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ORIGINAL ARTICLE

Trauma and the endocrine system

Joana Mesquita[a,b,*], Ana Varela[a,b] and José Luís Medina[a,b]

[a]*Endocrinology Department of Hospital de São João-EPE, 4200-319 Porto, Portugal*
[b]*Faculty of Medicine, Oporto University, Portugal*

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Abstract
The endocrine system may be the target of different types of trauma with varied consequences. The present article discusses trauma of the hypothalamic–pituitary axes, adrenal glands, gonads, and pancreas. In addition to changes in circulating hormone levels due to direct injury to these structures, there may be an endocrine response in the context of the stress caused by the trauma.

PALABRAS CLAVE
Trauma;
Sistema Endocrino;
Estrés

Trauma y sistema Endocrino

Resumen
El sistema endocrino puede estar sujeto a diferentes tipos de trauma con consecuencias muy variables. Podemos referenciar los traumas del eje hipotálamo-hipófisis, glándulas suprarrenales, gónadas y páncreas. Además de cambiar los niveles de hormonas circulantes por perjuicio directo de las estructuras antes mencionadas, puede haber una respuesta endocrina en el contexto del propio estrés causado por el trauma.

Introduction

The authors review some of the distinct types of trauma that can affect the endocrine system and their consequences. A brief reference is also made to the main endocrine characteristics of the stress response.

Traumatic brain injury

Traumatic brain injury (TBI) is a worldwide health problem and a major cause of death and disability among young adults[1,2] living in industrialized countries.[3] TBI has an overall incidence of 200/100,000 population per year in developed countries[4] and is increasingly common.[2,3] The population at greatest risk consists of young adult males under the age of 35 years,[5] although the number of females sustaining TBI appears to be rising steadily.[1,5] The consequences of TBI range from physical disabilities to

*Corresponding author.
E-mail address: joanamesquita1@gmail.com (J. Mesquita).

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long-term cognitive, behavioral, psychological, and social defects.[6]

In 1918, Cyran described the first case of post-traumatic hypopituitarism (PTHP)[1,7,8] and since then several studies have convincingly shown that hypopituitarism is a common complication of head trauma with a prevalence of 25–50%,[1–3,7,9,10] with severe growth hormone (GH) deficiency reported in 15–20% of adult patients.[7] This frequency is much higher than previously thought and suggests that many cases of PTHP remain undiagnosed and untreated.[3,11] In some patients undiagnosed hypopituitarism may be responsible for some of the cognitive and neuropsychiatric dysfunction typical of TBI,[3] but may be masked or overlooked because of the underlying primary diagnosis.[3,7,8,10] Undiagnosed hypopituitarism has the potential to adversely affect recovery from, and rehabilitation after, TBI but is easily treatable with hormone replacement.[3,7]

Approximately 50% of TBIs are the result of motor vehicle,[1,11] bicycle, or pedestrian–vehicle accidents. Falls are the second most common cause of TBI (20–30% of all TBI) and are more frequent among the elderly and the very young. Violence-related incidents account for approximately 20% of TBI, almost equally divided into firearm and non-firearm assaults.[1]

A very wide time interval has been reported between the occurrence of TBI and diagnosis of PTHP: from 5 months to 23 years. PTHP seems to occur mainly within 1 year.[1]

Hypopituitarism in survivors of TBI

Pituitary dysfunction following traumatic events can be divided into functional alterations during the acute phase post-TBI, which result in a temporary increase or decrease in blood pituitary hormone concentrations, or alterations in pituitary hormone secretion that may occur at any time after TBI, resulting in permanent hypopituitarism caused by damage to the pituitary gland and/or hypothalamus.[1]

Although symptom severity is not necessarily related to severity of the injury, systematic screening of pituitary function is recommended for all patients with moderate-to-severe TBI at risk of developing pituitary deficits.[7]

Most patients tested in various published studies had closed head injury and therefore it is unclear whether penetrating brain trauma, such as that caused by gun shots, carries a different risk of hypopituitarism.[3]

Pituitary dysfunction presents more frequently as an isolated deficiency (75%) and more rarely as a complete deficiency (3.4%). The most common hormone deficiencies are GH (ranging from 14.6% to 60%) and gonadotropin deficiency (ranging from 2.1% to 62.5%), in accordance with the anatomical site of gonadotrope and somatotrope cells in the vascular territory of the long hypophyseal portal system, which can be easily affected by TBI.[1] These deficiencies are followed by corticotrophin (ACTH) – ranging from 0% to 44.8% – and thyrotropin (TSH) deficiency – ranging from 3.6% to 31%. Hyper- or hypoprolactinemia may also be present. Diabetes insipidus may be frequent in the early, acute phase post-TBI but it is rarely permanent.[1]

The factors that predict likelihood of developing hypopituitarism after TBI remain poorly understood.[3] Published studies have used the Glasgow Coma Scale (GCS) score, which is widely used in clinical practice, to assess the severity of injury.[1,3,5] This is a 15-point scale: 1–4 points are given for eye opening, 1–5 points for best verbal response, and 1–6 points for best motor response. Severe head injury is defined by a post-resuscitation GCS score of 8/15 or less, moderate injury by a GCS score of 9/15–13/15, and mild injury by a score of 14/15 to 15/15.[3,12] The clinical severity of TBI is also defined by the duration of loss of consciousness, loss of memory for events immediately before or after the accident (post-traumatic amnesia), and the intracranial lesions identified.[1] Most studies have found no association between initial post-resuscitation and pre-intubation GCS scores and anterior pituitary dysfunction in TBI survivors.[3,12]

Neuroendocrine dysfunction in the acute phase of TBI

The pituitary gland responds to acute traumatic events with two secretory patterns: ACTH, prolactin (PRL), and GH levels increase, while luteinizing hormone, follicle-stimulating hormone, and TSH levels may either decrease or remain unchanged, associated with a decreased activity of their target organ. Changes in circulating hormone levels become apparent during the first hours or days after trauma and may persist for the duration of the acute critical illness. These alterations represent part of the acute adaptive response to injury[1,13] and may be influenced by the type of injury and pharmacological therapy used to treat the critical illness (glucocorticoids, narcotic analgesics, or dopaminergic agents).[13]

Serum cortisol concentrations have been found to increase immediately after head injury, with a subsequent gradual decline toward normality.[1,3,9,14] This elevation is associated with increased ACTH release,[1,9,15] presumably driven by corticotropin-releasing hormone (CRH), cytokines, and noradrenergic system activation.[1] Several days after severe TBI, serum cortisol values have been reported to be similar to those of controls.[3,16] In contrast with the above reports, one study found patients with severe penetrating head injury to have low serum cortisol on days 1–3, but high levels on days 5–7 after trauma.[3,14] In some cases, cortisol secretory dynamics (fasting hypercortisolemia, abolition of the normal diurnal rhythm, and inadequate suppression after dexamethasone) may persist for many months after TBI. In contrast, adrenal insufficiency has been found in 16% of patients during the early post-TBI phase, suggesting post-traumatic damage at the hypothalamic–pituitary level.[1]

As with the cortisol response, several studies have shown activation of the somatotrophic axis following head injury. Basal serum GH concentrations were found to increase following TBI.[1,3,9,13] Low basal circulating GH levels[1,7] and a decrease in frequency of GH bursts have also been reported.[1]

Suppression of the hypothalamic–pituitary–gonadal axis has frequently been observed after head injury,[1,3,14,16] as in other conditions of acute and chronic critical illnesses.[3,17] Switching off the production of anabolic androgens may be appropriate in critical illness to reduce the use of energy and metabolic substrates by the less vital organs.[3,18] Therefore, hypogonadism in this situation is likely to represent an adaptive response to injury.[3]

There are considerable inconsistencies in the post-TBI alterations of the thyroid axis reported in the literature. Some have shown no significant change in serum thyroxine (T4) concentration following head injury,[1,3,14] while others have shown reduced,[1,3,9] or even elevated, levels.[3,16] Serum triiodothyronine (T3) concentrations were found to be low,[1,3,9,14] or low-normal after acute TBI,[3] partly due to decreased T4 conversion to T3 and/or increased thyroid hormone turnover. These changes are consistent with the occurrence of low T3 syndrome.[1,9] Similarly, conflicting results on serum TSH concentrations have been reported by several authors; serum TSH concentration was found to be low[1,3,14] or normal[3] after severe TBI, but increased on days 1–3 following mild head trauma.[3,14] The clinical significance of these changes remains uncertain.[3]

Serum PRL (which can be regarded as a stress hormone) concentration was found to be elevated, unchanged,[3] or even low in acute TBI patients.[3,16] Hyperprolactinemia is present in more than 50% of patients in the early acute phase post-TBI and may persist in 31% of patients during rehabilitation. A blunted PRL response to thyrotropin-releasing hormone has also been reported.[1]

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) can manifest during the immediate post-TBI period as a result of damage to the pituitary stalk or the posterior pituitary.[1] Studies on SIADH after TBI have yielded conflicting results, showing a prevalence ranging from 2.3% to 36.6%.[1,7] Cytokines, in particular interleukin-6, which stimulate vasopressin secretion, may also be involved in the pathogenesis of SIADH after TBI.[19]

The wide variations in hormone responses to acute head injury reported in these studies reflect differences in patient selection, severity of the head injury, and timing of hormonal assessment.[3] Whether the reported hormone deficiencies are secondary to structural hypothalamic–pituitary injury and permanent or whether they reflect adaptive mechanism to acute illness remains unclear.[9]

Natural history of PTHP

Posterior pituitary abnormalities after head injury are usually transient.[3,20] Anterior pituitary hormone abnormalities, which occur soon after TBI, can also disappear in some patients.[1,3,2,8] Since recovery usually occurs by 6 months,[3] periodic endocrine evaluation and monitoring in patients with head trauma is required.[3] Hyperprolactinemia and gonadotropin deficiencies seem to be particularly likely to be lost completely in most patients. Recovery of normal GH production in two-thirds and of cortisol production in one-half of patients was demonstrated in the post-acute phase, and persistent deficiency in the two axes was associated with more severe acute-phase GH and cortisol hyposecretion. Conversely, some patients judged to have normal responses in the acute phase developed late pituitary dysfunction, particularly ACTH deficiency.[3]

Mechanisms of injury

Cerebral damage resulting from trauma can be divided into primary and secondary brain injuries. Primary injury is due to mechanical disruption of brain tissue occurring at the time of the initial trauma. Secondary injury develops in the hours or days following the initial insult and may lead to further damage and a worse neurological outcome.[1,21,22] Both primary and secondary injuries can be focal or diffuse. Focal injury tends to be caused by contact forces, whereas diffuse injury is more likely to be caused by non-contact, acceleration–deceleration, and rotational forces.[1]

Hypothalamic lesions have been reported in more than 50% of head trauma cases, affecting hypothalamic nuclei and resembling the lesions found in ruptured cerebral aneurysms.[5] Pituitary function is at particular risk because of the vulnerable physiologic location of the gland within the sella turcica as well as its delicate infundibular hypothalamic structure and fragile vascular supply.[7,23] At present, there are no studies suggesting that injuries of a certain type or in a certain location are more likely to produce hypopituitarism.[7]

GH deficiency is most often seen in patients with TBI because the GH-secreting somatotrope cells are located in the wings of the pituitary gland and vascular supply and oxygen they receive come from the hypothalamic–pituitary portal vessels. Consequently, damage in this area impairs the blood and oxygen supply, resulting in cell death. In contrast, cells secreting ACTH and TSH are located ventrally in the more protected medial portion of the pituitary, and they receive blood from the portal vessels and the anterior pituitary artery branch, which provide nutrients and oxygen to this area and to all the cells located in the sub-capsular part.[7,23]

Diagnosis

Diagnosis of hypopituitarism is based on clinical and biochemical criteria.[1] Abnormal or questionable results from basal hormonal testing (serum cortisol in the morning, 24-h urinary free cortisol, insulin-like growth factor I, free T3, free T4, TSH, follicle-stimulating hormone, luteinizing hormone, testosterone/17β-estradiol, PRL, and – in the patients with polyuria – diuresis, urine density, plasma sodium, and plasma osmolality)[7] should always be examined by an endocrinologist. Patients should be referred to an endocrinologist for provocation testing if the results of their basal evaluations are unclear or indicate the need for further testing.[7]

The imaging method of choice for studying the hypothalamic–pituitary region is magnetic resonance imaging.[3]

Pituitary screening after TBI

Although most of the available data fail to show an association between PTHP and severity of the head injury,[3,8,11] most patients are classified as having severe or moderate injury (defined as those with GCS scores of 3–13 or evidence of brain injury on computed tomography (CT) scan). However, even patients with milder head injury should be screened if clinically indicated.[3,7,11] Particular attention should be paid to this problem in children and adolescents, as the burden of the disease on their development may be extensive.[11] Additionally, patients in a permanent vegetative state should generally be evaluated

for diabetes insipidus, inappropriate antidiuretic hormone syndrome, hypoadrenalism, and thyroid deficiency, if indicated, but should not undergo further endocrinological testing.[7,10]

The clinical, neuropsychological, and endocrine evaluation of patients should be performed between 6 and 12 months after TBI.[11]

Patients with PTHP require periodic evaluation in the first year after TBI.[3] In the acute phase of TBI, the diagnosis of adrenal insufficiency should not be missed because it can be life-threatening.[2,3] However, the diagnosis of glucocorticoid deficiency is challenging during the acute phase, due to the difficulty of selecting a reliable test to assess cortisol secretion.[1,15,24] A basal cortisol concentration of less than 200 nmol/L (7 μg/dL) might suggest ACTH deficiency and glucocorticoid treatment is indicated, pending full assessment in the post-acute phase. Glucocorticoid replacement is also indicated in patients with basal cortisol levels greater than 200 nmol/L, if they exhibit features of adrenal insufficiency.[2] In contrast, the insulin tolerance test is regarded as potentially dangerous in these patients owing to the risk of seizures in the acute phase post-TBI. Moreover, the low-dose ACTH test may evoke false-normal cortisol responses, as the time elapsed since TBI might be insufficient for the development of adrenal failure. Alternatively, some authors propose the use of the glucagon stimulation test in the early phase after TBI.[1]

Routine cortisol assays measure total levels of the hormone, although only the free hormone is biologically active.[15,24] Indeed, more than 90% of circulating cortisol in human serum is bound to proteins (cortisol-binding globulin (CBG) and albumin) . Therefore, alterations in the levels of the binding proteins affect measured serum total cortisol levels.[15] This issue is important given the decrease of serum CBG during critical illness.[15,24] Accordingly, appropriate levels and responses of free cortisol have been observed in patients despite abnormalities in total cortisol levels, partly invalidating the use of total hormone levels in the diagnosis of relative adrenal insufficiency.[24] Direct determination of free cortisol level is, however, labor intensive and impractical for routine use.[15,24] Alternative surrogate markers are the free cortisol index (defined as the ratio of serum cortisol over serum CBG concentrations),[15] free cortisol levels calculated from total cortisol, cortisol-binding globulin using the formula introduced by Coolens et al.,[25] and salivary cortisol levels.[15,24] Salivary cortisol measurement is reliable, simple, and can be performed in a timely manner, although the data in critically ill patients are currently scarce. One limiting factor is the ability to obtain saliva from some patients, particularly those who are intubated.[15] Another confounding factor is the wide variety of total cortisol assays that are commercially available, with different specificities, sensitivities, and reproducibilities that overestimate or underestimate actual cortisol levels.[24]

Assessment of the GH, gonadal, and thyroid axes is not necessary in the acute phase of TBI because there is currently no evidence that acute phase replacement of these hormones in patients with deficiency improves outcome.[3] If hypopituitarism is detected, replacement therapy with glucocorticoids, sex steroids, and levothyroxine should be given, as appropriate.[2,3,8]

Traumatic lesions of adrenal glands

Adrenal gland injuries (AGIs) are rare[26–29] (2–3% of blunt abdominal trauma cases),[27] because of the position of the adrenal gland deep within the abdomen, well cushioned by surrounding soft tissue structures,[27] and because of its relatively small size.[28,30] Nevertheless, these injuries may be more frequent than previously suggested, and therefore careful inspection of the adrenal gland is required in patients with CT detection of lower thoracic or upper abdominal injuries. Indeed, at autopsy, adrenal injury may be found in up to 28% of patients with significant abdominal trauma.[31] Advances in modern diagnostic imaging over the last two decades have contributed to the increased frequency of AGI diagnosis.[26,30] In addition to the better technical quality of CT scans produced with more rapid scan times and power injection of intravenous contrast material, there is also increased awareness of the potential for adrenal injury and greater scrutiny of adrenal glands after trauma.[28,31]

AGIs most often result from blunt trauma,[29] associated with high injury severity,[26,28,30] and are rarely seen in penetrating trauma.[29] These injuries most frequently occur in the setting of multisystem organ injury,[26,28] accompanied by other intra-abdominal, retroperitoneal, or intrathoracic injuries.[27] However, detailed knowledge of the mechanisms and injury patterns associated with AGI is still poor.[30] These injuries are usually self-limited and do not require surgery, with less than 1% of patients requiring long-term steroid supplementation.[26] Adrenal insufficiency can occur, especially with bilateral adrenal trauma.[26,31,32] Thus, if a bilateral lesion is found, adrenal function should be checked and an adrenal crisis treated if the patient's condition deteriorates.[33]

The difficulty of diagnosing hypocortisolism in critically ill patients in the context of TBI, discussed above, may also apply to AGIs.

Injury to the thyroid gland after cervical trauma

Soft tissue injuries to the neck and superior mediastinum present the clinician with a broad differential diagnosis. These injuries may precipitate acute airway obstruction and may require prompt airway intervention. Often, a variety of imaging modalities may be needed that should be correctly diagnosed. For instance, thyroid hematoma is a rare cause of airway obstruction in victims of blunt trauma that occurs in the context of normally rich vascularity of the thyroid gland and the absence of a true capsule in adenomatous goiter.[34] Indeed, pre-existing goiters, adenomas, and cysts potentially render the thyroid gland more fragile and prone to injury. However, this phenomenon has also been reported in normal thyroid glands.[35]

Respiratory compromise, a paratracheal or pretracheal cervical mass, and a prior history of goiter appear to be the hallmarks of hemorrhage into the thyroid gland and have been reported in most cases.[34] Published case reports are few and result mainly from direct trauma to the neck and deceleration injury. Surgical and nonsurgical managements have been advocated but there is no consensus.[35]

Importantly, trauma can be a rare inciting factor of thyroid storm, which is a potentially life-threatening

endocrinologic emergency usually due to an exacerbation of an already hyperthyroid state.[36]

High-resolution ultrasonography is a fast and excellent method for first-line evaluation of patients with suspected thyroid gland rupture but CT scan with contrast is the diagnostic method of choice for the examination of extensive hematomas or whenever airway compromise is suspected.[35]

Trauma-related testicular injury

Scrotal trauma accounts for less than 1% of all trauma-related injuries, because of the anatomic location and mobility of the scrotum. The peak occurrence of these lesions is in the age range of 10–30 years.[37] Blunt trauma is the most commonly occurring form and usually results from athletic injury (about 50% of blunt trauma cases), motor vehicle collision (9–17% of cases), or assault.[37] Since sports injuries are one of the most common causes of significant testicular injury, all male athletes should be encouraged to wear adequate protective equipment.[38]

Scrotal blunt trauma is often associated with severe injuries of the scrotal contents, including testis rupture (46–48.5%), testis avulsion, testicular hematoma, hematocele, and epididymis injuries.[39,40] The right testis is injured more often than the left testis because of its greater propensity to be trapped against the pubis or inner thigh. Patients with scrotal trauma usually present as an emergency, and an accurate diagnosis is required to guide treatment and prevent loss of the testis.[37,38] Delay in diagnosis or inaccurate diagnosis may result in decreased fertility, delayed orchiectomy, infection, ischemia or infarction, and atrophy.[37,39,40] Patients usually have severe testicular pain, with varying degrees of scrotal swelling and ecchymosis.[41] Nevertheless, clinical examination is often limited because of scrotal pain and swelling, and may lead to the misdiagnosis of severe injuries and, in particular, testis fracture.[39,40]

Ultrasonography plays a major role in the initial evaluation of patients with scrotal injury.[39–41] This examination is noninvasive, can be rapidly performed, and is accurate in determining whether there is solely hematocoele, intratesticular hematoma, testicular contusion, or associated testicular rupture. Color Doppler ultrasonography should also be performed in all cases of scrotal injury to evaluate vascular supply to the testis.[41]

Ovarian trauma and premature ovarian failure

Premature ovarian failure (POF) is a primary ovarian defect characterized by absent menarche (primary amenorrhea) or premature depletion of ovarian follicles before the age of 40 years (secondary amenorrhea).[42–45] This abnormality affects about 1% of women,[43,44] and the heterogeneity of POF is reflected by the variety of possible causes, including autoimmunity, toxicity, drugs, infections, genetic defects, and idiopathic, as well as iatrogenic, origin (surgery, chemotherapy, radiation).[43–46] There are no specific references to POF due to ovarian trauma in the literature. Essentially, the reports that can be found describe the damage that can happen following cancer treatment or after an invasive gynecological/obstetric, diagnostic, or therapeutic, procedure.

POF presents with typical manifestations of climacterium: infertility associated with palpitations, heat intolerance, flushes, anxiety, depression, and fatigue. Biochemically, POF is characterized by low levels of sex hormones (estrogens and inhibins) and high levels of gonadotropins. Apart from infertility, hormone deficiency may cause severe neurological, metabolic, or cardiovascular consequences and lead to the early onset of osteoporosis.[42]

Management of POF must address the two major medical issues: hormone replacement therapy and infertility.[43,45] Women also require personal and emotional support to deal with the impact of the diagnosis on their health and relationships.[43]

Pancreatic trauma

The pancreas lies in a privileged position, high up in the retroperitoneum, protected by the spine and paraspinal muscles posteriorly and the intra-abdominal organs anteriorly.[47] Consequently, injuries to the pancreas are rare and account for only 1–4% of severe abdominal injuries.[48]

Pancreatic trauma is a diagnostic and therapeutic challenge,[47] but accurate and timely diagnosis is of utmost importance.[49] In many instances, diagnosis is missed during the primary survey and becomes apparent only after complications develop.[47] Consequently, reported mortality rates in patients with blunt pancreatic trauma range from 10% to 30%, with most deaths occurring within the first 48 hours after the traumatic event.[49]

Pancreatic trauma usually results from the delivery of a force to the mid-abdomen. Road traffic accidents are a major cause of blunt pancreatic trauma, but sports-associated injuries are increasingly common. Blunt injuries to the pancreas result in the organ being compressed over the spinal column. Compressive forces may result in a pancreatic contusion, hematoma, laceration, or fracture, depending on the magnitude of the force.[48]

CT has become the investigation of choice for hemodynamically stable patients that present after blunt abdominal trauma. Although highly accurate in diagnosing intraperitoneal injuries, pancreatic injury is often missed on initial scans and may be diagnosed only after repeating imaging procedures.[47]

Complications after pancreatic trauma are usually caused by missed pancreatic duct injury. There should be a low threshold for performing magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography if there is clinical, biochemical, or radiological suspicion of pancreatic duct disruption.[47,49]

There are few data on outcomes after pancreatic trauma, particularly with respect to endocrine and exocrine function. In a small series of 25 patients with pancreatic injury, endocrine deficiency was found post-trauma in 16%.[50]

Hormones and stress response

Since trauma can be considered a cause of stress, the main endocrine consequences of stress will be briefly discussed.

Hans Selye introduced and popularized stress as a nonspecific response of the body to any demand, emphasizing that the same pathological response would result from exposure to any stressor. According to Selye, these demands on the body included bacterial infection, toxins, X-irradiation, and various physical stimuli such as surgery and muscular exercise.[51]

The stress response is subserved by the stress system, which has both central nervous system and peripheral components.[52] The central components are located in the hypothalamus and the brainstem and include the parvocellular neurons of corticotrophin releasing hormone (CRH), the arginine vasopressin neurons of the paraventricular nuclei of the hypothalamus, the CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla and the locus ceruleus, and other mostly noradrenergic cell groups in the medulla and pons.[52,53] The peripheral components of the stress system include the peripheral limbs of the hypothalamic–pituitary–adrenal axis, the efferent sympathetic–adrenomedullary system, and the components of the parasympathetic system.[52,53]

The adaptive stress response is determined by genetic, environmental, and developmental factors, which dictate the characteristics of the defenses mobilized against intrinsic and extrinsic stressors. Inappropriate responses to stressors may turn deleterious and contribute to disease.[53,54]

During stress, there can be many changes in normal endocrine function, including the inhibition of growth axis, thyroid function, reproductive axis,[52] and digestive functions[53] so that energy becomes abundantly available to critical organs.[53,55] Meantime, there are increased circulating levels of stress hormones (glucocorticoids, catecholamines, glucagon) and metabolic changes toward catabolism.[56] Stress can even cause manifestations of the metabolic syndrome, such as visceral obesity, hypertension, dyslipidemia, cardiovascular disease, osteoporosis, insulin resistance,[52] and hyperglycemia,[56] which will be discussed below.

Stress hyperglycemia

Stress hyperglycemia generally refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes. No guidelines specifically define stress hyperglycemia. In a technical review written by the Diabetes in Hospitals Writing Committee of the American Diabetes Association, patients are classified into one of three groups: known diabetes, newly diagnosed diabetes, and hospital-related hyperglycemia.[57] A considerable percentage of people who have diabetes are unaware of their status[57,58] and, therefore, many hospital inpatients with apparent stress hyperglycemia have underlying diabetes or prediabetes.[57]

Mechanisms leading to the increase in blood glucose during critical illness are complex and are a part of the stress reaction and the inflammatory response. The stress response is associated with activation of the hypothalamic–pituitary–adrenal axis with consequent cortisol release, and is also associated with increased secretion of other hormones that can induce hyperglycemia such as catecholamines, glucagon, and GH. In addition, proinflammatory cytokines, such as interleukin-1 and tumor necrosis factor alpha, cause hyperglycemia and peripheral insulin resistance by promoting the same counter-regulatory hormone release and by altering insulin receptor signalling, respectively. In muscle and fat cells, insulin resistance decreases glucose uptake, while in hepatocytes it causes ongoing gluconeogenesis despite hyperglycemia and increased insulin release. Even with hyperglycemia and peripheral insulin resistance, insulin concentrations may be normal or even decreased, due to suppression of pancreatic beta-cells caused by proinflammatory cytokines and stimulation of alpha receptors by catecholamines.[59]

Hemoglobin A_{1c} remains the only tool available for differentiating between diabetes and stress hyperglycemia once the patient is critically ill and may be appropriate for risk stratification.[58] Nevertheless, patients with hyperglycemia during critical illness, who are discharged from the hospital with normal glucose control, should be regarded as being at increased risk of developing impaired glucose tolerance or diabetes and should as such be regularly monitored and treated appropriately. Changes in dietary habits, weight reduction, and physical activity should be recommended to all of these patients.[59]

Stress hyperglycemia was long deemed a beneficial, adaptive response to provide organs that predominantly rely on glucose as a metabolic substrate, such as the brain and the blood cells, with additional energy. However, it can also be associated with an adverse outcome. More precisely, large observational studies revealed a J-curved relationship between blood glucose levels and mortality risk, with the nadir roughly between 90 and 140 mg/dL.[60]

Therefore, better definition of the appropriate aims of glycemic control in critically ill patients was required, specifically in randomized controlled trials. The first randomized controlled trial of the effects of intensive insulin therapy in critically ill surgical patients was performed by Van den Berghe *et al*.[60,62] in Leuven, Belgium, in 2001.[61] In this landmark study, maintaining tight glycemic control (glucose levels between 79 and 100 mg/dL) in the intention-to-treat population lowered both intensive care unit (ICU) and in-hospital mortality (an absolute risk reduction of $>3\%$). The population involved in this study was predominantly cardiothoracic surgical patients and the study compared intensive insulin treatment targeting a glycemic range of 180–215 mg/dL.[61] After this first study, there were others, for instance in medical ICU populations, who produced different results.[60]

More recently, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study was a much larger multicenter study, which included 6100 patients.[63] Instead of tolerating hyperglycemia, a policy of insulin therapy to target intermediate blood glucose levels in the ICU (140–180 mg/dL) was chosen for the control group, in line with levels widely adopted in clinical practice.[61] The aim of this study was to assess whether further lowering of blood glucose levels to less than 108 mg/dL would exert additional benefit.[60] This study reported a significant 3% increase in mortality in the intensive insulin therapy group.[61]

Notably, there are some differences between the original Leuven study and the NICE-SUGAR study, which may explain,

at least partially, the dissimilar results, such as the glycemic range of the control group, the feeding regimens, and the accuracy of blood glucose monitoring.[24] Consequently, some authors assert that the two studies cannot be directly compared.[61] Other authors believe that the control group in the NICE-SUGAR study had glycemic levels that were much closer to physiologic levels and that may be ''ideal'' in critical illness.[61] Importantly, a recent meta-analysis does not support the widespread adoption of intensive insulin therapy in critically ill patients, although some patients may benefit from this treatment modality. However, the characteristics of these patients remain to be clearly defined, as does the effect of different blood glucose algorithms, the method of measuring blood glucose, and the influence of nutritional strategies.[24]

Conflict of interest

None to declare.

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