Review Article

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Effect of Insulin Therapy on Traumatic Patients: A Scoping Review

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Abstract

Background: Trauma is one of the most important causes of death in. Therefore, proper management and treatment of these patients can be very beneficial. Therefore, the aim of this literature was to investigate the extent, scope and nature of researches on the effect of insulin therapy on the treatment efficacy of traumatic patients.

Methods: This study is a scoping review of research that was conducted by searching in Scopus, PubMed, Embase and ScienceDirect databases with keywords related to insulin therapy and trauma. In this study, all reports with human and animals as well as cohort and clinical trial studies were reviewed.

Results: Of the 4365 studies, 73 studies met the inclusion criteria and were evaluated, most studies examining the effect of insulin on traumatic brain injury and immune system and the fewest were in trunk trauma patients, especially chest trauma. The findings of this study showed the effect of insulin therapy on decreasing levels of IL-6, IL-8, IL-10 and TNF-α thus decreasing the inflammatory response in trauma patients. Insulin therapy can reduce the risk of infection in patients with trauma and burns thereby reducing the number of days spent in intensive care units and dependence on ventilation.

Conclusion: Insulin therapy can be useful in treating trauma patients but increases the rate of hypoglycemic episodes that require careful monitoring of patients' blood glucose which can have a negative impact on treatment outcomes.

Keywords: Insulin therapy, Insulin treatment, Injury, Multiple traumas, Trauma, Traumatic patients

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Introduction

Trauma and injury account for 16% of the global burden of the disease, which is significant in low- and middle-income countries (1) and 90% of deaths from trauma occur in low-income countries (2). Trauma and its complications are the most costly health problems in the United States, with the fourth leading cause of death in all age groups and the first leading cause of death in children and individuals less than 45 years of age, and about 73% deaths of the individuals with 15 to 24 years old (3). In Iran, trauma-related deaths are the second leading cause of death (4). That the brain injury and motorcycle accidents are the first causes of death have been reported (5). It is estimated that 905 people in Iran per 1,000 people affected by traumas, which costs more than USD 6 billion to treat these non-fatal injuries (6). There are reports of increased trauma and injuries worldwide, with 16,000 people dying from trauma each day and thousands hospitalized, many of which become permanently disabled (1).

The two main causes of death in traumatic patients are hemorrhage and neurological injuries, accounting for about three quarters of all trauma-related deaths (7). 50% of deaths in the first 24 *hr* are caused by hemorrhage and hypovolemic shock and the cause of deaths after 24 *hr* is multiple organ dysfunction syndrome (8). Traumatic patients are affected by macro barriers including the skin, as well as micro barriers such as the cell wall, which in turn cause the release of dangerous molecules and compounds (9) so that bleeding in these patients can be due to oxidation and coagulation disorder (10,11). Insulin, as an antioxidant, can prevent the process of oxidation and cell death (12,13). In acute-phase inflammation in trauma, insulin levels decrease and increase levels of anti-insulin hormones such as glucagon and cortisol (14). Hyperglycemia is also one of the complications of trauma in patients which can affect the mortality rate of patients. This increase in glucose can be due to hypermetabolic response to the stress (15,16). This hyperglycemia may also be due to acute insulin resistance in traumatic patients (17).

Hyperglycemia and hemoglobin depletion have been found to be factors influencing trauma-induced coagulopathy (18). Also, studies showed that an increase in blood glucose levels of ≥200 *mg/dL* had an impact on the mortality rate of traumatic patients (19,20). But a study to clarify this issue compared blood glucose levels with mortality rates in the two types of blunt and penetrating trauma, and found that blood glucose levels were strongly correlated with mortality in penetrating trauma (21), but another study did not reach this conclusion and violated it (22).

Insulin is a peptide hormone secreted from the beta cells of the islets of Langerhans. Insulin is the main hormone in the body's metabolism, as it regulates carbohydrates, fats and proteins and produces many proteins in the body (23).

Insulin also has other effects on the body, including increased DNA transcription, enzyme production, reduced protein degradation, decreased autophagy, increased blood flow, especially in arterioles, and increased intracellular fluid, and other effects that may still be unknown (24,25). Other known effects of insulin are prevention of apoptosis and promotion of proliferation as well as cell differentiation (25-28). Studies on the effect of insulin on traumatic patients have yielded different results.

In this regard, a review study of 16 RCT studies demonstrated that insulin therapy did not affect the mortality rate of traumatic patients and only increased the risk of hypoglycemia, which could have a negative impact on treatment outcomes in this group of patients (29). One of the complications of traumatic and critically ill patients is multiple organ failure in which studies have shown that insulin therapy can be effective in acute renal and liver failure (30,31).

Various studies have indicated that insulin can be effective in treating trauma patients. For instance, Wang has shown that insulin therapy in traumatic brain injury is associated with reduced mortality as well as reduced neurological disorders (32). But studies have rejected that finding and showed insulin therapy cannot be effective on mortality rate in traumatic brain injury but can reduce the risk of infection and length of stay on intensive care unit (33,34)

Given the conflicting information about the impact of insulin on traumatic patients, the aim of this study is to review studies on the impact of insulin therapy on traumatic patients to help clarify this ambiguity.

Materials and Methods

Introducing research question

This study is a scoping review to answer the question of what effects can insulin therapy have on traumatic patients.

Inclusion criteria: In this study, all types of articles except case reports, case series, systematic review and meta-analysis were reviewed. Also, all articles with English language abstract were selected and included all articles in which the type of patients, insulin dose or blood glucose level, number of samples and place of study were mentioned in the article and just, one of these factors is not mentioned. Also inclusion criteria included articles with human and laboratory animals.

Exclusion criteria: They included insulin therapy in traumatic patients or animals with type 1 and 2 diabetes and the effects of insulin therapy on cells in vitro, but such studies were cited for further emphasis outside the final selected articles. Trauma refers to all bodily injuries caused by an external force, so the study included traumas to different organs as well as burns (3).

Determining the relevant studies

Search was completed on December 11, 2022 at ScienceDirect, PubMed, Embase, Scopus and Google Scholar databases. This was the search strategy at PubMed (insulin therapy [Title/Abstract]) OR (insulin treatment [Title/Abstract]) AND (trauma [Title/Abstract]) OR (traumatic [Title/Abstract]) OR (polytrauma [Title/Abstract]) OR (injury [Title/Abstract]) OR (injuries [Title/Abstract]).

But on the Google Scholar database, the keywords were searched only on the title of the articles. The PRISMA checklist was used to conduct the study (Figure 1).

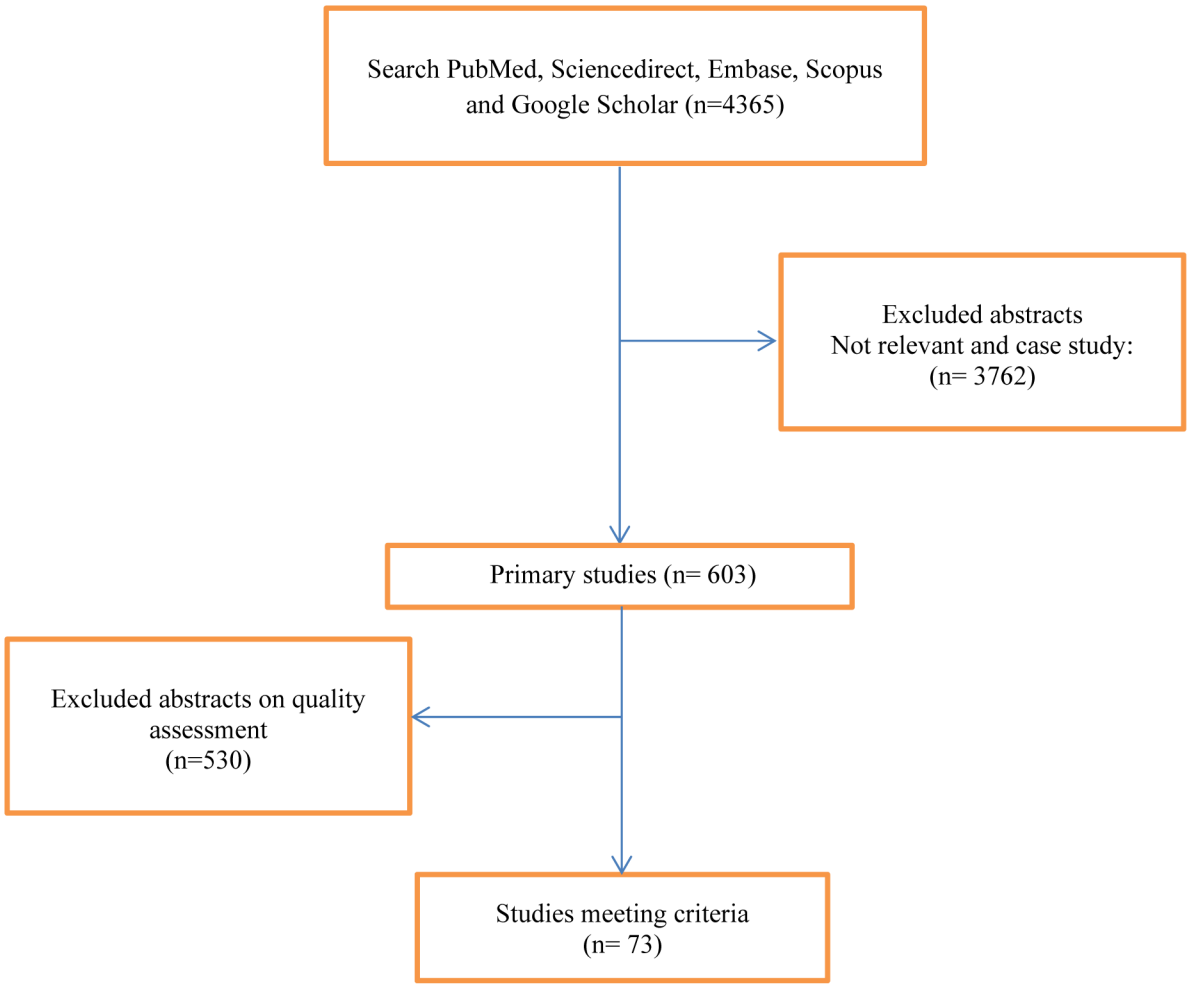

Figure 1. Flow diagram of the literature search and study selection.

Selecting the studies and charting data

The articles were first entered into Endnote 16 software, and after removal of duplicates of titles and abstracts based on investigators' agreed checklist, two investigators reviewed the inclusion criteria. And the data was charted in Excel software. Any disagreements were examined by the other investigators and a final agreement was reached. Data included first author of the study, year of publication, type of study, country, patient characteristics, blood glucose level in the intervention group, amount of insulin administered in the intervention group, number of participants, and important study findings.

Collecting, summarizing and reporting the results

The findings of this study are categorized into four areas that include the effect of insulin on the immune system and blood factors in traumatic patients, the effect of insulin on traumatic brain injury, the effect of insulin on traumatic and critically ill patients, and ultimately the effect of insulin therapy on burn patients.

Results

The findings of this study consisted of 73 articles examining insulin therapy on head trauma patients and types of cerebral hemorrhage, chest trauma, burns, and a number of articles examining the impact of insulin therapy on immune response from the perspective of laboratory parameters. Articles reviewed from 11 countries, respectively, China (35 articles), America (19 articles), Germany (4 articles), Belgium (5 articles), Brazil (3 articles), Italy (2 articles), Netherlands (1 article), Spain (1 article), Canada (2 article) and Bulgaria (1 article). In this review study, more than 16463 patients and over 1191 laboratory animals were studied (Table 1).

Table 1. Evaluation of the effects of insulin therapy on patients with trauma

First author, country	Country	Study design	Characteristics of the patients	level of blood glucose or insulin units' administration in intervention group	Number of participants	Important outcomes
Coester (2010) [64]	Brazil	A randomized trial	Traumatic brain injury	80-110 *mg/dL*	88 Pt	Insulin therapy did not improve the neurologic outcome
Badenes (2009) [65]	Spain	A microanalysis study	Traumatic brain injury	72-144 *mg/dL*	15 Pt	Insulin therapy decrease of cerebral glucose and an increase in micro-dialysis markers of cellular distress
Katakam (2019) [49]	USA	Controlled experimental study	-----	3 *U/kg* body weight	18 Rats	acute hypoglycemia induces impaired mitochondrial respiratory dysfunction in the cerebral microvasculature
Bilotta (2008) [66]	Italy	A randomized clinical trial	Traumatic brain injury	80–120 *mg/dL*	97 Pt	ICU stays and infection rates similar to those receiving conventional insulin therapy
Wang (2017) [69]	USA	A randomized controlled trial	Traumatic brain injury	79-109 *mg/dL*	88 Pt	Insulin therapy reduced infection rate, shorter stays in ICU, and improved neurological outcome
Clarito (2010) [70]	USA	Retrospective database review	Traumatic brain injury or stroke	80-140 *mg/dL*	125 Pt	Intensive insulin therapy worsening of neurological, as well as clinical outcomes
Zhao (1988) [71]	China	A randomized controlled trial	Head injury	70-110 *mg/dL*	46 Pt	Insulin therapy ameliorates the accumulation of lactate and decrease ICP

Contd. table 1.

Zygun (2004) [72]	Canada	Retrospective analysis of a prospectively collected database	Traumatic brain injury	131-172 *mg/dL*	34 Pt	Blood glucose is associated with brain tissue acidosis
Zhu (2019) [36]	China	A randomized controlled trial	Traumatic brain injury	79-140 *mg/dL*	61 Pt	Intensive insulin therapy inhibits the inflammatory response
Zhu (2014) [35]	China	A controlled trial study	Craniocerebral trauma	---	62 Pt	Remit hyperglycemia after traumatic brain injury and control the inflammatory reaction rapidly
Li-jun (2012) [37]	China	A controlled trial study	Traumatic brain injury	79-109 *mg/dL*	78 Pt	Intensive insulin therapy can depress the inflammatory response and improve prognosis
Birnbaum (2009) [74]	Germany	Before and after retrospectively study	Elevated intracranial pressure	80-140 *mg/dL*	64 Pt	Intensive insulin therapy could be helpful in the management of intracranial hypertension
Hill (2010) [79]	USA	Controlled experimental study	Moderately brain-injury	15 *U/kg*	21 Rats	Intervention with insulin therapy to lower blood glucose levels in TBI patients may increase secondary brain damage
Brabazon (2017) [80]	USA	Randomized controlled experimental study	Traumatic brain injury	6 IU *per day*	43 Rats	Intranasal insulin improves memory, increases cerebral glucose uptake and decreases neuroinflammation
Xu (2020) [84]	China	Randomized controlled experimental study	Subarachnoid Hemorrhage	1.5 *IU* each naris at 0, 24, and 48 *hr* post-trauma	72 Rats	Intranasal insulin improves metabolic distress after SAH
Sonneville (2011) [75]	Belgium	Randomized, controlled trials	Critically ill	95-111 *mg/dL*	10 Pt	Insulin therapy reduces brain inflammation and may be neuroprotective
[Arib (2016) [76	Belgium	Cohort study	Subarachnoid hem-orrhage	110–150 *mg/dL*	Pt 144	Insulin therapy resulted in lower proportion of glucose available in the CSF in patients with Subarachnoid hemorrhage
Bilotta (2007) [[77	Italy	A randomized pro-spective pilot trial	Acute subarachnoid hemorrhage	50 *IU* 80 to 120 *mg/dL*	Pt 78	Insulin therapy affects postoperative vasospasm and neurologic outcome
Lenhardt [(2012) [78	USA	A preliminary report	Intracranial hemor-rhage	80-110 *mg/dL*	Pt 44	Intensive insulin therapy did not reduce morbidity but may be a benefit of effect on outcome in patients with relatively minor neurologic injuries
Han (2014) [50]	China	Randomized con-trolled experimental study	Thermal injury	90-126 *mg/dL*	Rats 72	Insulin therapy inhibiting multiple organ failure after burn injury
Zhang (2011) [47]	China	Randomized con-trolled experimental study	Thermal injury	3 to 5 *U/kg/d* 90-126 *mg/dL*	Rats 56	Insulin therapy inhibited pulmonary microvascular endothelial cell dysfunction, decreased cell apoptosis, and inhibited acute lung injury after a burn
Dan (2010) [38]	China	Randomized, controlled trials	Polytrauma patients	79-109 *mg/dL*	Pt 54	Insulin therapy reduces the mortality and CRP, IL-6 and TNF-α in serum

Contd. table 1.

Zhao (2007) [39]	China	Randomized, controlled trials	Injured patients	72-108 *mg/dL*	----	Intensive insulin therapy can markedly improve immune function and enhance phagocytosis of monocytes
Zhang (2011) [59]	China	Randomized, controlled trials	Severe trauma	79-109 *mg/dL*	56 Pt	Insulin therapy can reduce the incidence rate of complication and mortality in severe traumatic patients
Barkhausen (2009) [52]	Germany	Controlled experimental study	Trauma	10 or 20 *IU/kg*	80 Rats	Insulin therapy was associated with improved survival rates and, in lungs and liver, fewer infiltrating neutrophils and reduced IL-6 and IL-10 mRNA expression
Ma (2012) [42]	China	A randomized controlled trial	Trauma	108-144 *mg/dL*	64 Pt	Intensive insulin therapy promoted immune suppression
Zhao (2005) [41]	China	A randomized controlled trial	Severe trauma	---	40 Pt	Insulin has anti-inflammatory actions and improved outcomes of patients
Peng (2015) [107]	China	A randomized controlled trial	Multiple trauma	---	53 Pt	Intensive insulin therapy can decrease the expressions of inflammatory, improve the prognosis, and reduce the incidence of nosocomial infection and mortality
Zhao (2007) [108]	China	A randomized controlled trial	Multiple trauma	72-109 *mg/dL*	62 Pt	Intensive insulin treatment might improve patient's general condition and decrease complications and mortality of severe multiple trauma
Ingels (2011) [44]	Belgium	Secondary analysis of 2 randomized clinical studies	Critical illness	80-110 *mg/dL*	1681 Pt	Reduced sCD163 with intensive insulin therapy supports reduced inflammation and may contribute to improved outcome
Dang (2011) [45]	China	A controlled trial study	Trauma patients	---	80 Pt	Early intensive insulin treatment could probably reduce multiple organ dysfunction syndrome and mortality
Zhao (2006) [40]	China	Before-after design	Trauma patients	108-144 *mg/dL*	32 Pt	Intensive insulin therapy improves blood glucose control and protects organ functions in injured patients
Liu (2012) [113]	China	A randomized controlled trial	Chest trauma patients	79-109 *mg/dL*	42 Pt	Intensive insulin therapy improves the short-term prognosis of chest trauma patients
Zhao (2007) [109]	China	A randomized controlled trial	Trauma patients	----	64 Pt	Intensive insulin therapy can protect organ functions of injured patients in ICU and reduce infection incidence and mortality of organ function failure patients

Contd. table 1.

Yang (2009) [73]	China	A randomized controlled trial	Traumatic brain injury	80-110 *mg/dL*	240 Pt	Mortality rates at 6 months follow-up are not affected by intensive glucose control in patients with severe TBI. Intensive insulin therapy decreases infection rate and days in NICU and improves the neurological outcome at 6 months follow-up
Van De Polder (2011) [122]	Nether-lands	Retrospective study	Traumatic brain injury	---	128 Pt	Insulin therapy decreases length of stay on the PICU
Van den Berghe (2005) [110]	Belgium	Prospectively planned subanalysis	Intracranial pressure, diabetes insipidus, seizures, and long-term rehabilitation	110 *mg/dL*	405 Pt	Preventing even moderate hyperglycemia with insulin during intensive care protected the central and peripheral nervous systems
Klein (2004) [31]	Germany	Randomized controlled experimental study	Thermal injury	5 *IU/kg* 120 *mg/dL*	56 Rats	Insulin attenuates the inflammatory response by decreasing the pro-inflammatory and increasing the anti-inflammatory cascade, thus restoring hepatic homeostasis
Azevedo (2009) [112]	Brazil	Analysis previously prospective study	Critically ill patients	132.6 *mg/dL*	228 Pt	Intensive insulin therapy does not reduce the incidence of acute kidney injury evaluated through the RIFLE criteria when compared with a carbohydrate restrictive strategy
Fram (2010) [127]	USA	Prospective, randomized study.	Thermal injury	80–110 *mg/dL*	20 Pt	Intensive insulin therapy protocol improves insulin sensitivity and mitochondrial oxidative capacity while decreasing resting energy expenditure in severely burned children
Gill (2015) [128]	USA	Retrospective chart review	Thermal injury	---	512 Pt	Insulin therapy protocol decreases in the number of complications of pneumonia, bacteremia, ARDS, DVT, PE and thrombosis
Hemmila (2008) [129]	USA	Retrospective cohort study	Thermal injury	100−140 *mg/dL*	152 Pt	Intensive insulin therapy for burn-injured patients admitted to the ICU was associated with a reduced incidence of pneumonia, ventilator-associated pneumonia, and urinary tract infection
Chu (2019) [134]	China	A randomized controlled experiment study	Thermal injury	1 *U/kg*	24 Rats	Insulin therapy may reduce skeletal muscle myocytes apoptosis and skeletal muscle wasting by alleviating endoplasmic reticulum stress in rats with severe scald
Jeschke (2011) [51]	USA	A randomized controlled experimental study	Thermal injury	2.5 *IU/kg*	20 Rats	Insulin alleviates burn-induced endoplasmic reticulum stress, hepatocyte apoptosis, mitochondrial abnormalities, and inflammation leading to improved hepatic structure and function significantly

Contd. table 1.

Solomon (2002) [135]	USA	A randomized controlled experimental study	Thermal injury	Firs day 0.25 *U* gradually increased, from day 2) to 0.5 *U* (day 3) to 1.0 *U* (day 4) *per* 100 *g* of body weight	Rat	Lower dose insulin particularly suppresses protein degradation without causing secondary effects
Jeschke (2010) [130]	USA	A prospective randomized trial	Thermal injury	80-110 *mg/dL*	239 Pt	Intensive insulin therapy improves post-burn morbidity
Lu (2008) [136]	China	A controlled experimental study	Thermal injury	81-93 *mg/dL*	80 Rats	Intensive insulin treatment possesses protective effect on cardiomyocytes after a severe burn
Madibally (2003) [137]	USA	Randomized controlled experimental study	Thermal injury	0.25 *U* (Day 1), to 0.5 *U* (Day 2), to 1.0 *U* (Day 3) *per* 100 *g* body wt	12 Rats	Insulin induces accelerated wound healing associated with diminished inflammation and increased collagen deposition
Yan (2013) [132]	China	A randomized controlled trial	Burn or trauma	108-144 *mg/dL*	60 Pt	Insulin therapy can alleviate insulin resistance of patients with severe burn or trauma
Jeschke (2002) [48]	Germany	A randomized controlled experimental study	Thermal injury	120 *mg/dL*	56 Rats	Insulin increased anti-inflammatory cytokines IL-2 and IL-4 at 5 and 7 days after trauma, and IL-10 at 2, 5 and 7 days after trauma
Patel (2009) [131]	USA	Retrospective, observational chart review	Thermal injury	107 *mg/dL*	71 Pt	No significant differences were found between the 2 groups with regard to mortality, ICU stay, or hospital stay
Ellger (2006) [138]	Belgium	A randomized controlled experimental study	Thermal injury	80-110 *mg/dL*	Rabbits	Mortality was significantly lower in the normoglycemic groups independent of insulin levels to increase myocardial systolic function, elevated insulin levels and prevention of hyperglycemia were required concomitantly
Hu (2010) [67]	China	A randomized controlled trial	Head trauma	80-110 *mg/dL*	65 Pt	The treatment of severe head injury with intensive insulin cannot decrease mortality rate, but increases the incidence of hypoglycemia
Yan (2009) [43]	China	A randomized controlled trial	Severe trauma	108-144 *mg/dL*	80 Pt	Intensive insulin therapy can mitigate systemic inflammatory response and improve prognosis of patients with severe trauma
Wang (2016) [32]	China	A randomized controlled trial	Traumatic brain injury	Three groups 80-126 *mg/dL* 127-180 *mg/dL* ≤181 *mg/dL*	60 Pt	Insulin therapy can reduce mortality and improve prognosis in patients with hyperglycemia after severe traumatic brain injury
Liu (2007) [68]	China	A randomized controlled trial	Severe head injury	---	62 Pt	Insulin therapy can promote recovery and decline the mortality of patients with acute severe head injury

Contd. table 1.

Du (2011) [106]	China	A randomized controlled trial	Traumatic shock combined with multiple organ dysfunction syndrome	80-110 *mg/dL*	114 Pt	The incidence of gastrointestinal dysfunction, the incidence of multiple organ dysfunction syndrome, the length of hospital stay and the mortality were markedly decreased
Duan (2009) [139]	China	A randomized controlled experimental study	Severe scald	0.25 *U*/ 100 *g* 24 *hr* after burn injury, and every 12 *hr* for 5 days (0.25, 0.50, 0.75, 1.00, 1.25 *U*/100 *g* each day	150 Rats	Insulin may inhibit apoptosis after burn by down-regulating secretion of apoptotic ligands
Tancheva (2008) [133]	Bulgaria	A prospective analysis	Severe burns	80-110 *mg/dL*	147 Pt	Insulin infusion significantly reduces morbidity and mortality and the stay in the ICU as well as the frequency of the septic episodes and prevents the acute renal failure
Treggiari (2008) [92]	USA	Cohort study	Critically ill patients	Two groups 80 to 130 *mg/dL* 80 to 110 *mg/dL*	10,456 Pt	Insulin therapy is not associated with a decrease in hospital mortality
Yan (2009) [61]	China	A randomized controlled trial	Severe trauma	108-144 *mg/dL*	80 Pt	Intensive insulin therapy can effectively restore serum proteins and improve the status of nutrition
Zhao (2008) [46]	China	A randomized controlled trial	Severe trauma	---	138 Pt	Insulin treatment can reduce the dysfunction of coagulation system
Zhang (2007) [140]	China	A randomized controlled trial	Severely scald	3 *U/kg*	21 Rats	Insulin exhibits protective effect on vascular endothelial cells
Pidcoke (2011) [141]	USA	Controlled experimental study	Burn	5 *units/kg/day*	20 Rats	Insulin therapy increased glucose disposal and attenuated loss of body mass
Xie (2009) [81]	China	A randomized controlled trial	Spinal cord injury	---	45 Rats	Insulin has protective effects on the injured spinal cord, which may promote expression of HSP70 and inhibit expression of NOS
Wu (2007) [82]	China	Controlled experimental study	Spinal cord injury	1 *IU/kg* day, for 7 days	120 Rats	Insulin affects the treatment of spinal cord injury
Baptista (2019) [142]	Brazil	A randomized controlled trial	Burn injury	5 *UI/Kg/day*	64 Rats	Insulin therapy improving the organization of thin collagen and increasing elastic fibers
Guo (2013) [114]	Canada	Controlled experimental study	Arterial injury	3 *U/day*	48 Rats	Insulin inhibits smooth muscle cell migration and supports a vasculoprotective role
Madihally (2006) [143]	USA	A randomized controlled trial	Burn injury	0.25 U (day 1), 0.5 *U* (day 2), and 1.0 *U* (day 3) per 100 grams of body weight	18 Rats	Muscle wasting can be significantly inhibited by the oral administration of insulin
Deng (2012) [115]	China	A randomized controlled trial	Acute lung injury	0.1 *U/kg/h* and at a rate of 2.5 *mU/h/rat via* micro-osmotic pumps	40 Rats	Insulin alleviated pulmonary edema

Contd. table 1.

Lv (2007) [53]	China	Controlled experimental study	Scalded rats	70-110 *mg/dL*	18 Rats	Intensive insulin treatment possesses a protective effect on myocardia function after severe burns
Pidcoke (2014) [116]	USA	Controlled experimental study	Burn injury	5 *UI/Kg/day*	26 Rats	Insulin treatment after burn and during disuse attenuated the hypermetabolic response, increased glucose clearance, and normalized circadian-metabolic protein expression patterns
Reed (2018) [83]	USA	Controlled experimental study	Burn injury	6 *IU/day*	----	Insulin therapy improves functional deficits, including learning, memory and hyperactivity on brain trauma patients

Insulin therapy and the immune response

Twenty-one articles met the inclusion criteria regarding the effect of insulin therapy on immune function and blood, of which studies on 2370 humans (35-46) and 300 rats (31,47-53) were implemented. Insulin therapy in head injury patients by High Mobility Group Box 1 and Nuclear factor kappa B pathway reduces inflammatory response in traumatic brain injury (36) in two studies of intensive insulin therapy vs conventional management in traumatic brain injury diverse immune markers such as plasma IL-6,IL-8 and TNF-α were improved, and in the same groups, mortality reduced tissue inflammation which in turn significantly reduces mortality (35,37). Insulin therapy in burned rats has also been shown to decrease inflammatory factors, which was shown in a study to decrease IL-1, IL-6, MIF, TNF and increase the anti-inflammatory factor such as IL-2, IL-4 and IL-10 (48).

TNF-α is one of the substances released in traumatic patients, which interferes with the function of the cardiovascular system and causes multiple organ failure (54,55) that insulin therapy can protect cardiac against this damage (53,54,56-58). In a study of 54 multiple trauma patients, the level of CRP levels in the insulin-treated intervention group decreased significantly on day 5 compared to the control group. Also, the same effect was observed for IL-6 and TNF-α (38).

Another study showed that insulin therapy in traumatic patients could improve immune function by lowering C3 and C4 levels but had no effect on A, G and M immunoglobulin levels but increased phagocytic function of monocytes (39).

A study examining the effect of insulin therapy in patients with severe trauma on T lymphocyte subgroups acknowledged that insulin therapy increased CD3+, CD4+, CD4+/CD8+ ratios on days 3, 7 and 14 after onset of insulin therapy in intervention group compared to the control group (59). In this regard, a study suggested that insulin therapy for 48 *hr* can reduce the level of inflammatory factors and has cardiac protective effects (60).

In an animal study performed by femoral fracture of rats and after one hour of bleeding, the results demonstrated that insulin therapy could decrease survival and infiltration of the lung and liver, as well as decreased levels of inflammatory factors IL-6 and IL-10 mRNA. This indicates the anti-inflammatory effects of insulin (52). However, there has been conflicting information about IL-10 as studies have shown that insulin therapy increases IL-10 induced burn in rats (48). Other human studies have also demonstrated the anti-inflammatory effects of insulin, which has shown that insulin therapy in traumatic patients decreases CRP, IL-6, C3 and C4 levels. Also, in insulin therapy group, HLA-DR and CD14+ monocytes levels were different from control

group (41,42), and IL-2 and IL-10 levels were lower in insulin-treated patients than in controls group (61). In a study of critically ill patients, insulin therapy was shown to reduce the plasma level of the inflammatory marker sCD163 and increase treatment efficacy (44). Insulin inhibits neutrophils apoptosis in traumatic patients by nicotine Amidophosphoribosyltransferase inhibition (62). Another study described the mechanism of inhibition of apoptosis by inhibition of oxidative esterification via phosphatidylinositol 3-kinase (27).

If insulin therapy starts less than 24 *hr* from the time of injury, its effects are greater so that early insulin therapy leads to a decrease in the serum level of High Mobility Group Box 1 (HMGB1). A study showed that after 36 hours of trauma, the level of HMGB1 in early intensive insulin therapy group was 41.3 *μg/L* versus 52.7 *μg/L* for conventional treatment group, which can be a clinical indicator for predicting the prognosis of traumatic patients and preventing lung injury (45,63). Insulin also boosts the function of immune cells by improving neutrophils function and glucose metabolism, modulating T cell differentiation and decreasing apoptosis of the macrophage cell (28). In a study of insulin therapy in traumatic patients, the results of the study showed that the intervention group had lower monocyte HLA-DR levels, which was increased following this protection of the organs (40). A review study indicated that insulin therapy can be effective in improving and preventing acute renal failure in critically ill patients (30). In this regard, a study demonstrated that insulin therapy in critically ill patients can prevent hepatic cell injury by increasing hepatic cytokine mRNA, IL-2 and IL-10 levels, and insulin by promoting B-cell lymphoma 2 (BCL-2) levels, increases the proliferation of hepatocytes, which in turn can affect the efficiency of treatment on poor condition patients (31).

In an animal study, it was reported that post-insulin hypoglycemia can impair the normal respiration of rat brain mitochondria, which may be due to mediators such as GRP75 and PRMT (49). Insulin therapy in burned mice also reduces pulmonary edema, bleeding and infiltration of inflammatory cells by decreasing the levels of inflammatory factors, such as stress fiber and zonula occludens-1 (50). Endoplasmic reticulum stress in the liver of burn patients can lead to liver dysfunction. An animal study has shown that insulin therapy can prevent liver damage in rats that have 60% of their body surface burned through mediators like IL-6, MCP-1, and CINC-1 (51). One study found that insulin use in trauma patients could be associated with a reduction in APTT, PT, and TT duration, increasing platelet aggregation, and ultimately improving trauma-induced coagulopathy (46).

Insulin therapy in brain and spinal cord injury

Twenty-two articles, covering 1260 people with head and brain injury (32,64-78) and 255 laboratory rats (79-84) reported on the effects of insulin on prognosis and treatment efficacy.

Several studies found that aggressive insulin therapy in traumatic patients, maintains a blood glucose level of between 80-110 *mg/dL* with the traditional protocol that maintains blood glucose between 180-200 *mg/dL*, thus there was no difference in clinical outcomes and mortality rate (85-88). It was also noted that conventional and intensive insulin therapy do not differ on the neurologic efficacy of patients with brain injury (64,89). A study also acknowledged that neurologic patients do not need precise blood glucose control (90).

Also, two studies have shown that invasive insulin therapy can lower brain glucose and increase brain microdialysis markers such as glutamate, lactate/pyruvate ratio which in turn increase mortality, as well as impairing the breathing of brain cell mitochondria (49,65). However, there were other studies that showed a positive effect of insulin therapy on head and brain injury patients, including a study that found that hypoglycemic attacks so that blood glucose levels reached 40 *mg/dL* or less cannot be considered as independent factor to increase mortality in traumatic patients (91). Studies have also demonstrated that insulin therapy in patients with head injury can cause severe hypoglycemia but decrease the days of hospitalization in the ICU ward, but no difference was observed in the rate of infection and mortality rate and neurological complications with conventional insulin therapy (66,67,92), as well as insulin therapy acts upon the hippocampus to reduce microglial activation through protein kinase B (AKT) mediated pathway. Therapeutically, this treatment can target a number of functional deficits, including learning, memory and

hyperactivity (83).

In contrast, studies have shown that insulin therapy can reduce mortality and improve the prognosis of patients with brain injury (32,68). Another study that examined insulin therapy on the risk of postoperative infection in traumatic brain injury patients concluded that insulin therapy was associated with reduced risk of postoperative infection (69), but if the hypoglycemic attacks are not treated well, they will decrease the efficiency of treatment as well as increasing hospitalization days (93), since hypoglycemia can lead to a shift in brain metabolism from glucose to lactate (94) and under hypoglycemic conditions, extracellular glucose depletion causes brain tissue energy crises, leading to increased mortality rate (95,96). In this regard, a study concluded that there was a higher cerebrospinal fluid lactate level and a lower glucose-to-lactate ratio in those who died than those who survived (97). It has been shown that insulin therapy in brain trauma patients can improve lactate accumulation in brain ischemia-induced brain injury (71), but a study also acknowledged that elevated blood glucose in traumatic brain patients is associated with brain acidosis (72). Another study to support this finding found that in traumatic patients with elevated blood glucose and lactate levels, the factor associated with multiple organ failure is lactate and is not hyperglycemia (98).

In 2010, Prisco also found that insulin therapy had an impact on the treatment outcomes of head trauma patients, but provided the blood sugar is above 180 *mg/dL* and the higher the blood sugar, the more effective the insulin therapy will be on treatment efficacy (99). Another study examining insulin therapy on brain trauma patients for up to 6 months found that the death rate at 6 months was not affected by insulin therapy, but the rate of infection and days spent in intensive care units in the intervention group with insulin was significantly lower. Also, during the 6-month period, neurological symptoms were better in the intervention group (73). In this regard, a review study showed that insulin therapy reduces the risk of infection and neurological complications in head trauma patients (100).

In patients with cerebrovascular disorders who have increased intracranial pressure, aggressive insulin therapy has led to a better management of increased intracranial pressure, reduced need for sedatives, and reduced number of days spent in intensive care units (74). A 2018 study found that elevated blood glucose in multiple trauma patients, even with insulin treatment, could have a worse prognosis than patients with normal blood sugar (20), but in contrast, the paper concludes that an increase in post-traumatic hyperglycemia in animals has no negative effect on treatment efficacy and that insulin therapy can cause brain damage (79) .On the other hand, an animal study in mice suggested that insulin-induced hypoglycemia in the brain could increase the functional capacity of the hypothalamus to reduce brain damage (101) but studies have contradicted this finding and show that aggressive insulin therapy increases the risk of hypoglycemia and does not affect the mortality rate of head injury patients (33,34,87,102,103). On the other hand, an animal study indicated that insulin therapy in mice with brain trauma improved memory, increased glucose uptake by brain cells, and decreased levels of inflammatory factors in the brain and reduced the extent of hippocampal lesion (75,80). A study noted that one of the factors causing brain cell damage in brain traumatic rats is Glutamate excitotoxicity that short-term insulin therapy may improve the potential drop of brain mitochondria due to glutamate, as well as promoting oxygen consumption and increasing respiration capacity in brain neurons but chronic insulin therapy has been reported to be a negative factor in improving glutamate stimulation (104).

Insulin therapy reduces glucose concentration in cerebrospinal fluid in patients with subarachnoid hemorrhage (76). Insulin therapy has also been associated with reduced risk of infection in subarachnoid hemorrhage surgery, but no evidence was found regarding reduced vascular spasm, postoperative efficacy and mortality (77). Also, evaluation of insulin therapy in patients with intracranial and subarachnoid hemorrhage based on Karnofsky scoring showed no effect on mortality of patient (78). A 2012 meta-analysis study found that insulin therapy in neurocritical patients had no effect on mortality, and insulin therapy increased the incidence of hypoglycemia, and lack of precise control of blood could have negative effects on treatment outcomes in these patients (29).

In traumatic patients without brain injury, the best

range of blood glucose that reduces mortality has been reported to be less than 110, however, there are no specific protocols for insulin therapy in this study, but it is recommended that injectable insulin levels should be adjusted according to the patients' nutritional conditions and adjust the body's response to insulin (105).

The findings of the two animal studies also indicate the effect of insulin on trauma to the spinal cord so that one of the articles expresses insulin may promote expression of HSP70 and inhibit expression of Nitric Oxide Synthases (NOS) and the other concluded insulin might improve neurologic recovery, increase the expression of anti-apoptotic bcl-2 proteins, inhibit caspase-3 expression decreasing neuronal apoptosis, reduce the expression of proinflammatory cytokines iNOS and COX-2, and ameliorate microcirculation of injured spinal cord after moderate contusive spinal cord injury in rats (81,82). Another animal study showed that treatment with nasal insulin improved metabolic distress in rats after Subarachnoid Hemorrhage (84).

Insulin therapy in critically ill and traumatic event

There were 13 studies on the impact of insulin therapy on critically ill and multiple trauma patients that met the inclusion criteria, which included the total number of insulin-treated samples comprising 11632 humans (43,92,106-113) and 88 rats (114-116).

Studies have shown that insulin therapy can reduce mortality in multiple organ failure in traumatic patients (106,117). This function appears to be achieved by protective effects of insulin on endothelial cells by reducing the permeability of lung endothelial cells to albumin leakage (50). A study demonstrated that insulin alleviated pulmonary edema and enhanced alveolar fluid clearance by increasing the expression of epithelial sodium channel which is dependent upon PI3K/Akt pathway by inhibition of Nedd4-2 (115). Insulin therapy prevents protein catabolism and reduced protein mass in critically ill patients admitted to intensive care units (118-120). Another study suggested that insulin therapy can control the blood sugar of traumatic patients and restore blood protein levels and improve body nutrition (43). In addition, it affects the prognosis of trauma patients and the reduction of nosocomial infections (107,108), but a cohort study also found that insulin therapy had no effect on mortality in critically ill patients (92). In this regard, a study examined the effect of insulin therapy on patients with chest trauma that found no hypoglycemic reactions were reported in insulin-treated patients. Also, duration of ICU admission, duration of ventilator dependence, and normalization of white blood cell levels were lower in the intervention group (113).

In another study evaluating the effect of insulin therapy on trauma patients based on the APACHE II index, the results showed that the score was reduced and the level of nosocomial infections and heart, liver and kidney failure were lower in this group of patients (109). In support of this finding, it was noted in another study that insulin therapy affects the days of hospitalization and the neurological symptoms of trauma patients but increases the mortality rate (121). In traumatic children, insulin therapy has also reduced days spent in intensive care units (122). Another study showed that insulin therapy could protect the central and peripheral nervous system and be effective in long-term rehabilitation of these patients, provided that the hypoglycemic attacks even moderate attacks due to insulin administration treated (110).

One study suggested that insulin therapy could prevent acute renal failure in traumatic patients (123) which may be related to a study showing that trauma and burns cause a large metabolic change in the body that insulin inhibits this process (118). On the other hand, a study showed that insulin therapy by RIFLE criteria, could not prevent kidney damage. Although kidney damage had a relationship with blood sugar levels, it was recommended that carbohydrate restriction be less risky than insulin use (112). Also, a study demonstrated that admission to the ICU ward causes muscle weakness, which is one of the contributing factors to hyperglycemia, thus insulin administration can be prevented (124). Furthermore, insulin treatment after burn and during disuse, attenuated the hypermetabolic response, increased glucose clearance, and normalized circadian metabolic protein expression patterns in burn rats (116).

In non-diabetic traumatic children, children with higher glucose levels have an increased risk of

ARDS (125). Invasive insulin therapy in patients' chest trauma compared to traditional has reduced the incidence of infection risk, time to ventilator dependence, and time to resume proper white blood cell count, but has not had an effect on chest drainage (113). However, one study suggested that insulin therapy and precisely blood glucose testing can reduce the incidence of ARDS in ill patients, but insulin administration and hypoglycemic attacks, as well as high age increase the risk of ARDS (126). An animal study found that insulin inhibits smooth muscle cell migration and supports a vasculoprotective role by reducing the gelatinolytic activity of pro-MMP-2, MMP-2 and MMP-9 (114).

Insulin therapy in burn

Total of 19 articles on the effect of insulin on burn treatment efficacy were found, of which 1201 were human samples (127-133) and more than 543 animal samples (47,50,134-143).

Due to the insulin resistance in burn patients, there is increase mortality due to increased blood sugar (144). Insulin therapy has made cells more susceptible to insulin and improved mitochondrial function. Also, insulin therapy in patients with severe burns has reduced mortality rate, wound healing and hospitalization (127,128). Insulin therapy has also reduced the risk of infection in burn patients (129).

In a study on rats, the results showed that insulin therapy could not affect bone health in burned rats (145). In another animal study of burned rats, insulin therapy was shown to reduce myocyte apoptosis and reduce endoplasmic reticulum stress and muscle atrophy (134). Moreover, a study concluded that muscle wasting can be significantly inhibited by the oral administration of insulin using pH-responsive hydrogels (143). Low-dose insulin therapy in burned rats also has protective effects on protein degradation and prevents loss of muscle tissue (116,135). However, a study found that insulin therapy in 50% of TBSA burn rats increased glucose disposal and attenuated loss of body mass (141).

In a clinical trial of burned children with levels above 30% TBSA, it was reported that insulin therapy reduced the acute phase of inflammation and reduced the mortality rate to 4%, while the mortality rate in the control group was 11% (130). But in the Hemmila's study, insulin therapy did not affect mortality and hospitalization but reduced the risk of UTI, pneumonia, and ventilator-associated pneumonia (129). Also, in Patel's study, there was no difference between control group and intervention in burn patients regarding death rate and number of days hospitalized (131).

An animal study on rats with 30% TBSA showed that insulin therapy could protect cardiac myocytes by regulating the level of phosphorylation of Protein kinase B (AKT) (136). In an animal study on dogs with 50% TBSA burns, the GIK diet was able to increase the cardiac function of the dogs and prevent hypoglycemic attacks (146). Insulin therapy in burn patients can also affect wound healing rate so that mice that received insulin had a faster rate of wound healing and collagen formation (137). Insulin therapy can also reduce post-burn insulin resistance (127,147).

An animal study found short insulin therapy able to stimulate reepithelization. It also reversed the damages to the collagen-elastic arrangement in the scald-burned group, improving the organization of thin collagen and increasing the Volume fraction (Vv) of elastic fibers (142).

Ellger in his study to clarify the effects of glucose and insulin, burned 20% TBSA of four groups of rabbits. In two groups, blood glucose was maintained at 80 to 110 *mg/dL*, but in one group, it increased insulin therapy to 4 *IU/kg*, and in the other two groups, it remained at a blood glucose level of 250 to 350 *mg/dL* and in one group insulin levels were elevated to 4 *IU/kg*. Results showed that mortality was lower in the two groups with normal blood glucose and this decrease in mortality has nothing to do with insulin levels. There was also less endothelial dysfunction in the two groups with normal glucose levels, but higher insulin and normal blood glucose levels were found to be associated with cardiac systolic function, which means insulin can protect heart function (138).

Insulin therapy and precise blood pressure control below 110 *mg/dL* reduce mortality in burn patients and reduce days in intensive care units and reduce the risk of infectious shock and kidney failure (133). In this regard, a review study confirmed this finding (148).

This finding was also confirmed in the burned rats in a study that exposed rats to water 92°*C* for 18 *s* and

then applied insulin therapy to the intervention group and the results demonstrated that the pulmonary microvascular endothelial injuries were less in this group than in the control group, which was followed by a decrease in cell apoptosis and pulmonary injury (47,139). Also, one study found that insulin has protective effects on vascular endothelial cells arising from increasing the conversion of cNOS to NO in severely scalded rats (140).

Discussion

According to the findings of this study, it seems that insulin therapy does not have much effect on mortality rate of head injury patients (34) but it can affect the treatment efficacy and reduce the neurological complications of these trauma patients (100). This effect through a variety of mechanisms, including the effects on the immune system that reduce inflammatory factors, subsequently shorten the inflammatory phase of brain tissue. It also seems that insulin therapy by reducing the level of inflammatory factors can affect trauma induced coagulopathy which reduces the mortality rate of traumatic patients. Insulin can also reduce the risk of infection by enhancing immune function and promoting white blood cells. However, all of these effects occur when the patient does not have hypoglycemic attacks, since hypoglycemia alters the body's metabolism, which can interfere with mitochondrial function.

Limitations of this study included unavailable main text of article, and some of the studies were in non-English languages. Also, all the information needed, including insulin dose or blood glucose level, was not included in the articles.

Conclusion

Insulin therapy reduces hospital stay, reduces neurological complications, and ultimately improves treatment outcomes in traumatic patients, but these results require careful control of blood glucose so that patients do not suffer from hypoglycemic attacks. It is suggested in future studies to evaluate the effect of insulin therapy on spinal cord injuries as well as on the efficacy of infectious diseases such as pneumonia.

Conflict of Interest

The authors report no declaration of interest.

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