Incidence, mechanisms and impact outcome of hyperglycaemia in severe scorpion-envenomed patients

Mabrouk Bahloul, Olfa Turki, Anis Chaari and Mounir Bouaziz

Abstract: Hyperglycaemia is often observed in severe scorpion-envenomed patients. It is due to a severe autonomic storm with a massive release of catecholamines, increased glucagon levels, cortisol levels, and either decreased insulin levels or insulin resistance. The presence of hyperglycaemia is an indicator of severity in this specific condition. Indeed, hyperglycaemia was associated with the severity of clinical manifestations of severe scorpion envenomation requiring intensive care unit (ICU) admission. In fact, the presence of hyperglycaemia was associated with the presence of respiratory failure, pulmonary oedema, haemodynamic instability, neurological failure, multisystem organ failure, and an increased mortality and ICU length of stay. As a consequence, we think the presence of hyperglycaemia in scorpion-envenomed patients at the emergency department prompts searching for presence of systemic manifestations or cardiorespiratory manifestations. As a consequence, the presence of hyperglycaemia can help screen severe patients at the emergency department.

The current management of severe scorpion envenomation involves the admission and close surveillance in the ICU, where vital signs and continuous monitoring enable early initiation of therapy for life-threatening complications. The use of antivenom for scorpion stings remains controversial. All patients with pulmonary oedema should receive prazosin and possibly dobutamine, according the scorpion’s species. Mechanical ventilation is usually used in severe cases. Insulin should be reserved for severe cases with confirmed excessive hyperglycaemia (>10 mmol/l).

Keywords: hyperglycaemia, outcome, pulmonary oedema, scorpion envenomation

Introduction
Scorpion envenomation is common in tropical and subtropical regions. In Tunisia, almost 40,000 stung patients are recorded per year.1–4 Around one thousand of them have systemic manifestations requiring hospitalization and about 10 patients eventually die.1–4 The severe form of scorpion envenomation requiring hospitalization in the ICU usually results from a sting by one of two species: Androctonus australis or Buthus occitanus.1–4 However, the dangerous forms of scorpion envenomation (including heart failure) were more observed with the A. australis species.1,2 Scorpion venoms contain toxins; better known for the buthoids (one family, Buthidae) than for the chactoides (the five other families) whose venoms are less dangerous for human beings.3 These toxins are small basic proteins containing about 65 amino acids that have a selective activity upon mammals or invertebrates. The scorpion venom has neuromuscular and cardiovascular toxic effects. The venoms have little enzymatic activity, especially the buthid venom.3

The main clinical features of scorpion envenomation are localized reactions that occur in up to 97% of affected people; systemic manifestations (e.g. fever, sweating, hypertension, vomiting) are uncommon.1–6 Cardiorespiratory manifestations, mainly cardiogenic shock and pulmonary oedema,
are the leading causes of death after scorpion envenomation.\textsuperscript{1-3}

Moreover, scorpion envenoming leads to the release of massive amounts of catecholamines (epinephrine and norepinephrine) and other counter-regulatory hormones (glucagon and cortisol) with suppressed insulin secretion or insulin resistance. Under these conditions, the metabolism of carbohydrate, protein, and fat is directed towards catabolism.\textsuperscript{7} As a consequence, hyperglycaemia has been well documented following scorpion stings and was associated with poor prognosis in several studies.\textsuperscript{4-6} However, hyperglycaemia secondary to severe scorpion envenomation requiring intensive care admission is rarely analysed in the literature. In fact, despite the fact that hyperglycaemia is frequently observed and was associated with cardiac dysfunction,\textsuperscript{4,5} the incidence and the impact outcome of this biological disturbance has, to the best of our knowledge, been poorly analysed in the literature.

In this review, we aimed to determine the incidence on ICU admission and 24 h later, the mechanisms and the impact outcome of hyperglycaemia in severe scorpion-envenomed patients requiring intensive care admission.

We used the PubMed database by using the following key words in MeSH research: scorpion envenomation, hyperglycaemia and intensive care unit (ICU).

**Incidence of hyperglycaemia in severe scorpion envenomation**

The definition of stress hyperglycaemia (i.e. like that induced by severe scorpion envenomation) in ICU is not well defined in the literature, and the cut-off value used in the literature ranged from 7.7 mmol/l to 11.1 mmol/l.\textsuperscript{8,9} Although critical illness hyperglycaemia is frequently studied,\textsuperscript{8} hyperglycaemia secondary to severe scorpion envenomation requiring intensive care admission is rarely analysed in the literature. In fact, while experimental studies have shown that severe scorpion envenomation is well associated with excessive hyperglycaemia,\textsuperscript{10-15} there are few data about the incidence of this metabolic complication in severe scorpion-stung patients, despite the fact that hyperglycaemia is frequently observed, and was associated with severity and with cardiac dysfunction.\textsuperscript{4-6} The incidence of hyperglycaemia reported in severe cases of scorpion envenomation requiring ICU admission ranges from 34\% to 54\%.\textsuperscript{4-6,10} Moreover, hyperglycaemia is more observed in children than in adult patients\textsuperscript{4-6,15-18} and the use of steroids was significantly associated with hyperglycaemia on ICU admission and 24 h later.\textsuperscript{17-18}

**Mechanisms of hyperglycaemia in severe scorpion envenomation**

Scorpion-envenoming syndrome results in a severe autonomic storm with a massive release of catecholamines, increased levels of glucagon, cortisol, thyroid hormones and either suppressed insulin levels or hyperinsulinaemia (insulin resistance).\textsuperscript{19,20} The rise in the counter-regulatory hormones (glucagon, cortisol, and catecholamines) opposes the anabolic actions of insulin, leading to hyperglycaemia. As a consequence, hyperglycaemia can be due to the increase in glycogenolysis\textsuperscript{19,20} or a resistance to insulin.\textsuperscript{21,22}

**Role of massive catecholamine release**

In severe cases, the clinical manifestations become more pronounced and reflect a massive catecholamine liberation (epinephrine and norepinephrine), secondary to a neurovegetative system disorder leading to a cellular hypermetabolism, and can be manifested by hyper sweating, myoclonias, agitation, priapism and heart failure.\textsuperscript{4,6,15,23-25} This hypothesis of catecholamine storm being due to a direct stimulatory effect of the venom on the adrenals and on sympathetic nerve endings has been confirmed by several studies.\textsuperscript{4,6,23-27}

In a clinical study,\textsuperscript{28} urinary catecholamine metabolites were investigated in 12 patients with severe scorpion envenomation. In this study, vanillylmandelic acid was elevated in seven patients. In an experimental study, Zeghal and colleagues\textsuperscript{27} showed that \textit{B. occitanus} venom, administered intravenously to anesthetized rats in the absence of different pretreatments, induced a 30–40-fold increase in plasma epinephrine and norepinephrine levels. In another experimental study, Nouira and colleagues\textsuperscript{25} have studied the effects of scorpion (\textit{A. australis Hector}) venom on haemodynamics and on the release of catecholamines, neuropeptide Y (NPY), endothelin-1 (ET-1) and atrial natriuretic peptide (ANP) in dog model of severe scorpion envenomation. In this study, scorpion venom leads to rapid haemodynamic changes, associated with a rapid and
significant increase of all measured hormones. The highest increase was for norepinephrine (28-fold) and epinephrine (25-fold).

The association between a catecholamine release and hyperglycaemia can be explained by many mechanisms. First, epinephrine elevates blood glucose and lactate concentration by a series of enzyme activities. Indeed, catecholamine storm is associated with enhanced rates of aerobic glycolysis (resulting in adenosine triphosphate production), leading to glucose release (both from glycogenolysis and gluconeogenesis). Second, adrenalin inhibits secretion of insulin from the beta (β) cells of islets in endocrine pancreas. Sudden cessation of insulin secretion leads rapidly to hyperglycaemia. In addition, adrenalin leads to the inhibition of insulin-mediated glycogen synthesis due to alpha (α) receptor stimulation. In fact, catecholamines antagonize insulin by increasing cyclic adenosine monophosphate formation in the liver, fat and muscle; in the liver, this activates phosphorylase, endorses glycogenolysis, and leads to hyperglycaemia. This hypothesis was supported by several clinical and experimental studies.

Finally, severe forms of scorpion envenomation (characterized by a catecholamine storm) are categorized by shock and multi organ failure (MOF). It is also well established that shock states are characterized by a hypermetabolic condition, with insulin resistance and increased oxygen demands that coincide with both compromised tissue microcirculatory perfusion and mitochondrial dysfunction. This, in turn, causes impaired glucose utilization and may lead to inadequate glucose supply and, ultimately, metabolic failure.

Role of glucagon release
Severe scorpion envenomation causes an autonomic storm resulting in a massive release of counter-regulatory hormones (catecholamines, angiotensin II, glucagon, and cortisol). The rises in the counter-regulatory hormones oppose the anabolic actions of insulin, resulting in a variety of clinical manifestations. The effect of scorpion venom on the circulating levels of blood sugar and glucagon was established in human and experimental studies. In an experimental study, venom in saline (3.0 mg/kg) was given to a group of nine dogs by subcutaneous injection. The blood samples from these animals were collected before venom administration and after 60 and 120 min. The dogs showed several biological changes. In fact, there was an increase in blood sugar following venom injection associated with a significant stimulation of glucagon secretion (160%) within 60 min after venom injection. This glucagon oversecretion can be explained by a massive release of this hormone caused by scorpion venom toxin. In fact, it is possible that norepinephrine released from the adrenergic nerve terminals of the pancreas may be an effective stimulus to glucagon secretion. Glucagon hypersecretion leads to glycogenolysis (in the atria, ventricle, liver and skeletal muscles) with simultaneous suppressed insulin secretion or insulin resistance, leading to an increase of blood glucose concentration. Moreover, by promoting gluconeogenesis from lactate, pyruvate, glycerol and amino acids, glucagon exacerbates hyperglycaemia.

Role of glucocorticoid release
Glucocorticoids can be released following injury or stress, such as severe scorpion envenomation. Several studies have shown that severe scorpion envenomation was associated with glucocorticoid hypersecretion. In a recent human study including 42 children with scorpion envenomation and 20 apparently healthy children as controls, Ahmed and colleagues found that children with severe envenomation had significantly higher levels of cortisol and aldosterone compared with the control and mild cases (severe scorpion envenomation induced a 3–4-fold increase in plasma cortisol and aldosterone levels in comparison with control cases). However, insulin levels decreased significantly in severe cases of scorpionism compared with mild ones, leading to hyperglycaemia. The same results were published in some experimental studies.

Glucocorticoids contribute to the development of hyperglycaemia by several mechanisms: inhibiting glucose uptake in muscles, increasing hepatic gluconeogenesis, and exerting multiple effects on the receptor and postreceptor activity of the β cells in the pancreas. However, the major hyperglycaemic effect of glucocorticoids is mediated through increased insulin resistance in skeletal muscle.

Role of the renin–angiotensin–aldosterone system
As mentioned above, changes in insulin secretion leading to hyperglycaemia have been observed in severe scorpion envenomation. The renin–angiotensin–aldosterone system is also involved in
scorpion sting victims. Consequently, elevated circulating levels of catecholamines and renin angiotensin had been observed in clinical and experimental envenomation. In fact, change in insulin secretion influences the renin–angiotensin–aldosterone system via insulin-induced potassium changes. At a cellular stage, angiotensin II and aldosterone provoke insulin resistance by increasing oxidative stress and altering insulin signalling. Aldosterone diminishes glucose-stimulated insulin secretion in vivo and in vitro from isolated pancreatic islets and cultured β cells through a mineralocorticoid-receptor-independent mechanism.

Role of hyperinsulinaemia (insulin resistance)

Severe scorpion envenoming causes an autonomic storm that results in a massive release of catecholamines, glucagon and cortisol, and changes in insulin secretion. In fact, scorpion envenoming alters insulin secretion. Insulin levels are either inhibited or elevated after envenoming.

In previous studies, intravenous injection of scorpion venom (Mesobuthus tamulus concanesis, Pocock) (4 mg/kg) in experimental dogs resulted in a suppressed insulin secretion, and subcutaneous injection of scorpion venom (3 mg/kg) in dogs resulted in suppression of insulin secretion 30 min after venom injection, and elevated insulin levels 60 min after venom injection. In other experimental studies, both insulin and blood glucose were found to be higher after 60 and after 120 min of venom injection. In a human study recently published, Ahmed and colleagues found that severe scorpion-envenomed patients had decreased insulin levels compared with mild cases (8.40 ± 0.58 versus 7.91 ± 0.79 μu/ml, respectively; p < 0.05).

In fact, adrenalin storms inhibit glucose-induced secretion of insulin from the β cells of islets in endocrine pancreas. Sudden stopping of insulin secretion leads to hyperglycaemia.

Role of cytokines (tumour necrosis factor alpha, interleukin-1 beta, interleukin 6 and interleukin 8) release

Severe scorpion envenomation is accompanied with a stress and pro-inflammatory cytokine hyperproduction. Pro-inflammatory cytokines may directly inhibit insulin release by β pancreatic cells. Moreover, insulin release during stress is decreased mainly through the stimulation of α-adrenergic pancreatic receptors.

Role of development of multiorgan failure

Severe scorpion envenomation can be associated with heart failure, neurological failure and respiratory failure, with uncontrolled release of pro-inflammatory mediators that can lead to MOF. In a retrospective study including 685 children, systemic inflammatory response syndrome (SIRS) was observed in 555 patients (81%), and 552 patients (80.6%) developed organ failure in at least one organ. Cardiac failure was observed in 542 (79.1%) patients, respiratory failure was observed in 444 (64.8%) patients. Moreover, most patients (64.7%) had more than two organ failures. In the same study, all organ failures were associated with death or poor outcome. In addition, high value of blood glucose level was significantly associated with a poor outcome. Moreover, a significance between blood glucose levels above 15 mmol/l and the presence of pulmonary oedema (p = 0.001), neurological failure (p < 0.05) and heart failure (p = 0.003) was found. This association between hyperglycaemia and the development of organ failures was confirmed by several studies. As a consequence, heart failure, neurological failure and respiratory failure are often associated with SIRS in severe scorpion envenomation, which in turn increases stress, leading to insulin resistance.

Other mechanisms of hyperglycaemia

Other mechanisms, including corticosteroid administration and perfusion of glucose, can be associated with hyperglycaemia. In a pair-wise, case-control study including 184 children admitted to intensive care for severe scorpion envenomation to study the efficacy and safety of systemic hydrocortisone hemisuccinate infusion, the comparison of biological findings between two groups showed that glycaemia was significantly higher in the cases group (who received hydrocortisone hemisuccinate), both on ICU admission and 24 h later. The same results were observed in adult patients.

In conclusion, endocrinological changes have been frequently observed in scorpion envenomation and they are more obvious in cases of severe envenomation compared with mild cases. Severe scorpion envenomation causes an autonomic storm resulting in a massive release of catecholamines, glucagon and cortisol, accompanied by changes in
insulin secretion. This rise in the counter-regulatory hormones (glucagon, cortisol, and catecholamines) opposes the anabolic actions of insulin, leading to hyperglycaemia (Figure 1). Moreover, heart failure, neurological failure, and respiratory failure are often associated with SIRS in severe scorpion envenomation, which in their turn increase the stress observed, leading to insulin resistance (Figure 2). The use of steroids increases this hyperglycaemia. As a consequence, hyperglycaemia is often observed.

**Impact outcome of hyperglycaemia in severe scorpion envenomation**

Scorpion-envenoming syndrome results in a severe autonomic storm with a massive release of catecholamines, increased levels of angiotensin II, an increase in glucagon and cortisol and either suppressed insulin levels or hyperinsulinaemia (insulin resistance).32–39 These changes may lead to hyperglycaemia with a syndrome of fuel–energy deficits and to an inability of the vital organs to utilize the existing metabolic substrates (like glucose), ultimately resulting in multisystem organ failure (MSOF) and death.4,5,16 In a recently published study16 including 626 severe scorpion-envenomed children, it was established that more than 50% of the analysed population developed hyperglycaemia on ICU admission. Moreover, it was established that the presence of hyperglycaemia was associated with the presence of respiratory failure, pulmonary oedema, haemodynamic instability, neurological failure, MSOF, and an increased mortality and ICU length of stay.16 Moreover, the presence of hyperglycaemia was associated with an increase of nosocomial infections.16

In another study including 685 severe scorpion-envenomed children, Bahloul and colleagues4 found a significant association between blood glucose levels above 15 mmol/l and the presence of pulmonary oedema \((p = 0.001)\), heart failure \((p = 0.003)\), respiratory failure \((p = 0.001)\), and agitation \((p = 0.009)\). Additionally, blood glucose levels above 15 mmol/l were associated with the diagnosis of pulmonary oedema, with a sensitivity of 27.5%, a specificity of 87.4%, and a positive predictive value of 88.2%. The correlation between the severity of scorpion envenomation (in particular, heart failure) and hyperglycaemia is well established.4–6,16,17,23 As a consequence, we think that the presence of hyperglycaemia in scorpion-envenomed patients at the emergency department should prompt investigation for presence of systemic manifestations (e.g. fever, sweating, hypertension, vomiting) and possibly cardiorespiratory manifestations. As a result, the presence of hyperglycaemia can help screen severe patients at the emergency department.

Hyperglycaemia enhances left ventricular dysfunction by several mechanisms. First, the stress accompanying scorpion envenomation leads to the secretion of catecholamines, steroids, glucagon and a resistance to insulin. These hormonal changes

---

**Figure 1.** Endocrinological changes associated with hyperglycaemia in severe scorpion-envenomed patients. TNF-\(\alpha\), tumour necrosis factor alpha; IL, interleukin.
lead to lipolysis and an increase in free fatty acids,\textsuperscript{1,4,5,23} inducing myocardial membrane cell damage, disturbances in calcium movement, and arrhythmia.\textsuperscript{1,4,5,23} Second, hyperglycaemia leads to the stimulation of thromboglobulin secretion by platelets leading to myocardial dysfunction.\textsuperscript{1,4,5,23,42} The last mechanism is the effect of endothelin-1.\textsuperscript{43} Indeed, hyperglycaemia can lead to endothelin-1 liberation by cardiomyocytes, which is responsible for intracellular calcium accumulation and a disturbance in myocardial contractility.\textsuperscript{1,4,5,23,43}

The association between neurological failure and hyperglycaemia is well documented.\textsuperscript{4,16,41} Neurological manifestations can be explained by two physiopathological phenomena. The first was hypertensive encephalopathy. Indeed, scorpion envenomation leads to high arterial blood pressure by a massive catecholamine discharge.\textsuperscript{41} When arterial blood pressure is excessive (sometimes exceeding the cerebral autoregulation plateau), it leads to a cerebral damage (oedema and ischaemia) explaining observed neurological signs.\textsuperscript{41} The second hypothesis is that the brain damage can result from a defect of oxygen transport secondary to the pulmonary oedema and cardiogenic shock observed in severe scorpion envenomation.\textsuperscript{41} As a consequence, the hyperglycaemic and neurological damage states have the same aetiologies (massive catecholamine discharge and brain ischaemia).

\textbf{Figure 2.} Association between the development of multiorgan failure and hyperglycaemia in severe scorpion envenomation.
Moreover, it has been well established that hyperglycaemia exacerbates brain damage and ischaemia via several mechanisms.44

Moreover, it was well established that there is a good association between high values of leucocyte levels and the presence of hyperglycaemia.16

This association may be explained by two mechanisms. The first is the stress which is due to the envenomation and the release of corticosteroids and catecholamines. The second is the liberation of cytokines (tumour necrosis factor alpha, interleukin (IL)-1β, IL-6, IL-8) secondary to envenomation.16 These two mechanisms lead to hyperglycaemia and hyperleucocytosis, and indicate the severity of scorpion envenomation.16

We concluded that hyperglycaemia was associated with the severity of clinical manifestations of severe scorpion envenomation requiring ICU admission. In fact, the presence of hyperglycaemia was associated with the presence of respiratory failure, pulmonary oedema, haemodynamic instability, neurological failure, MSOF, and an increased mortality and ICU length stay. As a consequence, we think that the presence of hyperglycaemia in scorpion-envenomed patients at the emergency department should prompt investigation for systemic manifestations (e.g. fever, sweating, hypertension, vomiting) and cardiorespiratory manifestations. Consequently, the presence of hyperglycaemia can help to screen severe patients in the emergency department. However, hyperglycaemia can indicate hospitalization only when it is associated with systemic (e.g. fever, sweating, hypertension, vomiting) or cardiorespiratory manifestations.

Management of severe scorpion envenomation

General management

Scorpion envenomation is common in tropical and subtropical regions. Cardiorespiratory manifestations, mainly cardiogenic shock and pulmonary oedema, are the leading causes of death after scorpion envenomation. Acute pulmonary oedema has been attributed to acute left ventricular failure. The current management of severe scorpion envenomation involves admission and close surveillance in ICU, where vital signs and continuous monitoring enable early initiation of therapy for life-threatening complications.

The use of antivenom for scorpion stings remains controversial, since the results of clinical trials have been both negative and positive.25,45,46 However, this treatment should be prescribed in patients admitted within 3–4 h after scorpion envenomation.45,46

All patients with pulmonary oedema should receive prazosin and possibly dobutamine according the scorpion’s species.4,6,24,26 Mechanical ventilation is usually used in severe cases (Figure 3).

Management of hyperglycaemia

Stress hyperglycaemia (i.e. like that induced by severe scorpion envenomation) in ICU is not well defined, and the cut-off value used in the literature ranged from 7.7 mmol/l to 11.1 mmol/l.8,9,16 However, the general consensus now is that excessive hyperglycaemia (>10 mmol/l) should be avoided in critically ill adults and children8,9,16 with target values between 6 and 8 mmol/l. However, we think that further studies for personalized blood glucose treatment targets are needed in this specific condition.

Insulin–glucose infusion seems to be the physiological basis for the control of the metabolic response in severe scorpion sting victims having hyperglycaemia. In fact, insulin administration reverses the metabolic changes (hyperglycaemia). In addition, the infusion of insulin in patients with hyperglycaemia leads to reversal of cardiovascular, haemodynamic, respiratory and neurological manifestations induced by scorpion envenoming.11–14,21,47 This hypothesis was confirmed, in six previously healthy children aged
between 18 months and 11 years admitted to hospital after scorpion stings (5–17 hours after scorpion envenomation).\textsuperscript{47} In this study,\textsuperscript{47} insulin (0.3 units/g of glucose) was administered when the standard therapy failed to produce an improvement, and at the earliest sign of haemodynamic instability. Consequently, reversal of pulmonary oedema and haemodynamic changes, and attainment or normal respiratory rate, blood pressure and central venous pressure, were observed. It was concluded that insulin administration may be useful in reversing haemodynamic changes and pulmonary oedema in victims of scorpion stings.

For these reasons, we think that insulin has a metabolic role in preventing and reversing the cardiovascular, haemodynamic, respiratory and neurological manifestations induced by scorpion envenoming.\textsuperscript{11–13,21} However, insulin should be reserved for severe cases with confirmed excessive hyperglycaemia (>10 mmol/l). In the absence of clinical studies in diabetic patients with this specific condition (scorpion envenomation), we advise the infusion of insulin in excessive hyperglycaemia (>10 mmol/l; Figure 3).

**Conclusion**

Hyperglycaemia is often observed in severe scorpion-envenomed patients. It is due to a severe autonomic storm with a massive release of catecholamines, increased glucagon levels, cortisol levels, and either suppressed insulin levels or hyperinsulinaemia (insulin resistance). The presence of hyperglycaemia is an indicator of severity in this specific condition. Insulin should be reserved for severe cases with excessive hyperglycaemia (>10 mmol/l).

**Acknowledgements**

All authors thank Professor Chokri Khalaf and Miss Nour Bahloul for their help in the redaction of this manuscript.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Conflict of interest statement**

The authors declare that there is no conflict of interest.

**References**


35. La Grange RG. Elevation of blood pressure and plasma renin levels by venom from scorpions, centruroides sculpturatus and Leiuirus quinquestriatus. Toxicon 1977; 15: 429–433.


