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Burned adults develop profound glucose intolerance

Sarah Rehou, MSc¹, Stephanie Mason, MD^{1,2}, Marjorie Burnett, BSc¹, and Marc G. Jeschke, MD PhD FACS FCCM FRCS(C)^{1,3,4}

¹Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

²Division of General Surgery, Department of Surgery, Faculty of Medicine, University of Toronto

³Division of Plastic and Reconstructive Surgery, Department of Surgery, Faculty of Medicine, University of Toronto

⁴Department of Immunology, Faculty of Medicine, University of Toronto

Abstract

Objective—Metabolic alterations after burn injury have been well described in children; however, in adult patients, glucose metabolism and insulin sensitivity are essentially unknown. We sought to characterize metabolic alterations and insulin resistance after burn injury and determine their magnitude and persistence at discharge.

Design—Prospective, cohort study.

Setting—Tertiary burn centre.

Patients—Non-diabetic adults with an acute burn involving 20% total body surface area (TBSA).

Measurements and Main Results—An oral glucose tolerance test (OGTT) was administered at discharge. Glucose, insulin, and C-peptide levels were measured to derive surrogate measures of insulin resistance and β -cell function, including: QUICKI, HOMA2-% β , HOMA2-%S, HOMA2-IR, and the ISI (composite). Patients were grouped according to the degree of glucose tolerance: normal glucose tolerance (NGT), impaired fasting glucose (IFG)/impaired glucose tolerance (IGT), or diabetes. Forty-five adults, aged 44 ± 15 years and $38 \pm 14\%$ TBSA burned underwent an OGTT at discharge. Median QUICKI [0.348 (0.332-0.375)] and median HOMA-IR [1.13 (0.69-1.45)] were abnormal, indicating insulin resistance along and impaired insulin production at discharge. Two-thirds of patients ($n=28$) met criteria for IFG/IGT, or diabetes.

Corresponding author and person to whom reprint requests should be addressed: Marc G. Jeschke MD PhD FACS FCCM FRCS(C), Sunnybrook Health Sciences Centre, 2075 Bayview Ave. D7 04, Toronto, ON, Canada, M4N 3M5, (T) 416-480-6703; (F) 416-480-6763; marc.jeschke@sunnybrook.ca.

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Conclusions—We have demonstrated that burn-injured adults remain hyperglycemic, are insulin resistant, and express defects in insulin secretion at discharge. Patients with lower burn severity (TBSA 20–30%) express similar metabolic alterations as patients with larger burns (TBSA 30%). Glucose tolerance testing at discharge offers an opportunity for early identification of burn patients that may be at high risk of pre-diabetes and diabetes. Our findings demonstrated that two-thirds of burn patients had some degree of glucose intolerance. With this in mind, surveillance of glucose intolerance post-discharge should be considered. As hyperglycemia and insulin resistance are associated with poor outcomes, studies should focus on how long these profound alterations persist.

Key terms

burns; hyperglycemia; insulin resistance; glucose tolerance test

INTRODUCTION

A hallmark of severe burns is hypermetabolism associated with hyperglycemia and insulin resistance (1–3). In these patients, hyperglycemia occurs due to increased glucose output in tandem with decreased glucose uptake. Ultimately, this leads to a hyperglycemic, hyperinsulinemic response. Hyperglycemic patients have impaired wound healing, and a higher incidence of infection, organ dysfunction, and mortality (2, 4, 5). Tight glycemic control aims to avoid these hyperglycemic peaks and associated complications, though it must be balanced against the risks of hypoglycemia. Hypoglycemia occurs in 15–20% of burn patients and is associated with an up to 9-fold increase in mortality (6). Thus, tight glucose control in burn patients is a balancing act; both hypo- and hyperglycemia can lead to poor outcomes.

To date, some post-burn metabolic alterations have been delineated, though the majority of studies have been conducted in children (5, 7, 8). There is strong evidence that the post-burn hyperglycemic, hyperinsulinemic response persists following the acute phase of injury. Studies in pediatric burn patients demonstrate elevated levels of fasting glucose for up to six months and insulin resistance for up to three years post-injury (7). Despite the well-documented metabolic alterations in the pediatric population (5, 7, 8), no studies have examined glucose regulation and insulin resistance in adults after burn injury using the oral glucose tolerance test (OGTT). We aimed to determine the metabolic and physiological alterations in severely burned adults, and to assess insulin resistance both during acute hospitalization and at the time of discharge.

The factors that contribute to insulin resistance in adult burn patients are poorly defined; this might occur through insulin resistance, impaired insulin secretion, or loss of β -cell function. Insulin resistance is defined as a reduced response to insulin (9), resulting in reduced glucose uptake in the presence of insulin. Prolonged hyperglycemia can induce β -cell dysfunction by exhausting β -cells. The insulin clamp technique is considered the gold standard for determining insulin resistance, but is limited by its clinical impracticality. Rather, the 2-hour OGTT is used to diagnose glucose intolerance by simulating the postprandial state after ingestion of 75 g of glucose. OGTT-derived indices are noninvasive

alternatives to the insulin clamp that are used to estimate surrogate markers of peripheral and hepatic insulin resistance, and β -cell function (9). The final aim of our study was to describe metabolic and physiologic alterations after burn, and to compare these responses in clinically relevant subgroups.

MATERIALS AND METHODS

Study design and participants

We conducted a prospective cohort study of adults (≥ 18 years of age) with a severe burn injury, defined as $\geq 20\%$ total body surface area (TBSA), admitted to our provincial burn center between June 1, 2011 and June 1, 2015. Patients were excluded if they had a history of diabetes, abnormal glycosylated hemoglobin (Hb A1C) levels upon admission, cardiovascular disease, or liver or renal failure. The Canadian Diabetes Association guidelines for Hb A1C levels are diagnostic criteria of 0.060–0.064 for pre-diabetes and 0.065 for diabetes (10). The research ethics board at our institution approved the study protocol and informed consent was obtained from all patients.

The following patient demographics and injury characteristics were recorded: age at injury, sex, weight, height, percent TBSA burned, presence of inhalation injury, length of stay (LOS) in hospital, and days to OGTT from injury. Body mass index (BMI) was calculated as weight (kg) / height² (m²). All patients received care in accordance with evidence-based protocols established at our burn centre. This includes a glucose control protocol, targeting a blood glucose range between 90 to 144 mg/dL (5 to 8 mmol/L) (6). None of the patients in our study received any anabolic agents, and all inpatient glucose levels and insulin administration were recorded. The Canadian Diabetes Association criteria were used to classify glucose tolerance as: (a) normal glucose tolerance (NGT), defined as fasting plasma glucose <110 mg/dL (<6.1 mmol/L) and 2-hour plasma glucose <140 mg/dL (<7.8 mmol/L); (b) impaired fasting glucose (IFG), defined as fasting plasma glucose 110 to 125 mg/dL (6.1 to 6.9 mmol/L) and 2-hour plasma glucose <140 mg/dL (<7.8 mmol/L); (c) impaired glucose tolerance (IGT), defined as fasting plasma glucose <110 mg/dL (<6.1 mmol/L) and 2-hour plasma glucose 140 to 200 mg/dL (7.8 to 11.0 mmol/L); or (d) diabetes, defined as fasting glucose ≥ 125 mg/dL (≥ 7.0 mmol/L) or 2-hour glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) (10). For the purposes of this study, IFG/IGT is defined as meeting one or both of the aforementioned criteria for IFG or IGT.

Oral glucose tolerance test

Subjects meeting inclusion criteria were administered an OGTT at discharge and wounds were 95% healed. Patients were not on insulin or beta-blockers at the time of OGTT. Patients were fasted overnight and blood samples were collected at 0, 30, 90, and 120 minutes after ingestion of a standard 75 g glucose load. Plasma glucose concentrations were determined using a hexokinase assay, and serum insulin and C-peptide concentrations were determined by common enzyme-linked immunosorbent assay ELISA techniques. Total glucose, insulin, and C-peptide secretion was estimated from the area under the curve (AUC) from 0 to 120 minutes using the trapezoidal rule.

Surrogate measures of insulin resistance and β -cell function

The following insulin sensitivity indices were calculated:

- a. The quantitative insulin sensitivity check index (QUICKI): $1/[\log(\text{fasting insulin } (\mu\text{U/mL})) + \log(\text{fasting glucose } (\text{mg/dL}))]$ (11).
- b. The composite whole-body insulin sensitivity index [ISI (composite)]: $10,000/ (G_0 \times I_0 \times G_{120} \times I_{120})$ where G = glucose (mg/dL), I = insulin ($\mu\text{U/mL}$) at times 0 and 120 minutes (12, 13).
- c. The insulinogenic index (IGI): $[\delta \text{ insulin } (0 - 30 \text{ min}) (\mu\text{U/mL}) / \delta \text{ glucose } (0 - 30 \text{ min}) (\text{mg/dL})]$ (14).
- d. The homeostasis model assessment (HOMA) calculator v2.2 .3, using the HOMA2 model, was utilized to determine quantitative estimates of insulin resistance calculated from a freely available calculator (available at: <http://www.dtu.ox.ac.uk/homacalculator/>) (15). Estimates of β -cell function (HOMA-% β), insulin sensitivity (HOMA-%S), and insulin resistance (HOMA-IR) were derived from simultaneously measured fasting plasma glucose, fasting specific insulin, and C-peptide values (15). C-peptide and fasting specific insulin were used to determine β -cell function and insulin sensitivity respectively, as reported by Wallace and colleagues (16).

Statistical analysis

The data are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (17). Data are expressed as mean $\pm$ SD, median (IQR), or number (%) as appropriate. To identify differences in OGTT profiles and insulin indices, we compared patients based on degree of glucose tolerance, injury severity (TBSA < 30% vs. TBSA $\geq$ 30%), presence of inhalation injury, sex, and complications (bacteremia, sepsis, pneumonia). Groups were compared using Student's t-test, one-way ANOVA, Kruskal-Wallis, Mann-Whitney *U*, Fisher's exact, and χ^2 test as appropriate. All tests were 2-tailed and calculated using SPSS version 20.0 software with a *P* value of < 0.05 considered statistically significant.

RESULTS

Patients

Fifty-four patients were assessed for eligibility at our burn center during the study period, of which 45 (83%) met inclusion criteria (Supplemental Figure 1). Patient demographics and injury characteristics are summarized in Table 1. Mean age was 44 ± 15 years and the majority of patients (76%) were male. The median LOS for patients was 33 days (IQR 22 – 58 days) and 1.1 ± 0.5 days per percent TBSA burn. The median time to OGTT from injury was 24 days (IQR 20–50 days). Of those undergoing OGTT, 27 patients (60%) had bacteremia, 12 (27%) had sepsis, and 20 (44%) had pneumonia during their acute hospital stay. The mean Hb A1C on patients measured was 0.0572 ± 0.003 , which indicates that patients were not preexisting diabetics. Additionally, the average admission glucose was 141 ± 29 mg/dl and there was no significant difference when stratified by degree of glucose

tolerance. Admission glucose values were 146 ± 32 , 137 ± 24 , and 143 ± 37 ($p = 0.660$) for the NGT, IFG/IGT, and diabetic groups, respectively. Glucose levels and insulin administration are displayed in Supplemental Figure 2. Across all patients, daily average glucose levels were within the ideal range (Supplemental Figure 2A).

Oral glucose tolerance test and surrogate measures of insulin resistance and β -cell function

The OGTT profile (Figure 1) demonstrated that severely burned adults had a hyperglycemic response (Figure 1A) and elevated fasting insulin levels (Figure 1B). Surrogate measures of insulin resistance and sensitivity were also abnormal, including QUICKI, and HOMA2 (Table 1).

Overall, two-thirds ($n=28$) of burn patients had some degree of impaired glucose metabolism or diabetes (Figure 2). Seventeen patients (38%) were classified as NGT, 20 (44%) as IFG/IGT, and 8 (18%) as diabetic. Patient demographics and injury characteristics compared by glucose tolerance classification are summarized in Table 1. There was a significant difference in age among the three groups ($p = 0.017$); patients with NGT were the youngest, while IFG/IGT were the oldest (Table 1).

The OGTT profile (Figure 3) of adult burn patients, based on the degree of glucose tolerance, demonstrated significant differences in serum glucose at 0, 90, and 120 minutes among the three groups ($p = 0.001$, $p < 0.0001$, $p < 0.0001$ respectively; Figure 3A). As expected, patients classified as diabetic had the highest glucose levels at all time points and those with NGT had the lowest glucose levels at all time points (Figure 3A). Elevated fasting insulin levels were observed among all patients, with a significant difference among the three groups at the 120-minute time point ($p = 0.0009$; Figure 3B). Patients meeting criteria for diabetes had a delayed peak in insulin levels after ingestion of the glucose load (Figure 3B). In contrast, peak insulin levels for NGT patients occurred at the 30-minute time point. IFG/IGT patients had elevated insulin levels throughout the 120-minute time point (Figure 3B). C-peptide levels followed a similar pattern to insulin levels and there was a significant difference at 120 minutes ($p = 0.002$; Figure 3C). The AUC glucose was significantly different across the three groups ($p < 0.0001$; Figure 5D). Patients classified as diabetics had the largest AUC for glucose (Figure 3D), insulin (Figure 3E), and C-peptide (Figure 3F), followed by IFG/IGT, and NGT.

There was no significant difference among patients classified with NGT, IFG/IGT, or diabetes for QUICKI, IGI, or HOMA2 estimates of insulin resistance and β -cell function (Table 1). In subjects with NGT, QUICKI, IGI, and HOMA2 estimates were normal. Subjects with IFG/IGT had abnormal QUICKI, IGI, and decreased HOMA2 estimates of insulin sensitivity and β -cell function. The diabetic group had the largest deviation from normal values for all indices (Table 1). There was a significant difference among the three groups in the ISI (composite); those with diabetes had diminished values, suggesting whole-body insulin resistance ($p = 0.001$; Table 1).

To determine how OGTT profiles vary with injury severity, inhalation injury, gender, and complications, we performed several subgroup analyses. No significant differences in OGTT

values or insulin indices were identified based on burn size, inhalation injury, or gender (Figure 4, Supplemental Figures 3–4, and Supplemental Tables 1–3). Patients with bacteremia had a significantly lower IGI, or a decrease in β -cell function compared to patients that did not have bacteremia ($p = 0.048$; Supplemental Table 4) while patients diagnosed with sepsis had a significantly higher c-peptide concentration measured at 90 minutes after ingestion of the glucose load ($p = 0.043$; Supplemental Figure 6). No other significant differences in the OGTT profile or insulin indices based on the presence of bacteremia, sepsis, or pneumonia were observed (Supplemental Figures 5–7 and Supplemental Tables 4–6).

DISCUSSION

This study demonstrated that burned adults have abnormal glucose metabolism, with degrees of impaired insulin secretion and insulin resistance. Hb A1C values were within the normal range at admission, and average glucose levels throughout the study were within the ideal glucose target range. This suggests that patients did not have elevated glucose levels pre-injury and that glucose was well controlled during their acute hospitalization. However, at discharge, two-thirds of burn patients in have abnormal glucose regulation and are classified with IFG/IGT or diabetes.

IFG and IGT are intermediate states that may ultimately lead to diabetes. While not equivalent metabolically, individuals can be classified as having both IFG and IGT. IFG refers to fasting glucose levels that are higher than normal due to abnormalities in basal insulin secretion or hepatic glucose output. Conversely, in IGT, postprandial plasma glucose levels are higher than normal. Typically, this is due to a defect in insulin production by the β -cells or a defect in insulin action (18). Previous studies in the pediatric burn population (7, 8) observed higher fasting insulin levels than in the current study. This suggests that insulin production does not mediate the observed insulin resistance in children. Rather, hyperinsulinemia occurs as a compensatory response to insulin resistance; increasing insulin levels ultimately resulting in reduced sensitivity to circulating insulin (18). In contrast, we found that insulin resistance in adults is mediated by β -cell dysfunction and decreased insulin sensitivity. Thus, children experience hyperglycemia associated with hyperinsulinemia, while adults experience impaired insulin secretion in addition to hyperglycemia. The hyperinsulinemia in adults is less severe, while insulin resistance is a more prominent feature.

Insulin indices demonstrate that burn-injured adults have defective insulin secretion, though this was less profound than that observed in severe diabetics. Utilizing C-peptide concentration as a surrogate for β -cell function, we estimate that β -cell function in this cohort was 91% of normal. Similar results were seen when using the IGI as a surrogate for insulin secretion. Taken together, these results suggest that burned adults have impaired early-phase insulin secretion, perhaps a consequence of the hypermetabolic response of the pancreas after β -cell exhaustion. This is consistent with abnormal 2-hour glucose levels. This is a key finding as defects in insulin secretion in IFG and IGT individuals can lead to overt diabetes. Previous work has suggested that insulin resistance may develop as a consequence

of decreased muscle mass after burn injury that ultimately leads to decreased glucose uptake by skeletal muscle (3).

Previous work in our laboratory has characterized the molecular and physiological mechanisms that might be underlying these metabolic derangements. After burn injury, hyperglycemia and insulin resistance are associated with endoplasmic (ER) stress in muscle, skin, and fat that persists for up to 250 days after injury (19). ER stress is associated with (a) conformational changes that prevent insulin receptor signaling, and (b) mitochondrial dysfunction and damage (19–23). These changes contribute to impairments in insulin-stimulated glucose uptake and fat metabolism, leading to increased concentrations of glucose, fatty acids, and cholesterol (19). While both adult and pediatric burn populations demonstrate altered glucose regulation, the current study suggests that adults are more likely to develop insulin resistance in response to the metabolic sequelae of burn injury than children. The underlying mechanism of how acquired insulin resistance is associated with subsequent development of diabetes is yet to be elucidated and may represent a significant source of long-term morbidity following major burn injury.

Defects in the insulin-signaling cascade after burn injury are similar to those observed in patients with type II diabetes (3, 23). This suggests that burn patients quickly move through the compensatory hyperinsulinemia state, to the second stage characterized by increased glucose levels and impaired early insulin release (24, 25). Efforts to prevent or attenuate this progression may be dependent on the underlying pathophysiology. As such, further characterization of the pathophysiologic mechanisms underlying this impaired glucose metabolism is required.

With age being a known risk factor for development of diabetes, we expected diabetic patients to be oldest. Interestingly, despite the observed difference among groups in terms of age, IFG/IGT were the oldest. No association between gender, inhalation injury, or burn size and subsequent glucose classification was identified. This is in contrast to a previous study in children that demonstrated an association between increasing burn size and increased hypermetabolism (26). Our study might be underpowered to detect an effect of burn size, as a very small proportion of patients (n=3) had a burn injury larger than 60% TBSA. Though a burn size was not associated with differences in OGTT profiles and insulin indices, a difference may be revealed by future studies with a greater distribution of burn size. However, our results are clinically significant, as they suggest that all patients with 20% TBSA are at risk for the sequelae of glucose intolerance and insulin resistance.

Several limitations of the OGTT and OGTT-derived indices merit discussion. Biological differences in fasting insulin values may result in more accurate fasting insulin values in patients that have NGT in comparison to patients that have diabetes (27). Fortunately, several indices are available for use in determining insulin resistance. We employed several indices in order to overcome the limitations and potential biases associated with using a single measure of insulin resistance. Another limitation is that estimates of “normal” can vary depending on conversion factors and the assay used (28). To decrease assay bias, the same assay sources were used throughout the study. Caution is required when interpreting insulin indices, as normal values can vary across different study populations. However, to

the best of our knowledge, there are no established normal values for burn-injured patients at the time of discharge. Our results are consistent with previously published studies in the pediatric burn population that have shown a hyperglycemic response and insulin resistance, providing external validity to our study (5, 7, 8). A further limitation is the lack of a control group; OGTTs are not routinely performed unless there is a clinical indication. Even in high-risk populations, not all institutions measure insulin or c-peptide and laboratories may vary by measurement technique.

In summary, abnormal glucose metabolism and insulin resistance was observed in this cohort of 45 burn-injured patients at the time of discharge. In some patients, these metabolic alterations result in glucose levels associated with frank diabetes. This is a consequence of two pathophysiologic events: (a) impaired insulin secretion and (b) concomitant peripheral insulin resistance. Monitoring burn-injured adults for metabolic alterations might guide therapeutic interventions, such as glucose control post-discharge. The trajectory of these derangements in glucose metabolism merits elucidation, as it remains unknown whether these changes are transient responses to injury or permanent alterations. It is also unknown whether patients with burns less than 20% TBSA manifest a similar response, and if those identified with intermediate states of impaired fasting glucose and impaired glucose tolerance, or with diabetes have poorer outcomes. Future work should determine the long-term impact of impaired glucose metabolism on patient outcomes, specifically whether or not these patients are at increased risk of developing diabetes compared to their non-injured counterparts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Burn injury leads to a hyperglycemic response and elevated fasting insulin levels. Mean glucose (A), insulin (B), and C-peptide (C) levels and mean area under the curve for glucose (D), insulin (E), and C-peptide (F) of burn patients during the 2-hour oral glucose tolerance test. Error bars indicate SD.

Figure 2.

Two-thirds of burn patients classified with abnormal glucose regulation using diagnostic criteria. NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Figure 3.

Mean glucose (A), insulin (B), and C-peptide (C) levels and mean area under the curve for glucose (D), insulin (E), and C-peptide (F) of burn patients assessed with diagnostic criteria during the 2-hour oral glucose tolerance test. Error bars indicate SD; * $P < 0.05$. NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Figure 4.

Mean glucose (A), insulin (B), and C-peptide (C) levels and mean area under the curve for glucose (D), insulin (E), and C-peptide (F) of burn patients by burn size during the 2-hour oral glucose tolerance test. Error bars indicate SD; TBSA, total body surface area.

Table 1

Demographics, burn injury characteristics, outcomes, and insulin indices assessed from 2-hour oral glucose tolerance test.

	Normal	All	NGT	Diagnostic criteria		<i>p^a</i>
				IFG/IGT	Diabetes	
No. of patients	45		17	20	8	
Age, mean $\pm$ SD	44 $\pm$ 15		37 $\pm$ 14	51 $\pm$ 15	41 $\pm$ 12	0.017
Male, No. (%)	34 (76%)		12 (71%)	18 (90%)	4 (50%)	0.070
BMI, mean $\pm$ SD, kg/m ²	27.0 (5.6)		28.0 $\pm$ 5.4	25.3 $\pm$ 3.4	29.2 $\pm$ 9.2	0.202
TBSA, mean $\pm$ SD	38 $\pm$ 14		43 $\pm$ 15	34 $\pm$ 14	39 $\pm$ 9	0.162
3 rd degree TBSA, median (IQR)	23 (3–40)		31 (2–42)	22 (12–31)	29 (0–43)	0.779
Inhalation injury, No. (%)	18 (40%)		8 (47%)	7 (35%)	3 (38%)	0.747
Bacteremia, No. (%)	27 (60%)		12 (71%)	9 (45%)	6 (75%)	0.181
Sepsis, No. (%)	12 (27%)		3 (18%)	7 (35%)	2 (25%)	0.489
Pneumonia, No. (%)	20 (44%)		7 (41%)	9 (45%)	4 (50%)	0.916
Insulin indices, median (IQR)						
QUICKI	0.357	0.348 (0.332–0.375)	0.359 (0.344–0.375)	0.348 (0.328–0.389)	0.335 (0.33–0.338)	0.124
ISI (composite)	> 3.0	6 (4–10)	8 (8–14)	6 (4–10)	2 (2–4)	0.001
IGI	> 0.4	0.4 (0.23–0.6)	0.41 (0.33–0.48)	0.4 (0.22–0.61)	0.25 (0.16–0.66)	0.580
HOMA2-IR	1	1.13 (0.69–1.45)	0.94 (0.78–1.33)	0.95 (0.57–1.66)	1.43 (1.38–1.47)	0.174
HOMA2 % β^b	100	91 (76–131)	129 (94–138)	87 (76–111)	72 (58–184)	0.131
HOMA2 % S	100	81 (68–135)	103 (74–122)	89 (60–169)	70 (68–72)	0.223

Numbers may not add to 100 due to rounding

TBSA, total body surface area; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; QUICKI, quantitative insulin sensitivity check index; ISI (composite), composite whole-body insulin sensitivity index; IGI, insulinogenic index; HOMA2-IR, homeostasis model assessment of insulin resistance; β , β -cell function; S, insulin sensitivity

^a *P*-value indicated for comparison of groups assessed by diagnostic criteria

^b Assessed using c-peptide data.