

Original article

Effect of Insulin Treatment to Systemic Inflammatory Response in Burn Injury

(Yanıkta insülin tedavisinin sistemik inflamatuvar yanıt üzerindeki etkileri)

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Amaç: Sistemik inflamatuvar ve hepatik akut faz yanıtı hipermetabolizmaya, çoklu organ yetmezliğine ve mortaliteye katkıda bulunur. Bu çalışmada, ciddi biçimde yanmış ve kan şekeri düzeyleri normal sınırlarda olan hastalarda, insülin verilen ve verilmeyen grupları karşılaştırarak insülinin sistemik inflamatuvar yanıtı, pro-inflamatuvar proteinlere ve hepatik akut faz yanıtı etkilerini incelemeyi amaçladık.

Materyal ve Metot: Oniki yanık hastasına kan şekeri düzeyini 120-180 mg/dl aralığında tutmak için insülin verilirken, kontrol grubundaki kan şekeri düzeyleri 120-180 mg/dl arasında olan 11 hastaya insülin verilmedi. Ölçümlerimiz, insülinin pro-inflamatuvar proteinlere, yağ ve hepatik akut faz yanıtına etkilerini kapsadı.

Bulgular: İnsülin uygulaması, pro-inflamatuvar proteinleri azaltırken hepatik proteinleri artırdı ($p<0,05$). İnsülin verilen hastalar, kontrol ile karşılaştırıldığında ($p<0,05$) normal düzeylerin sağlanması için anlamlı olarak daha az albumin replasmanına ihtiyaç duydular. İnsülin serbest serum trigliserid düzeylerini azalttı ($p<0,05$). İnsülin uygulaması ile hastanede kalış süresi ve sepsis insidansı azaldı ($p<0,05$).

Sonuçlar: İnsülin, pro-inflamatuvar yanıtı azaltıp hepatik fonksiyonları geri kazandırarak inflamatuvar yanıtı azaltır. Bu sonuç bize yanık hastalarında insülinin mortaliteyi, morbideyi azaltabileceğini düşündürmektedir.

Anahtar Kelimeler: Yanık; sistemik inflamatuvar yanıt; glukoz; insülin

ABSTRACT

Background: The systemic inflammatory and hepatic acute-phase-response contributes to hypermetabolism, multi-organ failure, and mortality. We aimed the effect of insulin on the systemic inflammatory response, pro-inflammatory proteins, and hepatic acute-phase-response in severely burned patients that received insulin but had glucose levels in the normal range, and compared the findings to patients who had similar glucose levels but did not receive insulin.

Material and Methods: Twelve burn injured patients received insulin to maintain blood glucose at a range from 120 to 180 mg/dl, 11 patients received no insulin with blood glucose levels also at range from 120 to 180 mg/dl and served as controls. Our outcome measures encompassed the effect of insulin on pro-inflammatory proteins, the hepatic acute-phase-response, and fat.

Results: Insulin administration decreased pro-inflammatory proteins, while increasing hepatic proteins ($P<0.05$). Burned patients receiving insulin required significantly less albumin substitution to maintain normal levels compared with control ($P<0.05$). Insulin decreased serum triglycerides ($P<0.05$). Incidence of sepsis and length of hospital stay decreased with insulin administration ($P<0.05$).

Conclusions: Insulin attenuates the inflammatory response by decreasing the pro-inflammatory, thus restoring hepatic functions. Therefore, we suggest that insulin may decrease morbidity and mortality in burn patients.

Key Words: Burn; systemic inflammatory response; glucose; insulin

INTRODUCTION

The systemic inflammatory response (SIRS) after trauma leads to hypermetabolism and catabolism. As a consequence, the structure and function of essential organs are compromised and contribute to multi-organ failure and mortality^{1,2}.

Under physiologic conditions the liver synthesizes mainly constitutive-hepatic proteins, such as albumin, prealbumin. After trauma the synthesis shifts from constitutive-hepatic proteins to acute-phase proteins, such as C-reactive protein (CRP)³.

This reaction of the liver is called the hepatic acute-phase-response.

The goal of the hepatic acute-phase-response is to restore homeostasis; however, a prolonged and exaggerated response leads to the enhancement of hypermetabolism and catabolism, thus to increased morbidity and mortality⁴. Insulin improves hypermetabolism by affecting pro-inflammatory cytokine production and hepatic signal transcription factor expression⁵. However, it remains unclear whether insulin affects the systemic inflammatory response and the hepatic acute-phase response and whether insulin directly exerts its effects or through glucose metabolism.

We determined the effect of insulin on the systemic inflammatory response, hepatic acute-phase-response in severely burned patients that received insulin but had glucose levels in the normal range, and compared the findings to

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patients who had similar glucose levels but did not receive insulin.

MATERIAL AND METHODS

We retrospectively analyzed patients with admission to our institute within 24 hours after burn injury in 2011 year. Patients who were 20–56 years of age and burns covering 40–60% total body surface area (TBSA) with a 3rd degree component of >10% are included to study.

Patients were randomized in the study groups. The patients with concomitant injuries, and inhalation injury were not included. Patient demographics (age, date of burn and admission, sex, burn size, and depth of burn) were recorded.

Insulin group was severely burn injured patients who required insulin substitution to maintain normal blood glucose levels of a range 120 to 180 mg/dl (<200 mg/dl). Insulin was administered as a continuous drip according to the blood glucose concentration. Control group was severely burn injured patients who did not require insulin substitution and their blood glucose levels without insulin were in the normal range of 120 to 180 mg/dl.

Ringer lactate solution was started by Parkland formula. The patients were fed by enteral feeding. If serum albumin concentrations were less than 2.0 g/dl, albumin was supplemented based upon body weight to maintain albumin at 2.0 g/dl. Grams of albumin infused per meter square burn were compared for patients receiving insulin and control patients. Serum calcium, phosphate, prealbumin, albumin, CRP and triglycerides were measured.

Analyses of variance (ANOVA) with post hoc Bonferroni's correction, paired and unpaired Student t test, were used. Data are expressed as percentages, means±SD or means±SEM. Significance was accepted at P<0.05.

RESULTS

With the administration of insulin a target blood glucose concentration of 120 to 180 mg/dl could be achieved in insulin group. The control group demonstrated also a blood glucose range of 120 to 180 mg/dl. There was no statistical significant difference between the two groups at each time point.

There were no significant differences between patients receiving insulin or control in age, sex, size, and depth of burns. By looking at infection rate, it was mostly burn wound infection that resulted in a SIRS. Onset of sepsis was with a range from 19 to 27 days (23 days) in the insulin group and from 13 to 19 days (16 days) in the control group. Incidence of sepsis was significantly

different in both groups. Significant differences in length of hospital stay between insulin and control treated patients could be shown (Table 1).

Table 1. Patient Demographics

	Insulin Group	Control Group	P
n	12	11	
Age (yr)	38±17	41±15	0.7
Sex (F/M)	5/7	4/7	0.8
TBSA (%)	48±8	51±7	0.8
3 rd degree (%)	31±6	23±9	0.6
Length of hospital	34±13*	46±17	0.4
Incidence of sepsis	41*	68	0.2
Onset of sepsis	23±4*	16±3	0.2
Mortality	4*	8	0.1

* P< 0.05

The amount of albumin required for substitution or as albumin per square meter burned surface area, was significantly reduced in patients receiving insulin compared with controls (P<0.05) (Table 2).

Table 2. Albumin Substitution Requirements

	Insulin Group	Control Group	P
Total albumin (g)	126±78*	230±97	0.02
Albumin per day (g)	43±31*	78±61	0.02
Albumin/m ² burn, g/m ²	174±82*	340±193	0.01

* P<0.05

The range of serum calcium was from 2.8 to 5.2 mg/dl in the insulin group, while the range was from 2.9 to 5.8 mg/dl in the control group. Four patients required calcium substitution in the insulin group and 2 patients in the control group, respectively. The range of serum phosphate was from 1.6 to 6.2 mg/dl insulin group, while the range was from 1.5 to 6.4 mg/dl in the control group. Phosphate substitution was required in 2 patients in the insulin group and 1 patient in the control group. Serum calcium and phosphate levels and requires were not statistically significant different in the both of groups.

All constitutive-hepatic-proteins dropped below normal levels within 1 day after burn. Over time constitutive-hepatic-proteins increased but still remained below normal levels. Insulin significantly increased serum prealbumin at days 30 and 40 post trauma when compared with controls (P<0.05) (Figure 1).

CRP determined in this study increased above normal levels at fifth day. Insulin further significantly decreased CRP levels at days 10, 30, and 40 after burn injury when compared with controls (P<0.05) (Figure 2).

Insulin decreased serum triglycerides on days 25, 30, and 40 when compared with controls ($P<0.05$) (Figure 3).

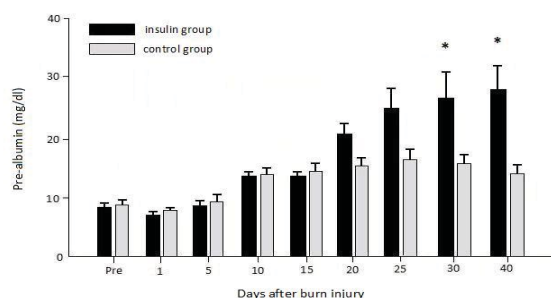


Figure 1. Insulin increased serum prealbumin at days 30 and 40. * $P<0.05$

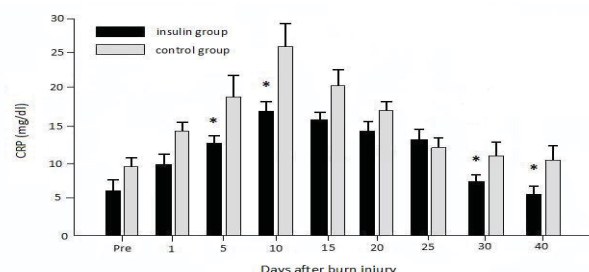


Figure 2. CRP was significantly decreased to normal range in the insulin group. * $P<0.05$

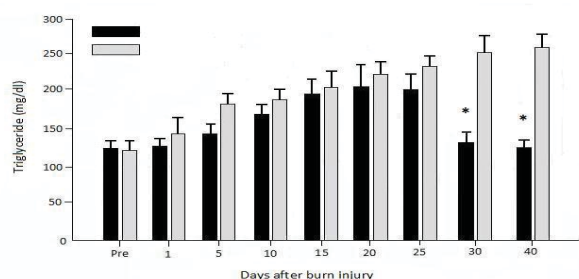


Figure 3. Insulin significantly decreased serum triglycerides at days 30 and 40. * $P<0.05$

DISCUSSION

The reaction of trauma, sepsis, or major operations is characterized by hypermetabolism and catabolism^{1,2}. These reactions causes to the systemic inflammatory response. During the aftermath of these multiple reactions, the liver has been shown to play a crucial role³. Insulin therapy (blood glucose below 110 mg/dl) was shown to decrease the incidence of multi-organ failure and mortality in critically ill patients². However, it is still unknown whether insulin exerts its effects directly through modulating pro-inflammatory mediators or indirectly through modulating glucose

concentration. Several studies suggested that even mild hyperglycemia is detrimental and it aggravates endotoxemic shock and hypermetabolism^{6,7}.

Hyperglycemia may further contribute to morbidity and mortality after burns or surgery^{1,8}. The possible detrimental mechanisms of hyperglycemia are increased production of superoxide and increased stress⁹.

Our results showed that insulin decreased pro-inflammatory proteins and hepatic acute-phase-protein concentrations. Given the fact that the insulin treated group and the control group had normal blood glucose levels, these data suggest that insulin acts as an anti-inflammatory molecule through direct cellular effects rather than through indirect effects, which would be by modulating glucose concentration.

Acute-phase-protein (CRP) concentrations decreased in insulin group. Decreased acute-phase-protein expression was associated with increased synthesis of constitutive-hepatic-proteins, such as albumin, prealbumin. As a clinical relevant consequence, albumin substitution requirement to maintain normal serum albumin levels was significantly decreased in the insulin group when compared with the control group. Improved constitutive-hepatic-protein synthesis may result from either direct cellular signalling effects of insulin or indirect from a better liver synthesis capacity. Insulin decreases the pro-inflammatory signal transcription factors⁵. An up-regulation of both transcription factors lead to impaired organ function and protein synthesis, such as albumin^{10,11}. Therefore, it appears that insulin improves organ function and protein synthesis during the hypermetabolic response⁵. Thus insulin may act as an antiinflammatory molecule by two different pathways by decreasing pro-inflammatory mediators and by increasing anti-inflammatory mediators.

Insulin is known to have vasodilatory properties and to increase glucose uptake in ischemic tissues for anaerobic ATP production after augmented glycolysis¹². Insulin may also stimulate pyruvate dehydrogenase during ischemia and thereby exerts a beneficial effect associated with an improved energy state and less lactate production¹³. Furthermore it was speculated that insulin may inhibit the synthesis and release of free fatty acids^{11,12}. Increased levels of free fatty acids lead to increased hepatic triglyceride accumulation, and thus to fatty liver infiltration and consecutively to hepatic failure, which is associated with increased incidence of sepsis and mortality^{14,15}. We have shown that insulin administration decreases serum triglycerides after

burn injury. This metabolic action of insulin represents an advantage, as liver failure and death due to increased fat accumulation could be prevented.

In our study, insulin increased constitutive proteins after severe burn. Insulin further decreased serum triglycerides which could attenuate fatty liver infiltration and thus liver function and liver homeostasis. As blood glucose was kept in the same range in both groups, these

data suggest that insulin acts through direct cellular mechanisms rather than indirect mechanisms, which would be through modulation of glucose concentrations. In conclusion, we have shown that insulin attenuates hypermetabolism after severe trauma, and we suggest that insulin may decrease morbidity and mortality in a variety of critical conditions.

Conflict of interest statement none declared.

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