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Hyperglycemia as a Predictor of High Morbidity and Mortality in Burn Patients

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Abstract

As one of the major public health problems, burns present an important challenge for patients and medical teams due to its high morbidity and mortality. Burns lead to profound metabolic alterations, trigger a systemic inflammatory response, decrease the immune defense, and impair the function of numerous organs. The metabolism is shifted towards a hypermetabolic state, and if this situation persists, it will have deleterious consequences for the patient's health. One of the things that plays an important role is the stress-induced hyperglycemia (SIH) that results from the hypermetabolic response in burn patients. High blood glucose levels are almost always found amongst patients suffering from burns. Poor glucose control has shown poorer outcomes and has been associated with a significant risk of complications. In the univariate analysis, mean admission patient glucose levels greater than 140 mg/dL was associated with a significant risk of mortality. This non-systematic review was performed to present the evidence for the hyperglycemia as a predictor of high morbidity and mortality in burn patients.

Keywords: hyperglycemia, burns, morbidity, mortality

Introduction

Burns represent one of the major public health problems, accounting for an estimated 180.000 deaths annually. The majority of these occur in low- and middle-income countries [1]. The average patient per year is reaching 141 per year and is considered high, meaning that Indonesia, as a low middle income country, still does not have the necessary effort to prevent the incidents of burn injury effectively. Admission of patients between 2013-2017 has inclined throughout the year, from 97 in 2013 to 166 in 2017, meaning there is an increase in incidence rate. The most condition triggering death in the Cipto Mangunkusumo Burn Unit is Septic Shock with a total of 48.6% (89 cases) [2].

Burned patients react with a systemic inflammatory response and a hypermetabolic response [3]. If the response and its consequences persist, they will start to have numerous organ dysfunctions, which could result in death [4]. One of the results from the hypermetabolic response is persistently elevated glucose, also called stress-induced hyperglycemia (SIH). SIH is almost found amongst burned patients [5].

Possible mechanisms for post-burn hyperglycemia include insulin resistance and elevated endogenous glucose production [6]. Hyperglycemia is recognized to be associated with adverse events including higher incidence of infection (such as wound infection and pneumonia that can lead to sepsis condition) and decreases the success rate of skin graft survival [7] [8] [9].

Methods

We performed a non-systematic review of the literature to present the evidence for the hyperglycemia as a predictor of high morbidity and mortality in burn patients. We search for articles about "hyperglycemia" and "burns patients".

Results

Hyperglycemia In Burned Patients

Patients who have suffered burns frequently undergo a systemic response that includes elevated metabolism, inflammation, altered immunological and cardiac function, and associated hyperglycemia [5]. From Gore DC *et al*., over 50% of severely burned children had persistently elevated glucose during a significant percentage of their hospitalization [10].

Hyperglycemia has been considered as an organism's response to stress and is linked to an elevated risk of morbidity and mortality. In burns patients, poor glucose control has shown poorer outcomes and have been associated with a significant risk of complications. A glucose level greater than 140mg/dl seems to increase the clinical suspicion of an infection in patients with burn injury [5] [10].

Stress-induced hyperglycemia (SIH) is an almost universal finding amongst patients suffering from burn injuries, especially major burn injuries. SIH has been defined as plasma glucose levels >200mg/ml in non-diabetic patients occurring as a result of injury. Patients with burn injuries exhibit increased gluconeogenesis and glycogenolysis (an increase in glucose production), as well as insulin resistance, leading to decreased glucose uptake and reduced clearance [10].

The patient's metabolic state and glucose metabolism change significantly after experiencing severe burns. The metabolic response to burns covering more than 20% of the TBSA (Total Body Surface Area) has been divided into two phases: the "ebb" phase and the "flow" phase. The "ebb" phase, which lasts for the first 2-4 days following burn, is characterized by a decrease in metabolic rate, circulation blood volume, cardiac output, tissue perfusion, and oxygen consumption [4].

The "flow" phase is initiated, amplified and maintained by the continuous action of stress hormones (cortisol, catecholamine, glucagon) and cytokines (TNFα, IL-1β, IL-6). This "flow" phase is characterized by [4][6] :

1. Increased heart rate and blood pressure
2. Peripheral insulin resistance
3. Increased glycolysis
4. Augmented glycogenolysis
5. Accentuated gluconeogenesis
6. Elevated lipolysis
7. Persistent proteolysis

Burn wound healing is an anabolic process that uses enormous amounts osf amino acids, which are obtained through the breakdown of skeletal muscle. The prognosis of these patients is heavily influenced by hyperglycemia and the loss of muscle mass that comes with catabolism. To improve the energy supply to the wound, enhanced gluconeogenesis primarily occurs in the liver. Gluconeogenesis increases energy expenditure in burn patients and its main substrates are amino acids derived from muscle catabolism and lactate produced by the burn wound itself. Increased gluconeogenesis after burn is characterized by inefficient use of metabolic substrates [11] [12] [13].

The first 48 hours after burn injury ('ebb' phase) are characterized by decreased metabolic rate and soon give way to hypermetabolism ('flow phase') accompanied by hyperinsulinemia and hyperglycemia, the hallmark of insulin resistance. Burn patients were hypermetabolic, had greater resting energy expenditure (REE) from weeks 2 to 4. Seven to fourteen days after the injury, hyperglycemia and hyperinsulinemia peak [11 [13] [14].

These acute changes are referred to as an "adaptive response" [15]. However, if the hypermetabolic response and its consequences persist, patients become exhausted and lose their ability to respond. They start to have numerous organ dysfunction, which could result in death [4] [6].

Hyperglycemia Increases Risk Of Infections

Both in adults and pediatric populations, critically-ill patients with hyperglycemia have a higher incidence of infections and sepsis [5]. Persistent hyperglycemia after severe burn injury is associated with a detrimental clinical outcome. A hyperglycemia-induced detriment in immune function results in an

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incompetence of the wound barrier that manifests as an increased incidence of bacteremia and fungemia. Another alleged negative effect of hyperglycemia is a delay in wound healing [10]. Ray JJ et al., has shown that the incidences of bacteremia, pneumonia, and urinary tract infection are higher in burn patients with admission hyperglycemia [9].

Kraft R *et al*., study found that systemic hyperglycemia with blood glucose levels over 150 mg/dl are associated with significantly increased post-burn pulmonary complications. One of the major infectious complications is pneumonia, which has been shown to increase burn mortality by 40%. The development of pneumonia is because of their vast hypermetabolic and inflammatory responses, profound immune compromise, prolonged bed rest, and need for mechanical ventilation [8].

Hyperglycemia Decreases The Success Rate Of Skin Graft Survival

Graft survival depends on the diffusion of nutrients and oxygen from the wound bed known as imbibition. Inosculation then follows when the blood vessels of the graft and from the wound bed grow together to make end-to-end contact. Neovascularization occurs when new blood vessels grow from the wound bed into the graft. Early failure of graft survival is attributable to seroma and hematoma formation, which lifts the graft off the wound bed, preventing imbibition. Other factors that lead to graft failure include shearing forces, edematous tissue, and infected tissue.

Hyperglycemia, as an acute phase response, has been consistently observed in burn patients. The increase in glucose levels has been attributed by increased rates of glucose production resulting from increased rates of gluconeogenesis as well as insulin resistance. To provide precursors for gluconeogenesis, substantial protein catabolism occurs, resulting in potential inhibition of wound healing. Elevated level of glucose during the few days after the injury induced edema that inhibited diffusion of metabolites in wound bed.

Authors	**Study Design**	**No of Patients**	**TBSA**	**Glucose Level**	**Skin Graft Survival**
Mowlavi et.al (2000)	Retrospective	· Normoglycemic group (n : 28)	>10%	Hyperglycemia : >126 mg/dL	· Hyperglycemic : 62,5 %
		· Hyperglycemic group (n : 24)			· Normoglycemic : 92,8%
Gore et.al (2001)	RCT	· Poor Glucose Control (n:33)	>60 %	Hyperglycemia : > 140 mg/dL	· Skin graft survival in poor glucose control patients : 64%
		· Adequate Glucose Control (n:25)			· Skin graft survival in adequate glucose control patients : 88%

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Nishat et.al	Retrospective	· Non Diabetic	TBSA >10%	Diabetes : 221 mg/dl ± 12,6 SD	· Rejection of skin grafts in diabetic individuals were 32.3% ± 11.12 SD.
-2022		(n : 30)			· The hematoma occur in diabetic individuals were 12.1% ± 10 SD,
		· Diabetic (n : 42)			· Pus pooling occur in diabetic individuals were 18.1% ± 4.8 SD
					· Rejection of skin grafts in non diabetic patients were 15.10 % ± 12.15 SD
					· The hematoma occur in non diabetic individuals were 7.1% ± 11 SD
					· Infection occur in non diabetic individuals were 7.5 % ± 6.2 SD
					· Pus pooling occur in non diabetic individuals were 9.4% ± 5.3 SD
McCampbell et.al (2002)	Retrospective	· Poor Glucose Control (n:50)	TBSA > 5%	Diabetes : >180 mg/dL	· Partial graft slough was 6% in diabetics with a 3% regraft rate, whereas nondiabetics had a

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		· Adequate Glucose Control (n:44)			1% regraft rate.

Insulin Therapy In Hyperglycemia

Pre-existing diabetes and hyperglycemia that occurs in burn injury patients, from the study above, shows that two conditions can lead to low skin graft survival on the treatment of burn injury and increase risk of infection. Blood glucose control is one of the key elements in critical burn care and treatment. Insulin improved muscle protein synthesis and therefore post-burn lean body mass. Furthermore, insulin increased protein synthesis in the skin, accelerated wound healing and had a massive impact on inflammatory and acute phase responses.

In pediatric patients with greater than or equal to 60% total body surface area burn, poor glucose control (>40% of all plasma glucose values >140 mg/dL) was associated with bacteremia, fungemia, reduced skin graft take, and increased mortality [10]. Intensive insulin therapy to maintain blood glucose levels of 90 to 120 mg/dL in pediatric patients with a greater than or equal to 30% total body surface area burn has been compared with ‘‘conventional insulin therapy.’’ In the intensive insulin therapy group, there was a reduced rate of urinary tract infections [16].

A study that conduct by Hemila in 2008, one hundred adult burn patients (control group n : 53) and (intensive insulin therapy group n : 47) were admitted to the burn intensive care unit of the University of Michigan Burn Service with > 15% total body surface area burn. Intensive insulin therapy group received insulin drip protocol for use in ICU patients with sustained blood glucose levels (>12 hours) over 150 mg/dL. The control group of burn patients experienced proportionately more infectious complications (52%) when compared with the intensive insulin therapy group (35%). Positive quantitative wound culture is higher in the control group (11%) than in the intensive insulin therapy group (4%). Bacteremia and Urinary tract infection are also higher in the control group than in the intensive insulin therapy group. In univariate analysis, admission glucose greater than 200 mg/dL, mean patient glucose greater than 140 mg/dL, and maximum glucose greater than 200 mg/dL were all associated with a significant risk of mortality

Conclusion

Hyperglycemia in burn patients is recognized to be associated with a higher incidence of infection, including wound infections, bacteremia, and pneumonia that can lead to sepsis conditions. Furthermore, the alleged negative effect of hyperglycemia is a delay in wound healing and decrease in the success rate of skin graft survival. Nevertheless, hyperglycemia is a condition that can be managed. Knowing hyperglycemia as a predictor factor for high morbidity and mortality and how to manage it in burn patients can help decrease the morbidity and mortality itself.

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