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Predictors of insulin resistance in pediatric burn injury survivors 24 to 36 months post-burn

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Abstract

Background—Burn injury is a dramatic event with acute and chronic consequences including insulin resistance. However, factors associated with insulin resistance have not been previously investigated.

Purpose—To identify factors associated with long-term insulin resistance in pediatric burn injury survivors.

Methods—The study sample consisted of 61 pediatric burn injury survivors 24 to 36 months after the burn injury, who underwent an oral glucose tolerance test. To assess insulin resistance, we calculated the area under the curve for glucose and insulin. The diagnostic criteria of the American Diabetes Association were used to define individuals with impaired glucose metabolism. Additional data collected include body composition, anthropometric measurements, burn characteristics and demographic information. The data were analyzed using multivariate linear regression analysis.

Results—Approximately 12% of the patients met the criteria for impaired glucose metabolism. After adjusting for possible confounders, burn size, age and percent body fat were associated with the area under the curve for glucose ($p<0.05$ for all). Time post-burn and lean mass were inversely

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CONFLICTS OF INTEREST: None

associated with the area under the curve for glucose ($p<0.05$ for both). Similarly, older age predicted higher insulin area under the curve.

Conclusion—A significant proportion of pediatric injury survivors suffer from glucose abnormalities 24–36 months post-burn. Burn size, time post-burn, age, lean mass and adiposity are significant predictors of insulin resistance in pediatric burn injury survivors. Clinical evaluation and screening for abnormal glucose metabolism should be emphasized in patients with large burns, older age and survivors with high body fat.

Keywords

Insulin resistance; oral glucose tolerance test; long-term; burn; pediatric

INTRODUCTION

Burn injury is a dramatic event with acute and chronic consequences including systemic stress, inflammation, hypermetabolism, muscle wasting and insulin resistance (1–3). The catabolic hormonal milieu after burn injury (i.e., increased circulating levels of epinephrine, norepinephrine, glucagon and cortisol) has been associated with increased hepatic gluconeogenesis and impaired glucose uptake from peripheral tissues (4–8). Moreover, burn injury survivors often have elevated levels of fasting serum insulin (9). In the absence of studies with longer follow-up periods, current evidence suggests that the deregulation of glucose metabolism, in some cases, may persist up to three years post-injury (1).

In the acute phase of the burn injury, hyperglycemia is associated with impaired wound healing and immune response, muscle catabolism, sepsis and mortality (10–12). Nevertheless, the long-term consequences of impaired glucose metabolism in pediatric burn injury survivors remain largely unknown. In non-burn populations, impaired glucose metabolism has been associated with impaired wound healing and infection (13, 14), atherosclerosis (15), cancer (16), peripheral neural damage (17), and macro- and micro-vascular dysfunction affecting different systems (18, 19).

The purpose of this study was to identify predictors/factors associated with insulin resistance in pediatric burn injury survivors 24 to 36 months after the burn injury. A large percentage of burn injury survivors do not follow up with their burn care team two years after burn (20). Therefore, long-term or secondary consequences of burn injury may not receive adequate clinical care. Considering the persistence and the potential long-term implications of insulin resistance in burn injury survivors, it is of major importance to ensure adequate medical attention, especially for individuals who are more prone to impaired insulin sensitivity.

METHODS

SAMPLE

The study sample consisted of 61 long-term (24 to 36 months post-burn) pediatric burn injury survivors. Subjects included in this study consist of a subset of a previously-published study investigating the short- and long-term impact of burn injury on insulin sensitivity (1). Approval to conduct the study was obtained from the University of Texas Medical Branch

Institutional Review Board. Written consent was obtained from all participants over the age of 18 years. Written assent was obtained from participants younger than 18, and written consent was obtained from their parents or guardians. Inclusion criteria included patients admitted with ≥ 40% total body surface area (TBSA) burns, requiring at least one surgery, aged 0–21 years. Exclusion criteria included pregnancy, cancer within 5 years or myocardial infarction (within 6 weeks). The majority of the patients had no significant past medical history, except from one patient with a congenital hearing deficit, one with asthma, one with migraines and one with anemia.

For comparison, our control sample was from previously-published data on non-burn high-risk (obese, a suspicion of gestational diabetes or a family history of diabetes) children and adolescents who performed an oral glucose tolerance test (OGTT) for clinical purposes (1).

BURN-RELATED AND DEMOGRAPHIC CHARACTERISTICS

Data on burn-related characteristics of participants were obtained from their medical records. The variables of interest included gender, date of burn, date of admission, etiology of burn injury, burn size (expressed in percent of TBSA, TBSA%), third degree burn (also expressed in TBSA%), age at burn injury, current age, and time post-burn (in months). Burn size and third degree burn was assessed during surgery using the “rule of nines” method (21). Third degree burn included the areas with full thickness burns involving destruction of the dermis and epidermis, extending to the subcutaneous tissue (22).

ANTHROPOMETRIC AND BODY COMPOSITION MEASUREMENTS

Subjects’ height and weight were measured using an electronic scale (ST Scale-Tronix Model 5102 409, Scale-Tronix White Plains, NY) and a stadiometer (PE-WM-BASE, Perspective Enterprises, Portage, MI), respectively. Participants’ body mass index (BMI) was calculated using the following formula: BMI = weight (kg) / height^2 (m^2). The weight status of subjects older than 20 years was defined using the World Health Organization’s (WHO) criteria for BMI: underweight (BMI < 18.45), normal weight (BMI 18.5–24.95), overweight (BMI > 25–29.9), or obese (BMI >30). For participants younger than 20 years old, we used the age- and gender-specific International Obesity Task Force (IOTF) criteria to classify subjects (23, 24).

Body composition measurements were conducted using Dual X-Ray Absorptiometry (Hologic model QDR-4500W, Hologic Inc, Waltham, MA) as previously described (3). Total body fat percentage has been used as an index of adiposity and lean mass as an index of muscle mass, both previously associated with insulin sensitivity in non-burn child and adult populations (25, 26)

ORAL GLUCOSE TESTING AND CALCULATION OF INSULIN RESISTANCE AND SENSITIVITY

A 2 h OGTT was performed 24 to 36 months post burn. Blood samples were collected in the fasted state and every 30 min for 120 min after ingestion of a standardized glucose load to determine concentrations of plasma glucose and serum insulin. The amount of glucose administered was calculated using the following formula: 1.75 g per kg bodyweight, up to

75 g (27).The diagnostic criteria of the American Diabetes Association (ADA) were used to define individuals with impaired glucose metabolism (fasting plasma glucose > 100 mg/dL and 2 hr OGTT plasma glucose levels > 140 mg/dL) (28). To assess insulin resistance, we used the trapezoid rule to calculate the 0–120 min area under the curve area for glucose (AUC_{glu}) and insulin (AUC_{ins}). To assess insulin sensitivity, we calculated the AUC_{glu} /AUC_{ins} ratio.

Plasma glucose concentrations were measured using a hexokinase assay on a Dimension Instrument (Dade Behring/Siemens Healthcare Diagnostics, Rockville, MD), while serum insulin concentrations were measured using enzyme-linked immunosorbent assay ELISA assays (Diagnostic System Laboratories/Beckmann-Coulter, Webster, TX).

STATISTICAL ANALYSIS

All continuous variables are presented as mean ± standard deviation (SD) or standard error of the mean (SEM). All categorical variables are presented as absolute and relative frequencies. To identify differences in the OGTT measurements between control patients and burn injury survivors, we conducted Student's t-test. We also performed multiple linear regression analyses to evaluate possible predictors of insulin sensitivity and insulin resistance. Data analysis was performed using the PASW Statistics 18, Release Version 18.0.0 (SPSS Inc, 2010, Chicago, IL).

RESULTS

The study sample consisted of pediatric burn injury survivors 11.3 ± 5.5 years old (Table 1). The mean burn size was 59 ± 15 % TBSA% and the mean time post-burn was 27.5 ± 4.3 months. Seven of the patients (11.5%) met the ADA criteria for impaired glucose metabolism. The majority of participants were male (63.9%), of normal weight (73.7%) and the main cause of injury was fire/flame (78.7%). Table 1 also contains the sample characteristics of the high-risk control children and adolescents (1). The control high-risk children were significantly older and had higher BMI compared to the sample of burn injury survivors.

The OGTTs from burned survivors were compared to those from a high-risk reference group (Table 2). Burned patients had significantly higher insulin concentrations under fasting conditions than reference subjects (12.2 ± 1.7 vs 8.2 ± 0.6 μIU/mL, $p = 0.008$). Moreover, burn injury survivors had larger area under the curve for insulin (147.1 ± 12.3 vs 104 ±4 μIU/mL, $p<0.001$) than control high-risk children and adolescents.

To investigate the possible predictors of glucose secretion (AUC_{glu}), we conducted multiple regression analyses. Burn size, age and percent body fat were associated with AUC_{glu} ($p<0.05$ for all), while time post-burn and lean body mass (kg) were inversely associated with AUC_{glu} ($p<0.01$ for both) (Table 3).

Similarly, using multiple regression models, we investigated the possible predictors of insulin secretion (AUC_{ins}) as a measure of insulin resistance. The results in Table 4 show

that age was associated with higher insulin secretion ($p<0.001$) after adjusting for sex, burn size, weight status and percent body fat.

Moreover, we examined potential predictors of the AUC_{glu}/AUC_{ins} ratio as a measure of insulin sensitivity (Table 5). According to our results, age was inversely associated with insulin sensitivity after adjustment for sex, burn size, weight status and body fat percent ($p<0.001$).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the predictors of insulin resistance long-term in pediatric burn injury survivors (24 to 36 months post-burn). The results of this study indicate that pediatric burn injury survivors may still experience abnormal glucose metabolism even 2–3 years post-burn. Moreover, burn size, time post-burn, lean body mass, adiposity and age were significant predictors of insulin resistance in pediatric burn injury survivors.

Previous literature has well established that burn injury acutely causes hyperglycemia and resistance in the action of insulin. The results of this study support the idea that burn injury survivors continue to experience insulin resistance and abnormalities of glucose metabolism two to three years after the burn. Specifically, plasma glucose levels (fasting and 2 hr value during an OGTT), 2 hr insulin levels during an OGTT and the area under the curve for glucose are similar to the levels in obese patients, patients with suspicion of gestational diabetes and family history of diabetes. Further, pediatric burn injury survivors have higher levels of fasting insulin and overall insulin secretion during the OGTT compared to children at high risk for diabetes.

In addition, our results suggest that increased body fat percentage is associated with insulin resistance in long-term pediatric burn injury survivors. Adiposity has been previously associated with decreased insulin sensitivity in healthy children and adolescents (29–31). To the best of our knowledge this is the first study to support this relationship in a population of pediatric burn injury survivors. Adiposity leads to increased availability of free fatty acids (FFAs) in plasma, decreasing insulin resistance (32). Interestingly, overweight or obese weight status, defined according to the age- and gender-specific BMI cut-offs (24), was not a significant predictor of insulin resistance. The lack of significance unveils the intrinsic limitations of BMI as an index of adiposity (33), especially in this clinical population, which experiences dramatic changes in body composition during the clinical course of burn injury.

Conversely, lean body mass was inversely associated with insulin resistance in long-term burn injury survivors. This specific finding is consistent with the previous literature, as the role of muscle tissue as a major glucose disposal organ has been widely recognized (34). In healthy adults, muscle mass has been directly associated with insulin resistance (35). Similarly to type 2 diabetic patients, burn injury survivors acutely experience abnormalities in the insulin signaling pathway (36). Specifically, burn injury survivors manifest mitochondrial dysfunction in muscle cells (37), impaired activation of insulin receptor (IR)

and insulin receptor substrate-1 (IRS-1) (38), and disruption of the serine/threonine-specific protein kinase AKT (39).

Moreover, burn size was independently associated with increased insulin resistance in pediatric burn injury survivors. In support of our results, Jeschke et al. (40) previously reported that, at 40 days post-burn, pediatric burn injury survivors with burns >80% TBSA have higher fasting insulin levels compared to those with smaller burns. Patients with larger burns experience more pronounced muscle catabolism (40) and undergo more excision and other surgeries. During excision surgery, a significant amount of adipose tissue (affected and not affected) is removed, leaving patients depleted of adipose tissue mass. According to the lipotoxicity theory (41), low levels of subcutaneous adipose tissue can result in ectopic fat accumulation and insulin resistance.

According to the results of this study, time post-burn was inversely associated with insulin resistance in pediatric burn injury survivors. Previous studies indicate that the impact of the burn injury abates with time (1, 42). Similar to our study, Gauglitz et al. (1) reported that insulin resistance gradually decreases up to 36 months after burn. The gradual improvement in the metabolic profile of burn injury survivors may be attributable to numerous concurrent physiologic adaptations: suppression of circulating catecholamines and inflammatory factors (1) and increase in lean body mass (42).

Age was an additional factor independently associated with insulin resistance. Studies conducted in non-burn pediatric subjects report similar results. Specifically, in healthy children and adolescents, age was associated with higher fasting insulin levels (31). Moreover, puberty (specifically, Tanner stage 1) also has been associated with insulin resistance (30). Puberty is a stage of the lifecycle associated with changes in the circulating levels of sex hormones and growth factors, conditions which can influence glucose homeostasis (43–46).

Several factors limit the generalizability of our study. Specifically, the majority of the participants of our small sample were males of Hispanic origin. Moreover, the study is of cross sectional design. As a result, it cannot be used to establish causation. Although the hyperinsulinemic euglycemic clamp is considered to be the “gold-standard” approach for measuring insulin sensitivity (47), we used the OGTT approach to minimize patient burden. The OGTT method has also been extensively used in pediatric populations and its results are strongly correlated with those of the hyperinsulinemic euglycemic clamp (48, 49).

Nevertheless, our study has numerous strengths. Namely, to the best of our knowledge, this study is the first to investigate the predictors of insulin resistance in long-term burn injury survivors. Most studies have focused on the acute consequences of burn injury. However, as the survival rates of burn injury have increased, it is increasingly important to consider the long-term consequences of burn injuries. Moreover, body composition was assessed using DXA and not just BMI, which may be a suboptimal index of adiposity (33). Nevertheless, we could not differentiate between subcutaneous and visceral adipose tissues, which have been differentially associated with insulin resistance (50, 51).

In conclusion, the results of this study support the notion that age, burn size, time post-burn, lean body mass and body adiposity are significant predictors of insulin resistance in long-term pediatric burn injury survivors. Weight status was not a significant predictor of insulin resistance. Future studies should investigate the role of these factors in a larger study sample using a prospective study design. Moreover, the underlying mechanisms of insulin resistance in pediatric burn injury survivors and possible lifestyle (physical activity, nutrition) and/or pharmacological interventions remain to be elucidated. Considering the low follow-up rates two years after burn (20), clinical evaluation and screening for abnormal glucose metabolism should be emphasized in patients with large burns, older age and survivors with high body fat.

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TABLE 1

Subject characteristics.

Parameters	Burn Survivors (n =61)	High Risk Subjects[#] (n =95)
Age (yrs)	11.3 ± 5.5 (3.6 –20.8)	13.2 ± 3.6[*]
Sex		
Male	39 (63.9%)	NA
Female	22 (36.1%)	NA
Etiology		
Flame / Fire	48 (78.7%)	NA
Scald / Grease	10 (16.4 %)	NA
Electricity	3 (4%)	NA
Burn Size (TBSA%)	59 ± 15 (40–95%)	NA
Third (TBSA%)	50 ± 22 (0–95%)	NA
Time post-burn (mo)	27.5 ± 4.3 (24–36)	NA
Weight Status		
Normal weight	45 (73.7 %)	NA
Overweight	14 (23%)	NA
Obese	2 (3.3 %)	NA
BMI (kg/m^2)	19.6 ± 4.4	24.3 ± 5.6[*]

Data are presented as means ± standard deviations (SD), or absolute and relative frequencies. TBSA: Total body surface area

[*] Statistically significant differences between burn injury survivors and high-risk subjects ($p<0.05$)

[#] Data as previously published Gauglitz et al (1)

TABLE 2

Glucose and insulin concentrations during the oral glucose tolerance test in burn survivors and high-risk subjects.

Parameters	Burned Survivors (n = 61)	High Risk Subjects[#] (n = 95)	p-value
Fasted glucose (mg/dL)	83.7 ± 1.3	83.4 ± 11.0	0.9769
2hr glucose (mg/dL)	108.7 ± 2.9	109.2 ± 2.5	0.879
Fasted insulin (μIU/mL)	12.2 ± 1.7	8.2 ± 0.6	0.008
2hr insulin (μIU/mL)	63.4 ± 7.1	57.5 ± 5	0.4587
AUC glucose (mg/dL)	228.7 ± 5.0	236 ± 4	0.255
AUC insulin (μIU/mL)	147.1 ± 12.3	104 ±4	<0.001

Data are presented as means ± standard errors of the mean (SEM)
AUC: area under the curve

[#]Data as previously published Gauglitz et al (1).

TABLE 3

Multiple logistic regression models: Predictors of glucose area under the curve (AUC_{glu}) in pediatric burn injury survivors 24 to 36 months post burn.

	Model 1		Model 2		Model 3	
	Beta ± SE	**p-value**	**Beta ± SE**	**p-value**	**Beta ± SE**	**p-value**
Burn Size (TBSA%)	0.8 ± 0.3	0.008	0.7 ± 0.3	0.010	0.9 ± 0.3	0.003
Sex	2.6 ± 8.9	0.771	12.9 ± 10.6	0.228	9.9 ± 9.2	0.286
Age (yrs)	2.6 ± 0.8	0.002	2.5 ± 0.8	0.002	8.0 ± 2.1	0.001
Time post burn (mo)	−3.0 ± 1.0	0.005	−2.8 ± 1.0	0.011	−3.2 ± 1.0	0.002
Weight Status	−2.3 ± 9.7	0.816	-	-	-	-
Total Body Fat (%)	-	-	1.5 ± 0.8	0.047	-	-
Lean Mass (kg)	-	-	-	-	−2.0 ± 0.7	0.009

TBSA: Total body surface area
Weight Status: overweight/obese vs normal weight
Positive beta values denote a positive association

TABLE 4

Multiple logistic regression models: Predictors of insulin area under the curve (AUC_{ins}) in pediatric burn injury survivors 24 to 36 months post burn.

	Model 1		Model 2	
	Beta ± SE	**p-value**	**Beta ± SE**	**p-value**
Burn Size (TBSA%)	−0.1 ± 0.7	0.952	−0.1 ± 0.8	0.884
Sex	−22.9 ± 23.1	0.902	− 9.3 ± 28.4	0.745
Age (yrs)	9.7 ± 2.1	<0.001	9.2 ± 2.1	<0.001
Time post burn (mo)	−3.3 ± 2.6	0.206	−3.1 ± 2.7	0.253
Weight Status	3.8 ± 25.0	0.635	-	-
Total Body Fat (%)	-	-	−0.7 ± 0.3	0.736

TBSA: Total body surface area
Weight Status: overweight/obese vs normal weight
Positive Beta values denote a positive association

TABLE 5

Multiple logistic regression models: Predictors of insulin sensitivity (AUCglucose/AUCinsulin ratio) in pediatric burn injury survivors 24 to 36 months post burn.

	Model 1		Model 2	
	Beta ± SE	**p-value**	**Beta ± SE**	**p-value**
Burn Size (TBSA%)	0.03 ± 0.015	0.96	0.03 ± 0.015	0.110
Sex	0.4 ±0.5	0.496	0.3 ± 0.6	0.620
Age (yrs)	−0.25 ±0.043	<0.001	−0.2 ±0.1	<0.001
Time post burn (mo)	0.1±0.1	0.154	0.1± 1.1	0.152
Weight Status	−0.1 ± 0.5	0.910	-	-
Total Body Fat (%)	-	-	0.1 ± 0.1	0.256

TBSA: Total body surface area
Weight Status: overweight/obese vs normal weight
Positive Beta values denote a positive association.