test was used where appropriate to compare variables. Multiple linear regression analysis was performed using (1) new-onset stress diabetes requiring insulin therapy and (2) mean daily dose of insulin as a dependent factor. Several clinical and laboratory variables including age, body mass index (BMI), ABSI, APACHE II, total body surface area (TBSA), inhalation scores, A_{1c} on the first day, GA on the first day, glucose on the fourth and 21st days, insulin on the fourth and 21st days, HOMA-β on the fourth and 21st days, insulin sensitivity index (HOMA-IR, QUICKI) on the fourth and 21st days, corticotropin, cortisol, 24-hour u-free cortisol and creatinine clearance on the fourth and 14th days, and β-cell reserve (bCP, sCP, and C-peptide increment) on the fourth and 21st days of post–burn injury were entered as independent factors.

Sample-size calculations were based on the A_{1c} using primary data [14-16], where a threshold A_{1c} of high risk was greater than or equal to 6.1 and a threshold A_{1c} of low risk was less than or equal to 5.4 with a ratio of sample size (3 = diabetes/normal glucose). In addition, expected mortality in the enrolled subjects was based on our previous report [9]. Statistical significance was defined as a conventional P value < .05. All statistical analyses were conducted using PRISM version 3.0 (GraphPad Software, San Diego, CA).

3. Results

Of the sixty patients with critical burn injuries who were admitted to the burn ICU, 11 patients died and 2 patients dropped out during the study, resulting in the overall mortality rate of 18.3%. The patients' demographics and clinical data are summarized in Table 2. The mean and median times to death after the burn injury were 12.2 and 11 days, respectively, in the nonsurvivor group. When only comparing the survivor group (n = 45), there was a trend or significant difference in extent and severity of burn injuries in the nonsurvivor group (n = 11). Forty-seven had unrecognized diabetes, but 2 subjects showed A_{1c} levels of 10.5% and 8.5%. The subjects were classified into the following 2 groups: insulin analogue free (n = 10) and insulin requiring (n = 35). Finally, 45 were analyzed in the study. Mean patient age was 45.7 years, and considerable male dominance was shown. The patients suffered from severe burn injury of a mean 35.2% TBSA. There were no significant differences in age, BMI, total burn surface area, degree of inhalation injuries, ABSI, and APACHE II scores found between the insulin-free and insulin-requiring groups.

The serum and 24-hour urinary cortisol levels, β-cell secretory function, and insulin sensitivity parameters according to insulin-free and insulin-requiring statuses are shown in Table 3. The subjects requiring insulin therapy were leaner (lower BMI, 22.8 ± 2.3) and more insulin sensitive (lower HOMA-IR, 3.18 ± 2.87 and 1.67 ± 1.76 on fourth and 21st days, respectively) than insulin-free subjects (23.8 ± 3.9, 5.30 ± 7.23, and 2.59 ± 1.87, respectively). Twenty-four–hour u-free cortisol level on the 14th day post–burn injury was significantly higher in the insulin-requiring group (271.1 ± 181.1) than in the insulin-

Table 2
The patients' demographic and clinical parameters

	Patients demographics			
	All subjects (n = 45)	Insulin analogue–free (n = 10)	Insulin analogue–requiring (n = 35)	*t* test *P*
Age (y)	45.7 ± 13.5 (44)	45.0 ± 18.2 (44.5)	45.9 ± 12.2 (44)	*P* = .862
Sex (F/M)	13:32	3:7	10:25	*P* = 1.00
TBSA (%)	35.2 ± 14.9 (34.0)	36.0 ± 13.5 (34.5)	34.9 ± 15.5 (34.0)	*P* = .896
BS points	0.9 ± 18.0 (0.0)	0.4 ± 1.27 (0.0)	1.0 ± 1.6 (0.0)	*P* = .271
ABSI	8.3 ± 1.6 (8.0)	8.0 ± 1.2 (8.0)	8.4 ± 1.7 (8.0)	*P* = .460
APACHE II	5.8 ± 2.9 (6.0)	4.9 ± 2.6 (5.0)	6.1 ± 3.0 (7.0)	*P* = .249
BMI	23.0 ± 2.7 (23.3)	23.8 ± 3.9 (23.9)	22.8 ± 2.3 (23.3)	*P* = .456

Data are expressed as mean ± SD (median). BS indicates bronchoscopic.

Table 3
The serum and 24-hour urinary cortisol levels, β-cell secretory function, and insulin sensitivity parameters according to insulin-free and insulin-requiring status

		Glucose control markers and β-cell function and insulin sensitivity			
		All subjects (n = 45)	Insulin analogue–free (n = 10)	Insulin analogue–requiring (n = 35)	*t* test *P*
A_{1c}	D + 1	5.66 ± 0.41	5.46 ± 0.25	5.72 ± 0.43	*P* = .074
	D + 21*	5.76 ± 0.34	5.64 ± 0.10	5.79 ± 0.38	*P** = .036
GA	D + 1	13.26 ± 3.63	12.28 ± 4.09	13.54 ± 3.50	*P* = .340
	D + 21	12.86 ± 2.79	11.72 ± 2.84	13.19 ± 2.73	*P* = .144
ACTH	D + 4	28.10 ± 18.49	27.74 ± 11.24	28.20 ± 20.22	*P* = .946
s-cortisol		23.15 ± 6.17	25.45 ± 4.47	22.49 ± 6.47	*P* = .184
24-h u-cortisol	D + 4	367.7 ± 261.2	352.8 ± 198.1	371.0 ± 279.0	*P* = .841
	D + 14†	245.1 ± 168.4	154.0 ± 53.3	271.1 ± 181.1	*P*† = .002
D + 4					
Glucose		122.3 ± 38.2	114.7 ± 20.1	124.5 ± 41.9	*P* = .482
Insulin		11.64 ± 11.71	17.52 ± 20.94	9.96 ± 6.96	*P* = .288
bCP		2.63 ± 1.28	2.43 ± 1.20	2.69 ± 1.32	*P* = .577
sCP		3.87 ± 2.07	4.58 ± 2.61	3.67 ± 1.89	*P* = .225
HOMA-β		84.1 ± 74.2	117.1 ± 99.8	74.4 ± 63.5	*P* = .111
ΔC-peptide		1.24 ± 1.68	2.15 ± 2.08	0.98 ± 1.48	*P* = .051
Incline of ΔC-peptide		0.56 ± 0.80	0.97 ± 0.99	0.45 ± 0.72	*P* = .067
HOMA-IR		3.65 ± 4.22	5.30 ± 7.23	3.18 ± 2.87	*P* = .386
QUICKI		0.34 ± 0.04	0.34 ± 0.06	0.34 ± 0.04	*P* = .922
D + 21					
Glucose		98.7 ± 19.9	101.8 ± 8.9	97.8 ± 22.2	*P* = .585
Insulin		7.47 ± 6.53	10.23 ± 7.07	6.68 ± 6.25	*P* = .131
bCP		2.05 ± 1.88	2.18 ± 1.00	2.02 ± 2.07	*P* = .814
sCP†		3.49 ± 2.51	5.37 ± 2.87	2.92 ± 2.12	*P*† = .005
HOMA-β		86.3 ± 70.3	99.3 ± 75.3	82.5 ± 69.5	*P* = .512
ΔC-peptide*		1.28 ± 2.85	3.20 ± 2.59	0.74 ± 2.71	*P** = .014
Incline of ΔC-peptide		1.17 ± 1.95	1.59 ± 1.31	1.04 ± 2.10	*P* = .457
HOMA-IR		1.88 ± 1.80	2.59 ± 1.87	1.67 ± 1.76	*P* = .153
QUICKI		0.37 ± 0.05	0.35 ± 0.05	0.38 ± 0.05	*P* = .160

ACTH indicates adrenocorticotropic hormone.
The statistical significances were tested by *t* test.
* $P < .05$.
† $P < .01$.

free group (154.0 ± 53.3) ($P = .002$). The sCP level and C-peptide increments on the 21st day post–burn injury were statistically lower in the insulin-requiring group (2.92 ± 2.12 and 0.74 ± 2.71, respectively) than in the insulin-free group (5.37 ± 2.87 and 3.20 ± 2.59, respectively) ($P = .005$ and $P = .014$, respectively). The HOMA-β values of the insulin-free group and insulin-requiring group were 117.1 ± 99.8 and 74.4 ± 63.5, respectively, on the fourth day post–burn injury and 99.3 ± 75.3 and 82.5 ± 69.5, respectively, on the 21st day post–burn injury (without significance).

During multiple linear regression analysis, new-onset stress diabetes requiring insulin therapy was used as a dependent factor; and variable factors described in statistical analyses were entered in stepwise procedure. We found that sCP on the 21st day ($\beta = -0.420$, $P = .005$) and 24-hour u-free cortisol on the 14th day ($\beta = 0.328$, $P = .022$) in the stepwise procedure could predict new-onset stress diabetes requiring insulin therapy in subjects with unrecognized diabetes before burn injuries. The above independent variables were also entered in a stepwise manner after mean daily doses of insulin had entered the model in the multiple regression analysis. Of the independent factors entered, A_{1c} on the first day ($\beta = 0.676$, $P < .001$), sCP on the 21st day post–burn injury ($\beta = -0.372$, $P < .001$), HOMA-IR on the fourth day ($\beta = 0.391$, $P < .001$), age ($\beta = -0.365$, $P < .001$), and serum insulin level on the 21st day ($\beta = -0.240$, $P = .012$) had a significant influence on the mean daily dose of insulin. The demographic characteristics and glucose homeostasis parameters of subclassified patients according to requiring insulin analogue types are summarized in Table 4. Subjects requiring only basal insulin analogue were significantly younger and suffered from more severe inhalation burns. Compared with subjects requiring only basal insulin, subjects requiring both basal and short-acting insulin analogues showed significantly lower pancreatic β-cell function on the 21st day post–burn injury (54.6 ± 32.1 vs 156.0 ± 126.6, $P = .018$). Compared with subjects requiring only short-acting insulin, subjects requiring both basal and short-acting insulin analogues showed significantly increased A_{1c} levels on the first day (5.92 ± 0.45 vs 5.49 ± 0.26, $P = .012$) and increased insulin analogue demand to control the glucose.

Table 4
The demographic characteristics and glucose homeostasis parameters of subclassified patients according to insulin-requiring analogue types

		Demographic and glucose homeostasis parameter			
		Basal insulin-requiring (n = 4)	Short-acting insulin-requiring (n = 12)	Basal and short-acting insulin-requiring (n = 19)	ANOVA *P*
Age (y)		30.5 ± 8.5‖	46.1 ± 11.5	49.0 ± 11.0	*P** < .05
Sex (F/M)		1:3	5:7	4:15	NS
TBSA (%)		44.5 ± 22.2	30.8 ± 13.9	36.2 ± 14.7	NS
Bronchoscopic points		2.75 ± 2.22§	0.25 ± 0.45	1.21 ± 1.78	*P** < .05
ABSI		9.0 ± 2.8	8.3 ± 1.4	8.4 ± 1.7	NS
APACHE II		4.0 ± 3.5	5.8 ± 2.9	6.8 ± 2.8	NS
BMI		21.5 ± 2.4	23.1 ± 2.6	22.9 ± 2.1	NS
Transfusion					
p-RBC		10.5 ± 5.5	9.0 ± 6.9	9.8 ± 7.4	NS
FFP		7.6 ± 6.7	5.1 ± 4.7	5.6 ± 4.8	NS
Albumin		17.0 ± 6.4	10.9 ± 8.2	17.5 ± 10.5	NS
A_{1c}	D + 1	5.45 ± 0.17	5.49 ± 0.26¶	5.92 ± 0.45	*P** < .05
	D + 21*	5.60 ± 0.18	5.59 ± 0.31¶	5.96 ± 0.38	*P** < .05
GA	D + 1	13.05 ± 0.90	11.76 ± 2.64	14.76 ± 3.88	NS
	D + 21	11.50 ± 2.08	11.84 ± 3.19¶	14.39 ± 1.93	*P** < .05
ACH	D + 4	21.70 ± 10.02	30.03 ± 27.66	28.41 ± 16.63	NS
s-cortisol	D + 4	23.55 ± 6.22	20.38 ± 5.99	23.61 ± 6.80	NS
24-h u-cortisol	D + 4	636.4 ± 520.7	265.4 ± 104.6	383.7 ± 268.1	NS
	D + 14	286.3 ± 226.8	258.8 ± 192.5	275.6 ± 174.9	NS
Creatinine clearance	D + 4	160.5 ± 44.7	153.6 ± 37.4	143.4 ± 44.5	NS
	D + 14	110.2 ± 72.7	152.2 ± 72.9	144.4 ± 43.6	NS
Mean daily insulin dose					
Lantus		11.7 ± 6.6	0.0 ± 0.0#	20.9 ± 14.3	*P*‡ < .001
Lispro		0.0 ± 0.0	0.8 ± 0.8¶	4.2 ± 4.0	*P*† < .01
Lantus/lispro		11.7 ± 6.6	0.8 ± 0.8#	25.11 ± 16.6	*P*‡ < .001
D + 4					
Glucose		100.3 ± 8.1	113.4 ± 21.6	136.5 ± 51.6	NS
Insulin		7.03 ± 3.33	10.05 ± 4.47	10.52 ± 8.67	NS
bCP		1.79 ± 0.75	2.61 ± 1.16	2.93 ± 1.45	NS
sCP		3.85 ± 2.24	3.38 ± 1.07	3.82 ± 2.27	NS
HOMA-β		70.8 ± 38.7	83.7 ± 55.2	68.9 ± 74.1	NS
ΔC-peptide		2.07 ± 1.51	0.77 ± 1.16	0.89 ± 1.62	NS
Incline of ΔC-peptide		1.03 ± 0.60	0.51 ± 0.92	0.28 ± 0.53	NS
HOMA-IR		1.74 ± 0.86	2.85 ± 1.49	3.68 ± 3.64	NS
QUICKI		0.36 ± 0.04	0.33 ± 0.02	0.33 ± 0.04	NS
D + 21					
Glucose		93.8 ± 9.3	100.3 ± 21.9	99.3 ± 23.9	NS
Insulin		6.75 ± 3.42	9.47 ± 9.03	4.89 ± 3.66	NS
bCP		2.04 ± 0.92	3.03 ± 3.07	1.37 ± 1.02	NS
sCP†		1.99 ± 1.48	3.95 ± 2.32	2.57 ± 2.01	NS
HOMA-β		156.0 ± 126.6‖	99.8 ± 70.4	54.6 ± 32.1	*P** < .05
ΔC-peptide*		1.28 ± 2.85	3.20 ± 2.59	0.74 ± 2.71	NS
Incline of ΔC-peptide		−0.11 ± 0.46	0.81 ± 1.36	1.40 ± 2.54	NS
HOMA-IR		1.38 ± 0.72	2.43 ± 2.56	1.26 ± 1.07	NS
QUICKI		0.37 ± 0.03	0.35 ± 0.04	0.40 ± 0.06	NS

p-RBC indicates packed red blood cells; FFP, fresh frozen plasma.
The statistical significances were tested by 1-way ANOVAs among groups. *P* values by ANOVA are provided for the 3-group comparisons.

* $P < .05$.
† $P < .01$.
‡ $P < .001$.
§ $P < .05$ vs short-acting insulin-requiring.
‖ $P < .05$ vs basal and short-acting insulin-requiring.
¶ $P < .05$ vs basal and short-acting insulin-requiring.
# $P < .001$ vs basal and short-acting insulin-requiring.

We evaluated the occurrences of the burn-related morbidities and insulin-induced hypoglycemia during the study periods (Table 5). With regard to infectious complications including blood culture and wound culture, the percentages of wound cultures with more than 10^5 organisms per gram concentration for gram-positive organisms, gram-

Table 5
Morbidities and Major hypoglycemia event

	Insulin analogue-free (n = 10)	Insulin analogue-requiring (n = 35)	*t* test *P* value
Stay in ICU (d)	39.9 ± 17.0 (45.0)	32.9 ± 20.1 (32.0)	*P* = .342
ABSI D + 1	8.3 ± 1.6 (8.0)	8.4 ± 1.7 (8.0)	*P* = .460
D + 14	7.3 ± 1.6 (7.5)	7.4 ± 1.7 (7.0)	*P* = .833
D + 21	6.7 ± 1.6 (6.5)	6.7 ± 1.9 (7.0)	*P* = .958
APACHE II D + 1	4.9 ± 2.6 (5.0)	6.1 ± 3.0 (7.0)	*P* = .249
D + 14	5.0 ± 2.9 (4.0)	5.2 ± 2.6 (5.0)	*P* = .835
D + 21	4.9 ± 3.9 (4.0)	4.2 ± 3.0 (4.0)	*P* = .593
No. of graft operations/patient	3.0 ± 1.9 (2.0)	3.3 ± 1.9 (3.0)	*P* = .616
No. of debridements/patient	1.9 ± 1.7 (1.5)	1.7 ± 1.3 (1.0)	*P* = .584
Major hypoglycemia			
No. of patients/total no. (%)	0.0	5/35 (14.3)	
No. of frequency/patient	0.0	1.6	
Wound infection			
% (+) Blood culture	30	14.3	
% (+) Op site culture	0.0	8.6	

negative organisms, and yeast were statistically indifferent between insulin-requiring and insulin-free groups. Furthermore, when indexed by the length of ICU stay and numbers of burn-related operations including grafts and debridement, these patient groups were statistically similar in the number of ICU stays and surgeries. Of the 35 insulin-requiring subjects, 5 subjects suffered from major hypoglycemia, which averaged 1.6 times during the study period.

4. Discussion

In the present study, our attention was focused on the glucose metabolic homeostasis in stress diabetes in Korean subjects with unrecognized diabetes before severe burn injuries. Based on previous reports that the characteristic pathogenesis of the development of Korean type 2 diabetes mellitus is deterioration of early-phase insulin secretion [17], we hypothesized that glucose metabolism in severe insulin resistance induced by inflammation and excessive counterregulatory hormones could be more dependent on underlying insulin secretory function and reserve. To do this, we tried to identify the following: (1) which surrogate markers or indices for average BG could reflect the glycemic excursion and be suitable for evaluating the effectiveness of glycemic control protocol with insulin analogues in subjects with critical burn injuries and (2) which biomarkers could predict or reflect the development or aggravation of new-onset stress-induced hyperglycemia in Korean subjects with severe burns.

To investigate these questions, we used A_{1c} and GA as surrogate markers for an average BG excursion and adopted a mean daily dose of insulin analogues in the given 21 days as an indirect index of an average glycemic excursion. Although A_{1c} and GA are widely used in the general diabetic population, neither A_{1c} (which reflects the BG level over 120 days preceding the test) nor GA (which reflects glycemic control over 2-3 weeks preceding the assay) [18] reflected glycemic excursions and was suitable for evaluating the efficiency of glycemic control protocol in this critical situation. Their unreliability as suitable biomarkers in the situation of severe burn could be due to the unique pathologic conditions in which blood, plasma products, and albumin administrations were needed when clinically indicated because they suffer from hypoalbuminemia in the hypermetabolic state and excision of eschar and allograft skin grafts related blood loss [4]. Despite a lack of clinical validation, we only surrogated the mean daily dose of insulin for further evaluation and analysis of glycemic excursions in this study. From this point of view, the mean daily dose of insulin could indirectly reflect the development or aggravation of stress-induced hyperglycemia and poor glycemic excursion. The optimal target range for BG in critically ill patients remains unclear because trials examining the effects of tighter glucose control have had conflicting results [19,20]. Nevertheless, many professional organizations recommended tight glucose control for patients treated in ICUs [21]. Our study was designed to investigate glucose metabolic homeostasis in stress diabetes, not to compare intensive glucose control and conventional glucose control. In this study, interventions with subcutaneous insulin by combined basal insulin analogue and sliding scale regimen with short-acting insulin were taken to achieve target fasting and postprandial BG levels (<140 and 200 mg/dL, respectively). Severely burned patients were divided into 35 who were deemed to require insulin supplement and 10 who were deemed not to require insulin to maintain target BG levels. These 2 groups were statistically similar in demographic characteristics. During the ICU-based 21-day study period, there was no significant difference between the 2 groups with regard to infectious complications, length of ICU stay, and numbers of burn-related operation. Although this modified glucose protocol could not demonstrate or confer

the effectiveness of achieving and maintaining target BG, indexed by burn-related morbidities, there were similar morbidities between the insulin-free group and insulin-requiring group. In this regard, modified glucose protocol and proposed glucose target goals might confer the clinical relevance in subjects with severe burn injuries.

In this study, we adopted the ABSI [7], APACHE II, serum cortisol, and 24-hour u-free cortisol to provide objective clinical and laboratory parameters for burn-induced stress. According to previous reports, the criterion standard for assessing cortisol overproduction is the 24-hour u-free cortisol determination, especially in Cushing syndrome [22,23]; and increases in cortisol production were roughly proportional to the severity of the inhalation burn [9], with statistical significance. The proposed minimal levels of adrenal insufficiency have ranged from 10 to 34 μg/dL [24], but several studies have suggested that a threshold of 15 μg/dL best identifies persons with clinical features of corticosteroid insufficiency [25]. To rule out the possible inclusion of relative adrenal insufficiency, we excluded subjects whose serum cortisol level was less than 15 μg/dL on post–burn injury day 4.

Several studies have shown that the C-peptide response to glucagon correlates well with the initial β -cell response to mixed meals or to other stimuli commonly used to characterize endogenous insulin secretion, is used to determine endogenous reserves, and has the advantage of shorter duration and simple standardization [12,26,27]. In this regard, we measured C-peptides and calculated the C-peptide increments and incline of C-peptide increments for β-cell secretory function or insulin reserve.

To investigate the second question, multiple linear regression analyses were performed using (1) new-onset stress diabetes requiring insulin therapy and (2) mean daily dose of insulin as a dependent factor in insulin-requiring subjects. Several clinical and laboratory factors were entered as independent variables. Of the independent factors entered, sCP on the 21st day and 24-hour u-free cortisol on the 14th day post–burn injury predicted the new onset of stress diabetes demanding insulin to control the high glucose. Despite a lack of statistical significance, bronchoscopic scores assessing inhalation burn injury, ABSI, and APACHE II were higher in subjects requiring insulin therapy. We may interpret the meanings of higher 24-hour u-free cortisol level on the 14th day as the long-standing severity of burn injuries and of lower sCP level on the 21st day as the magnitude of the insulin secretory dysfunction or insulin reserve in response to both prolonged 21-day stress and hyperglycemia. In contrast to expectations, the subjects requiring insulin therapy were insignificantly leaner as assessed by BMI and more insulin sensitive as assessed by HOMA-IR and QUICKI than insulin-free subjects. However, there was a significant difference in u-free cortisol excretion on the 14th day post–burn injury. Taking into account that clinical implications of u-free cortisol and calculation equation of HOMA-IR (HOMA-IR = fasting insulin/[22.5 × $e^{-\ln \text{ fasting glucose}}$]), this discrepancy could be explainable. In this study, we measured 24-hour u-free cortisol to provide objective parameters for burn-induced stress. Pearson correlations between 24-hour u-free cortisol level on the 14th day and ABSI, TBSA, bronchoscopic points, APACHE II scores, and HOMA-IR were 0.448 (P = .003), 0.345 (P = .024), 0.310 (P = .043), 0.257 (P = .096), and −0.077 (P = .625). The fasting glucose levels were higher in the insulin-requiring group (124.5 ± 41.9 mg/dL) than in the insulin-free group (114.7 ± 20.1 mg/dL), but insulin levels were lower in the insulin-requiring group (9.96 ± 6.96 μIU/mL) than in the insulin-free group (17.52 ± 20.94 μIU/mL) on the fourth day post–burn injury. On the 21st day post–burn injury, similar glucose levels of around 100 mg/dL were found; but more decreased insulin levels were noticed in the insulin-requiring group (10.23 ± 7.07 vs 6.68 ± 6.25 μIU/mL). Therefore, the discrepancy between HOMA-IR and u-free cortisol excretion could be explained by the insulin secretory dysfunction to burn injuries-induced stress, resulting in hyperglycemia.

In our limited number of subjects, this discordant insulin secretory and resistant pathogenesis were quite different from those of type 2 diabetes mellitus. The likely postulation for important pathophysiologic defects in the development of stress diabetes in Korean subjects could be clued from the bCP levels in subjects requiring insulin therapy on the fourth and 21st days post–burn injury. In contrast to the wide differences in sCP levels on the fourth and 21st days (3.67 ± 1.89 vs 4.58 ± 2.61, 2.92 ± 2.12 vs 5.37 ± 2.87, respectively), differences in bCP levels are negligible on the fourth and 21st days (2.43 ± 1.20 vs 2.69 ± 1.32, 2.18 ± 1.00 vs 2.02 ± 2.07, respectively). This finding partially reflected the characteristics of pathogen-

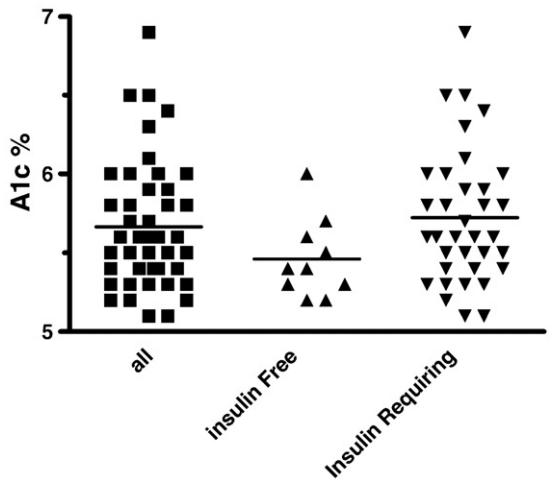

Fig. 1. Glycated hemoglobin levels of insulin analogue–free and insulin-requiring groups on the first day post–burn injury is shown. Glycated hemoglobin levels of insulin-requiring subjects (5.72 ± 0.43) were insignificantly higher than those of insulin-free subjects (5.46 ± 0.25).

esis of Korean type 2 diabetes mellitus, in which deterioration of early-phase insulin secretion plays an important role in the development of this disease [17]. From these results, insulin secretory dysfunction or insulin reserve and severity of the illness were the predictors of stress diabetes.

Glycated hemoglobin on the first day post–burn injury, sCP on the 21st day, HOMA-IR on the fourth day, age, and serum insulin level on the 21st day had significant influence on the mean daily dose of insulin. The most significant factor found to be associated with the dependent variable in this study was A_{1c} on the first day ($\beta = 0.676$, $P < .001$) (Fig. 1). Moreover, despite a lack of statistical significance, A_{1c} levels increased more in subjects requiring insulin therapy. Because we studied subjects with hyperglycemia occurring after the burn injury, these stress diabetic subjects demonstrated by slightly elevated A_{1c} might be diabetes prone or have unrecognized impairment of glucose tolerance, including occult frank diabetes. In addition, these subjects showed the magnitude of insulin secretory dysfunction or insulin reserve in response to both prolonged 21-day stress and hyperglycemia. However, despite numerous calculations, our data were weakened by the fact that we could not use matched controls from our exact referral area because of the regulatory restrictions on studies in healthy adults.

Based on these results, it is likely that the magnitude of burn stress affects stress-induced glycemic excursion on vulnerable subjects who show relatively higher levels of A_{1c} and have dysfunctional pancreatic β-cells and insulin reservoir. Moreover, A_{1c} level is considered an important monitoring tool in treating patients with diabetes; but it is not currently recommended as a screening or diagnostic test in the outpatient setting [28]. We suggest that the A_{1c} is an attractive option as an inpatient screening test for those who are critically ill.

In conclusion, our present data show that Korean subjects with dysfunctional pancreatic β-cells of critical stress are prone to become stress diabetic and require more insulin to control the hyperglycemia.

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