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Impaired glucose tolerance in pediatric burn patients at discharge from the acute hospital stay

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Abstract

Objective—Hyperglycemia, secondary to the hypermetabolic stress response, is a common occurrence after thermal injury. This stress response has been documented to persist up to 9 months post burn. The purpose of this study was to measure insulin sensitivity in severely burned children prior to discharge when wounds are 95% healed.

Methods—Twenty-four children, aged 4–17 years, with burns >40% total body surface area (TBSA) underwent a 2 hour oral glucose tolerance test (OGTT) prior to discharge from the acute pediatric burn unit. Plasma glucose and insulin levels, as well as the Homeostasis Model Assessment for Insulin Resistance (HOMA_{IR}) were compared to published OGTT data from healthy, non-burned children.

Results—There was a significant difference between severely burned children and non-burned, healthy children with respect to the HOMA_{IR}. Severely burned children had a HOMA_{IR} of 3.53 ± 1.62 compared to the value in non-burned healthy children was 1.28 ± 0.16 ($p < 0.05$).

Conclusion—Insulin resistance secondary to the hypermetabolic stress response persists in severely burned children when burn wounds are at least 95% healed. The results of this study warrant future investigations into therapeutic options for the burned child during the rehabilitative phase of their care after injury.

Keywords

Burns; Pediatrics; Children; Insulin Resistance; Oral Glucose Tolerance Test

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INTRODUCTION

The demonstrated impaired glucose tolerance in the critically ill patient has resulted in an emerging interest in the role of hyperglycemia and insulin therapy in clinical outcomes. The presence of insulin resistance has been clearly identified during traumatic physical events, including thermal injury^{1–7}. Historically, hyperglycemia is a result of the hypermetabolic stress response common to the critically ill patient. The cause is uncertain, but it is thought that gluconeogenic hormones, such as glucagon, cortisol and catecholamine, are released at much higher levels and result in elevated plasma glucose concentrations^{8, 9}. Additionally, insulin resistance taking place at the cellular receptor level leads to a decrease in peripheral glucose uptake and an increase in hepatic glucose production and release^{1, 10–12}.

The clinical implications of hyperglycemia during the acute hospital stay are substantial. Animals studies have illustrated elevated blood glucose levels lead to impairment in immune function and wound healing^{13–17}. In humans, uncontrolled diabetes mellitus produces difficulties in wound healing, and increased rates of infection and mortality¹⁸. Similar complications have been shown in trauma patients¹⁹. Specifically, hyperglycemia in severely burned children has led to elevations in muscle protein breakdown, a reduction in skin graft adherence, an increased incidence in positive blood cultures and higher mortality rates^{20, 21}.

In a landmark study, Van den Berghe et al. found that euglycemia, secondary to an intensive insulin therapy protocol, in critically ill patients had statistically significant decreases in mortality, infectious complications, lower incidences of acute renal failure, polyneuropathy, a smaller number of blood transfusions, a decrease in ventilator days and shorter length of stay in the ICU²². This study has led to further investigations into the role of “tight glycemic control” in critically ill patients and its benefit in clinical outcomes during the acute hospital stay^{23–29}.

In a review of the literature, there are no investigations examining the duration of insulin resistance after an acute traumatic injury. Hart and associates found that the hypermetabolic response continued for at least 9 months after injury³⁰. For the insulin resistant state to follow the same pattern of persistence is of importance, particularly in severely burned patients. Although patients are discharged at approximately 30 days post burn injury, their rehabilitation includes extended physical and occupational therapy, and years of reconstructive surgeries; additional stressors that require adequate physiologic, immune and wound healing functions. Therefore, the aim of our study was to determine the presence of insulin resistance in severely burned children at discharge from their acute hospital stay.

METHODS

Patients and Clinical Care

This study was approved by the institutional review board of the University of Texas Medical Branch. Informed written consent was obtained from each patient’s guardian with assent of patients aged ≥ 7 years before enrollment into the study. This was a prospective, clinical study.

Children, aged 4–18 years, with total body surface area (TBSA) burn ≥ 40% requiring skin grafting, who arrived to the Shriners Hospital for Children Galveston within one week after injury, were eligible for enrollment. Children were older than 4 due to limitations in sample collection and disproportionate non-insulin sensitive glucose use by the brain in smaller children. None of the children enrolled were receiving anabolic agents, such as growth hormone and oxandrolone, which are commonly used in the treatment of burns³¹. In the

initial resuscitation, some patients received low-dose propranolol, or dopamine as clinically indicated however, even at higher doses peripheral glucose metabolism is not altered, and they were not receiving these medications at the time of study³². Finally, none of the children had type 1 or type 2 diabetes before or after their thermal injury. All patients were treated in a similar surgical manner by the same team of burn surgeons. Standard treatment included early excision of the burn wound, wound revision approximately every 5–8 days as needed, systemic antibiotic therapy, and continuous enteral feeding³³.

During the acute hospitalization, patients were fed with Vivonex T.E.N. (Sandoz Nutritional, Minneapolis, MN) through a nasoduodenal tube. The daily caloric intake was calculated to deliver 1500 kcal/m² BSA + 1500 kcal/m² TBSA burned. Initially, then after the first week, the resting energy expenditure was directly measured in each patient and they were then fed 120% of their estimated caloric needs. Enteral nutrition was started at admission and continued until the child tolerated an adequate intake of calories which was a requirement for discharge.

Study Design

An oral glucose tolerance test (OGTT) was performed once the child's wounds were 95% healed, and the child was ready to be discharged from the pediatric burn intensive care unit. The determination of 95% healed is equivalent to only 5% of TBSA still without good epithelialization and was determined by consensus of the 3 faculty Surgeons. The time between injury and 95% healed was 67.9±15 days. The two-hour OGTT was performed following a 10- to 12- hour overnight fast. We used existing peripheral intravenous catheters that were placed for medical treatment during the patients acute hospital stay. A blood sample was drawn at 0 minutes to measure a baseline plasma level of glucose and insulin. Then, a flavored glucose load (Sundex, Fisher Healthcare, Houston, TX) was given orally at 1.75 g/kg body weight, up to 75 g. Subsequent blood samples were drawn at 30, 60, 90 and 120 minutes to again determine plasma levels of glucose and insulin.

Sample Analysis

Plasma levels of glucose were determined using a Stat-5 Analyzer (Novel Biomedical, Waltham, MA). Plasma levels of insulin were analyzed using enzyme linked immunosorbent assays (Diagnostic Systems Laboratories, Inc., Webster, TX). We compared our results in pediatric burn patients to previously published literature on the response of healthy children to an OGTT³⁴.

Calculations

Homeostasis Model Assessment for Insulin Resistance (HOMA_{IR})—HOMA_{IR} was developed by Matthews et al.³⁵ as a measurement for estimating insulin sensitivity from fasting serum insulin (FI) and fasting plasma glucose (FG) using the following formula:

$$\text{HOMA}_{\text{IR}} = \text{FI} \times \text{FG} / 22.5,$$

where FI is measured in µU/ml and FG is measured in mmol/L.

Statistics

Data are presented as mean ± standard error of the mean (SEM). Comparisons between burned and control mean values were made using unpaired t-tests. P values < 0.05 were considered statistically significant. All statistics were performed using Sigma Stat software package, version 2.03.

RESULTS

A total of 24 severely burned children were enrolled in this study when their burn wounds were diagnosed as 95% healed. The demographic characteristics of the severely burned children and the non-burned, healthy children published in the literature are presented in Table 1. The groups were similar in age, gender, weight, height and body mass index (BMI).

Measurements from the oral glucose tolerance test (OGTT) are shown in Table 2. Gunczler et al. published values for insulin and glucose at 0 (fasting) and 120 minutes³⁴. Fasting glucose levels were significantly higher in severely burned children as compared to non-burned, healthy children (92.3 ± 4.5 mg/dl vs. 73.6 ± 1.3 mg/dl, respectively; $p < 0.001$). Plasma insulin levels at 120 minutes in severely burned children were almost twice that of non-burned, healthy children (41.2 ± 10.8 μ U/ml vs. 24.9 ± 2.3 μ U/ml, respectively; $p < 0.05$). Moreover, there was a significant difference in the HOMA_{IR}. Severely burned children had a HOMA_{IR} of 3.53 ± 1.62 , and the value in non-burned healthy children was 1.28 ± 0.16 ($p < 0.05$).

DISCUSSION

Hyperglycemia in the critically ill population has become a forefront of interest in healthcare in the last decade. It seems only natural considering diabetes mellitus is a widespread disease with related complications that lead to greater morbidity to the patient and a rising burden to the healthcare industry. Stress-induced hyperglycemia was described in the literature as early as 1854 when Goolden illustrated the presence of glycosuria soon after injury³⁶. Further publications have described the adverse outcomes that are associated with hyperglycemia including impaired immune function leading to increased risk of infection, poor wound healing, polyneuropathy, longer stays in the intensive care unit and increased mortality^{19, 37}.

These adverse events led to the publication of the landmark study by Van den Berghe et al. identifying a positive role of intensive insulin therapy protocols in ICU patients²². Although her original investigation focused on surgical patients, continued interests led to further studies in other acutely ill population illustrating that euglycemia is extremely beneficial^{23–29}.

The goal of our study was to evaluate the level of insulin sensitivity in the severely burned pediatric patients once their total burn wounds were 95% healed. Thermal injury alone causes an extreme hypermetabolic response and the acute care enhances this catabolic reaction with frequent excision and grafting and daily wound care^{33, 38}. These events do not stop at discharge. In fact, once the patient reaches the rehabilitation phase he is involved with intense physical and occupational therapy and sequential scar revisions for years which act as constant strain and can augment the stress response. Thus, the continued presence of an insulin resistant state will further complicate rehabilitative outcomes.

There are numerous assessment tools available for quantifying insulin resistance. The hyperinsulinemic-euglycemic clamp technique, originally identified by DeFronzo³⁹ is considered the “gold standard” for identifying insulin sensitivity. However, the method is labor intensive and difficult to perform in the pediatric population. Simple indices using the oral glucose tolerance test is a more suitable method for the pediatric population.

HOMA_{IR} is an index of insulin sensitivity developed by Matthews et al.³⁵ that incorporates fasting insulin and fasting glucose in its formula. HOMA_{IR} correlates well with the metabolic clearance rate calculated from the hyperinsulinemic euglycemic clamp^{40, 41}. Our study found the HOMA_{IR} was significantly higher in severely burned children at 95%

healed as compared to non-burned healthy children. The higher the HOMA_{IR} indicates a low insulin sensitivity⁴². Severely burned children at 95% healed had almost twice the HOMA_{IR} index as non-burned healthy children. As expected, fasting glucose levels and insulin levels 2 hours after a glucose load were significantly higher in severely burned children at 95% healed. However, because little has been published regarding insulin resistance after the acute phase of thermal injury, the use of HOMA_{IR} for measuring insulin resistance remains to be validated in the trauma and burn setting.

Limitations to our study exist which relate to the daily care of the patients in the acute pediatric burn unit. Many patients may have experienced stress from intractable pain and possibly post traumatic stress disorder. All patients were placed on a conventional insulin therapy protocol which ordered intravenous boluses of insulin using a sliding scale when blood glucose levels were greater than 215 mg/dl. However, this protocol was stopped once the patient was able to tolerate adequate food intake by mouth. Additionally, medication usages varied depending on the patient. Therefore, medications that influence glucose control (i.e., epinephrine, dopamine, propranolol) could have been given during the acute medical treatment course, but patients were not receiving these at the time of sample collection. Further, no patient that received study medications such as growth hormone or oxandrolone, were included in our study.

The other major limitation to our study is the lack of a control population within our institution, due to IRB constraints of studying healthy children. However, the study we selected had several time points during the OGTT for which we could compare data. Other studies in children have also shown similar baseline data to those found by Guznler^{43–45}. Further, baseline norms have been established for fasted concentrations by clinical pediatric endocrinologists and whereas the glucose concentrations are at the upper level of normal (70–100 mg/dL), the insulin levels are elevated (1–10 μU/ml)^{46, 47}. So despite the lack of controls within our institution, our comparison group is similar to other published norms, and the differences detected in the burn patients are real.

There is no literature describing the detrimental effects of chronic insulin resistance after an acute trauma. In individuals with type 2 diabetes, insulin resistance leads to an increased incidence of hypertension, dyslipidemia, cardiovascular disease, diabetes mellitus⁴⁸ and impaired wound healing⁴⁹. It is likely that the morbidity associated with hyperglycemia that can occur secondary to insulin resistance continues to be a risk in the chronic phase. It has been shown that hyperglycemia slows the wound healing process described by a decrease in skin graft take in burn patients²⁰. Changes in the immune and inflammatory response may be associated in delayed wound healing and in the increase risk of septicemia. Further, hyperglycemia has been shown to inhibit platelet function and the phagocyte response^{50, 51}. Additional more detailed long-term studies are needed to determine how much of a role insulin resistance has in morbidity following the acute phase of burn trauma.

The mechanism behind the physiological response of insulin resistance continues to be under investigation. One limitation of the HOMA_{IR} is its inability to differentiate between insulin sensitivity in the liver versus peripheral tissues⁵². During acute trauma, impairment of the GLUT-4 receptors in the liver and skeletal muscle occurs leading to increases in plasma insulin levels⁵³. Inactivation of insulin receptor β subunits and downstream modulators such as AKT/PKB and MTOR has been linked to insulin resistance in the animal burn model⁵⁴. Moreover, we have found that changes in mitochondrial function occur after burn injury in severely burned children⁵⁵, and increases in mitochondrial pyruvate oxidative capacity improves insulin sensitivity in vivo⁵⁶. Also, the release of reactive oxygen species (ROS) caused by a higher rate of uncoupled oxidation can decrease insulin action⁵⁷.

These proposed mechanisms of actions lead us toward future studies in the role of pharmacological mediators in glucose metabolism during the long-term rehabilitative phase in burn injury. At our institution, we found that metformin given for 7 days during the acute burn trauma period demonstrated a significant anabolic effect on muscle protein⁵⁸. Furthermore, we studied the efficacy of the PPAR- α agonist, fenofibrate, immediately following burn trauma and found significant improvements in insulin sensitivity, insulin signaling and maximal mitochondrial ATP production from pyruvate⁵⁶. The results of these acute studies may provide the rationale for evaluating options in treatment of insulin resistance after discharge from the acute care setting.

CONCLUSION

This study demonstrates that insulin resistance persists even when 95% of the burn wounds have healed in thermally injured pediatric patients who are over the age of 4, and whom have sustained greater than 40% TBSA burns. This finding suggests the potential for new therapeutic methods during rehabilitation of the severely burned child.

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Table 1**Demographics**

Demographic characteristics comparing the severely burned children in our study to data published in healthy, non-burned children³⁴. Data are presented as mean±SEM.

Measurement	Normal	Burned
Author	Gunczler et al. ³⁴	
Subjects (n)	59	24
Age (years)	8.3±3.6	8±4.6
Gender (M:F)	29:30	15:9
Weight (kg)	28.7±13.2	28±13
Height (cm)	127.5±22.5	123±28
BMI (kg/m ²)	16.7±2.8	18±5
TBSA (%)	N/A	66±15
Third Degree (%)	N/A	62±19

Table 2
Measurement comparisons between severely burned children and healthy, non-burned children

Laboratory measurements taken during a 2 hour OGTT. Data are presented as mean±SEM. Glucose was measured in mg/dl. Insulin measured in μ IU/ml.

Measurement	Normal [†]	Burned	Reference Values [‡]
Fasting Glucose	73.6±1.3	92.3±4.5*	60–110
60 Minute Glucose	N/A	134.3±5.9	N/A
120 Minute Glucose	N/A	62±19	N/A
Fasting Insulin	7.4±1.0	16.6±7.8	2.1–30.8
60 Minute Insulin	N/A	67.2±13.8	N/A
120 Minute Insulin	24.9±2.3	41.2±10.8*	N/A
HOMA_{IR}	1.28±0.16	3.53±1.62*	N/A

Fasting glucose and insulin at 120 minutes were significant (*p<0.05) between the burned children and healthy, non-burned children.

[†] Normal values taken from published data from healthy, non-burned children in Gunczler et al.³⁴.

[‡] Reference values taken from the clinical laboratory at the Shriners Hospital for Children Galveston.