Changes in Fat Distribution in Children Following Severe Burn Injury

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Abstract

Background: Children with severe cutaneous burn injury show persistent metabolic abnormalities, including inflammation and insulin resistance. Such abnormalities could potentially increase their future risk for developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). This could be related to changes in body composition and fat distribution.

Methods: We studied body composition, fat distribution, and inflammatory cytokines changes in children with severe burn injury up to 6 months from discharge. Sixty-two boys and 35 girls (burn $\geq 30\%$ of total body surface area) were included.

Results: We found a decrease in total body fat and subcutaneous peripheral fat at 6 months (6% and 2%, respectively; $P < 0.05$ each). An inverse correlation between the decrease in peripheral fat content at 6 months and the extent of burn injury ($r = -0.41$, $P = 0.02$) was also observed. In addition, there was a 12% increase in serum tumor necrosis factor- α (TNF- α) ($P = 0.01$ vs. discharge) and 9% decrease in serum interleukin-10 (IL-10) ($P < 0.0001$ vs. discharge) over 6 months after burn.

Conclusion: Severe burn injury in children is associated with changes in body fat content and distribution up to 6 months from hospital discharge. These changes, accompanied by persisting systemic inflammation, could possibly mediate the observed persistence of insulin resistance, predisposing burn patients to the development of T2DM and CVD.

Introduction

BURN INJURY IS ONE OF THE most severe forms of critical illness associated with long-term complications. Among known long-term effects of severe burn injury, metabolic abnormalities of glucose and lipid metabolism have been areas of intense investigation given the associated risk for complications during the hospitalization period.¹ The hypermetabolic state immediately following burn injury is characterized by increased resting energy expenditure, glycogenolysis, proteolysis, lipolysis, and inflammation.² However, growing evidence has shown that metabolic abnormalities similar to those found in obese patients, including inflammation and insulin resistance, persist long after hospital discharge and could be related to changes in body composition and fat distribution. These metabolic abnormalities could potentially increase the lifetime risk for developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) and have not been studied in sufficient detail. Therefore, we conducted a longitudinal analysis of changes in

body composition, fat distribution, and inflammatory cytokines in a cohort of children with severe burn injury up to 6 months from discharge. The reported data will provide the necessary springboard for future mechanistic studies and therapeutic intervention to minimize risk of chronic metabolic complications of both children and adults with severe burn injury.

Materials and Methods

We conducted a prospective study involving a total of 97 children with burn injury admitted to Shriners Hospital for Children in Galveston, TX, between February, 2002, and May, 2013. Only patients randomized to the control arm of ongoing clinical trials (*clinicaltrials.gov*, ID NCT00675714) were included in this analysis. All studies and procedures were approved by the Institutional Review Board at the University of Texas Medical Branch (UTMB), Galveston, TX, and all participants and/or their care takers provided signed consent for this study. Total body fat, peripheral fat, visceral fat, and truncal

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TABLE 1. DEMOGRAPHICS OF BURN SUBJECTS

Characteristics	n or mean $\pm$ SD
Total subjects	97
Age (years)	8.7 $\pm$ 5.4
Gender	
Male	62
Female	35
Ethnicity	
Non-Hispanic whites	10
Hispanic whites	87
TBSA (%)	55.95 $\pm$ 14.6
BMI percentiles at discharge (D/C)	46.7 $\pm$ 31.7
BMI percentiles at 6 months	53.2 $\pm$ 32.8 ($P=0.2$ vs. D/C)

SD, standard deviation; TBSA, total body surface area; BMI, body mass index.

fat were measured using dual-energy X-ray absorptiometry (DEXA; Hologic APEX Software, v. 4, Discovery™ QDR Series, Model 010-1549, Bedford, MA). Fat content in whole body and specific fat depots was analyzed and calculated as percentage of body weight at each time point. Visceral fat content could be assessed only in 45 study patients using the Hologic APEX Software (v. 4.02). The remaining subjects could not be analyzed for this variable due to corrupted electronic files.

Cytokine levels of interleukins (IL) IL-1 β , IL-10, and tumor necrosis factor- α (TNF- α) were measured in the plasma of 45 study subjects using the Bioplex human 17-plex assay kit using Luminex technologies (Bio-Rad Laboratories, Inc. Hercules, CA).

Statistical analysis

Statistical analysis was done using SAS version 9.3. A paired *t*-test was used to compare data sets at two different time points. Values are reported as mean $\pm$ standard deviation. Pearson correlation analysis was used to evaluate correlation between total burn surface area and body fat content after 6 months from burn injury.

Results

Sixty-two boys and 35 girls with burn injury more than 30% of total body surface area (TBSA) were included in this study. Subject demographics are detailed in Table 1. Figure 1A depicts the changes of body fat distribution over 6 months from burn injury. Total body fat declined by 6% at 6 months compared to discharge ($P<0.05$). Subcutaneous peripheral fat was decreased by almost 2% at 6 months following burn injury compared to discharge ($P<0.05$). Both visceral and subcutaneous truncal fat were virtually identical over the observation period ($P=0.5$ each). The decrease in peripheral fat content at 6 months was found to be inversely correlated with the extent of burn injury (Fig. 2; $r=-0.41$, $P=0.015$).

To gain some insight into possible variables associating with peripheral fat loss, we evaluated plasma cytokine levels known to be increased in the acute phase of burn injury. The data shown in Fig. 1B illustrate our findings on significant increase in serum TNF- α , an inflammatory cytokine, after 6 months from burn injury as compared to discharge, whereas serum IL-10, an anti-inflammatory cytokine, was found to be decreased ($P=0.01$ and <0.0001 for TNF- α and IL-10, respectively). However, the levels of these cytokines did not correlate with the observed changes in body fat content.

Discussion

This study is the first to examine the changes in fat content of different adipose tissue depots in children following severe burn injury. We observed a decrease in peripheral areas of subcutaneous fat content 6 months after the acute injury, with no change in subcutaneous truncal or visceral fat content. This long-term reduction in subcutaneous peripheral fat content was responsible for about 6% loss in total body fat that surprisingly was associated with increased systemic inflammatory activation. Our results suggest that the changes in body fat distribution appear to be determined by burn injury, because there was an inverse relationship between the extent of burn and peripheral fat content.

Following severe burn injury, the increase in resting energy expenditure and catecholamines may persist up to 3 years.^{1,3-6} Thus, it is conceivable that the consequent excessive

FIG. 1. Burn injury associates with significant changes in body fat distribution and low-grade systemic inflammation. (A) Significant decrease of subcutaneous peripheral fat content 6 months after burn as compared to discharge from the hospital ($*P<0.05$). (B) Changes in cytokines concentration [proinflammatory tumor necrosis factor- α (TNF- α) and anti-inflammatory interleukin-10 (IL-10)] suggestive of systemic inflammatory activation ($*P=0.01$ and <0.0001 for TNF- α and IL-10, respectively).

FIG. 2. Correlation between extent of burn injury and peripheral fat content at 6 months following burn injury. The decrease in peripheral fat content at 6 months was found to be inversely correlated with the extent of burn injury ($r = -0.41$; $P = 0.015$).

mobilization of triglycerides from adipose tissue (*i.e.*, lipolysis) can result in fat depletion in various depots.³ Of interest, we found that the decrease in fat content was exclusively localized to the subcutaneous peripheral area and did not include the abdominal depots, neither subcutaneous truncal nor visceral adipose tissue. Yet, peripheral fat deposition is known to be protective against the development of insulin resistance and related health complications, including T2DM and CVD.^{7,8} On the other hand, subcutaneous truncal and visceral adipose tissue depots are detrimental to glucose metabolism and associate with severe insulin resistance^{9,10} independently of overall body fat content.¹¹

Therefore, it is possible that the reduction of peripheral fat and lack of reduction of the subcutaneous truncal area overcomes the potentially beneficial effects of decreased total body fat. Although we did not directly measure insulin resistance or lipid metabolism in our cohort, previous studies in children with burn have shown persisting insulin resistance to glucose disposal, up to 1 year after burn.¹ However, we could measure markers of inflammation in our study sample, and the finding of persisting systemic inflammatory activation burn is consistent with persisting systemic metabolic complications, possibly including insulin resistance. In fact, inflammatory activation worsened after 6 months from the acute burn injury.

Whereas TNF- α , a proinflammatory cytokine increased significantly, the plasma levels of IL-10, an anti-inflammatory cytokine, was found to decrease over time. TNF- α is known to suppress adipocyte differentiation.¹² Therefore, it is possible that increased TNF- α long term after burn injury may prevent adequate adipocyte maturation and triglyceride storage, thus resulting in decreased total body fat content. Our study design does not allow mechanistic conclusions and in fact, our results are also compatible with a primary effect of fat distribution changes on systemic inflammation. Previous studies have associated preferential deposition of fat in the truncal area as a condition of elevated TNF- α and overall systemic inflammatory activation.¹³ It is possible that burn-induced changes in body fat distribution can be determinants of worsening inflammation over time in this population. This by itself could significantly contribute to increased risk for persistence of insulin resistance over time that overcomes the potential

benefits of total body fat content decrease observed in our study. Future mechanistic studies will be needed to further clarify the nature of the associations here reported.

In conclusion, extensive burn injury in children associates with longitudinal changes in body fat content and distribution up to 6 months from hospital discharge. These changes, as well as the persisting systemic inflammation, could contribute to the observed persistence of insulin resistance to glucose disposal in these patients and significantly impact lifetime risk for complicating diseases, including T2DM and CVD.

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Author Disclosure Statement

No competing financial interests exist.

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