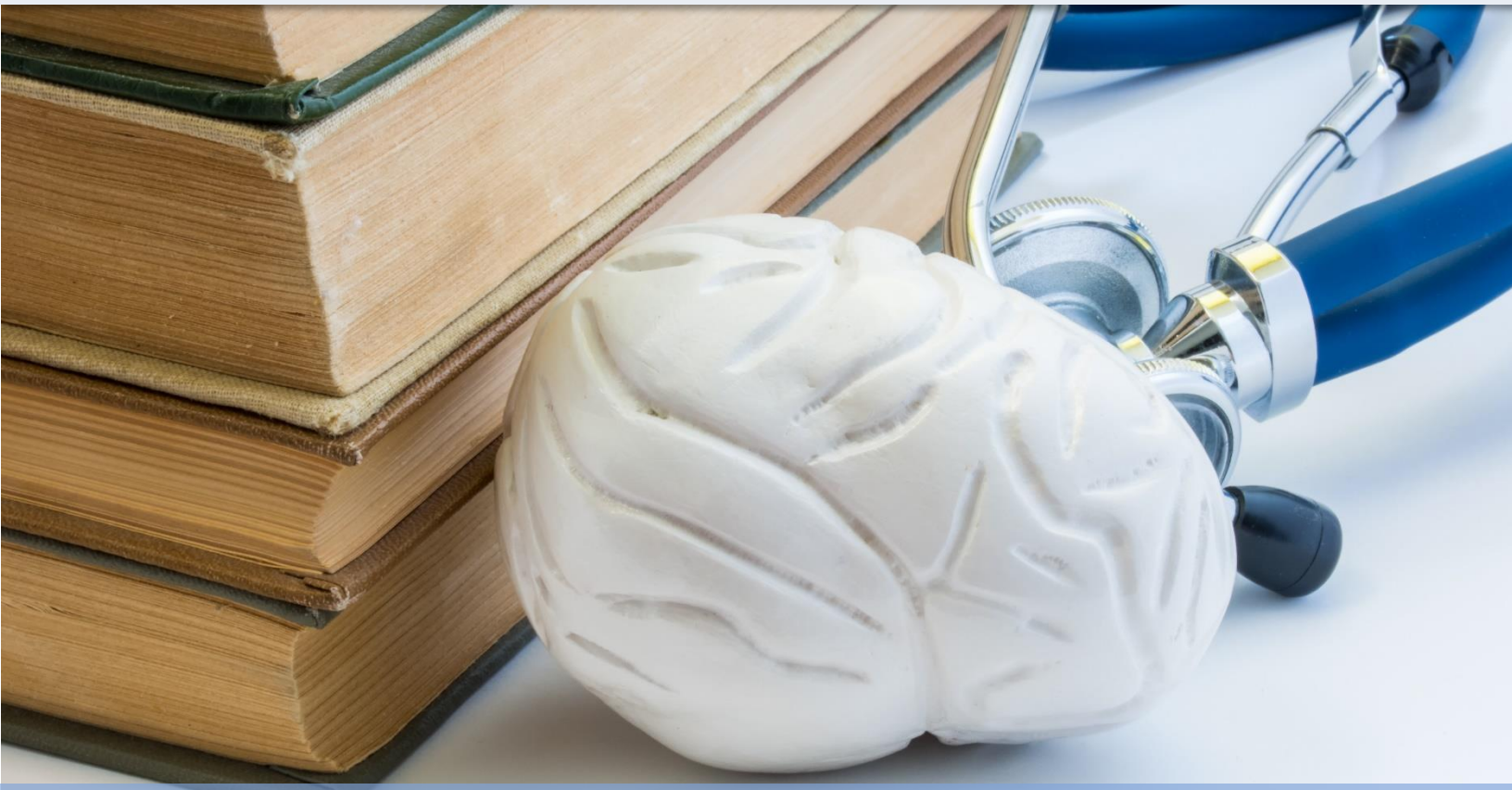
ERABI
EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY



NEUROENDOCRINE FUNCTION & DISORDERS

POST ACQUIRED BRAIN INJURY

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Disclaimer

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Conflict of Interest

In the context of ERABI development, the term “conflict of interest” (COI) refers to situations in which an author or ERABI staff member’s financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of moderate to severe Acquired Brain Injury (ERABI) *Neuroendocrine Function and Disorders post Acquired Brain Injury*. Through collaboration of researchers, clinicians, administrators, and funding agencies, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and is committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto) and Dr. Shawn Marshall (University of Ottawa) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

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Preface

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

E. Ali Bateman, MD, FRCPC is a consultant physiatrist in acquired brain injury, spinal cord injury, and electromyography at Parkwood Institute in London, Ontario, and an assistant professor in the Department of Physical Medicine & Rehabilitation at Western University. She completed undergraduate training at McGill University, medical school and residency at Western University, and is completing a masters in quality improvement and patient safety at the University of Toronto.

Amber Harnett, MSc, BScN (candidate), CNF scholar, completed her MSc in pathology at Western University and is currently a first-year nursing student in the accelerated BScN program at Western University. Passionate about supporting and advocating for those with brain injuries, she also works as a research coordinator to improve the rehabilitation system through research synthesis, guideline development, knowledge translation, education and outreach, in the CORRE lab at Parkwood Institute.

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Dr. Robert Teasell is Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University and a Clinical Researcher at Lawson Research Institute in London, Ontario. He is a clinician at Parkwood Institute, St. Joseph's Health Care London.

Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies.

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amyotrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Brain Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA). Another factor used to distinguish moderate and severe brain injury is evidence of intracranial injury on conventional brain imaging techniques which distinguish severity of injury from a mild or concussion related brain injury.

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–March 2020 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the

database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the study population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury (as defined in Table 2), and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high quality randomized controlled trials (RCTs) (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate and the intensity with which it should be provided, based on their individual patient's needs. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with the known limitations in mind.

TABLE 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6
	Prospective Controlled Trial (PCT)	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post Trial	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each randomized controlled trial (RCT) was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

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Summary of the Evidence

Intervention	Key Point Level of Evidence
Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)	
Thyrotropin-Releasing Hormone	Syndrome of inappropriate antidiuretic hormone secretion may be effectively controlled through thyrotropin-releasing hormone (TRH) stimulation. *There is level 4 evidence (from one pre-post test; Zhang et al., 2010) that TRH stimulation may be effective in treating hyponatremia post ABI.*
Growth Hormone Deficiency	
Hormone Replacement Therapy	Growth hormone deficiency may be effectively treated with hormone replacement therapy and insulin growth like factor-1 therapy. *There is level 1b evidence (from one RCT; Dubiel et al., 2018) that growth hormone replacement therapy may improve clinical outcomes compared to placebo in patients with GHD post ABI.* *There is level 1b evidence (from one RCT; Dubiel et al., 2018) and level 4 evidence (from one pre-post test; Devesa et al., 2013) that growth hormone replacement therapy effectively elevates serum IGF-1 levels in individuals with growth hormone deficiency post ABI.* *There is level 2 evidence (from one randomized controlled trial; Hatton et al., 1997) that pharmacological concentrations of IGF-1 may improve recovery, as well as glucose and nitrogen utilization post moderate to severe TBI.* *There is level 2 evidence (from one prospective controlled trial; Moreau et al., 2013) and 3 evidence (from one case control; Gardner et al., 2015) that growth hormone replacement therapy improves quality of life post ABI.* *There is level 4 evidence (from one pre-post test; Mossberg et al., 2017) that growth hormone replacement therapy may be effective in treating GHD, fatigue, and depression post ABI.*
Androgen Replacement in Men	
Testosterone Therapy	More research is needed to determine the efficacy of testosterone therapy in hypogonadal men post ABI. *There is level 1b evidence (from one randomized controlled trial; Ripley et al., 2020) that testosterone therapy is safe and well-tolerated in hypogonadal men with severe TBI; however, it may not improve functional outcomes.*
Estrogen Replacement in Women	
Progesterone	Progesterone may be effective in treating long-term outcomes in gonadotropic deficiency.

There is level 1b evidence (from one randomized controlled trial; Soltani et al., 2017) that progesterone treatment improves long-term outcome and functionality; however, benefits may not be observed short-term in ABI populations.

Introduction

Hypopituitarism is a common and treatable condition resulting from an acquired brain injury (ABI). Post-traumatic neuroendocrine disorders result from injury to, or disruption of the hypothalamic-pituitary axis within the brain and can involve one or more hormones from the anterior and/or posterior lobes of the pituitary gland, depending on which anatomical areas are involved. This module explores the variety of disorders which can arise from neuroendocrine dysfunction, their etiologies, and discusses relevant evidence-based interventions within the ABI population. However, evidence specific to post-ABI neuroendocrine dysfunction is not always available; in these instances, the most relevant research is discussed and provides an opportunity for further research.

Anatomy of the Pituitary Gland

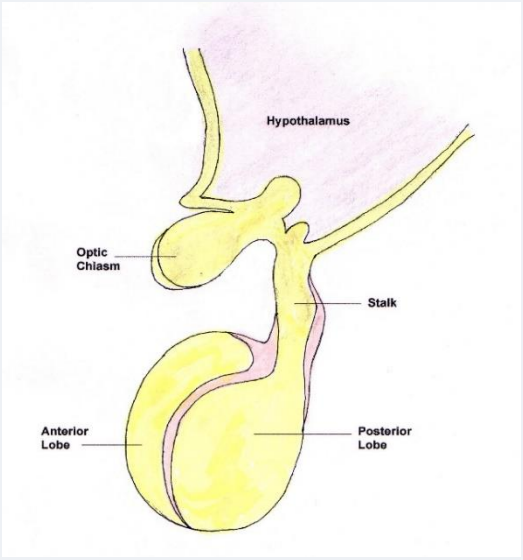


Figure 1 | Diagram of the Hypothalamic Pituitary Axis

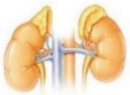
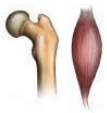
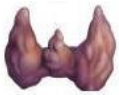
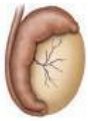
The pituitary gland (Figure 1) consists of two lobes derived from two different embryological pouches, the anterior lobe (or adenohypophysis) and the posterior lobe (or neurohypophysis). The pituitary gland is connected to the hypothalamus through the pituitary stalk; together, the hypothalamus and pituitary gland regulate neuroendocrine function and serve a critical role in maintaining homeostasis. The hypothalamus determines which hormones should be secreted from either the anterior or posterior lobe based on complex feedback loops from the systemic circulation. The hormones secreted by both the anterior and posterior pituitary and their target function are shown in Table 4. Following ABI, there may be notable changes in hormones released by the pituitary gland (Popovic et al., 2005).

The **anterior lobe** contains glandular cells which secrete hormones into the systemic circulation. It is controlled by the hypothalamus through the vascular portal system, a network of blood vessels inside the pituitary stalk, which also provides the blood supply for the anterior lobe. These vessels within the pituitary stalk are vulnerable to injury in ABI, and such injuries can produce ischemia in the anterior lobe. The anterior lobe is responsible for the production of six important hormones: prolactin (PRL), adrenocorticotropic

hormone (ACTH), growth hormone (GH), thyrotropin-stimulating hormone (TSH), follicle stimulating hormone (FSH), and luteinizing hormone (LH) (Blumenfeld, 2002).

The **posterior lobe** contains the axons and nerve terminals of neurons which have their cell bodies in the hypothalamus. These axons project from the cell bodies in the hypothalamus through the pituitary stalk and into the posterior lobe, where they secrete hormones directly into the systemic circulation. The axons within the pituitary stalk are vulnerable to injury in ABI but can regrow from the hypothalamus; the posterior lobe is less vulnerable to ischemia than the anterior lobe as its blood supply does not travel through the pituitary stalk. The posterior lobe of the pituitary is responsible for the production of two important hormones: antidiuretic hormone (ADH, also referred to as vasopressin) and oxytocin (Blumenfeld, 2002).

TABLE 4 | Pituitary Hormones and Bodily Responses

Glands	Hormones	Part of Body Affected	Body Response
Anterior Pituitary	PRL	Mammary glands 	Lactation
	ACTH	Adrenal glands 	Glucocorticoid production
	GH	Liver, muscle, bone and other tissues 	Stimulation of growth and metabolism
	TSH	Thyroid gland 	Stimulation of growth and metabolism
	FSH	Testes (men) & Ovaries (women) 	Androgen secretion and sperm production
	LH		Menstruation, estrogen and progesterone secretion
Posterior Pituitary	ADH	Kidney 	Water regulation
	Oxytocin	Uterus and mammary glands 	Labour contractions and lactation

Note: ACTH=adrenocorticotropic hormone; ADH=antidiuretic hormone; FSH=follicle stimulating hormone; GH=growth hormone; LH=luteinizing hormone; PRL=prolactin; TSH=thyroid stimulating hormone

History and Epidemiology

Hypopituitarism due to head trauma was first reported by the German researcher Cyran in 1918 (Benvenga, 2005; Lieberman et al., 2001; Makulski et al., 2008). In the early 1950s, the incidence of hypopituitarism post injury was thought to be only 1%; however, more recent research indicates that neuroendocrine disorders due to ABI may affect 8-80% of persons post-ABI in the acute, subacute, and chronic phases of injury (Benvenga, 2005; Bondanelli et al., 2005; Ghigo et al., 2005; Makulski et al., 2008; Sirois, 2009). Two reviews of the literature by Lauzier et al. (2014) and Schneider et al. (2007) found that the pooled prevalence of hypopituitarism in the chronic phase post-ABI was 27-32%.

Until recently, damage to the hypothalamus and pituitary gland following trauma was often not diagnosed until the post-mortem examination (Yuan XQ, 1991). Now, blood and urine analysis are the most common methods to diagnose neuroendocrine disorders, which allows for functional assessment of hormonal imbalances and more accurate diagnosis (Tan et al., 2017). Neuroendocrine disorders can develop in the early days post injury, while the patient is still in the acute stage of recovery, or in the later sub-acute or chronic stages.

Timing of Onset and Recovery of Hormone Deficiencies

The likelihood of experiencing neuroendocrine dysfunction varies based on a number of factors, including the time since injury. In the acute period following an ABI, neuroendocrine dysfunction may develop as a consequence of critical illness and/or interventions required for acute ABI management and therefore may not represent sequelae of injury to the hypothalamic-pituitary axis (Klose et al., 2007). As a result, some acute neuroendocrine dysfunction may not persist beyond the acute phase of injury (Klose et al., 2007). However, monitoring for some neuroendocrine disorders during this period, such as signs of potentially life-threatening ACTH or ADH deficiency, is critical even if these deficiencies are temporary, because they warrant intervention (Hadjizacharia et al., 2008; Hannon et al., 2013; Kelly et al., 2000; Olivecrona et al., 2013; Sesmilo et al., 2007).

In general, hypothalamic-pituitary axis dysfunction is most common in the acute phase post injury, when it affects 8-80% of persons with moderate or severe ABI (Benvenga, 2005; Bondanelli et al., 2005; Ghigo et al., 2005; Makulski et al., 2008; Sirois, 2009). Typically, the incidence of hormone dysfunction decreases as patients move into the subacute and chronic phases. Many patients who develop early neuroendocrine dysfunction experience recovery within the first 6 months post injury (Aimaretti, Ambrosio, Benvenga, et al., 2004). Various studies have shown that the majority of patients with low-grade or single hormone deficiencies recover during the first 6 months post injury and tend to have a much better prognosis than those who do not recover (Aimaretti, Ambrosio, Benvenga, et al., 2004; Bondanelli et al., 2004; Ghigo et al., 2005). Although neuroendocrine dysfunction typically arises in the acute phase post-injury, one study reported that 5.5% of patients who showed no signs of neuroendocrine dysfunction at 3 months did so at 12 months, demonstrating that hormone deficiencies can develop in the subacute and/or chronic phases as well. Moreover, with time, persons with

neuroendocrine dysfunction may experience spontaneous recovery or may develop additional hormone deficiencies (Aimaretti, Ambrosio, Benvenga, et al., 2004; Ghigo et al., 2005).

Isolated and Combined Hormone Deficiencies

Which hormones are affected depends on which areas of the hypothalamic-pituitary axis have been affected. Patients may develop abnormalities in one or more hormones. Single hormone deficiencies are more common than multiple hormone deficiencies, in which two or more hormones are affected (Krewer et al., 2016). Single hormone deficiencies may affect 30-40% of persons with moderate to severe ABI, whereas 10-15% of persons with moderate to severe ABI may develop multiple hormone deficiencies (Aimaretti, Ambrosio, Di Somma, et al., 2004; Bondanelli et al., 2004; Kelly et al., 2000; Lieberman et al., 2001). In one study, 13.3% of patients who demonstrated single hormone deficiencies at 3 months developed multiple hormone deficiencies at 12 months (Ghigo et al., 2005).

There is significant variability in the reported incidence of different types of hormonal abnormalities post ABI. Of the single hormone deficiencies, elevated PRL (30%), GH deficiency (20-30%), ADH deficiency (also termed diabetes insipidus, DI; 15-50%), ACTH deficiency (9-80%), LH and/or FSH deficiency (also termed hypogonadism; 10-30%), and hypothyroidism (10-30%) are the most commonly reported (Bondanelli et al., 2004; Hadjizacharia et al., 2008; Hannon et al., 2013; Olivecrona et al., 2013). The pattern of involvement in combined hormone deficiencies is not well-established.

Risk Factors for Neuroendocrine Dysfunction

To date, there is no consensus on what factors predict who will develop neuroendocrine dysfunction post ABI. This is due, in part, to differences in rates of screening to detect hormonal abnormalities, variability in the timing of onset, variability in cut-offs for diagnosis, and likely other factors that have not yet been elucidated. In general, there are five factors which are thought to increase a person's risk of developing neuroendocrine dysfunction post ABI: greater injury severity, lower initial Glasgow Coma Scale (GCS) score, specific injury features, raised intracranial pressure, length of intensive care unit stay, and time post-injury (Klose et al., 2007; Schneider, Aimaretti, et al., 2007).

TBI Severity

Persons with moderate or severe TBI are more likely to develop neuroendocrine dysfunction than individuals who sustain mild TBI (concussion)(INESSS-ONF, 2015; Klose et al., 2007; Schneider, Kreitschmann-Andermahr, et al., 2007). Accordingly, persons with an initial GCS score between 3 and 12 should be considered higher risk for hormonal disorders or deficiencies and considered for screening (Behan et al., 2008). For persons with a TBI and initial GCS score <12, there is inconclusive evidence for the relationship between lower initial GCS score and neuroendocrine dysfunction; however, on the balance of evidence, there is likely a greater risk of neuroendocrine dysfunction in persons with severe injuries compared to moderate injuries (Bondanelli et al., 2004; Cernak et al., 1999; Kleindienst et al., 2009; Klose et al., 2007; Lauzier et al., 2014; Nemes et al., 2015; Prasanna et al., 2015; Sirois, 2009; Tanriverdi et al., 2013). This is supported by recent guidance from both the American College of

Endocrinology, the American Association of Clinical Endocrinologists, and the British Neurotrauma Group (Tan et al., 2017; Tritos et al., 2015).

Some studies suggest an increased risk in persons with the most severe disability including disorders of consciousness (i.e., coma or unresponsive wakefulness(Estes & Urban, 2005; Klose et al., 2007; Sesmilo et al., 2007). In addition, longer length of stay in the intensive care unit (ICU), longer hospitalization, and a prolonged loss of consciousness may also be associated with the development of hypopituitarism (Klose et al., 2007; Schneider, Kreitschmann-Andermahr, et al., 2007). Although prolonged ICU admission and prolonged coma may be attributable to factors other than severity of injury, these factors suggest patients with more severe clinical presentations are at increased risk for developing neuroendocrine dysfunction.

Other Risk Factors for Neuroendocrine Dysfunction

Numerous studies have evaluated whether or not the Individuals at greatest risk for post-traumatic hypopituitarism are those who have sustained a specific type of injury or who were older at the time of injury.

Ultimately, there is conflicting evidence regarding whether hormone deficiencies are associated with specific types or patterns of brain injury. Neuroendocrine dysfunction may develop as a result of any type of ABI or TBI (Klionsky et al., 2016). Several studies found no relationship between the type of injury and hypothalamic-pituitary axis dysfunction (Ghigo et al., 2005; Lauzier et al., 2014). Some studies found that diffuse axonal injury (Estes & Urban, 2005; Hadjizacharia et al., 2008; Schneider et al., 2008)and penetrating injury may be associated with increased risk of neuroendocrine dysfunction(Hadjizacharia et al., 2008). In one study, cerebral edema was associated with increased risk of diabetes insipidus due to ADH deficiency (Behan et al., 2008). Several studies reported that subarachnoid hemorrhage was correlated with increased risk of Syndrome of Inappropriate ADH (SIADH), or excess ADH production (Behan et al., 2008), as well as anterior pituitary hormone deficiencies (Khajeh et al., 2015). The incidence of basal skull fractures and neurosurgical procedures has been reported to be similar in patients with hypopituitarism when compared to those with normal pituitary function in some studies (Bondanelli et al., 2007) whereas other studies have reported that basal skull fractures increase the risk of developing ADH deficiency (diabetes insipidus) (Born et al., 1985; Schneider et al., 2008) and anterior pitiuitary dysfunction (Lauzier et al., 2014) after ABI. Further, one study by Schneider et al. (2008) suggested that greater diffuse axonal injury and basal skull fracture are associated with a higher risk of pituitary impairment, although this finding has not been reproduced across all studies.

Older age was associated with the development of anterior pituitary hormone deficiencies in a systematic review in which all included studies had a mean age <50 years old (Lauzier et al., 2014). Other studies have yielded similar results, and similarly included relatively young patients, although the older patients within these cohorts were more likely to develop neuroendocrine dysfunction (Agha et al., 2004; Bondanelli et al., 2004; Schneider et al., 2006). However, younger patients in these studies also developed neuroendocrine dysfunction, indicating that all ages are at risk. This finding is supported by

Benvenga et al. (2000), who noted that post ABI hypopituitarism occurred primarily in male survivors between the ages of 11 and 39. In two studies, high body mass index was found to be a risk factor for pituitary dysfunction (Klose et al., 2007; Ulfarsson et al., 2013).

Pathophysiology of Hypopituitarism Post ABI

Neuroendocrine disorders post TBI result from injuries to the areas of the brain that regulate endocrine functions within the hypothalamic-pituitary axis (Sandel ME et al., 2007). In addition to pituitary trauma, hormonal alterations may reflect adaptive responses to injury and critical illness, particularly in the acute phase of injury; these alterations are not necessarily associated with long-term hypopituitarism. Figure 2 shows the pituitary gland under normal conditions and how it can be altered following a traumatic injury.

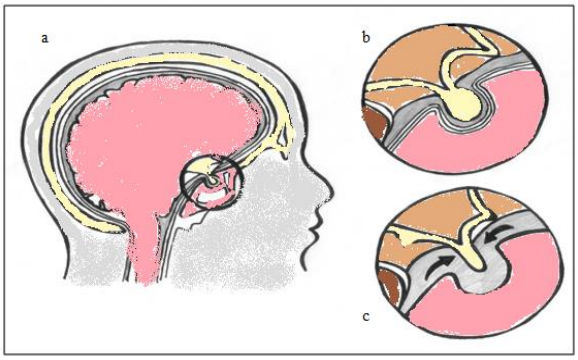


Figure 2 | Pituitary Gland: Normal (b) & Post-Traumatic Conditions (c)

Mechanism of Injury

ABI can affect any component of the hypothalamic-pituitary axis via direct trauma or indirect injury; direct trauma can arise from hematoma, compression, or shearing of the pituitary stalk and indirect injury can arise from medications, ischemia from hemorrhage or hypotension, or systemic illness gland (Behan et al., 2008; Benvenga et al., 2000; Sirois, 2009). Direct injury most often occurs at the level of the pituitary stalk or within the pituitary gland. This may be the result of direct trauma (Behan et al., 2008; Benvenga et al., 2000; Sirois, 2009) (i.e., skull fracture), edema, hemorrhage, elevated intracranial pressure, or hypoxic shock. Direct mechanical injury to the hypothalamus, the pituitary stalk, or the pituitary gland may also result in hypopituitarism. Disruption of the long hypophyseal vessels, which travel through the vulnerable pituitary stalk to provide the blood supply to the anterior lobe of the pituitary, may produce an anterior lobe infarct (Stanfield, 1960). An infarction of the posterior lobe is much less common because the posterior lobe's blood supply does not travel through the pituitary stalk. However, compression, inflammation, and/or edema involving the posterior pituitary gland can produce posterior lobe dysfunction; this has been shown to improve with time (Behan et al., 2008). Potential lesions of the hypothalamic-pituitary axis known to be associated with TBI are shown in Table 5. The types of injuries and respective rates are listed below in Table 6.

TABLE 5 | Hypothalamic-Pituitary-Adrenal Lesions Associated with TBI (Sirois, 2009)

Lesion	Causes of Injury	Location of Injury
Primary Lesion (direct)	Acceleration-deceleration	Traumatic lesion of the stalk
		Anterior lobe necrosis
		Posterior lobe hemorrhage

	Basal skull fracture	Direct lesion to pituitary, stalk, or hypothalamus
Secondary Lesion (non-direct)	Brain edema	
	Hypoxia	
	Intracranial pressure	
	Hemorrhage	
	Inflammatory mediators	

TABLE 6 | Type and Rate of Injury (Benvenga et al., 2000)

Type of Injury	Percentage
Hemorrhage of hypothalamus	29%
Hemorrhage of posterior lobe	26%
Infarction of anterior lobe	25%
Infarction of posterior lobe	1%
Stalk resection	3%

Note that although this section emphasizes the pathophysiology and mechanisms of injury thought to contribute to the development of neuroendocrine dysfunction, neuroendocrine dysfunction can develop post ABI in the absence of these mechanisms and neuroimaging findings. For instance, in 7% of cases, neuroendocrine disorders are not associated with neuroimaging abnormalities (Benvenga et al., 2000). The gold standard for neuroendocrine dysfunction includes serum tests assessing hormonal function (Benvenga et al., 2000).

Signs & Symptoms

Neuroendocrine dysfunction may present at any time post injury. The presenting features vary significantly depending on which hormones are affected. Patients with neuroendocrine dysfunction may present with fatigue, temperature lability, disturbances in appetite, weight fluctuations, sodium dysregulation, sexual dysfunction, hypertension or hypotension, increased anxiety and depression, cognitive deficiencies, reduced bone and muscle mass, exercise intolerance, and immunologic disorders (Sesmilo et al., 2007; Sirois, 2009). Due to the overlapping symptoms and signs that may occur, clinical determination of which hormones are affected may not be possible, and thus typically requires diagnostic testing (Sesmilo et al., 2007; Sirois, 2009). Moreover, these symptoms and signs can overlap with the sequelae of ABI, even in the absence of neuroendocrine dysfunction, underscoring the need for diagnostic testing.

Clinical Presentation of Hypopituitarism

- Fatigue
- Sleep Disturbance
- Decreased muscle mass, increased fat mass
- Reduced exercise tolerance and muscle strength
- Amenorrhea, decreased libido, erectile dysfunction
- Decreased cognitive function, concentration, memory
- Mood disturbances, depression, irritability
- Social isolation, decreased quality of life

Due to the nature of its features and the delay of its presentation, neuroendocrine dysfunction may be missed following any type of ABI (Klionsky et al., 2016; Schneider, Kreitschmann-Andermahr, et al., 2007); thus, the diagnosis of hypopituitarism following an ABI remains a challenge. Further complicating the assessment of hypopituitarism are normal variations in different populations, such as low serum insulin-like growth factor in older patients due to normal aging and not due to a pathological or ABI-related process. However, some symptoms of hypopituitarism do not routinely occur due to ABI, loss of hair growth (loss of axillary hair or decreased need for facial shaving), impaired sexual function, weight changes, polydipsia, or secondary amenorrhea. The most common signs and symptoms of pituitary dysfunction are outlined in Table 7.

TABLE 7 | Hormone Abnormalities and Accompanying Signs and Symptoms

Type of Injury	Percentage
Hemorrhage of hypothalamus	29%
Hemorrhage of posterior lobe	26%
Infarction of anterior lobe	25%
Infarction of posterior lobe	1%
Stalk resection	3%

Current research suggests that anyone who suffers a brain injury (due to a stroke or TBI) and has a Glasgow Coma Scale (GCS) score between 3 and 12 should be tested for hormonal disorders or deficiencies (Behan et al., 2008). Due to the consequences associated with pituitary dysfunction, it represents a negative prognostic factor for post ABI recovery (Benvenga et al., 2000).

Screening & Diagnosis of Hypopituitarism

Diagnosis of neuroendocrine dysfunction is based on clinical evaluation and laboratory testing. According to the INESSS-ONF Guidelines (2015) and Sesmilo et al. (2007), screening for neuroendocrine dysfunction should be performed in all patients with an initial GCS score between 3 and 12 (i.e., moderate to severe TBI). The INESSS-ONF Guidelines recommend screening these patients any time they

present with clinical features suggestive of neuroendocrine dysfunction and/or between 3-6 months post ABI; recommended screening tests are described in Table 8. However, there is some dispute in the literature as to how soon after injury testing should be performed, if it should be repeated, and if so, how often it should be conducted. As indicated previously, because clinical assessment of hypopituitarism is difficult since the signs and symptoms are often nonspecific, may overlap between specific hormones, and can mimic the neuropsychological sequelae of TBI, screening and diagnostic testing are critical to making the diagnosis.

TABLE 8 | Screening Tests for the Hypothalamic-Pituitary Axis post ABI (INESSS-ONF, 2015)

Anterior Pituitary*	**Pituitary-Gonadal Axis** LH, FSH, PRL, and serum testosterone (men) or estrogen (women) **Pituitary-Adrenal Axis** Plasma cortisol and serum glucose **Pituitary-Thyroid Axis** TSH and free T3 or free T4 **Pituitary-Growth Hormone Axis** Insulin-like growth factor 1 (IGF-1)[#]
Posterior Pituitary	Clinical evaluation of volume (hydration) status Serum sodium and urine sodium Serum osmolality and urine osmolality

*According to the INESSS-ONF guidelines, all testing should be performed in the morning to account for expected diurnal variation.
[#]IGF-1 testing is controversial and may not need to be completed due to uncertainty regarding the need for and/or benefit of treatment (Behan et al., 2008; Molitch et al., 2011; Sesmilo et al., 2007).

In the acute phase of after an ABI, patients should be monitored clinically for the development of signs and/or symptoms indicative of neuroendocrine dysfunction. Specifically, patients should be monitored for signs or symptoms of adrenal insufficiency and DI, as these can have serious, life-threatening consequences (Bernard et al., 2006; INESSS-ONF, 2015). During the acute phase, plasma cortisol levels of less than 193 nmol/L (7.2 µg/dL) or serum glucose <4 mmol/L (72 mg/dL) may indicate adrenal insufficiency if alternative explanations are absent and warrant immediate attention; low plasma cortisol (496 nmol/L or <18 ug/dL) may also warrant consideration for treatment for adrenal insufficiency (Schneider, Aimaretti, et al., 2007).

Screening for other neuroendocrine abnormalities during the acute period is not recommended due to the risks and harms associated with over diagnosis and overtreatment in the critically ill patient (Tan et al., 2017). For patients in the subacute or chronic phases after an ABI, clinicians should screen for signs and/or symptoms of neuroendocrine dysfunction including asking about signs/symptoms, checking blood pressure, and, if appropriate or warranted, arranging for the screening tests outlined in Table 9.

Given that hypopituitarism can evolve over time following injury, it is important to consider it as a diagnostic possibility in all stages of recovery. In the acute stage, screening for adrenal insufficiency and diabetes insipidus is particularly important due to their life-threatening potential. Although a recent study found that elevated levels of luteinizing hormone during early hospitalization are significantly associated with higher rates of mortality, the clinical utility of testing in the acute phase is limited (Hohl et al., 2018). In the acute stage of recovery it is not necessary to routinely assess growth, gonadal, or thyroid hormones as there is no evidence to suggest that supplementation of these hormones during this phase is beneficial (Ghigo et al., 2005; Schneider, Aimaretti, et al., 2007); however, during the post recovery stage, between 3 and 6 months, a clinical assessment for hypopituitarism should be completed (Agha, Phillips, et al., 2005; Powner & Boccalandro, 2008; Powner et al., 2006; Schneider, Aimaretti, et al., 2007).

Neuroendocrine screening and diagnostic tests are outlined in Table 9. Anterior pituitary screening should include morning serum cortisol and random blood glucose, TSH and either free T_3 or free T_4, FSH, LH, PRL, IGF-1, and morning testosterone in men or estrogen in women. Posterior pituitary screening should include serum and urine sodium and osmolality. For patients who screen positive for neuroendocrine dysfunction, confirmatory tests are required to diagnose ACTH and GH deficiency. For suspected ACTH deficiency, morning cortisol levels <100nmol/L (3.6 µg/dL) are sufficient for diagnosis; other patients may require referral to an endocrinologist for definitive diagnosis (Tan et al., 2017). For suspected GH deficiency, provocative testing may be warranted if IGF-1 levels are below the 25th percentile of age-related normal limits (Ghigo et al., 2005). However, GH deficiency treatment is controversial in adults and provocative testing may not be appropriate; consultation with an endocrinologist is recommended (Molitch et al., 2011).

TABLE 9 | Screening and Diagnostic Testing for Neuroendocrine Dysfunction Post ABI (Molitch et al., 2011; Tan et al., 2017).

Hypothalamic-Pituitary Axis	Screening Tests	Abnormalities Indicating Need for Referral or Further Testing	Diagnostic Tests
Adrenal	Morning serum cortisol Serum glucose	Low cortisol (<7 ug/dL or 193 nmol/L) Low glucose (<4 mmol/L without other explanation)	Morning cortisol <100 nmol/L is diagnostic Consider consulting an endocrinologist for CRH stimulation test or insulin-induced hypoglycemia test
Gonadal	LH, FSH, morning testosterone (men) or estrogen (women)	Low LH, FSH, and low testosterone or estrogen	No additional tests required for diagnosis

Hypothalamic-Pituitary Axis	Screening Tests	Abnormalities Indicating Need for Referral or Further Testing	Diagnostic Tests
Prolactin	PRL	Low or high PRL (note that disorders of PRL can occur due to medications or other causes)	No additional tests required for diagnosis; consider referral for low PRL if interested in lactation
Thyroid	TSH Free T_4 or free T_3	Low TSH + low free T_4 or free T_3 indicates hypothalamic-pituitary axis abnormality (note that high TSH + low free T_4 or free T_3 indicates a primary thyroid problem)	No additional tests required for diagnosis
Growth Hormone	IGF-1	Low IGF-1	Consider consulting an endocrinologist for insulin tolerance test or glucagon stimulation test
Diabetes Insipidus (ADH deficiency)	Simultaneous serum and urine sodium and osmolality Urine output (mL/hr) Clinical assessment of volume status	Serum sodium >145 mmol/L Serum osmolality >290 mmol/L Urine osmolality <300 mmol/L Urine output >3L/24h, or >200 mL/hr for 2+ consecutive hours, or >5 mL/kg/hr Dehydrated (low volume status)	No additional tests required for diagnosis if meets these criteria; consider desmopressin test if concern for nephrogenic DI
SIADH (ADH excess)	Simultaneous serum and urine sodium and osmolality Clinical assessment of volume status	Serum sodium <135 mmol/L Serum osmolality <280mmol/L Urine osmolality >300 mmol/L Normal volume status	No additional tests required for diagnosis

Neuroimaging

Neuroimaging is not required for the diagnosis of neuroendocrine dysfunction. However, in patients for whom neuroimaging is needed, Makulski et al. (2008) concluded from a systematic review that magnetic resonance imaging (MRI) is the preferred imaging technique for the pituitary gland, as it can readily distinguish between the anterior and posterior lobes. MRI allows for both visualization of structural abnormalities and indirect imaging of the blood supply. The most common pathological findings are hemorrhage of the hypothalamus and posterior lobe, and infarction of the anterior lobe (Maiya et al., 2008; Makulski et al., 2008). While widely regarded as the best imaging technique, MRI may still fail to show pathological abnormalities in some patients with PTHP (Makulski et al., 2008). Benvenga et al. (2000) found that 6% to 7% of those with post-traumatic hypopituitarism showed no abnormalities on MRI. Regarding testing, blood tests remain the gold standard. Neuroimaging can be a useful adjunct to ensure there are no reversible structural causes of pituitary dysfunction, such as a mass.

Provocative Testing

Growth Hormone Provocative Tests

Approximately 20% of those with a TBI or subarachnoid hemorrhage are at risk for severe growth hormone deficiency (Klionsky et al., 2016); provocative testing has been recommended to rule it out. Due to the expense of this test, it is recommended that other hormonal tests are conducted first, such as the IGF-I, and that provocative testing is used only to rule out other transitory hormone deficits (Sesmilo et al., 2007). It is not recommended to use Insulin Growth Factor (IGF) levels as an assessment of overall growth hormone as multiple studies have found no association between the two (Bondanelli et al., 2005; Popovic et al., 2005).

Adrenocorticotropic Hormone Provocative Tests

The diagnosis of ACTH insufficiency often requires provocative tests in addition to measurement of early morning basal serum cortisol levels. The normal basal morning serum cortisol values are between 150 nmol/L and 800 nmol/L (5.3–28.6 lg/dL). Basal morning serum cortisol <100 nmol/L (<3.6 ug/dL) is diagnostic for secondary ACTH insufficiency related to hypothalamic-pituitary axis dysfunction; if this value is >500 nmol/L (>18 lg/dL) ACTH insufficiency can be excluded. When basal serum cortisol values are borderline, a provocative test is necessary (Auernhammer & Vlotides, 2007). These tests include the the insulin-induced hypoglycemia test, the cortotropin-releasing hormone stimulation test, and the metyrapone test. Consultation with an endocrinologist is recommended prior to proceeding with provocative testing (Tan et al., 2017).

During the insulin-induced hypoglycemia test, the peak serum cortisol levels in healthy people are between 555 nmol/L and 1,015 nmol/L (19.8–36.2 lg/dL) (Auernhammer & Vlotides, 2007). ACTH insufficiency is diagnosed when there is a serum cortisol peak <500 nmol/L. Although this test has been

shown to be the gold standard, caution is recommended when using the test because it produces hypoglycemia; the test is contraindicated in some persons with cardiac disease and epilepsy.

In the corticotropin-releasing hormone (CRH) stimulation test, patients receive recombinant CRH intravenously; CRH is normally produced by the hypothalamus and is responsible for stimulating ACTH release from the anterior pituitary. If serum cortisol increases to <350–420 nmol/L (<12.5–15 ug/dL), this suggests ACTH insufficiency; if serum cortisol increases to >515-615 nmol/L (18.5–22.0 lg/dL), insufficiency can be excluded (Auernhammer & Vlotides, 2007).

The metyrapone test is considered only when other tests are inconclusive. Metyrapone blocks the last step in the biochemical pathway between cholesterol and cortisol, leading to a reduction in serum cortisol; in turn, this should increase of ACTH secretion and an increase of cortisol precursors including 11b-deoxycortisol. The peak serum 11b-deoxycortisol levels in healthy people range between 195 nmol/L and 760 nmol/L. During the test, if the serum 11-deoxycortisol increase to >200 nmol, adrenal insufficiency is excluded. Another variant of the test is the ‘‘multiple dose metyrapone test’’, which requires other diagnostic cut-offs of serum 11b-deoxycortisol levels. In order to support this multistep testing, patients must be monitored in hospital because metyrapone may cause gastrointestinal upset and may lead to adrenal insufficiency (Auernhammer & Vlotides, 2007).

Because ACTH insufficiency is not the only cause of low serum cortisol/adrenal insufficiency, some patients may require an ACTH stimulation test. In this test, intravenous recombinant ACTH is injected, and patients’ serum cortisol is measured; failure of the intravenous ACTH to stimulate cortisol production indicates a problem with the adrenal glands (primary adrenal insufficiency). This testing does not diagnose hypothalamic-pituitary axis causes of low serum cortisol.

TABLE 10 | Tests of Hypothalamic-Pituitary-Adrenal Axis Function (Auernhammer & Vlotides, 2007)

Tests	Methods
Insulin-induced hypoglycemia test	- Insulin (0.1–0.15 IU/kg) intravenously sufficient to cause adequate hypoglycemia (<40mg/dL, <2.2 nmol/L) - Blood samples are collected for measurement of serum cortisol at –15, 0, 30, 45, 60 and 90 min
Metyrapone test	- 30 mg/kg orally at midnight with a snack to minimize gastrointestinal discomfort - Blood for serum 11b-deoxycortisol, ACTH and cortisol are obtained at 8 AM
CRH test	- 100 µg recombinant human CRH is given intravenously - Blood samples for serum cortisol are collected at –15, 0, 30, 45 and 60 min
ACTH stimulation test	- 250 µg recombinant human ACTH and serum cortisol, given intravenously - Responses are assessed at 0, 30 and 60 min - This tests the adrenal glands’ ability to produce cortisol and does not test the hypothalamic-pituitary-adrenal axis

Management of Neuroendocrine Disorders

Timing of Assessment and Interventions

To date, there have been no consensus guidelines to advise when to assess for or how to treat endocrine dysfunction post ABI; however, the American Association of Clinical Endocrinologists and American College of Endocrinology produced an approach to post-traumatic neuroendocrine dysfunction in 2015 and the British Neurotrauma Group produced guidance for screening and management of post TBI pituitary dysfunction in 2017 (Tan et al., 2017; Tritos et al., 2015). Both of these groups recommend monitoring for signs and/or symptoms of ACTH and ADH dysfunction in the acute phase after moderate to severe TBI, particularly in the first two weeks post-injury, and assessing anterior and posterior pituitary hormones in the subacute and/or chronic phase. These recommendations are consistent with those from the INESSS-ONF (INESSS-ONF, 2015), which recommend screening clinically and/or with blood tests at 3-6 months or any time signs/symptoms develop. All of these guidelines are specific to persons with moderate to severe TBI and are not applicable to persons with mild TBI. Specific guidance for non-traumatic ABI is lacking. When there is clear indication of anterior or posterior pituitary dysfunction, consulting an endocrinologist is strongly recommended (Estes & Urban, 2005; Tan et al., 2017; Tritos et al., 2015).

Posterior Pituitary Dysfunction and Available Interventions

Sodium Disorders: Hyponatremia and Hypernatremia

The most common manifestation of posterior pituitary dysfunction after ABI is sodium dysregulation. Early studies investigating the impact of ABI on the posterior pituitary gland have demonstrated a disruption in sodium and fluid balance (Doczi et al., 1982). Makulski et al. (2008) noted that the more common medical consequences of acute TBI are disorders of salt and water balance resulting in hyponatremia, which may be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or due to cerebral salt wasting (CSW), and hypernatremia, which is typically the result of diabetes insipidus (DI) from insufficient ADH. Abnormalities of ADH represent one of the most common endocrine disturbances that occur in patients following TBI (Powner et al., 2006).

Hyponatremia, defined as a serum sodium concentration below 135 mEq/L, can arise after ABI as a result of SIADH, in which too much ADH is produced by the posterior pituitary, as a result of CSW, which is not the result of a pituitary abnormality, or due to other medical conditions or medical treatments. In addition to SIADH and CSW, numerous medications, such as carbamazepine, selective serotonin

reuptake inhibitors (Li et al., 2016), loop diuretics, vasopressin analogs, and chlorpromazine, may lead to hyponatremia (Agha, Phillips, et al., 2005; Goh, 2004; Haugen, 2009). Signs and symptoms of hyponatremia include low serum sodium, anorexia, nausea, vomiting, altered mental status—ranging from confusion to lethargy to coma—and seizures. From three studies, the prevalence of hyponatremia post ABI ranged from 15% to 40% (Agha, Phillips, et al., 2005; Hannon et al., 2013; Moro et al., 2007; Zhang et al., 2010). Findings suggest that hyponatremia is more common in patients with severe, as opposed to mild or moderate, ABI (Zhang et al., 2010). Hyponatremia is undesirable during recovery as it is associated with longer length of stay and worse outcomes at 1 month post ABI (i.e., limited 'good' recovery, higher number of patients with moderate disability) (Moro et al., 2007).

Hypernatremia, defined as a serum sodium concentration above 145 mEq/L, can arise after ABI as a result of inadequate ADH secretion. Like hyponatremia, other medical conditions or interventions, including the use of hypertonic saline or mannitol (for the management of raised intracranial pressure) or diuretics, can cause hypernatremia (Tritos et al., 2015). Commonly prescribed medications and those frequently used in persons with ABI that can cause hyponatremia are listed in Table 11; however, this list is not exhaustive.

TABLE 11 | Medications Associated with Hyponatremia and SIADH. Adapted from (Shepshelovich et al., 2017)

Class of Medication	Medications
Antidepressants	Citalopram, escitalopram, sertraline, paroxetine, venlafaxine, duloxetine, mirtazapine, amitriptyline
Antipsychotics	Haloperidol, risperidone, chlorpromazine, olanzapine, quetiapine,
Anti-seizure medications	Phenytoin, valproate, carbamazepine, lamotrigine, phenobarbital
Neuropathic pain agents	Pregabalin, venlafaxine, duloxetine
Opioid agonists	Oxycodone, tramadol
Endocrine medications	Glyburide, desmopressin

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

SIADH is diagnosed in patients when sodium serum levels drop below 135 mEq/L (hyponatremia) (Goh, 2004), coupled with an inappropriate elevation of urine osmolality (Blumenfeld, 2002). Most evidence for the treatment of SIADH is not specific to ABI. The incidence of SIADH post ABI can range from 2.3 to 36.6%, and for most patients will be transient (Agha et al., 2004; Tan et al., 2017). The onset of SIADH may present as early as 2 to 3 days post injury (Born et al., 1985), and may persist beyond 12 months (Moreau et al., 2012). Depending on the diagnostic criteria, SIADH is categorized as "severe" if serum sodium is <125-130 mmol/L (Born et al., 1985; Doczi et al., 1982). Severe syndromes may be associated with poorer neurological function compared to moderate syndromes.

TABLE 12 | Interventions for SIADH Post ABI

Author, Year	Methods	Outcome

Country Study Design Sample Size		
Zhang et al. (2010) China Pre-Post N=68	**Population:** Craniocerebral Injury (CI); Mean Age=27.8yr; Gender: Male=51, Female=17; Time Post Injury ≤24hr; Injury Severity: Mild=17, Moderate=18, Severe=33. **Intervention:** Patients hospitalized within 24hr of CI were assessed for post-injury hyponatremia, which was defined as blood [Na^+] <135mmol/L. Those with hyponatremia received thyrotropin-releasing hormone (TRH) stimulation. **Outcome Measure:** Incidence of hyponatremia, Level of ADH.	1. TRH stimulation was shown to mitigate symptoms of hyponatremia caused by SIADH by reducing blood ADH concentration from baseline to 60min post TRH stimulation (130.87±4.32 to 72.64±3.11pg/mL; p<0.01). TRH stimulation was not effective in resolving hyponatremia caused by cerebral salt-wasting syndrome.

Discussion

Recommendations for the management of hyponatremia resulting from SIADH include limiting daily fluid intake and TRH stimulation (Zhang et al., 2010). These interventions may be administered alone or with loop diuretics (Arai et al., 2009). The former, in particular, directly decreases the level of circulating ADH in blood, and thus may represent an effective therapy for SIADH-induced hyponatremia. Its effectiveness, however, is limited against hyponatremia resulting from CSW (Zhang et al., 2010). Other ways to manage post-injury hyponatremia include intravenous or oral sodium supplementation . Higher doses of sodium may be necessary if hyponatremia persists. Hydrocortisone may be appropriate if sodium supplementation and fluid restriction are ineffective (Hannon et al., 2013; Moro et al., 2007). Moro et al (2007) reported that in such cases, hydrocortisone administration returned the serum sodium to within normal range after 2 days of therapy. Other treatments for SIADH which have not been studied in the ABI population may be effective; consultation with an endocrinologist is recommended.

In one prospective study, Zhang et al. (2010) reported that TRH stimulation mitigated the symptoms of hyponatremia caused by SIADH but did not resolve hyponatremia caused by CSW. Retrospective studies have identified several successful treatments for SIADH including intravenous saline (Chen et al., 2014; Moro et al., 2007), restricting fluid intake (Chen et al., 2014), hydrocortisone (2007), and enteral urea (Annoni et al., 2016). There optimal target range for fluid restriction has not been established post ABI: Doczi et al. (1982) suggested limiting daily fluid intake to less than 600-800mL, whereas Born et al. (1985) suggest limiting intake to 250-500mL.

Conclusions

There is level 4 evidence (from one pre-post test; Zhang et al., 2010) that TRH stimulation may be effective in treating hyponatremia post ABI.

KEY POINT

- Syndrome of inappropriate antidiuretic hormone secretion may be effectively controlled through thyrotropin-releasing hormone (TRH) stimulation.

Cerebral Salt Wasting (CSW)

Hyponatremia is often multifactorial; in addition to SIADH, medications, and other causes, CSW may also cause hyponatremia (Moro et al., 2007; Zhang et al., 2010). CSW is a rare clinical condition resulting in low volume status (dehydration) and low blood pressure (hypovolemia) from excessive loss of sodium in the urine (Yee et al., 2010). Because CSW results in hyponatremia, the symptoms are similar to SIADH, but patients may also experience clinical signs of dehydration, polyuria, significant thirst (polydipsia), low blood pressure, and salt cravings which can help distinguish them from SIADH (Yee et al., 2010). The treatment for CSW is to correct the dehydration; CSW will not respond to fluid restriction or TRH, unlike SIADH (Yee et al., 2010). As with SIADH, most evidence for the treatment of CSW is not specific to the post ABI population.

Diabetes Insipidus (DI)

DI develops when there is inadequate secretion of ADH from the posterior lobe of the pituitary gland. In DI, insufficient ADH causes the kidneys to produce large amounts of dilute urine (polyuria), resulting in dehydration, incredible thirst (polydipsia), and hypernatremia (Blumenfeld, 2002). Post-ABI DI has been shown to occur in 2% to 51% of patients (Bondanelli et al., 2007; Bondanelli et al., 2004; Born et al., 1985; Ghigo et al., 2005; Hannon et al., 2013). In a large observational study by Hadjizacharia et al. (2008), 15% patients with either blunt or penetrating head injury were diagnosed with DI. Typically, DI develops early, usually occurring within a few days to a week of injury as a result of cerebral edema and transient compression of the hypothalamus and/or posterior pituitary (Hadjizacharia et al., 2008; Kelly et al., 2000). While most studies suggest that post-injury DI is transient (Bondanelli et al., 2004; Hannon et al., 2013; Kelly et al., 2000; Schneider et al., 2006; Schneider et al., 2008), there is some evidence that DI may persist up to 12 months post injury (Agha & Thompson, 2005; Ghigo et al., 2005; Tsagarakis et al., 2005). With regards to treatment, desmopressin—an analogue to ADH which can be taken orally or nasally—has been shown to be effective in treating DI post ABI (Alaca et al., 2002; Born et al., 1985; Hannon et al., 2013).

DI has been reported as significantly associated with higher mortality in individuals with TBI (Hannon et al., 2013), as well as a leading cause of death in those who sustain a severe TBI (Maggiore et al., 2009). Multiple risk factors for DI post ABI have been identified (Hadjizacharia et al., 2008): multivariable analysis showed that patients with severe injury, brain edema, Abbreviated Injury Scale score for the head greater than or equal to 3, and/or intraventricular hemorrhage were at a greater risk of developing DI following ABI. Others reported that extensive fractures at the base of the skull may also be an

important risk factor for DI, as these more often produce injury to the posterior pituitary gland (Born et al., 1985). Presence of DI may also predict deficiencies in other pituitary axes, such as hypogonadism (Schneider et al., 2008).

Anterior Pituitary Dysfunction and Available Interventions

Anterior pituitary dysfunction may lead to a compromise in production of GH, TRH, PRL, glucocorticoid, and sex hormones (Sandel ME et al., 2007). Clinical presentation of anterior pituitary dysfunction varies widely, depending on the particular neuroendocrine axes affected, as well as the severity and rapidity of damage to that axis. The clinical presentation can range from subclinical disease to life-threatening cardiovascular collapse (Sandel ME et al., 2007).

Several studies have examined the prevalence of anterior pituitary deficiencies following ABI. In the past, anterior pituitary dysfunction was likely unreported post ABI (Yuan XQ, 1991); however, anterior pituitary dysfunction is now increasingly recognized (Sandel ME et al., 2007). The rate varies widely across studies, ranging from 15.4% to 76.4% (Bondanelli et al., 2007; Hannon et al., 2013; Klose et al., 2007; Kopczak et al., 2014; Moreau et al., 2012; Nemes et al., 2015; Prodam et al., 2013; Rosario et al., 2013; Ulfarsson et al., 2013). The onset of anterior pituitary deficiencies may occur within 24 hours of injury (Olivecrona et al., 2013; Tanriverdi et al., 2007) and may persist up to 12 months post injury or lifelong (Agha, Phillips, et al., 2005; Agha et al., 2004; Bondanelli et al., 2007; Bondanelli et al., 2004; Ghigo et al., 2005; Kelly et al., 2000; Lieberman et al., 2001; Moreau et al., 2012; Nemes et al., 2015; Schneider et al., 2006).

Risk factors for anterior pituitary deficiencies post ABI vary across studies. As reviewed above (see History and Epidemiology) most studies conclude that greater injury severity is a significant risk factor for post-injury hypopituitarism (Bondanelli et al., 2004; Klose et al., 2007; Nemes et al., 2015; Prasanna et al., 2015; Tan et al., 2017; Tritos et al., 2015). However, not all studies demonstrate this relationship: Tanriverdi et al. (2007) and Agha et al. (2004) did not find differences in pituitary dysfunction by injury severity. Lieberman et al. (2001) reported that injury severity was not related to the number of affected pituitary axes affected in individuals presenting with hypopituitarism. Other risk factors for hypopituitarism are less well-established.

Pituitary abnormalities may to occur in one or more axes (Agha et al., 2004; Kelly et al., 2000; Klose et al., 2007; Kopczak et al., 2014; Lieberman et al., 2001; Schneider et al., 2006). As there is no way to predict which axes, if any, will be affected following an ABI, clinical and laboratory evaluations are paramount to making the diagnosis. In a systematic review (n=66), Lauzier et al. (2014) reported the prevalence, predictors, and clinical outcomes of anterior pituitary disorders following TBI. In the long term, 31.6% (n=27) of individuals were found to have at least one involved neuroendocrine axis.

Predictors of these disorders were older age (RR=3.19; n=19), greater injury severity (RR=2.15; n=7), and the presence of skull fracture (RR=1.73; n=6). In this review, anterior pituitary disorders were associated with increased ICU mortality (RR=1.79; n=4), but not predictive of better/worse Glasgow Outcome Scale scores (n=3). In general, there is conflicting evidence as to whether outcomes for persons with post ABI anterior pituitary dysfunction may be worse than their unaffected counterparts.

Rosario et al. (2013) reported that daily Functional Independence Measure gain was significantly lower in patients with hypopituitarism compared to those with normal function. However, the authors did not find any differences between those with and without endocrine function when comparing hospital length of stay. Individuals with hypopituitarism have also been shown to have poorer Disability Rating Scores at discharge compared to those with normal function (Bondanelli et al., 2007). Prasanna et al. (2015) found that lower Glasgow Outcome Scale Extended scores were associated with pituitary dysfunction, although Ulfarsson et al. (2013) did not find such results. Other studies have reported alterations in hormone patterns in persons with worse outcomes post ABI. For instance, Marina et al. (2015) reported that Glasgow Outcome Scale Extended and Functional Independence Measure scores at both 3 months and 1 year were associated with elevated stress hormones as well as suppressed thyroidal and gonadal hormones. Similarly, Prodam et al. (2013) found that individuals with hypopituitarism had higher prevalence of dyslipidemia and altered glucose metabolism. In all of these studies, causation cannot be established; worse outcomes in some of these studies may reflect the greater severity of initial injury, premorbid or other factors.

Growth Hormone Deficiency

The signs and symptoms of GH deficiency include fatigue, decreased muscle mass, osteoporosis, exercise intolerance, dyslipidemia, and truncal obesity, as well as several cognitive deficits and a poorer quality of life (Sandel ME et al., 2007; Schneider, Aimaretti, et al., 2007). Many of these symptoms overlap with the neuropsychiatric sequelae of ABI and may therefore be difficult to diagnose. Consequently, although GHD is not uncommon following ABI, may not be as readily diagnosed as other hormone deficiencies (Lieberman et al., 2001). This observed difference in diagnosis of GH deficiency may also reflect the controversies regarding GH replacement in skeletally mature adults (Behan et al., 2008; Molitch et al., 2011; Sesmilo et al., 2007; Tan et al., 2017; Tritos et al., 2015). Laboratory findings of GH deficiency include low IGF-1 levels (Agha et al., 2004; Agha, Sherlock, et al., 2005; Bondanelli et al., 2007; Lieberman et al., 2001; Olivecrona et al., 2013; Schneider et al., 2006; Tanriverdi et al., 2013), although provocative testing may be required for diagnosis.

Clinical Presentation of Growth Hormone Deficiency

- Headaches, sleep disturbances, energy loss, fatigue, insomnia
- Attention/concentration disorders, decrease cognitive performance
- Irritability, depression
- Low self-esteem, poor quality of life
- Muscle wasting, decrease lean body mass, weight gain (visceral obesity
- Decrease VO_2 max, decrease exercise tolerance, fatigability
- Atherosclerosis, osteoporosis, dyslipidemia

The prevalence of post-injury GHD varies considerably across studies, ranging from 2.8% to 63.6% (Agha, Phillips, et al., 2005; Agha et al., 2004; Bondanelli et al., 2007; Bondanelli et al., 2004; Ghigo et al., 2005; Kelly et al., 2000; Kleindienst et al., 2009; Klose et al., 2007; Kopczak et al., 2014; Lieberman et al., 2001; Moreau et al., 2012; Schneider et al., 2006; Tanriverdi et al., 2007). GH deficiency may be transient or may persist up to and beyond 12 months(Agha, Phillips, et al., 2005; Agha et al., 2004; Bondanelli et al., 2004; Ghigo et al., 2005; Kelly et al., 2000; Kleindienst et al., 2009; Lieberman et al., 2001; Schneider et al., 2006; Tanriverdi et al., 2013). As with other anterior pituitary hormones, multiple studies have evaluated putative risk factors for the development of GH deficiency with conflicting results. Some studies report that higher body mass index (Agha et al., 2004; Lieberman et al., 2001; Schneider et al., 2006; Tanriverdi et al., 2013), and more severe injury (Kleindienst et al., 2009; Tanriverdi et al., 2013) are associated with a higher incidence of post-injury GH deficiency. Conversely, other studies have not found GH deficiency to be associated with body mass index (Agha, Phillips, et al., 2005; Aimaretti et al., 2005; Bondanelli et al., 2004) or injury severity (Agha, Phillips, et al., 2005; Bondanelli et al., 2004).

In patients with a confirmed GH deficiency, GH replacement therapy can be considered (Auernhammer & Vlotides, 2007; Behan et al., 2008; Molitch et al., 2011; Sesmilo et al., 2007; Tritos et al., 2015). Guidance from experts recommends treating all other neuroendocrine disorders, if present, before considering GH treatment (Sesmilo et al., 2007; Tritos et al., 2015). The goal of therapy is to elevate serum IGF-I levels to within the normal range for age and gender without developing adverse consequences of GH excess.

TABLE 13 | Interventions for Growth Hormone Deficiency Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Dubiel et al. (2018) United States RCT PEDro=7 N=40	**Population:** Mean age=31.1yr; Gender: Male=34, Female=6; Mean Time Post-injury=64.1d. GCS: mild=4, Moderate=3, Severe=32, unknown=1. **Intervention:** Individuals were randomized to receive either recombinant human growth hormone or placebo. Follow-up was at 1-mo, 3-mo, 6-mo and 12-mo. 1-mo and 3-mo follow-up was only taken for IGF-1 concentrations.	1. At 3-mo and 6-mo follow-up the rhGH group had significantly higher IGF-1 concentrations (p=0.035, p=0.005), these were not observed at 1-mo or 12-mo follow-up. 2. At 6-mo follow-up the rhGH group had a significantly higher positive change in FIM motor scores (p=0.02), FIM cognitive scores (p=0.02), and total change in FIM scores

Author, Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measure: Disability rating scale scores (DRS), Functional Independence Measure (FIM) motor, FIM Cognitive, FIM total, IGF-1, Peak L-Arginine, California Verbal Learning Test (CVLT), Trail making test-A, Trail Making test-B.	(p=0.02). There were no other significant differences at 6-mo. At 12-mo follow-up the rhGH group had maintained significantly higher positive scores in FIM motor scores (p=0.02), and total FIM change (p=0.01). There were no other significant differences at 12-mo follow-up.
Hatton et al. (1997) USA RCT PEDro=5 N=33	**Population:** TBI; *Intervention Group (n=17)*: Mean Age=27.6yr; Gender: Male=14, Female=3; Mean GCS=7; Mean Time Post Injury=56.5hr; *Control Group (n=16)*: Mean Age=27.8yr; Gender: Males=14, Females=2; Mean GCS=6.1; Mean Time Post Injury=57.1 hr. **Intervention:** Patients were randomly allocated to receive either continuous IV IGF-1 (0.01mg/kg/hr, treatment) or no IV treatment (control). IGF-I treatment began within 72hr of injury and continued for up to 14d. Both groups received nutritional support and neurosurgical intensive care. Patient assessments were made on 15d, 30d, discharge, and 3 and 6mo follow-up. **Outcome Measure:** Glasgow Outcome Scale, Weight Loss, Glucose Concentrations, Nitrogen Balance.	1. IGF-1 treatment resulted in lower daily glucose concentration and nitrogen output (p=0.03) when compared to placebo. 2. Patients receiving IGF-1 treatment showed weight gain while those receiving placebo showed significant weight loss (p=0.02). 3. In patients with GCS=5-7, those receiving IGF-1 showed better outcome on GOS than those receiving placebo (p=0.06).
Mossberg et al. (2017) United States Pre-Post N=15	**Population:** TBI=15: Mean Age=45.5yr; Gender: Males=10, Females=5; Mean Time Post-Injury=11.2yr. **Intervention:** Daily injections of recombinant human growth hormone (rhGH) for 12 mo. **Outcome Measure:** Cardiorespiratory symptoms, Muscle force testing, Body composition, Cognitive function (BDI, Fatigue Severity Scale (FSS)).	1. There were no significant differences between pre and post measures of cardiorespiration (oxygen uptake, heart rate, minute ventilation, respiratory exchange ratio, oxygen pulse). 2. Although skeletal muscle fatigue did not decrease over the course of treatment, there was a strong trend for a decrease in perceived fatigue (p=0.06). 3. There was a strong trend for an increase in lean mass (p=0.06) post-treatment. 4. There was a significant improvement in both BDI (p=0.019) and FSS (p=0.039) scores post-treatment.
Gardner et al. (2015) Sweden Case Control N=1429	**Population:** *TBI (n=161):* Mean Age=42.6yr; Gender: Male=93, Female=68. *Tumour (n=1268):* Mean Age=53.2yr; Gender: Male=786, Female=482. **Intervention:** Participants diagnosed with GHD and treated with GH therapy were included in retrospective analysis. **Outcome Measures:** Quality of Life Assessment of GHD in Adults (QOL-AGHDA).	1. At baseline, mean QOL-AGHDA scores were significantly worse in the TBI group than in the Tumour group (p<0.0001) 2. After 1yr of treatment, mean improvement in QOL-AGHDA was greater in the TBI group than in the Tumour group (p=0.04), but the score remained worse in the TBI group. 3. Over 8yr of treatment, mean improvement in QOL-AGHDA was maintained in both groups, but the score remained worse in the TBI group.
Devesa et al. (2013) Spain	**Population:** TBI; Mean Age=28.4yr; Gender: Male=8, Female=4; Mean Time Post	1. GHD was diagnosed in 42% of participants.

Author, Year Country Study Design Sample Size	Methods	Outcome
Pre-Post N=12	Injury=5.3yr. **Intervention:** Participants received GH therapy (1mg/d, 5d/wk, 8mo) and clinical rehabilitation (3-4hr/d, 5d/wk, 6-12mo). Diagnosis of GHD was made by the following criteria: plasma GH <7ng/mL. **Outcome Measures:** Plasma IGF-1.	2. Before treatment, mean plasma IGF-1 levels were significantly lower in the GHD group than in the non-GHD group ($p<0.05$). 3. After treatment, mean plasma IGF-1 levels significantly increased in both the GHD group ($p<0.01$) and non-GHD group ($p<0.05$), such that the two groups were no longer significantly different ($p>0.05$). Percentage increase in IFG-1 levels was significantly higher in the GHD group than in the non-GHD group ($p<0.01$).
Moreau et al. (2013) France PCT N=50	**Population:** TBI; *Intervention Group (TG, n=23):* Mean Age=37.9yr; Gender: Male=19, Female=4; Mean Time Post Injury=7.8yr; Mean GCS=8.1. *Control Group (CG, n=27):* Mean Age=37.1yr; Gender: Male=24, Female=3; Mean Time Post Injury=5.5yr; Mean GCS=9.4. **Intervention:** Participants were allocated to receive GH therapy (TG, 0.2-0.6mg/d) or no treatment (CG) for 1yr. GHD was diagnosed with an insulin tolerance test or GHRH assay. Outcomes were assessed before and after treatment. **Outcome Measures:** Quality of Life Brain Injury (QOLBI); Activities of Daily Living (ADL); Cognitive Function.	1. The TG showed significantly greater improvement in QOLBI functional ($p=0.023$) and personal ($p=0.019$) subscores. No significant differences between groups were found for ADL or tests of cognitive function.

Discussion

Recent research has found that GH replacement therapy effectively elevates serum IGF-I levels in individuals with GH deficiency post ABI (Devesa et al., 2013; Dubiel et al., 2018) and improves their quality of life (Gardner et al., 2015; Moreau et al., 2013). In a randomized controlled trial (RCT) of individuals with TBI, patients received IGF-I (5mg) via continuous intravenous infusion within 72 hours after injury and continued for 14 days, or placebo (Hatton et al., 1997). The authors found that patients receiving IGF-I treatment showed better outcomes in terms of glucose concentration, nitrogen balance, body weight, and recovery (Hatton et al., 1997). These findings were not replicated in a more recent study, in which Mossberg et al. (Mossberg et al., 2017) found that although recombinant human GH did not improve respiratory capacity or symptoms, fatigue and depression scores significantly improved with treatment. Similarly, another RCT (Dubiel et al., 2018) found that more than just IGF-1 concentrations improved with recombinant GH treatment. Cognitive and Motor Functional Independence Measure scores were seen to significantly increase in those receiving GH treatment at 6-month follow-up (Dubiel et al., 2018). These findings indicate that, in selected patients, replacement of GH or IGF-1 may improve symptoms and some outcome measures in persons with post ABI GH deficiency; however, treatment intervention may need to be tailored over time to an individual's specific needs.

Conclusions

There is level 1b evidence (from one RCT; Dubiel et al., 2018) that growth hormone replacement therapy may improve clinical outcomes compared to placebo in patients with GHD post ABI.

There is level 1b evidence (from one RCT; Dubiel et al., 2018) and level 4 evidence (from one pre-post test; Devesa et al., 2013) that growth hormone replacement therapy effectively elevates serum IGF-I levels in individuals with growth hormone deficiency post ABI.

There is level 2 evidence (from one randomized controlled trial; Hatton et al., 1997) that pharmacological concentrations of IGF-1 may improve recovery, as well as glucose and nitrogen utilization post moderate to severe TBI.

There is level 2 evidence (from one prospective controlled trial; Moreau et al., 2013) and level 3 evidence (from one case control; Gardner et al., 2015) that growth hormone replacement therapy improves quality of life post ABI.

There is level 4 evidence (from one pre-post test; Mossberg et al., 2017) that growth hormone replacement therapy may be effective in treating GHD, fatigue, and depression post ABI.

KEY POINT

- Growth hormone deficiency may be effectively treated with growth hormone replacement therapy and insulin growth like factor-1 replacement therapy.

Gonadotropic Deficiency

Hypogonadism is often one of the earliest symptoms of hypopituitarism in those who survive a TBI (Lee et al., 1994). In both men and women, hypogonadism has been associated with sexual dysfunction, reduced vigour, mood disorders, insomnia, loss of facial, pubic and body hair, osteoporosis, and infertility (Hohl et al., 2009; Schneider, Aimaretti, et al., 2007). In men, additional symptoms include erectile dysfunction; in women, additional symptoms include secondary amenorrhea. Testing for hypogonadism requires assessing concentrations of LH and FSH in both men and women, and assessing serum testosterone concentrations in men and serum estradiol (estrogen) concentrations in women. Low levels of testosterone in men or low levels of estradiol in women in the absence of elevated FSH and LH levels may indicate hypogonadism. Interpreting these findings requires assessing the patient's age, menopausal status, oral contraceptive use, and other medications, as these can influence test results and expected normal values (Tritos et al., 2015).

Clinical Presentation of Gonadotropic Deficiency

- Testosterone and estrogen/progesterone deficiency
- Hypogonadism: oligomenorrhea, amenorrhea, infertility, sexual dysfunction, decreased libido
- Muscle atrophy, osteoporosis, hair loss (axillary and/or pubic), reduced need to shave facial hair
- Reduced tolerance to exercise
- Decreased memory and cognitive performance

Hypogonadism is common among individuals with ABI: in the acute phase, prevalence rates range from 13% to 80% (Agha, Phillips, et al., 2005; Aimaretti et al., 2005; Barton et al., 2016; Hohl et al., 2014; Kleindienst et al., 2009; Kopczak et al., 2014; Lee et al., 1994; Olivecrona et al., 2013; Rosario et al., 2013; Schneider et al., 2006; Tanriverdi et al., 2007). Persistent deficiencies up to and beyond 12 months have also been reported (Agha et al., 2004; Agha & Thompson, 2005; Aimaretti et al., 2005; Bondanelli et al., 2007; Bondanelli et al., 2004; Kelly et al., 2000; Kleindienst et al., 2009; Klose et al., 2007; Lieberman et al., 2001; Moreau et al., 2012; Schneider et al., 2006). Due to uncertainty around the clinical significance of hypogonadism in the acute period post-ABI, most authors suggest testing at the same time as for other neuroendocrine dysfunction, approximately 3 to 6 months post-injury or if signs/symptoms develop. Several authors, including Hohl et al. (2009) and. Agha and Thompson (2005) also suggest testing at 12 months post-injury.

Common predictors of post-injury hypogonadism include older age (Agha et al., 2004), transient DI, polytrauma, hypoxia, and greater injury severity (Cernak et al., 1999; Kleindienst et al., 2009), specifically lower initial GCS (Agha & Thompson, 2005; Cernak et al., 1999; Kleindienst et al., 2009; Schneider et al., 2006), although other studies have not reported this relationship (Bondanelli et al., 2007; Tanriverdi et al., 2007). Compared to individuals with normal hormone functioning, hypogonadism was also found to be associated with poorer scores for the Functional Independence Measure, Disability Rating Scale, cognitive function (Barton et al., 2016; Bondanelli et al., 2007), and Glasgow Outcome Scale scores (Agha & Thompson, 2005; Barton et al., 2016). In two studies, hypogonadism also correlated with lower Functional Independence Measure gains per day (Rosario et al., 2013) and less clinical improvement on the modified Rankin Scale (Schneider et al., 2006). Only one study has evaluated the mortality relationship with hypogonadism: this study reported that the rate of hypogonadism did not differ between individuals who survived and did not survive (Tanriverdi et al., 2007).

Management of Hypogonadism in Men

Treatments for hypogonadism in men include oral testosterone replacement therapy, subcutaneous testosterone implantation (3-6 pellets of 200mg unmodified testosterone every 4-6 months), intramuscular injections (testosterone esters), transdermal patches and gels, and buccal delivery (Nieschlag et al., 2004). Although several treatments are available and there are several evidence-based guidelines on when and how to treat hypogonadism, there is very little literature specific to the use of these treatments in the post ABI population.

TABLE 14 | Interventions for Hypogonadism in Men Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Ripley et al., (2020) USA RCT PEDro=6 $N_{Initial}$=70, N_{Final}=35	**Population:** TBI=35; *Intervention Group (Low testosterone intervention, LTI; n=11):* mean age=35.3±16.1yr; gender: male=11, female=0; time post injury=<6mo; severity: median GCS=3.5, range=3-15. *Control Group 1 (Low testosterone placebo, LTP; n=6):* mean age=35.2±11.0yr; gender: male=6, female=0; time post injury=<6mo; severity: median GCS=3, range=3-8. *Control Group 2 (Normal testosterone, NT; n=18):* mean age=34.4±12.2yr; gender: male=18, female=0; time post injury=<6mo; severity: median GCS=3, range=3-8. **Intervention:** Participants were assigned to the normal testosterone group or the low testosterone group (if testosterone was <260ng/dL). Participants in the low testosterone group were randomly allocated to receive 1% testosterone (50mg/d) or placebo transdermal gel. Outcome measures were assessed at baseline, 2, 4, 6 and 8wk. **Outcome Measures:** Serum hormonal measurements, Functional Independence Measure (FIM), grip strength, adverse events, Agitation Index, Aggression Index.	1. Testosterone therapy significantly improved testosterone levels by 3wk (p<.05). Levels returned to normal by 6wk. 2. No significant differences in functional independence (FIM, p>.05), grip strength (p>.05), or adverse events (p>.05) were observed between groups. However, participants receiving testosterone therapy demonstrated the greatest absolute improvement in function and strength compared to the placebo or normal testosterone groups. 3. Testosterone therapy was not associated with increased agitation or aggression.

Discussion

In one RCT, men with hypogonadism (low testosterone) who received transdermal testosterone therapy had significantly improved serum levels of testosterone, but did not experience improved functional outcomes in the short-term (<3mo), as indicated by Functional Independence Measure scores, compared to men with low testosterone who did not receive testosterone supplementation(Ripley et al., 2020). Importantly, the therapy was well tolerated with no significant differences in adverse events or increases in agitation or aggression. Although these results are promising, further research is necessary to determine the efficacy of testosterone therapy in persons with post ABI hypogonadism.

Conclusions

There is level 1b evidence (from one randomized controlled trial; Ripley et al., 2020) that testosterone therapy is safe and well-tolerated in hypogonadal men with severe TBI, although it may not improve functional outcomes.

KEY POINT

- Testosterone replacement may improve testosterone levels but not functional outcomes in men with hypogonadism post-TBI.

Other Treatments for Hypogonadism

In addition to reduced testosterone or estrogen levels, hypogonadism in men and women also results in low levels of progesterone. In animal models of TBI, progesterone has neuroprotective effects and is associated with improved outcomes. Unlike other studies, in which patients demonstrated hypogonadism, studies evaluating the benefit of progesterone supplementation do not require patients to have demonstrated hypogonadism. These studies are summarized in Table 15.

TABLE 15 | Progesterone Interventions Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Soltani et al. (2017) Iran RCT PEDro=7 N=48	**Population:** 48 men with TBI and diffuse axonal injury (DAI). *Experimental Group (n=20)*: Mean age=27.85yr; Mean GCS=7.7. *Control Group (n=24)*: Mean Age=30.37yr; Mean GCS=7.7. **Intervention:** 1 mg/kg of Progesterone was given intramuscularly every 12 hours for 5 days to the experimental group, while the control group received no treatment. Participants received treatment within 12 hours of initial trauma. **Outcome Measure:** Glasgow Outcome Scale-Extended (GOS-E), Functional Independence Measure (FIM), serum progesterone levels, mortality.	1. There were no significant differences between groups at 3 mo post-trauma based on treatment. However, at 6 mo post-trauma the progesterone group had significantly higher GOS-E scores (p=0.03), with only 1 death in the progesterone group compared to 7 in the control group. 2. FIM scores showed a similar trend with no significant difference between groups at 3 mo but 6 mo post-trauma the progesterone group had significantly higher FIM scores ($p<0.05$). 3. At baseline there was no significant difference between groups in terms of serum progesterone levels, however after the initiation of treatment the progesterone group maintained significantly higher progesterone levels until the end of the trial ($p<0.05$). The control group experienced significantly higher mortality compared to the progesterone group ($p<0.05$).
Wright et al., (2014) USA RCT PEDro= $N_{Initial}$=882, N_{Final}=882	**Population:** 882 patients with moderate to severe TBI (73.7% men). *Experimental group (n=442);* median age=36yr; injury severity= 29.2% moderate, 52.9% moderate-to-severe, 17.9% severe. *Control group (n=440)*; median age=34yr; injury severity= 28.4% moderate, 54.1% moderate-to-severe, 17.5% severe. **Intervention**: 0.05 mg/kg/mL of intravenous progesterone was infused continuously over 96 hours (1 hour loading dose, 14.53mL/hr; 71-hour maintenance dose, 10mL/hr; 8-hour taper, reducing dose by 2.5mL per hour); control subjects received a matched appearance placebo. Participants received treatment within 4 hours of admission. **Outcome Measures:** Glasgow Outcome Scale-Extended (GOS-E) at 6mos; secondary outcomes were mortality, Disability Rating Scale score, and safety data.	1. Trial was stopped early due to lack of benefit (882 of planned 1140 participants) 2. Early administration of progesterone did not improve functional outcomes (Glasgow Outcome Scale) at 6mos. 3. There was no significant difference in mortality between the progesterone and placebo groups. 4. There was no significant difference in Disability Rating Scale scores at 6mos. 5. Progesterone was not associated with greater frequency of safety or adverse events.

Discussion

In one single-centre RCT, progesterone treatment did not appear to improve functionality short-term (<3 mo); however, at 6mo follow-up, patients had significantly higher Glasgow Outcome Scale Extended (GOS-E) and Functional Independence Measure scores (Soltani et al., 2017). Furthermore, the control group experienced significantly higher mortality than the progesterone group. In contrast to these results, a multicentre randomized controlled trial by Wright et al. (2014) did not demonstrate benefit for functional outcomes (as measured by the GOS-E) or for mortality or disability rating scale scores for progesterone treatment for persons with moderate to severe TBI. This is in keeping with a systematic review of 5 studies which concluded that there are no sure benefits to progesterone administration compared to placebo (Ma et al., 2016). Authors consistently found no difference between disability or mortality between groups.

Conclusions

There is conflicting level 1a evidence (from one multicentre randomized controlled trial (Wright et al., 2014) and one single centre randomized controlled trial; Soltani et al., 2017) that progesterone treatment does not improve long-term outcome and functionality.

KEY POINT

- Acute progesterone supplementation may not be effective in improving long-term outcomes in persons with TBI.

Management of Hypogonadism in Women

The management of hypogonadism due to ABI in women has not been thoroughly evaluated. In general, premenopausal women who have central hypogonadism can receive estrogen and progesterone supplementation if they have an intact uterus, or estrogen supplementation alone if they have had a hysterectomy, provided there are no other contraindications (Tritos et al., 2015). In perimenopausal and menopausal women, hormone replacement therapy may be appropriate for symptom management on an individualized basis. However, long-term treatment is not recommended due to the negative benefit-risk ratio (Auernhammer & Vlotides, 2007). Other treatments for women may include the administration of daily dehydroepiandrosterone or testosterone. Although some success has been found using these treatments, none have been studied within the ABI population.

Hyperprolactinemia and Hypoprolactinemia

The rate of post-ABI hyperprolactinemia varies widely across studies, ranging from 5% to 50%(Agha, Phillips, et al., 2005; Aimaretti et al., 2005; Bondanelli et al., 2004; Kleindienst et al., 2009; Klose et al., 2007; Kopczak et al., 2014; Lieberman et al., 2001; Moreau et al., 2012; Olivecrona et al., 2013; Schneider et al., 2006; Tanriverdi et al., 2007). It is important to note, however, that the rate of post-injury

hyperprolactinemia may be lower if patients receiving hyperprolactinemia-inducing drugs are excluded from the analysis (Kopczak et al., 2014; Lieberman et al., 2001; Schneider et al., 2006). Hyperprolactinemia has been shown to be present in more than half of patients with ABI in the early acute phase and it is believed that approximately 30% of patients show symptoms (Bondanelli et al., 2005). Kilimann et al. (2007) found men had higher levels of PRL than women and more men were found to have hyperprolactinemia than women. Although hyperprolactinemia can result from disruption of the pituitary stalk whereby inhibitory signals from the hypothalamus fail to reach the PRL-secreting cells in the anterior lobe of the pituitary gland, it should be noted studies in which hyperprolactinemia was found report that all patients with hyperprolactinemia also had an infection, were hypoglycemic, or were on medications known to increase PRL levels (such as dopamine antagonists, GABA agonists, opiates or central catecholamine depletors). Post-injury hyperprolactinemia may persist up to 12 months post injury (Agha, Phillips, et al., 2005; Ghigo et al., 2005; Kleindienst et al., 2009; Schneider et al., 2006). However, it is difficult to predict whether individuals sustaining ABI will develop hyperprolactinemia. Agha et al. (2005; 2004) reported that post-injury hyperprolactinemia was not associated with factors such as age, sex, or GCS score (Agha, Phillips, et al., 2005; Agha et al., 2004); although a later study reported that GCS scores were negatively correlated to post-injury PRL levels (Tanriverdi et al., 2007). Given the apparent lack of association with negative outcomes, hyperprolactinemia may not be a significant deterrent to patient recovery (Olivecrona et al., 2013).

Data regarding hypoprolactinemia is very sparse. Based on a limited number of studies, the rate of post-ABI hypoprolactinemia ranged from <1% to 8% (Bondanelli et al., 2004). Similar to hyperprolactinemia, hypoprolactinemia may not be a significant factor in patient recovery.

Adrenocorticotropic Hormone (ACTH) Deficiency

Clinical Presentation of Adrenocorticotropic Hormone Deficiency

- Fatigue, weakness, anorexia, nausea, vomiting
- Hair loss
- Low blood pressure
- Hypoglycemia
- Absence of hyperpigmentation
- Poor quality of life
- If acute, may be life-threatening

ACTH secretion has a natural diurnal variation and increases with stress, physical activity, and chronic disease. ACTH-regulated cortisol release is imperative for stress responses and impaired ACTH release and resulting hypoadrenalism can be life-threatening. ACTH deficiency in the acute phase post-injury is associated with higher mortality (Hannon et al., 2013). Findings from multiple studies suggest that ACTH (or cortisol) deficiency within 1 week of injury can vary considerably in rate, ranging from 8.8% to 78% (Hannon et al., 2013; Olivecrona et al., 2013). Several studies concluded that greater injury severity is an important predictor of ACTH deficiency (Agha, Phillips, et al., 2005; Kleindienst et al., 2009; Tanriverdi et al., 2013; Tanriverdi et al., 2007). Other

reported risk factors for ACTH deficiency and hypoadrenalism include older age, basal skull fractures, and lack of cranial vault fracture (Schneider et al., 2008).

Individuals living with ABI may continue to demonstrate post-injury ACTH deficiency for up to 12 months (Ghigo et al., 2005) and beyond (Kleindienst et al., 2009; Tanriverdi et al., 2013). This may be problematic for recovery, as post-injury ACTH deficiency has been shown to be associated with poorer cognitive and physical outcomes (Moreau et al., 2012), as well as with other anterior pituitary disturbances such as hyperprolactinemia, low testosterone, and low tT_3 and fT_4 (Kleindienst et al., 2009), and higher mortality (Hannon et al., 2013).

Although there are many established and effective treatments for ACTH deficiency and hypoadrenalism, none have specifically been studied in the post ABI population. In the absence of ABI-specific evidence, prompt administration of glucocorticoid supplementation is recommended by expert consensus (Tritos et al., 2015).

Thyroid-Stimulating Hormone (TSH) Deficiency

TSH deficiency appears to be less common than other hormonal deficiencies post ABI (Schneider, Aimaretti, et al., 2007). Multiple studies found that post-ABI TSH deficiency is uncommon, with very few individuals displaying symptoms at or greater than 6 months post injury (Agha, Phillips, et al., 2005; Agha et al., 2004; Bondanelli et al., 2007; Kelly et al., 2000; Klose et al., 2007). Risk factors for TSH deficiency vary across studies. Kleindienst et al. (2009) found that more severe injuries were associated with greater incidence of low TSH and fT_4 levels; this association was also reported by Cernak et al. (1999), who found that TSH deficiency was more common in individuals with severe TBI than those with mild TBI in the first 7 days post-injury. In contrast, Tanriverdi et al. (2007) reported that no significant differences in mean TSH levels were found among individuals with mild, moderate, and severe injuries. The discrepancy across studies indicates that there is still considerable uncertainty regarding the epidemiology of TSH deficiency post ABI (Moreau et al., 2012).

Reduced thyroid function may lead to a decrease in an individual's basal metabolic rate and cognitive function, and an increase in fatigue (Elovic, 2003). In children, TSH deficiencies may lead to growth retardation (Alexopoulou et al., 2004). The signs and symptoms of TSH deficiency may not present until much later in the recovery period (Schneider, Aimaretti, et al., 2007). Signs and symptoms of TSH deficiency overlap with other hormone deficiencies and with the neuropsychiatric sequelae of ABI; diagnosis with laboratory testing is important. Untreated hypothyroidism, if present, is undesirable from a recovery standpoint, studies have shown a trend toward poorer cognitive outcomes in these individuals (Moreau et al., 2012; Zetterling et al., 2013). The treatment of TSH deficiency is replacement of thyroid hormones with levothyroxine (Yamada & Mori, 2008).

Conclusion

The prevalence of neuroendocrine dysfunction varies considerably among studies. The reasons for this are multifactorial, and may reflect the variability in timing of assessments, lack of established diagnostic criteria, or other provider- or patient-specific factors. Neuroendocrine disorders often result in a variety of symptoms including hypotension, hypertension, cognitive dysfunction, temperature lability, appetite disturbances, decreased muscle mass, sleep disturbances, hair loss, decreased libido, and disorders of fluid regulation (Sirois, 2009). In the acute phase, healthcare providers for persons with ABI should be vigilant for the identification and treatment of DI and ACTH deficiency. Testing should be conducted while the patient is in acute care for ACTH and ADH deficiencies; in the subacute to chronic period, such as at 3 to 6 months post-injury, providers should consider testing for all of the anterior and posterior pituitary hormones. Failure to identify neuroendocrine dysfunction could impact an individual's recovery process and their overall quality of life. Overall, the current state of research-based evidence for post ABI neuroendocrine dysfunction is lacking. There needs to be a specific focus in research to determine the potential interventions available to and beneficial for ABI populations.

References

Agha, A., Phillips, J., O'Kelly, P., Tormey, W., & Thompson, C. J. (2005). The natural history of post-traumatic hypopituitarism: Implications for assessment and treatment. *American Journal of Medicine, 118*(12), 1416.e1411-1416.e1417.

Agha, A., Rogers, B., Sherlock, M., O'Kelly, P., Tormey, W., Phillips, J., & Thompson, C. J. (2004). Anterior pituitary dysfunction in survivors of traumatic brain injury. *Journal of Clinical Endocrinology and Metabolism, 89*(10), 4929-4936.

Agha, A., Sherlock, M., & Thompson, C. J. (2005). Post-traumatic hyponatraemia due to acute hypopituitarism [3]. *QJM - Monthly Journal of the Association of Physicians, 98*(6), 463-464.

Agha, A., & Thompson, C. J. (2005). High risk of hypogonadism after traumatic brain injury: Clinical implications. *Pituitary, 8*(3-4), 245-249.

Aimaretti, G., Ambrosio, M. R., Benvenga, S., Borretta, G., De Marinis, L., De Menis, E., Di Somma, C., Faustini-Fustini, M., Grottoli, S., Gasco, V., Gasperi, M., Logoluso, F., Scaroni, C., Giordano, G., & Ghigo, E. (2004, Jun). Hypopituitarism and growth hormone deficiency (GHD) after traumatic brain injury (TBI). *Growth Horm IGF Res, 14 Suppl A*, S114-117.

Aimaretti, G., Ambrosio, M. R., Di Somma, C., Fusco, A., Cannavò, S., Gasperi, M., Scaroni, C., De Marinis, L., Benvenga, S., Degli Uberti, E. C., Lombardi, G., Mantero, F., Martino, E., Giordano, G., & Ghigo, E. (2004). Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: Screening study at 3 months after the brain injury. *Clinical Endocrinology, 61*(3), 320-326.

Aimaretti, G., Ambrosio, M. R., Di Somma, C., Gasperi, M., Cannavò, S., Scaroni, C., Fusco, A., Del Monte, P., De Menis, E., Faustini-Fustini, M., Grimaldi, F., Logoluso, F., Razzore, P., Rovere, S., Benvenga, S., Degli Uberti, E. C., De Marinis, L., Lombardi, G., Mantero, F., Martino, E., Giordano, G., & Ghigo, E. (2005). Residual pituitary function after brain injury-induced hypopituitarism: A prospective 12-month study. *Journal of Clinical Endocrinology and Metabolism, 90*(11), 6085-6092.

Alaca, R., Yilmaz, B., & Gunduz, S. (2002). Anterior hypopituitarism with unusual delayed onset of diabetes insipidus after penetrating head injury. *American Journal of Physical Medicine and Rehabilitation, 81*(10), 788-791.

Alexopoulou, O., Beguin, C., De Nayer, P., & Maiter, D. (2004, Jan). Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. *Eur J Endocrinol, 150*(1), 1-8.

Annoni, F., Fontana, V., Brimioulle, S., Creteur, J., Vincent, J. L., & Taccone, F. S. (2016). Early Effects of Enteral Urea on Intracranial Pressure in Patients With Acute Brain Injury and Hyponatremia [In Press]. *Journal of Neurosurgical Anesthesiology., 19*.

Arai, Y., Fujimori, A., Sasamata, M., & Miyata, K. (2009). New topics in vasopressin receptors and approach to novel drugs: Research and development of conivaptan hydrochloride (YM087), a drug for the treatment of hyponatremia. *Journal of Pharmacological Sciences, 109*(1), 53-59.

Auernhammer, C. J., & Vlotides, G. (2007). Anterior pituitary hormone replacement therapy - A clinical review. *Pituitary, 10*(1), 1-15.

Barton, D. J., Kumar, R. G., McCullough, E. H., Galang, G., Arenth, P. M., Berga, S. L., & Wagner, A. K. (2016). Persistent Hypogonadotropic Hypogonadism in Men After Severe Traumatic Brain Injury: Temporal Hormone Profiles and Outcome Prediction. *Journal of Head Trauma Rehabilitation, 31*(4), 277-287.

Behan, L. A., Phillips, J., Thompson, C. J., & Agha, A. (2008). Neuroendocrine disorders after traumatic brain injury. *Journal of Neurology, Neurosurgery and Psychiatry, 79*(7), 753-759.

Benvenga, S. (2005). Brain injury and hypopituitarism: The historical background. *Pituitary, 8*(3-4), 193-195.

Benvenga, S., Campennί, A., Ruggeri, R. M., & Trimarchi, F. (2000). Hypopituitarism secondary to head trauma. *Journal of Clinical Endocrinology and Metabolism, 85*(4), 1353-1361.

Bernard, F., Outtrim, J., Menon, D. K., & Matta, B. F. (2006). Incidence of adrenal insufficiency after severe traumatic brain injury varies according to definition used: Clinical implications. *British Journal of Anaesthesia, 96*(1), 72-76.

Blumenfeld, H. (2002). Pituitary and Hypothalamus. In B. H. (Ed.), *Neuroanatomy through Clinical Cases* (pp. 737-759). Sinauer Associates, Inc.

Bondanelli, M., Ambrosio, M. R., Cavazzini, L., Bertocchi, A., Zatelli, M. C., Carli, A., Valle, D., Basaglia, N., & Uberti, E. C. D. (2007). Anterior pituitary function may predict functional and cognitive outcome in patients with traumatic brain injury undergoing rehabilitation. *Journal of Neurotrauma, 24*(11), 1687-1697.

Bondanelli, M., Ambrosio, M. R., Zatelli, M. C., De Marinis, L., & degli Uberti, E. C. (2005, May). Hypopituitarism after traumatic brain injury. *Eur J Endocrinol, 152*(5), 679-691.

Bondanelli, M., De Marinis, L., Ambrosio, M. R., Monesi, M., Valle, D., Zatelli, M. C., Fusco, A., Bianchi, A., Farneti, M., & Degli Uberti, E. C. (2004). Occurrence of pituitary dysfunction following traumatic brain injury. *Journal of Neurotrauma, 21*(6), 685-696.

Born, J. D., Hans, P., Smitz, S., Legros, J. J., & Kay, S. (1985). Syndrome of inappropriate secretion of antidiuretic hormone after severe head injury. *Surgical Neurology, 23*(4), 383-387.

Cernak, I., Savic, V. J., Lazarov, A., Joksimovic, M., & Markovic, S. (1999). Neuroendocrine responses following graded traumatic brain injury in male adults. *Brain Injury, 13*(12), 1005-1015.

Chen, L., Xu, M., Zou, Y., & Xu, L. (2014, 01 Jul). Clinical analysis of brain trauma-associated SIADH. *Cell biochemistry and biophysics, 69*(3), 703-706.

Devesa, J., Reimunde, P., Devesa, P., Barberá, M., & Arce, V. (2013, 2016-08-22). Growth hormone (GH) and brain trauma. *Hormones and Behavior, 63*(2), 331-344.

Doczi, T., Tarjanyi, J., Huszka, E., & Kiss, J. (1982, Jun). Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after head injury. *Neurosurgery, 10*(6 Pt 1), 685-688.

Dubiel, R., Callender, L., Dunklin, C., Harper, C., Bennett, M., Kreber, L., Auchus, R., & Diaz-Arrastia, R. (2018, 10 Sep). Phase 2 randomized, placebo-controlled clinical trial of recombinant human growth hormone (rhGH) during rehabilitation from traumatic brain injury. *Frontiers in Endocrinology, 9 (SEP) (no pagination)*(520).

Elovic, E. P. (2003). Anterior Pituitary Dysfunction after Traumatic Brain Injury, Part I. *Journal of Head Trauma Rehabilitation, 18*(6), 541-543.

Estes, S. M., & Urban, R. J. (2005). Hormonal replacement in patients with brain injury-induced hypopituitarism: Who, when and how to treat? *Pituitary, 8*(3-4), 267-270.

Gardner, C. J., Mattsson, A. F., Daousi, C., Korbonits, M., Koltowska-Haggstrom, M., & Cuthbertson, D. J. (2015, 01 Apr). GH deficiency after traumatic brain injury: Improvement in quality of life with GH therapy: Analysis of the KIMS database. *European Journal of Endocrinology, 172*(4), 371-381.

Ghigo, E., Masel, B., Aimaretti, G., Léon-Carrión, J., Casanueva, F. F., Dominguez-Morales, M. R., Elovic, E., Perrone, K., Stalla, G., Thompson, C., & Urban, R. (2005). Consensus guidelines on screening for hypopituitarism following traumatic brain injury. *Brain Injury, 19*(9), 711-724.

Goh, K. P. (2004, May 15). Management of hyponatremia. *Am Fam Physician, 69*(10), 2387-2394.

Hadjizacharia, P., Beale, E. O., Inaba, K., Chan, L. S., & Demetriades, D. (2008). Acute Diabetes Insipidus in Severe Head Injury: A Prospective Study. *Journal of the American College of Surgeons, 207*(4), 477-484.

Hannon, M. J., Crowley, R. K., Behan, L. A., O'Sullivan, E. P., O'Brien, M. M., Sherlock, M., Rawluk, D., O'Dwyer, R., Tormey, W., & Thompson, C. J. (2013, Aug). Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality. *J Clin Endocrinol Metab, 98*(8), 3229-3237.

Hatton, J., Rapp, R. P., Kudsk, K. A., Brown, R. O., Luer, M. S., Bukar, J. G., Chen, S. A., McClain, C. J., Gesundheit, N., Dempsey, R. J., & Young, B. (1997). Intravenous insulin-like growth factor-I (IGF-I) in moderate-to-severe head injury: A phase II safety and efficacy trial. *Journal of Neurosurgery, 86*(5), 779-786.

Haugen, B. R. (2009). Drugs that suppress TSH or cause central hypothyroidism. *Best Practice and Research: Clinical Endocrinology and Metabolism, 23*(6), 793-800.

Hohl, A., Mazzuco, T. L., Coral, M. H., Schwarzbold, M., & Walz, R. (2009, Nov). Hypogonadism after traumatic brain injury. *Arq Bras Endocrinol Metabol, 53*(8), 908-914.

Hohl, A., Ronsoni, M. F., Debona, R., Ben, J., Schwarzbold, M. L., Diaz, A. P., Thais, M. E., Linhares, M. N., Latini, A., Prediger, R. D., Pizzol, F. D., & Walz, R. (2014). Role of hormonal levels on hospital mortality for male patients with severe traumatic brain injury. *Brain Inj, 28*(10), 1262-1269.

Hohl, A., Zanela, F. A., Ghisi, G., Ronsoni, M. F., Diaz, A. P., Schwarzbold, M. L., Dafre, A. L., Reddi, B., Lin, K., Pizzol, F. D., & Walz, R. (2018, 13 Feb). Luteinizing hormone and testosterone levels during acute phase of severe traumatic brain injury: Prognostic implications for adult male patients. *Frontiers in Endocrinology, 9 (FEB) (no pagination)*(29).

INESSS-ONF. (2015). *Clinical Practice Guidelines for the Rehabilitation of Adults with Moderate to Severe Traumatic Brain Injury*.

Kelly, D. F., Gaw Gonzalo, I. T., Cohan, P., Berman, N., Swerdloff, R., & Wang, C. (2000). Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: A preliminary report. *Journal of Neurosurgery, 93*(5), 743-752.

Khajeh, L., Blijdorp, K., Heijenbrok-Kal, M. H., Sneekes, E. M., van den Berg-Emons, H. J., van der Lely, A. J., Dippel, D. W., Neggers, S. J., Ribbers, G. M., & van Kooten, F. (2015). Pituitary dysfunction after aneurysmal subarachnoid haemorrhage: course and clinical predictors—the HIPS study. *Journal of neurology, neurosurgery, and psychiatry, 86*(8), 905-910.

Kilimann I, Stalla GK, & F., v. R. (2007). Hyperprolactinemia in post-acute phase after severe TBI or SAH is mostly iatrogenic or due to physical stress [Abstracts]. *Endocrine Abstracts*, 14 P448.

Kleindienst, A., Brabant, G., Bock, C., Maser-Gluth, C., & Buchfelder, M. (2009). Neuroendocrine function following traumatic brain injury and subsequent intensive care treatment: A prospective longitudinal evaluation. *Journal of Neurotrauma, 26*(9), 1435-1446.

Klionsky, D. J., Abdelmohsen, K., Abe, A., Abedin, M. J., Abeliovich, H., Acevedo Arozena, A., Adachi, H., Adams, C. M., Adams, P. D., Adeli, K., Adhihetty, P. J., Adler, S. G., Agam, G., Agarwal, R., Aghi, M. K., Agnello, M., Agostinis, P., Aguilar, P. V., Aguirre-Ghiso, J., Airoldi, E. M., Ait-Si-Ali, S., Akematsu, T., Akporiaye, E. T., Al-Rubeai, M., Albaiceta, G. M., Albanese, C., Albani, D., Albert, M. L., Aldudo, J., Algul, H., Alirezaei, M., Alloza, I., Almasan, A., Almonte-Beceril, M., Alnemri, E. S., Alonso, C., Altan-Bonnet, N., Altieri, D. C., Alvarez, S., Alvarez-Erviti, L., Alves, S., Amadoro, G., Amano, A., Amantini, C., Ambrosio, S., Amelio, I., Amer, A. O., Amessou, M., Amon, A., An, Z., Anania, F. A., Andersen, S. U., Andley, U. P., Andreadi, C. K., Andrieu-Abadie, N., Anel, A., Ann, D. K., Anoopkumar-Dukie, S., Antonioli, M., Aoki, H., Apostolova, N., Aquila, S., Aquilano, K., Araki, K., Arama, E., Aranda, A., Araya, J., Arcaro, A., Arias, E., Arimoto, H., Ariosa, A. R., Armstrong, J. L., Arnould, T., Arsov, I., Asanuma, K., Askanas, V., Asselin, E., Atarashi, R., Atherton, S. S., Atkin, J. D., Attardi, L. D., Auberger, P., Auburger, G., Aurelian, L., Autelli, R., Avagliano, L., Avantaggiati, M. L., Avrahami, L., Awale, S., Azad, N., Bachetti, T., Backer, J. M., Bae, D. H., Bae, J. S., Bae, O. N., Bae, S. H., Baehrecke, E. H., Baek, S. H., Baghdiguian, S., Bagniewska-Zadworna, A., Bai, H., Bai, J., Bai, X. Y., Bailly, Y., Balaji, K. N., Balduini, W., Ballabio, A., Balzan, R., Banerjee, R., Banhegyi, G., Bao, H., Barbeau, B., Barrachina, M. D., Barreiro, E., Bartel, B., Bartolome, A., Bassham, D. C., Bassi, M. T., Bast, R. C., Jr., Basu, A., Batista, M. T., Batoko, H., Battino, M., Bauckman, K., Baumgarner, B. L., Bayer, K. U., Beale, R., Beaulieu, J. F., Beck, G. R., Jr., Becker, C., Beckham, J. D., Bedard, P. A., Bednarski, P. J., Begley, T. J., Behl, C., Behrends, C., Behrens, G. M., Behrns, K. E., Bejarano, E., Belaid, A., Belleudi, F., Benard, G., Berchem, G., Bergamaschi, D., Bergami, M., Berkhout, B., Berliocchi, L., Bernard, A., Bernard, M., Bernassola, F., Bertolotti, A., Bess, A. S., Besteiro, S., Bettuzzi, S., Bhalla, S., Bhattacharyya, S., Bhutia, S. K., Biagosch, C., Bianchi, M. W., Biard-Piechaczyk, M., Billes, V., Bincoletto, C., Bingol, B., Bird, S. W., Bitoun, M., Bjedov, I., Blackstone, C., Blanc, L., Blanco, G. A., Blomhoff, H. K., Boada-Romero, E., Bockler, S., Boes, M., Boesze-Battaglia, K., Boise, L. H., Bolino, A., Boman, A., Bonaldo, P., Bordi, M., Bosch, J., Botana, L. M., Botti, J., Bou, G., Bouche, M., Bouchecareilh, M., Boucher, M. J., Boulton, M. E., Bouret, S. G., Boya, P., Boyer-Guittaut, M., Bozhkov, P. V., Brady, N., Braga, V. M., Brancolini, C., Braus, G. H., Bravo-San Pedro, J. M., Brennan, L. A., Bresnick, E. H., Brest, P., Bridges, D., Bringer, M. A., Brini, M., Brito, G. C., Brodin, B., Brookes, P. S., Brown, E. J., Brown, K., Broxmeyer, H. E., Bruhat, A., Brum, P. C., Brumell, J. H., Brunetti-Pierri, N., Bryson-Richardson, R. J., Buch, S., Buchan, A. M., Budak, H., Bulavin, D. V., Bultman, S. J., Bultynck, G., Bumbasirevic, V., Burelle, Y., Burke, R. E., Burmeister, M., Butikofer, P., Caberlotto, L., Cadwell, K., Cahova, M., Cai, D., Cai, J., Cai, Q., Calatayud, S., Camougrand, N., Campanella, M., Campbell, G. R., Campbell, M., Campello, S., Candau, R., Caniggia, I., Cantoni, L., Cao, L., Caplan, A. B., Caraglia, M., Cardinali, C., Cardoso, S. M., Carew, J. S., Carleton, L. A., Carlin, C. R., Carloni, S., Carlsson, S. R., Carmona-Gutierrez, D., Carneiro, L. A., Carnevali, O., Carra, S., Carrier, A., Carroll, B., Casas, C., Casas, J., Cassinelli, G., Castets, P., Castro-Obregon, S., Cavallini, G., Ceccherini, I., Cecconi, F., Cederbaum, A. I., Cena, V., Cenci, S., Cerella, C., Cervia, D., Cetrullo, S., Chaachouay, H., Chae, H. J., Chagin, A. S., Chai, C. Y., Chakrabarti, G., Chamilos, G., Chan, E. Y., Chan, M. T., Chandra, D., Chandra, P.,

Chang, C. P., Chang, R. C., Chang, T. Y., Chatham, J. C., Chatterjee, S., Chauhan, S., Che, Y., Cheetham, M. E., Cheluvappa, R., Chen, C. J., Chen, G., Chen, G. C., Chen, G., Chen, H., Chen, J. W., Chen, J. K., Chen, M., Chen, M., Chen, P., Chen, Q., Chen, Q., Chen, S. D., Chen, S., Chen, S. S., Chen, W., Chen, W. J., Chen, W. Q., Chen, W., Chen, X., Chen, Y. H., Chen, Y. G., Chen, Y., Chen, Y., Chen, Y., Chen, Y. J., Chen, Y. Q., Chen, Y., Chen, Z., Chen, Z., Cheng, A., Cheng, C. H., Cheng, H., Cheong, H., Cherry, S., Chesney, J., Cheung, C. H., Chevet, E., Chi, H. C., Chi, S. G., Chiacchiera, F., Chiang, H. L., Chiarelli, R., Chiariello, M., Chieppa, M., Chin, L. S., Chiong, M., Chiu, G. N., Cho, D. H., Cho, S. G., Cho, W. C., Cho, Y. Y., Cho, Y. S., Choi, A. M., Choi, E. J., Choi, E. K., Choi, J., Choi, M. E., Choi, S. I., Chou, T. F., Chouaib, S., Choubey, D., Choubey, V., Chow, K. C., Chowdhury, K., Chu, C. T., Chuang, T. H., Chun, T., Chung, H., Chung, T., Chung, Y. L., Chwae, Y. J., Cianfanelli, V., Ciarcia, R., Ciechomska, I. A., Ciriolo, M. R., Cirone, M., Claerhout, S., Clague, M. J., Claria, J., Clarke, P. G., Clarke, R., Clementi, E., Cleyrat, C., Cnop, M., Coccia, E. M., Cocco, T., Codogno, P., Coers, J., Cohen, E. E., Colecchia, D., Coletto, L., Coll, N. S., Colucci-Guyon, E., Comincini, S., Condello, M., Cook, K. L., Coombs, G. H., Cooper, C. D., Cooper, J. M., Coppens, I., Corasaniti, M. T., Corazzari, M., Corbalan, R., Corcelle-Termeau, E., Cordero, M. D., Corral-Ramos, C., Corti, O., Cossarizza, A., Costelli, P., Costes, S., Cotman, S. L., Coto-Montes, A., Cottet, S., Couve, E., Covey, L. R., Cowart, L. A., Cox, J. S., Coxon, F. P., Coyne, C. B., Cragg, M. S., Craven, R. J., Crepaldi, T., Crespo, J. L., Criollo, A., Crippa, V., Cruz, M. T., Cuervo, A. M., Cuezva, J. M., Cui, T., Cutillas, P. R., Czaja, M. J., Czyzyk-Krzeska, M. F., Dagda, R. K., Dahmen, U., Dai, C., Dai, W., Dai, Y., Dalby, K. N., Dalla Valle, L., Dalmasso, G., D'Amelio, M., Damme, M., Darfeuille-Michaud, A., Dargemont, C., Darley-Usmar, V. M., Dasarathy, S., Dasgupta, B., Dash, S., Dass, C. R., Davey, H. M., Davids, L. M., Davila, D., Davis, R. J., Dawson, T. M., Dawson, V. L., Daza, P., de Belleroche, J., de Figueiredo, P., de Figueiredo, R. C., de la Fuente, J., De Martino, L., De Matteis, A., De Meyer, G. R., De Milito, A., De Santi, M., de Souza, W., De Tata, V., De Zio, D., Debnath, J., Dechant, R., Decuypere, J. P., Deegan, S., Dehay, B., Del Bello, B., Del Re, D. P., Delage-Mourroux, R., Delbridge, L. M., Deldicque, L., Delorme-Axford, E., Deng, Y., Dengjel, J., Denizot, M., Dent, P., Der, C. J., Deretic, V., Derrien, B., Deutsch, E., Devarenne, T. P., Devenish, R. J., Di Bartolomeo, S., Di Daniele, N., Di Domenico, F., Di Nardo, A., Di Paola, S., Di Pietro, A., Di Renzo, L., DiAntonio, A., Diaz-Araya, G., Diaz-Laviada, I., Diaz-Meco, M. T., Diaz-Nido, J., Dickey, C. A., Dickson, R. C., Diederich, M., Digard, P., Dikic, I., Dinesh-Kumar, S. P., Ding, C., Ding, W. X., Ding, Z., Dini, L., Distler, J. H., Diwan, A., Djavaheri-Mergny, M., Dmytruk, K., Dobson, R. C., Doetsch, V., Dokladny, K., Dokudovskaya, S., Donadelli, M., Dong, X. C., Dong, X., Dong, Z., Donohue, T. M., Jr., Doran, K. S., D'Orazi, G., Dorn, G. W., 2nd, Dosenko, V., Dridi, S., Drucker, L., Du, J., Du, L. L., Du, L., du Toit, A., Dua, P., Duan, L., Duann, P., Dubey, V. K., Duchen, M. R., Duchosal, M. A., Duez, H., Dugail, I., Dumit, V. I., Duncan, M. C., Dunlop, E. A., Dunn, W. A., Jr., Dupont, N., Dupuis, L., Duran, R. V., Durcan, T. M., Duvezin-Caubet, S., Duvvuri, U., Eapen, V., Ebrahimi-Fakhari, D., Echard, A., Eckhart, L., Edelstein, C. L., Edinger, A. L., Eichinger, L., Eisenberg, T., Eisenberg-Lerner, A., Eissa, N. T., El-Deiry, W. S., El-Khoury, V., Elazar, Z., Eldar-Finkelman, H., Elliott, C. J., Emanuele, E., Emmenegger, U., Engedal, N., Engelbrecht, A. M., Engelender, S., Enserink, J. M., Erdmann, R., Erenpreisa, J., Eri, R., Eriksen, J. L., Erman, A., Escalante, R., Eskelinen, E. L., Espert, L., Esteban-Martinez, L., Evans, T. J., Fabri, M., Fabrias, G., Fabrizi, C., Facchiano, A., Faergeman, N. J., Faggioni, A., Fairlie, W. D., Fan, C., Fan, D., Fan, J., Fang, S., Fanto, M., Fanzani, A., Farkas, T., Faure, M., Favier, F. B., Fearnhead, H., Federici, M., Fei, E., Felizardo, T. C., Feng, H., Feng, Y., Feng, Y., Ferguson, T. A., Fernandez, A. F., Fernandez-Barrena, M. G., Fernandez-Checa, J. C., Fernandez-Lopez, A., Fernandez-Zapico, M. E., Feron, O., Ferraro, E., Ferreira-Halder, C. V., Fesus, L., Feuer, R., Fiesel, F. C., Filippi-Chiela, E. C., Filomeni, G., Fimia, G. M., Fingert, J. H., Finkbeiner, S., Finkel, T., Fiorito, F., Fisher, P. B., Flajolet, M., Flamigni, F., Florey, O., Florio, S., Floto, R. A., Folini, M., Follo, C., Fon, E. A., Fornai, F., Fortunato, F., Fraldi, A., Franco, R., Francois, A., Francois, A., Frankel, L. B., Fraser, I. D., Frey, N., Freyssenet, D. G., Frezza, C., Friedman,

S. L., Frigo, D. E., Fu, D., Fuentes, J. M., Fueyo, J., Fujitani, Y., Fujiwara, Y., Fujiya, M., Fukuda, M., Fulda, S., Fusco, C., Gabryel, B., Gaestel, M., Gailly, P., Gajewska, M., Galadari, S., Galili, G., Galindo, I., Galindo, M. F., Galliciotti, G., Galluzzi, L., Galluzzi, L., Galy, V., Gammoh, N., Gandy, S., Ganesan, A. K., Ganesan, S., Ganley, I. G., Gannage, M., Gao, F. B., Gao, F., Gao, J. X., Garcia Nannig, L., Garcia Vescovi, E., Garcia-Macia, M., Garcia-Ruiz, C., Garg, A. D., Garg, P. K., Gargini, R., Gassen, N. C., Gatica, D., Gatti, E., Gavard, J., Gavathiotis, E., Ge, L., Ge, P., Ge, S., Gean, P. W., Gelmetti, V., Genazzani, A. A., Geng, J., Genschik, P., Gerner, L., Gestwicki, J. E., Gewirtz, D. A., Ghavami, S., Ghigo, E., Ghosh, D., Giammarioli, A. M., Giampieri, F., Giampietri, C., Giatromanolaki, A., Gibbings, D. J., Gibellini, L., Gibson, S. B., Ginet, V., Giordano, A., Giorgini, F., Giovannetti, E., Girardin, S. E., Gispert, S., Giuliano, S., Gladson, C. L., Glavic, A., Gleave, M., Godefroy, N., Gogal, R. M., Jr., Gokulan, K., Goldman, G. H., Goletti, D., Goligorsky, M. S., Gomes, A. V., Gomes, L. C., Gomez, H., Gomez-Manzano, C., Gomez-Sanchez, R., Goncalves, D. A., Goncu, E., Gong, Q., Gongora, C., Gonzalez, C. B., Gonzalez-Alegre, P., Gonzalez-Cabo, P., Gonzalez-Polo, R. A., Goping, I. S., Gorbea, C., Gorbunov, N. V., Goring, D. R., Gorman, A. M., Gorski, S. M., Goruppi, S., Goto-Yamada, S., Gotor, C., Gottlieb, R. A., Gozes, I., Gozuacik, D., Graba, Y., Graef, M., Granato, G. E., Grant, G. D., Grant, S., Gravina, G. L., Green, D. R., Greenhough, A., Greenwood, M. T., Grimaldi, B., Gros, F., Grose, C., Groulx, J. F., Gruber, F., Grumati, P., Grune, T., Guan, J. L., Guan, K. L., Guerra, B., Guillen, C., Gulshan, K., Gunst, J., Guo, C., Guo, L., Guo, M., Guo, W., Guo, X. G., Gust, A. A., Gustafsson, A. B., Gutierrez, E., Gutierrez, M. G., Gwak, H. S., Haas, A., Haber, J. E., Hadano, S., Hagedorn, M., Hahn, D. R., Halayko, A. J., Hamacher-Brady, A., Hamada, K., Hamai, A., Hamann, A., Hamasaki, M., Hamer, I., Hamid, Q., Hammond, E. M., Han, F., Han, W., Handa, J. T., Hanover, J. A., Hansen, M., Harada, M., Harhaji-Trajkovic, L., Harper, J. W., Harrath, A. H., Harris, A. L., Harris, J., Hasler, U., Hasselblatt, P., Hasui, K., Hawley, R. G., Hawley, T. S., He, C., He, C. Y., He, F., He, G., He, R. R., He, X. H., He, Y. W., He, Y. Y., Heath, J. K., Hebert, M. J., Heinzen, R. A., Helgason, G. V., Hensel, M., Henske, E. P., Her, C., Herman, P. K., Hernandez, A., Hernandez, C., Hernandez-Tiedra, S., Hetz, C., Hiesinger, P. R., Higaki, K., Hilfiker, S., Hill, B. G., Hill, J. A., Hill, W. D., Hino, K., Hofius, D., Hofman, P., Hoglinger, G. U., Hohfeld, J., Holz, M. K., Hong, Y., Hood, D. A., Hoozemans, J. J., Hoppe, T., Hsu, C., Hsu, C. Y., Hsu, L. C., Hu, D., Hu, G., Hu, H. M., Hu, H., Hu, M. C., Hu, Y. C., Hu, Z. W., Hua, F., Hua, Y., Huang, C., Huang, H. L., Huang, K. H., Huang, K. Y., Huang, S., Huang, S., Huang, W. P., Huang, Y. R., Huang, Y., Huang, Y., Huber, T. B., Huebbe, P., Huh, W. K., Hulmi, J. J., Hur, G. M., Hurley, J. H., Husak, Z., Hussain, S. N., Hussain, S., Hwang, J. J., Hwang, S., Hwang, T. I., Ichihara, A., Imai, Y., Imbriano, C., Inomata, M., Into, T., Iovane, V., Iovanna, J. L., Iozzo, R. V., Ip, N. Y., Irazoqui, J. E., Iribarren, P., Isaka, Y., Isakovic, A. J., Ischiropoulos, H., Isenberg, J. S., Ishaq, M., Ishida, H., Ishii, I., Ishmael, J. E., Isidoro, C., Isobe, K., Isono, E., Issazadeh-Navikas, S., Itahana, K., Itakura, E., Ivanov, A. I., Iyer, A. K., Izquierdo, J. M., Izumi, Y., Izzo, V., Jaattela, M., Jaber, N., Jackson, D. J., Jackson, W. T., Jacob, T. G., Jacques, T. S., Jagannath, C., Jain, A., Jana, N. R., Jang, B. K., Jani, A., Janji, B., Jannig, P. R., Jansson, P. J., Jean, S., Jendrach, M., Jeon, J. H., Jessen, N., Jeung, E. B., Jia, K., Jia, L., Jiang, H., Jiang, H., Jiang, L., Jiang, T., Jiang, X., Jiang, X., Jiang, X., Jiang, Y., Jiang, Y., Jimenez, A., Jin, C., Jin, H., Jin, L., Jin, M., Jin, S., Jinwal, U. K., Jo, E. K., Johansen, T., Johnson, D. E., Johnson, G. V., Johnson, J. D., Jonasch, E., Jones, C., Joosten, L. A., Jordan, J., Joseph, A. M., Joseph, B., Joubert, A. M., Ju, D., Ju, J., Juan, H. F., Juenemann, K., Juhasz, G., Jung, H. S., Jung, J. U., Jung, Y. K., Jungbluth, H., Justice, M. J., Jutten, B., Kaakoush, N. O., Kaarniranta, K., Kaasik, A., Kabuta, T., Kaeffer, B., Kagedal, K., Kahana, A., Kajimura, S., Kakhlon, O., Kalia, M., Kalvakolanu, D. V., Kamada, Y., Kambas, K., Kaminskyy, V. O., Kampinga, H. H., Kandouz, M., Kang, C., Kang, R., Kang, T. C., Kanki, T., Kanneganti, T. D., Kanno, H., Kanthasamy, A. G., Kantorow, M., Kaparakis-Liaskos, M., Kapuy, O., Karantza, V., Karim, M. R., Karmakar, P., Kaser, A., Kaushik, S., Kawula, T., Kaynar, A. M., Ke, P. Y., Ke, Z. J., Kehrl, J. H., Keller, K. E., Kemper, J. K., Kenworthy, A. K., Kepp, O., Kern, A., Kesari, S., Kessel, D., Ketteler, R., Kettelhut Ido, C., Khambu, B.,

Khan, M. M., Khandelwal, V. K., Khare, S., Kiang, J. G., Kiger, A. A., Kihara, A., Kim, A. L., Kim, C. H., Kim, D. R., Kim, D. H., Kim, E. K., Kim, H. Y., Kim, H. R., Kim, J. S., Kim, J. H., Kim, J. C., Kim, J. H., Kim, K. W., Kim, M. D., Kim, M. M., Kim, P. K., Kim, S. W., Kim, S. Y., Kim, Y. S., Kim, Y., Kimchi, A., Kimmelman, A. C., Kimura, T., King, J. S., Kirkegaard, K., Kirkin, V., Kirshenbaum, L. A., Kishi, S., Kitajima, Y., Kitamoto, K., Kitaoka, Y., Kitazato, K., Kley, R. A., Klimecki, W. T., Klinkenberg, M., Klucken, J., Knaevelsrud, H., Knecht, E., Knuppertz, L., Ko, J. L., Kobayashi, S., Koch, J. C., Koechlin-Ramonatxo, C., Koenig, U., Koh, Y. H., Kohler, K., Kohlwein, S. D., Koike, M., Komatsu, M., Kominami, E., Kong, D., Kong, H. J., Konstantakou, E. G., Kopp, B. T., Korcsmaros, T., Korhonen, L., Korolchuk, V. I., Koshkina, N. V., Kou, Y., Koukourakis, M. I., Koumenis, C., Kovacs, A. L., Kovacs, T., Kovacs, W. J., Koya, D., Kraft, C., Krainc, D., Kramer, H., Kravic-Stevovic, T., Krek, W., Kretz-Remy, C., Krick, R., Krishnamurthy, M., Kriston-Vizi, J., Kroemer, G., Kruer, M. C., Kruger, R., Ktistakis, N. T., Kuchitsu, K., Kuhn, C., Kumar, A. P., Kumar, A., Kumar, A., Kumar, D., Kumar, D., Kumar, R., Kumar, S., Kundu, M., Kung, H. J., Kuno, A., Kuo, S. H., Kuret, J., Kurz, T., Kwok, T., Kwon, T. K., Kwon, Y. T., Kyrmizi, I., La Spada, A. R., Lafont, F., Lahm, T., Lakkaraju, A., Lam, T., Lamark, T., Lancel, S., Landowski, T. H., Lane, D. J., Lane, J. D., Lanzi, C., Lapaquette, P., Lapierre, L. R., Laporte, J., Laukkarinen, J., Laurie, G. W., Lavandero, S., Lavie, L., LaVoie, M. J., Law, B. Y., Law, H. K., Law, K. B., Layfield, R., Lazo, P. A., Le Cam, L., Le Roch, K. G., Le Stunff, H., Leardkamolkarn, V., Lecuit, M., Lee, B. H., Lee, C. H., Lee, E. F., Lee, G. M., Lee, H. J., Lee, H., Lee, J. K., Lee, J., Lee, J. H., Lee, J. H., Lee, M., Lee, M. S., Lee, P. J., Lee, S. W., Lee, S. J., Lee, S. J., Lee, S. Y., Lee, S. H., Lee, S. S., Lee, S. J., Lee, S., Lee, Y. R., Lee, Y. J., Lee, Y. H., Leeuwenburgh, C., Lefort, S., Legouis, R., Lei, J., Lei, Q. Y., Leib, D. A., Leibowitz, G., Lekli, I., Lemaire, S. D., Lemasters, J. J., Lemberg, M. K., Lemoine, A., Leng, S., Lenz, G., Lenzi, P., Lerman, L. O., Lettieri Barbato, D., Leu, J. I., Leung, H. Y., Levine, B., Lewis, P. A., Lezoualc'h, F., Li, C., Li, F., Li, F. J., Li, J., Li, K., Li, L., Li, M., Li, M., Li, Q., Li, R., Li, S., Li, W., Li, W., Li, X., Li, Y., Lian, J., Liang, C., Liang, Q., Liao, Y., Liberal, J., Liberski, P. P., Lie, P., Lieberman, A. P., Lim, H. J., Lim, K. L., Lim, K., Lima, R. T., Lin, C. S., Lin, C. F., Lin, F., Lin, F., Lin, F. C., Lin, K., Lin, K. H., Lin, P. H., Lin, T., Lin, W. W., Lin, Y. S., Lin, Y., Linden, R., Lindholm, D., Lindqvist, L. M., Lingor, P., Linkermann, A., Liotta, L. A., Lipinski, M. M., Lira, V. A., Lisanti, M. P., Liton, P. B., Liu, B., Liu, C., Liu, C. F., Liu, F., Liu, H. J., Liu, J., Liu, J. J., Liu, J. L., Liu, K., Liu, L., Liu, L., Liu, Q., Liu, R. Y., Liu, S., Liu, S., Liu, W., Liu, X. D., Liu, X., Liu, X. H., Liu, X., Liu, X., Liu, X., Liu, Y., Liu, Y., Liu, Z., Liu, Z., Liuzzi, J. P., Lizard, G., Ljujic, M., Lodhi, I. J., Logue, S. E., Lokeshwar, B. L., Long, Y. C., Lonial, S., Loos, B., Lopez-Otin, C., Lopez-Vicario, C., Lorente, M., Lorenzi, P. L., Lorincz, P., Los, M., Lotze, M. T., Lovat, P. E., Lu, B., Lu, B., Lu, J., Lu, Q., Lu, S. M., Lu, S., Lu, Y., Luciano, F., Luckhart, S., Lucocq, J. M., Ludovico, P., Lugea, A., Lukacs, N. W., Lum, J. J., Lund, A. H., Luo, H., Luo, J., Luo, S., Luparello, C., Lyons, T., Ma, J., Ma, Y., Ma, Y., Ma, Z., Machado, J., Machado-Santelli, G. M., Macian, F., MacIntosh, G. C., MacKeigan, J. P., Macleod, K. F., MacMicking, J. D., MacMillan-Crow, L. A., Madeo, F., Madesh, M., Madrigal-Matute, J., Maeda, A., Maeda, T., Maegawa, G., Maellaro, E., Maes, H., Magarinos, M., Maiese, K., Maiti, T. K., Maiuri, L., Maiuri, M. C., Maki, C. G., Malli, R., Malorni, W., Maloyan, A., Mami-Chouaib, F., Man, N., Mancias, J. D., Mandelkow, E. M., Mandell, M. A., Manfredi, A. A., Manie, S. N., Manzoni, C., Mao, K., Mao, Z., Mao, Z. W., Marambaud, P., Marconi, A. M., Marelja, Z., Marfe, G., Margeta, M., Margittai, E., Mari, M., Mariani, F. V., Marin, C., Marinelli, S., Marino, G., Markovic, I., Marquez, R., Martelli, A. M., Martens, S., Martin, K. R., Martin, S. J., Martin, S., Martin-Acebes, M. A., Martin-Sanz, P., Martinand-Mari, C., Martinet, W., Martinez, J., Martinez-Lopez, N., Martinez-Outschoorn, U., Martinez-Velazquez, M., Martinez-Vicente, M., Martins, W. K., Mashima, H., Mastrianni, J. A., Matarese, G., Matarrese, P., Mateo, R., Matoba, S., Matsumoto, N., Matsushita, T., Matsuura, A., Matsuzawa, T., Mattson, M. P., Matus, S., Maugeri, N., Mauvezin, C., Mayer, A., Maysinger, D., Mazzolini, G. D., McBrayer, M. K., McCall, K., McCormick, C., McInerney, G. M., McIver, S. C., McKenna, S., McMahon, J. J., McNeish, I. A., Mechta-Grigoriou, F., Medema, J. P., Medina, D. L., Megyeri, K., Mehrpour, M., Mehta,

J. L., Mei, Y., Meier, U. C., Meijer, A. J., Melendez, A., Melino, G., Melino, S., de Melo, E. J., Mena, M. A., Meneghini, M. D., Menendez, J. A., Menezes, R., Meng, L., Meng, L. H., Meng, S., Menghini, R., Menko, A. S., Menna-Barreto, R. F., Menon, M. B., Meraz-Rios, M. A., Merla, G., Merlini, L., Merlot, A. M., Meryk, A., Meschini, S., Meyer, J. N., Mi, M. T., Miao, C. Y., Micale, L., Michaeli, S., Michiels, C., Migliaccio, A. R., Mihailidou, A. S., Mijaljica, D., Mikoshiba, K., Milan, E., Miller-Fleming, L., Mills, G. B., Mills, I. G., Minakaki, G., Minassian, B. A., Ming, X. F., Minibayeva, F., Minina, E. A., Mintern, J. D., Minucci, S., Miranda-Vizuete, A., Mitchell, C. H., Miyamoto, S., Miyazawa, K., Mizushima, N., Mnich, K., Mograbi, B., Mohseni, S., Moita, L. F., Molinari, M., Molinari, M., Moller, A. B., Mollereau, B., Mollinedo, F., Mongillo, M., Monick, M. M., Montagnaro, S., Montell, C., Moore, D. J., Moore, M. N., Mora-Rodriguez, R., Moreira, P. I., Morel, E., Morelli, M. B., Moreno, S., Morgan, M. J., Moris, A., Moriyasu, Y., Morrison, J. L., Morrison, L. A., Morselli, E., Moscat, J., Moseley, P. L., Mostowy, S., Motori, E., Mottet, D., Mottram, J. C., Moussa, C. E., Mpakou, V. E., Mukhtar, H., Mulcahy Levy, J. M., Muller, S., Munoz-Moreno, R., Munoz-Pinedo, C., Munz, C., Murphy, M. E., Murray, J. T., Murthy, A., Mysorekar, I. U., Nabi, I. R., Nabissi, M., Nader, G. A., Nagahara, Y., Nagai, Y., Nagata, K., Nagelkerke, A., Nagy, P., Naidu, S. R., Nair, S., Nakano, H., Nakatogawa, H., Nanjundan, M., Napolitano, G., Naqvi, N. I., Nardacci, R., Narendra, D. P., Narita, M., Nascimbeni, A. C., Natarajan, R., Navegantes, L. C., Nawrocki, S. T., Nazarko, T. Y., Nazarko, V. Y., Neill, T., Neri, L. M., Netea, M. G., Netea-Maier, R. T., Neves, B. M., Ney, P. A., Nezis, I. P., Nguyen, H. T., Nguyen, H. P., Nicot, A. S., Nilsen, H., Nilsson, P., Nishimura, M., Nishino, I., Niso-Santano, M., Niu, H., Nixon, R. A., Njar, V. C., Noda, T., Noegel, A. A., Nolte, E. M., Norberg, E., Norga, K. K., Noureini, S. K., Notomi, S., Notterpek, L., Nowikovsky, K., Nukina, N., Nurnberger, T., O'Donnell, V. B., O'Donovan, T., O'Dwyer, P. J., Oehme, I., Oeste, C. L., Ogawa, M., Ogretmen, B., Ogura, Y., Oh, Y. J., Ohmuraya, M., Ohshima, T., Ojha, R., Okamoto, K., Okazaki, T., Oliver, F. J., Ollinger, K., Olsson, S., Orban, D. P., Ordonez, P., Orhon, I., Orosz, L., O'Rourke, E. J., Orozco, H., Ortega, A. L., Ortona, E., Osellame, L. D., Oshima, J., Oshima, S., Osiewacz, H. D., Otomo, T., Otsu, K., Ou, J. H., Outeiro, T. F., Ouyang, D. Y., Ouyang, H., Overholtzer, M., Ozbun, M. A., Ozdinler, P. H., Ozpolat, B., Pacelli, C., Paganetti, P., Page, G., Pages, G., Pagnini, U., Pajak, B., Pak, S. C., Pakos-Zebrucka, K., Pakpour, N., Palkova, Z., Palladino, F., Pallauf, K., Pallet, N., Palmieri, M., Paludan, S. R., Palumbo, C., Palumbo, S., Pampliega, O., Pan, H., Pan, W., Panaretakis, T., Pandey, A., Pantazopoulou, A., Papackova, Z., Papademetrio, D. L., Papassideri, I., Papini, A., Parajuli, N., Pardo, J., Parekh, V. V., Parenti, G., Park, J. I., Park, J., Park, O. K., Parker, R., Parlato, R., Parys, J. B., Parzych, K. R., Pasquet, J. M., Pasquier, B., Pasumarthi, K. B., Patschan, D., Patterson, C., Pattingre, S., Pattison, S., Pause, A., Pavenstadt, H., Pavone, F., Pedrozo, Z., Pena, F. J., Penalva, M. A., Pende, M., Peng, J., Penna, F., Penninger, J. M., Pensalfini, A., Pepe, S., Pereira, G. J., Pereira, P. C., Perez-de la Cruz, V., Perez-Perez, M. E., Perez-Rodriguez, D., Perez-Sala, D., Perier, C., Perl, A., Perlmutter, D. H., Perrotta, I., Pervaiz, S., Pesonen, M., Pessin, J. E., Peters, G. J., Petersen, M., Petrache, I., Petrof, B. J., Petrovski, G., Phang, J. M., Piacentini, M., Pierdominici, M., Pierre, P., Pierrefite-Carle, V., Pietrocola, F., Pimentel-Muinos, F. X., Pinar, M., Pineda, B., Pinkas-Kramarski, R., Pinti, M., Pinton, P., Piperdi, B., Piret, J. M., Platanias, L. C., Platta, H. W., Plowey, E. D., Poggeler, S., Poirot, M., Polcic, P., Poletti, A., Poon, A. H., Popelka, H., Popova, B., Poprawa, I., Poulose, S. M., Poulton, J., Powers, S. K., Powers, T., Pozuelo-Rubio, M., Prak, K., Prange, R., Prescott, M., Priault, M., Prince, S., Proia, R. L., Proikas-Cezanne, T., Prokisch, H., Promponas, V. J., Przyklenk, K., Puertollano, R., Pugazhenthi, S., Puglielli, L., Pujol, A., Puyal, J., Pyeon, D., Qi, X., Qian, W. B., Qin, Z. H., Qiu, Y., Qu, Z., Quadrilatero, J., Quinn, F., Raben, N., Rabinowich, H., Radogna, F., Ragusa, M. J., Rahmani, M., Raina, K., Ramanadham, S., Ramesh, R., Rami, A., Randall-Demllo, S., Randow, F., Rao, H., Rao, V. A., Rasmussen, B. B., Rasse, T. M., Ratovitski, E. A., Rautou, P. E., Ray, S. K., Razani, B., Reed, B. H., Reggiori, F., Rehm, M., Reichert, A. S., Rein, T., Reiner, D. J., Reits, E., Ren, J., Ren, X., Renna, M., Reusch, J. E., Revuelta, J. L.,

Reyes, L., Rezaie, A. R., Richards, R. I., Richardson, D. R., Richetta, C., Riehle, M. A., Rihn, B. H., Rikihisa, Y., Riley, B. E., Rimbach, G., Rippo, M. R., Ritis, K., Rizzi, F., Rizzo, E., Roach, P. J., Robbins, J., Roberge, M., Roca, G., Roccheri, M. C., Rocha, S., Rodrigues, C. M., Rodriguez, C. I., de Cordoba, S. R., Rodriguez-Muela, N., Roelofs, J., Rogov, V. V., Rohn, T. T., Rohrer, B., Romanelli, D., Romani, L., Romano, P. S., Roncero, M. I., Rosa, J. L., Rosello, A., Rosen, K. V., Rosenstiel, P., Rost-Roszkowska, M., Roth, K. A., Roue, G., Rouis, M., Rouschop, K. M., Ruan, D. T., Ruano, D., Rubinsztein, D. C., Rucker, E. B., 3rd, Rudich, A., Rudolf, E., Rudolf, R., Ruegg, M. A., Ruiz-Roldan, C., Ruparelia, A. A., Rusmini, P., Russ, D. W., Russo, G. L., Russo, G., Russo, R., Rusten, T. E., Ryabovol, V., Ryan, K. M., Ryter, S. W., Sabatini, D. M., Sacher, M., Sachse, C., Sack, M. N., Sadoshima, J., Saftig, P., Sagi-Eisenberg, R., Sahni, S., Saikumar, P., Saito, T., Saitoh, T., Sakakura, K., Sakoh-Nakatogawa, M., Sakuraba, Y., Salazar-Roa, M., Salomoni, P., Saluja, A. K., Salvaterra, P. M., Salvioli, R., Samali, A., Sanchez, A. M., Sanchez-Alcazar, J. A., Sanchez-Prieto, R., Sandri, M., Sanjuan, M. A., Santaguida, S., Santambrogio, L., Santoni, G., Dos Santos, C. N., Saran, S., Sardiello, M., Sargent, G., Sarkar, P., Sarkar, S., Sarrias, M. R., Sarwal, M. M., Sasakawa, C., Sasaki, M., Sass, M., Sato, K., Sato, M., Satriano, J., Savaraj, N., Saveljeva, S., Schaefer, L., Schaible, U. E., Scharl, M., Schatzl, H. M., Schekman, R., Scheper, W., Schiavi, A., Schipper, H. M., Schmeisser, H., Schmidt, J., Schmitz, I., Schneider, B. E., Schneider, E. M., Schneider, J. L., Schon, E. A., Schonenberger, M. J., Schonthal, A. H., Schorderet, D. F., Schroder, B., Schuck, S., Schulze, R. J., Schwarten, M., Schwarz, T. L., Sciarretta, S., Scotto, K., Scovassi, A. I., Screaton, R. A., Screen, M., Seca, H., Sedej, S., Segatori, L., Segev, N., Seglen, P. O., Segui-Simarro, J. M., Segura-Aguilar, J., Seki, E., Sell, C., Seiliez, I., Semenkovich, C. F., Semenza, G. L., Sen, U., Serra, A. L., Serrano-Puebla, A., Sesaki, H., Setoguchi, T., Settembre, C., Shacka, J. J., Shajahan-Haq, A. N., Shapiro, I. M., Sharma, S., She, H., Shen, C. K., Shen, C. C., Shen, H. M., Shen, S., Shen, W., Sheng, R., Sheng, X., Sheng, Z. H., Shepherd, T. G., Shi, J., Shi, Q., Shi, Q., Shi, Y., Shibutani, S., Shibuya, K., Shidoji, Y., Shieh, J. J., Shih, C. M., Shimada, Y., Shimizu, S., Shin, D. W., Shinohara, M. L., Shintani, M., Shintani, T., Shioi, T., Shirabe, K., Shiri-Sverdlov, R., Shirihai, O., Shore, G. C., Shu, C. W., Shukla, D., Sibirny, A. A., Sica, V., Sigurdson, C. J., Sigurdsson, E. M., Sijwali, P. S., Sikorska, B., Silveira, W. A., Silvente-Poirot, S., Silverman, G. A., Simak, J., Simmet, T., Simon, A. K., Simon, H. U., Simone, C., Simons, M., Simonsen, A., Singh, R., Singh, S. V., Singh, S. K., Sinha, D., Sinha, S., Sinicrope, F. A., Sirko, A., Sirohi, K., Sishi, B. J., Sittler, A., Siu, P. M., Sivridis, E., Skwarska, A., Slack, R., Slaninova, I., Slavov, N., Smaili, S. S., Smalley, K. S., Smith, D. R., Soenen, S. J., Soleimanpour, S. A., Solhaug, A., Somasundaram, K., Son, J. H., Sonawane, A., Song, C., Song, F., Song, H. K., Song, J. X., Song, W., Soo, K. Y., Sood, A. K., Soong, T. W., Soontornniyomkij, V., Sorice, M., Sotgia, F., Soto-Pantoja, D. R., Sotthibundhu, A., Sousa, M. J., Spaink, H. P., Span, P. N., Spang, A., Sparks, J. D., Speck, P. G., Spector, S. A., Spies, C. D., Springer, W., Clair, D. S., Stacchiotti, A., Staels, B., Stang, M. T., Starczynowski, D. T., Starokadomskyy, P., Steegborn, C., Steele, J. W., Stefanis, L., Steffan, J., Stellrecht, C. M., Stenmark, H., Stepkowski, T. M., Stern, S. T., Stevens, C., Stockwell, B. R., Stoka, V., Storchova, Z., Stork, B., Stratoulias, V., Stravopodis, D. J., Strnad, P., Strohecker, A. M., Strom, A. L., Stromhaug, P., Stulik, J., Su, Y. X., Su, Z., Subauste, C. S., Subramaniam, S., Sue, C. M., Suh, S. W., Sui, X., Sukseree, S., Sulzer, D., Sun, F. L., Sun, J., Sun, J., Sun, S. Y., Sun, Y., Sun, Y., Sun, Y., Sundaramoorthy, V., Sung, J., Suzuki, H., Suzuki, K., Suzuki, N., Suzuki, T., Suzuki, Y. J., Swanson, M. S., Swanton, C., Sward, K., Swarup, G., Sweeney, S. T., Sylvester, P. W., Szatmari, Z., Szegezdi, E., Szlosarek, P. W., Taegtmeyer, H., Tafani, M., Taillebourg, E., Tait, S. W., Takacs-Vellai, K., Takahashi, Y., Takats, S., Takemura, G., Takigawa, N., Talbot, N. J., Tamagno, E., Tamburini, J., Tan, C. P., Tan, L., Tan, M. L., Tan, M., Tan, Y. J., Tanaka, K., Tanaka, M., Tang, D., Tang, D., Tang, G., Tanida, I., Tanji, K., Tannous, B. A., Tapia, J. A., Tasset-Cuevas, I., Tatar, M., Tavassoly, I., Tavernarakis, N., Taylor, A., Taylor, G. S., Taylor, G. A., Taylor, J. P., Taylor, M. J., Tchetina, E. V., Tee, A. R., Teixeira-Clerc, F., Telang, S., Tencomnao, T., Teng, B. B., Teng, R. J., Terro, F., Tettamanti, G., Theiss, A. L., Theron, A. E., Thomas, K. J.,

Thome, M. P., Thomes, P. G., Thorburn, A., Thorner, J., Thum, T., Thumm, M., Thurston, T. L., Tian, L., Till, A., Ting, J. P., Titorenko, V. I., Toker, L., Toldo, S., Tooze, S. A., Topisirovic, I., Torgersen, M. L., Torosantucci, L., Torriglia, A., Torrisi, M. R., Tournier, C., Towns, R., Trajkovic, V., Travassos, L. H., Triola, G., Tripathi, D. N., Trisciuoglio, D., Troncoso, R., Trougakos, I. P., Truttmann, A. C., Tsai, K. J., Tschan, M. P., Tseng, Y. H., Tsukuba, T., Tsung, A., Tsvetkov, A. S., Tu, S., Tuan, H. Y., Tucci, M., Tumbarello, D. A., Turk, B., Turk, V., Turner, R. F., Tveita, A. A., Tyagi, S. C., Ubukata, M., Uchiyama, Y., Udelnow, A., Ueno, T., Umekawa, M., Umemiya-Shirafuji, R., Underwood, B. R., Ungermann, C., Ureshino, R. P., Ushioda, R., Uversky, V. N., Uzcategui, N. L., Vaccari, T., Vaccaro, M. I., Vachova, L., Vakifahmetoglu-Norberg, H., Valdor, R., Valente, E. M., Vallette, F., Valverde, A. M., Van den Berghe, G., Van Den Bosch, L., van den Brink, G. R., van der Goot, F. G., van der Klei, I. J., van der Laan, L. J., van Doorn, W. G., van Egmond, M., van Golen, K. L., Van Kaer, L., van Lookeren Campagne, M., Vandenabeele, P., Vandenberghe, W., Vanhorebeek, I., Varela-Nieto, I., Vasconcelos, M. H., Vasko, R., Vavvas, D. G., Vega-Naredo, I., Velasco, G., Velentzas, A. D., Velentzas, P. D., Vellai, T., Vellenga, E., Vendelbo, M. H., Venkatachalam, K., Ventura, N., Ventura, S., Veras, P. S., Verdier, M., Vertessy, B. G., Viale, A., Vidal, M., Vieira, H. L., Vierstra, R. D., Vigneswaran, N., Vij, N., Vila, M., Villar, M., Villar, V. H., Villarroya, J., Vindis, C., Viola, G., Viscomi, M. T., Vitale, G., Vogl, D. T., Voitsekhovskaja, O. V., von Haefen, C., von Schwarzenberg, K., Voth, D. E., Vouret-Craviari, V., Vuori, K., Vyas, J. M., Waeber, C., Walker, C. L., Walker, M. J., Walter, J., Wan, L., Wan, X., Wang, B., Wang, C., Wang, C. Y., Wang, C., Wang, C., Wang, C., Wang, D., Wang, F., Wang, F., Wang, G., Wang, H. J., Wang, H., Wang, H. G., Wang, H., Wang, H. D., Wang, J., Wang, J., Wang, M., Wang, M. Q., Wang, P. Y., Wang, P., Wang, R. C., Wang, S., Wang, T. F., Wang, X., Wang, X. J., Wang, X. W., Wang, X., Wang, X., Wang, Y., Wang, Y., Wang, Y., Wang, Y. J., Wang, Y., Wang, Y., Wang, Y. T., Wang, Y., Wang, Z. N., Wappner, P., Ward, C., Ward, D. M., Warnes, G., Watada, H., Watanabe, Y., Watase, K., Weaver, T. E., Weekes, C. D., Wei, J., Weide, T., Weihl, C. C., Weindl, G., Weis, S. N., Wen, L., Wen, X., Wen, Y., Westermann, B., Weyand, C. M., White, A. R., White, E., Whitton, J. L., Whitworth, A. J., Wiels, J., Wild, F., Wildenberg, M. E., Wileman, T., Wilkinson, D. S., Wilkinson, S., Willbold, D., Williams, C., Williams, K., Williamson, P. R., Winklhofer, K. F., Witkin, S. S., Wohlgemuth, S. E., Wollert, T., Wolvetang, E. J., Wong, E., Wong, G. W., Wong, R. W., Wong, V. K., Woodcock, E. A., Wright, K. L., Wu, C., Wu, D., Wu, G. S., Wu, J., Wu, J., Wu, M., Wu, M., Wu, S., Wu, W. K., Wu, Y., Wu, Z., Xavier, C. P., Xavier, R. J., Xia, G. X., Xia, T., Xia, W., Xia, Y., Xiao, H., Xiao, J., Xiao, S., Xiao, W., Xie, C. M., Xie, Z., Xie, Z., Xilouri, M., Xiong, Y., Xu, C., Xu, C., Xu, F., Xu, H., Xu, H., Xu, J., Xu, J., Xu, J., Xu, L., Xu, X., Xu, Y., Xu, Y., Xu, Z. X., Xu, Z., Xue, Y., Yamada, T., Yamamoto, A., Yamanaka, K., Yamashina, S., Yamashiro, S., Yan, B., Yan, B., Yan, X., Yan, Z., Yanagi, Y., Yang, D. S., Yang, J. M., Yang, L., Yang, M., Yang, P. M., Yang, P., Yang, Q., Yang, W., Yang, W. Y., Yang, X., Yang, Y., Yang, Y., Yang, Z., Yang, Z., Yao, M. C., Yao, P. J., Yao, X., Yao, Z., Yao, Z., Yasui, L. S., Ye, M., Yedvobnick, B., Yeganeh, B., Yeh, E. S., Yeyati, P. L., Yi, F., Yi, L., Yin, X. M., Yip, C. K., Yoo, Y. M., Yoo, Y. H., Yoon, S. Y., Yoshida, K., Yoshimori, T., Young, K. H., Yu, H., Yu, J. J., Yu, J. T., Yu, J., Yu, L., Yu, W. H., Yu, X. F., Yu, Z., Yuan, J., Yuan, Z. M., Yue, B. Y., Yue, J., Yue, Z., Zacks, D. N., Zacksenhaus, E., Zaffaroni, N., Zaglia, T., Zakeri, Z., Zecchini, V., Zeng, J., Zeng, M., Zeng, Q., Zervos, A. S., Zhang, D. D., Zhang, F., Zhang, G., Zhang, G. C., Zhang, H., Zhang, H., Zhang, H., Zhang, H., Zhang, J., Zhang, J., Zhang, J., Zhang, J., Zhang, J. P., Zhang, L., Zhang, L., Zhang, L., Zhang, L., Zhang, M. Y., Zhang, X., Zhang, X. D., Zhang, Y., Zhang, Y., Zhang, Y., Zhang, Y., Zhang, Y., Zhao, M., Zhao, W. L., Zhao, X., Zhao, Y. G., Zhao, Y., Zhao, Y., Zhao, Y. X., Zhao, Z., Zhao, Z. J., Zheng, D., Zheng, X. L., Zheng, X., Zhivotovsky, B., Zhong, Q., Zhou, G. Z., Zhou, G., Zhou, H., Zhou, S. F., Zhou, X. J., Zhu, H., Zhu, H., Zhu, W. G., Zhu, W., Zhu, X. F., Zhu, Y., Zhuang, S. M., Zhuang, X., Ziparo, E., Zois, C. E., Zoladek, T., Zong, W. X., Zorzano, A., & Zughaier, S. M. (2016). Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy, 12*(1), 1-222.

Klose, M., Juul, A., Poulsgaard, L., Kosteljanetz, M., Brennum, J., & Feldt-Rasmussen, U. (2007). Prevalence and predictive factors of post-traumatic hypopituitarism. *Clinical Endocrinology, 67*(2), 193-201.

Kopczak, A., Kilimann, I., von Rosen, F., Krewer, C., Schneider, H. J., Stalla, G. K., & Schneider, M. (2014, Jan 1). Screening for hypopituitarism in 509 patients with traumatic brain injury or subarachnoid hemorrhage. *J Neurotrauma, 31*(1), 99-107.

Krewer, C., Schneider, M., Schneider, H. J., Kreitschmann-Andermahr, I., Buchfelder, M., Faust, M., Berg, C., Wallaschofski, H., Renner, C., Uhl, E., Koenig, E., Jordan, M., Stalla, G. K., & Kopczak, A. (2016, Aug 15). Neuroendocrine Disturbances One to Five or More Years after Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage: Data from the German Database on Hypopituitarism. *J Neurotrauma, 33*(16), 1544-1553.

Lauzier, F., Turgeon, A. F., Boutin, A., Shemilt, M., Côté, I., Lachance, O., Archambault, P. M., Lamontagne, F., Moore, L., Bernard, F., Gagnon, C., & Cook, D. (2014). Clinical outcomes, predictors, and prevalence of anterior pituitary disorders following traumatic brain injury: a systematic review. *Critical Care Medicine, 42*(3), 712-721.

Lee, S. C., Zasler, N. D., & Kreutzer, J. S. (1994). Male pituitary-gonadal dysfunction following severe traumatic brain injury. *Brain Injury, 8*(6), 571-577.

Li, H., Zhu, H., Wallack, M., Mwamburi, M., Abdul-Hay, S. O., Leissring, M. A., & Qiu, W. Q. (2016). Age and its association with low insulin and high amyloid-beta peptides in blood. *J Alzheimers Dis, 49*(1), 129-137.

Lieberman, S. A., Oberoi, A. L., Gilkison, C. R., Masel, B. E., & Urban, R. J. (2001). Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. *Journal of Clinical Endocrinology and Metabolism, 86*(6), 2752-2756.

Ma, J., Huang, S., Qin, S., You, C., & Zeng, Y. (2016, Dec 22). Progesterone for acute traumatic brain injury. *Cochrane Database Syst Rev, 12*, Cd008409.

Maggiore, U., Picetti, E., Antonucci, E., Parenti, E., Regolisti, G., Mergoni, M., Vezzani, A., Cabassi, A., & Fiaccadori, E. (2009). The relation between the incidence of hypernatremia and mortality in patients with severe traumatic brain injury. *Critical Care, 13*(4).

Maiya, B., Newcombe, V., Nortje, J., Bradley, P., Bernard, F., Chatfield, D., Outtrim, J., Hutchinson, P., Matta, B., Antoun, N., & Menon, D. (2008). Magnetic resonance imaging changes in the pituitary gland following acute traumatic brain injury. *Intensive Care Medicine, 34*(3), 468-475.

Makulski, D. D., Taber, K. H., & Chiou-Tan, F. Y. (2008). Neuroimaging in posttraumatic hypopituitarism. *Journal of Computer Assisted Tomography, 32*(2), 324-328.

Marina, D., Klose, M., Nordenbo, A., Liebach, A., & Feldt-Rasmussen, U. (2015, 01 Jun). Early endocrine alterations reflect prolonged stress and relate to 1-year functional outcome in patients with severe brain injury. *European Journal of Endocrinology, 172*(6), 813-822.

Molitch, M. E., Clemmons, D. R., Malozowski, S., Merriam, G. R., & Vance, M. L. (2011). Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism, 96*(6), 1587-1609.

Moreau, O. K., Cortet-Rudelli, C., Yollin, E., Merlen, E., Daveluy, W., & Rousseaux, M. (2013, 01 Jun). Growth hormone replacement therapy in patients with traumatic brain injury. *Journal of Neurotrauma, 30*(11), 998-1006.

Moreau, O. K., Yollin, E., Merlen, E., Daveluy, W., & Rousseaux, M. (2012, Jan 1). Lasting pituitary hormone deficiency after traumatic brain injury. *J Neurotrauma, 29*(1), 81-89.

Moro, N., Katayama, Y., Igarashi, T., Mori, T., Kawamata, T., & Kojima, J. (2007). Hyponatremia in patients with traumatic brain injury: incidence, mechanism, and response to sodium supplementation or retention therapy with hydrocortisone. *Surgical Neurology, 68*(4), 387-393.

Mossberg, K. A., Durham, W. J., Zgaljardic, D. J., Gilkison, C. R., Danesi, C. P., Sheffield-Moore, M., Masel, B. E., & Urban, R. J. (2017, Feb 15). Functional Changes after Recombinant Human Growth Hormone Replacement in Patients with Chronic Traumatic Brain Injury and Abnormal Growth Hormone Secretion. *J Neurotrauma, 34*(4), 845-852.

Nemes, O., Kovacs, N., Czeiter, E., Kenyeres, P., Tarjanyi, Z., Bajnok, L., Buki, A., Doczi, T., & Mezosi, E. (2015, 01 Jul). Predictors of post-traumatic pituitary failure during long-term follow-up. *Hormones, 14*(3), 383-391.

Nieschlag, E., Behre, H. M., Bouchard, P., Corrales, J. J., Jones, T. H., Stalla, G. K., Webb, S. M., & Wu, F. C. W. (2004). Testosterone replacement therapy: Current trends and future directions. *Human Reproduction Update, 10*(5), 409-419.

Olivecrona, Z., Dahlqvist, P., & Koskinen, L. O. (2013). Acute neuro-endocrine profile and prediction of outcome after severe brain injury. *Scand J Trauma Resusc Emerg Med, 21*, 33.

Popovic, V., Aimaretti, G., Casanueva, F. F., & Ghigo, E. (2005). Hypopituitarism following traumatic brain injury. *Front Horm Res, 33*, 33-44.

Powner, D. J., & Boccalandro, C. (2008). Adrenal insufficiency following traumatic brain injury in adults. *Current Opinion in Critical Care, 14*(2), 163-166.

Powner, D. J., Boccalandro, C., Alp, M. S., & Vollmer, D. G. (2006). Endocrine failure after traumatic brain injury in adults. *Neurocritical Care, 5*(1), 61-70.

Prasanna, K. L., Mittal, R. S., & Gandhi, A. (2015, 01 Mar). Neuroendocrine dysfunction in acute phase of moderate-to-severe traumatic brain injury: A prospective study. *Brain Injury, 29*(3), 336-342.

Prodam, F., Gasco, V., Caputo, M., Zavattaro, M., Pagano, L., Marzullo, P., Belcastro, S., Busti, A., Perino, C., Grottoli, S., Ghigo, E., & Aimaretti, G. (2013). Metabolic alterations in patients who develop traumatic brain injury (TBI)-induced hypopituitarism [Article]. *Growth Hormone and IGF Research, 23*(4), 109-113.

Ripley, D. L., Gerber, D., Pretz, C., Weintraub, A. H., & Wierman, M. E. (2020). Testosterone replacement in hypogonadal men during inpatient rehabilitation following traumatic brain injury: Results from a double-blind, placebo-controlled clinical pilot study. *NeuroRehabilitation, 46*(3), 355-368.

Rosario, E. R., Aqeel, R., Brown, M. A., Sanchez, G., Moore, C., & Patterson, D. (2013, Sep-Oct). Hypothalamic-pituitary dysfunction following traumatic brain injury affects functional improvement during acute inpatient rehabilitation. *J Head Trauma Rehabil, 28*(5), 390-396.

Sandel ME, Delmonico R, & MJ, K. (2007). Sexuality, reproduction, and neuroendocrine disorders following TBI. In Zasler ND, Katz DI, & Z. RD. (Eds.), *Brain Injury Medicine: Principles and Practices* (pp. 673-695). Demos Medical Publishing.

Schneider, H. J., Aimaretti, G., Kreitschmann-Andermahr, I., Stalla, G. K., & Ghigo, E. (2007, Apr 28). Hypopituitarism. *Lancet, 369*(9571), 1461-1470.

Schneider, H. J., Kreitschmann-Andermahr, I., Ghigo, E., Stalla, G. K., & Agha, A. (2007). Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: A systematic review. *Journal of the American Medical Association, 298*(12), 1429-1438.

Schneider, H. J., Schneider, M., Saller, B., Petersenn, S., Uhr, M., Husemann, B., von Rosen, F., & Stalla, G. K. (2006). Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury. *European Journal of Endocrinology, 154*(2), 259-265.

Schneider, M., Schneider, H. J., Yassouridis, A., Saller, B., Von Rosen, F., & Stalla, G. K. (2008). Predictors of anterior pituitary insufficiency after traumatic brain injury. *Clinical Endocrinology, 68*(2), 206-212.

Sesmilo, G., Halperin, I., & Puig-Domingo, M. (2007). Endocrine evaluation of patients after brain injury: what else is needed to define specific clinical recommendations? *Hormones (Athens, Greece), 6*(2), 132-137.

Shepshelovich, D., Schechter, A., Calvarysky, B., Diker-Cohen, T., Rozen-Zvi, B., & Gafter-Gvili, A. (2017). Medication-induced SIADH: distribution and characterization according to medication class. *British journal of clinical pharmacology, 83*(8), 1801-1807.

Sirois, G. (2009). *Neuroendocrine problems in traumatic brain injury*.

Soltani, Z., Shahrokhi, N., Karamouzian, S., Khaksari, M., Mofid, B., Nakhaee, N., & Reihani, H. (2017). Does progesterone improve outcome in diffuse axonal injury? *Brain Inj, 31*(1), 16-23.

Stanfield, J. P. (1960). The blood supply of the human pituitary gland. *Journal of Anatomy, 94*, 257-273.

Tan, C. L., Alavi, S. A., Baldeweg, S. E., Belli, A., Carson, A., Feeney, C., Goldstone, A. P., Greenwood, R., Menon, D. K., & Simpson, H. L. (2017). The screening and management of pituitary dysfunction following traumatic brain injury in adults: British Neurotrauma Group guidance. *Journal of Neurology, Neurosurgery & Psychiatry, 88*(11), 971-981.

Tanriverdi, F., De Bellis, A., Ulutabanca, H., Bizzarro, A., Sinisi, A. A., Bellastella, G., Paglionico, V. A., Mora, L. D., Selcuklu, A., Unluhizarci, K., Casanueva, F. F., & Kelestimur, F. (2013, 2016-08-22). A five year prospective investigation of anterior pituitary function after traumatic brain injury: Is hypopituitarism long-term after head trauma associated with autoimmunity? *Journal of Neurotrauma, 30*(16), 1426-1433.

Tanriverdi, F., Ulutabanca, H., Unluhizarci, K., Selcuklu, A., Casanueva, F. E., & Kelestimur, F. (2007). Pituitary functions in the acute phase of traumatic brain injury: Are they related to severity of the injury or mortality? *Brain Injury, 21*(4), 433-439.

Tritos, N. A., Yuen, K. C., & Kelly, D. F. (2015). American association of clinical endocrinologists and American college of endocrinology disease state clinical review: a neuroendocrine approach to patients with traumatic brain injury. *Endoctrine Practice, 21*(7), 823-831.

Tsagarakis, S., Tzanela, M., & Dimopoulou, I. (2005). Diabetes insipidus, secondary hypoadrenalism and hypothyroidism after traumatic brain iInjury: Clinical implications. *Pituitary, 8*(3-4), 251-254.

Ulfarsson, T., Gudnason, G. A., Rosén, T., Blomstrand, C., Sunnerhagen, K. S., Lundgren-Nilsson, Å., & Nilsson, M. (2013, 2016-08-22). Pituitary function and functional outcome in adults after severe traumatic brain injury: The long-term perspective. *Journal of Neurotrauma, 30*(4), 271-280.

Wright, D. W., Yeatts, S. D., Silbergleit, R., Palesch, Y. Y., Hertzberg, V. S., Frankel, M., Goldstein, F. C., Caveney, A. F., Howlett-Smith, H., Bengelink, E. M., Manley, G. T., Merck, L. H., Janis, L. S., Barsan, W. G., & Investigators, N. (2014). Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med, 371*(26), 2457-2466.

Yamada, M., & Mori, M. (2008). Mechanisms related to the pathophysiology and management of central hypothyroidism. *Nature Clinical Practice Endocrinology and Metabolism, 4*(12), 683-694.

Yee, A. H., Burns, J. D., & Wijdicks, E. F. (2010). Cerebral salt wasting: pathophysiology, diagnosis, and treatment. *Neurosurgery Clinics, 21*(2), 339-352.

Yuan XQ, W. C. (1991). Neuroendocrine abnormalities in patients with traumatic brain injury. In F. Neuroendocrinology (Ed.), (Vol. 12, pp. 209-230).

Zetterling, M., Engstrom, B. E., Arnardottir, S., & Ronne-Engstrom, E. (2013, Nov). Somatotropic and thyroid hormones in the acute phase of subarachnoid haemorrhage. *Acta Neurochir (Wien), 155*(11), 2053-2062.

Zhang, W., Li, S., Visocchi, M., Wang, X., & Jiang, J. (2010, Aug). Clinical analysis of hyponatremia in acute craniocerebral injury. *J Emerg Med, 39*(2), 151-157.