Review Article

# A Narrative Review on Posttraumatic Hypopituitarism; Part 1: Definitions, epidemiology, pathophysiology and clinical feature

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## ABSTRACT

Posttraumatic hypopituitarism (PTHP) is a form of acquired hypopituitarism following traumatic brain injury (TBI). TBI is a common significant global health problem. TBI in its full range of severity can lead to hypopituitarism with consequent substantial impact on health and quality of life. We carried a narrative review of relevant cohort, case-control studies, systematic reviews, and meta-analyses since the year 2007 and after and published online in PubMed, EMBASE and Medline databases. The aim was to draw health care providers' (HCPs') attention to the existence of PTHP, and to raise their awareness about the approach to such cases. This review is divided into two parts; this part one covered the definitions, epidemiology, pathophysiology and clinical features of TBI and PTHP. The second part dealt with the predictors, diagnosis, treatment and prognosis of PTHP. We intervened by creation of two algorithms on investigations and treatment of PTHP (discussed in part 2 of this review). Results of this part of the review showed that road traffic accidents (RTAs), falls and child abuse are the major causes of brain injury. The age group vulnerable to TBI is 15 to 24 years with male preponderance. Different prevalence of PTHP derived by different studies are attributed to different methods and laboratory cut - off levels to diagnose hormone deficiencies. Africa and North America showed higher TBI incidence than central Asia, Central and Eastern Europe. Pathogenesis of PTHP is multifaceted intricate topic. Clinical manifestations of TBI may overlap with those of acute adrenal insufficiency during the acute phase of TBI. Awareness of the existence of PTHP should be further raised and maintained in the accidents and emergency departments.

***Objectives:*** To review relevant manuscripts and narrate the data available on epidemiology, pathophysiology and clinical features of TBI and PTHP. This is to draw HCP's attention to the existence of PTHP and how it manifest during different phases of TBI. This is to enable them approach PTHP cases in a timely manner.

***Methods:*** We searched PubMed, EMBASE and Medline databases using the words prevalence, incidence, brain injury, hypopituitarism, pathophysiology and clinical features. We narrated the literature derived from this search of manuscripts of cohort, case-control studies, systematic reviews and meta-analyses relevant to this topic

***Results:*** By reviewing the epidemiology of TBI and PTHP we found PTHP is existing with different prevalence. Road traffic accidents (RTAs), falls and child abuse are the major causes of brain injury. Prevalence differs by geographic area, gender and age. Pathogenesis is complicated.


## INTRODUCTION

Traumatic brain injury (TBI) is a major global health problem.[1,2] Post-traumatic hypopituitarism (PTHP) is a form of acquired hypopituitarism that is increasingly diagnosed following TBI.[2] Health care professionals are lacking knowledge on the existence of PTHP and how to properly approach such cases. There may be an overlap between symptomatology of TBI and that of PTHP.

Because of this, we carried this narrative review to improve clinicians' knowledge about definitions and

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**Access this Article Online**

**URL:**
https://jpes.org.pk/index.php/jpes/article/view/22

**Submitted:** June 15, 2024 **Revision Received:** October 15, 2024

**Accepted for Publication:** October 19, 2024



***How to cite this:*** *Mohammed AME, Wanjiru AW, Tsishutsina V. A Narrative Review on Posttraumatic Hypopituitarism; Part 1: Definitions, epidemiology, pathophysiology and clinical feature. JPES. 2024;1(2):69-82.*

classification of TBI severity and how it leads to PTHP, how PTHP presents in the context of TBI.TBI severity can be determined using different scales.[4] TBI in its two phases and of any severity can lead to PTHP. Single anterior pituitary hormone deficiencies were more common than multiple deficiencies.[3] PTHP showed different prevalence from different studies because of different methodology for diagnoses among other suggested reasons.[6] This review will improve HCP' knowledge on the existence of PTHP, its pathogenesis, how it presents at different phases of TBI. In addition we created approach algorithms to allow easy management of such cases. Algorithms were discussed in part 2 of this review.

### *Definitions and classification*

TBI is termed as an alteration in brain functions and controls due to external mechanical forces, which may be associated with neurologic deficits.[3] The pituitary gland and the hypothalamus are the most commonly involved central nervous system (CNS) organs in TBI and results in neuroendocrine dysfunction.

Different scales can be used to classify TBI and assess the severity:[1,4]

a. Glasgow Coma Scale (GCS) (see appendix A).
b. Abbreviated Injury Score for Head Injuries (AIS Head) also known as Head Abbreviated Injury Score (HAIS),
c. International Classification of Diseases (ICD) code.

TBI can also be classified by findings on computed tomography (CT) scan, clinical features,[9] and anatomical changes, according to whether the injury is closed (blunt) or open. Open injuries are always considered severe.[5]

Using the Glasgow Coma Scale, TBI is classified into Mild TBI (total GCS score of 13-15), moderate TBI (total GCS of 9-12), and severe TBI (total GCS of 3-8).[5,6]

GCS classification is the most commonly utilized scale in clinical trials on TBI as it offers excellent decision on clinical management and prognostication. It also has the advantage that it is a bed-side assessment. However, it has the cons of not accounting for the pathophysiological mechanisms causing the injury for targeted therapies and a limited ability to classify individuals with previously established neurological deficits.[7,8] The AIS Head score is preferable to GCS in predicting Glasgow Outcome Score (GOS).[8] The AIS Head score used points from one to six to define severity of TBI with one point denoting minimum severity while six points reflect maximum severity. The Trauma score is a modification of GCS with added vital signs measurement such as systolic BP and respiratory rate and can be used in acute settings.[8]

The following have been identified as causes of TBI: Roads traffic injuries (RTIs),[9,10] falls of different types[2], acts of assault, inflicted injuries (along with shaken baby syndrome),[11] accidents including work-related),[6] professional sportsman head traumas (including repetitive injuries in boxers, football and hockey players), and blast-related brain injuries.[9] New cases of TBI predominantly occurred after road traffic injuries and falls.[2]

The types of head injury documented on imaging studies include: subdural hematomas, intracerebral hemorrhage, extradural hematomas, diffuse axonal injury and base of skull fractures.[12]

Acquired hypopituitarism in most of the cases is due to TBI.[13] Deficiency of one, multiple or all of the anterior pituitary gland hormones is referred to as hypopituitarism.[5]

According to the number of anterior pituitary hormones involved, hypopituitarism can be categorized into three.[14]

a. Isolated hormone deficiency: when only one of the anterior pituitary hormones is deficient, e.g., isolated adrenocorticotropic hormone (ACTH) deficiency;
b. Partial hypopituitarism: when more than one of the pituitary hormones are affected;
c. Panhypopituitarism: when majority or the entire of the anterior pituitary hormones are deficient.

Tanriverdi *et al.* in 2015 noted that, isolated anterior pituitary hormone deficiencies present more often than multiple hormone deficiencies.[3]

Moreover, depending on the time-line between the TBI incidence and the occurrence of hypopituitarism, post-traumatic hypopituitarism (PTHP) can be classified into two[6]:

a. Acute: occurring within 2 weeks after TBI;
b. Chronic: occurring more than 3 months after TBI.

### *Incidence and prevalence of TBI*

Most of the epidemiological studies on incidence of TBI were limited by the inability to comprehensively measure the incidence of outcomes of different injuries and the extent to which TBI can occur. Alternatively, those studies had paid more attention to the types of injuries that led to TBI. Since survivors of such injuries could be burdensome to the community as a whole, and most of the leading injuries are preventable; it worth knowing the extent to which these injuries can lead to TBI.[2]

The Global Burden of Diseases, Injuries and Risk Factors study (GBD) in 2016 was systematically reviewed and revealed an incidence of TBI of 27.08 million new cases in the year 2016 with age-standardized incidence rate of 369/100,000 population.[2] This study reported also that the global prevalence of TBI ranged between 53-58 million (average 55 million) cases with an age-standardized prevalence rate of 759 cases per 100,000 persons. The prevalence and incidence rates had risen by 8.4% and 3.6% respectively in the time period between 1990 and 2016. There were 8.1 million disability-adjusted life years (DALYs) in the same span of time.[2]

By geographic region, Central Asia, Central and Eastern Europe recorded the highest age-standardized TBI incidence and prevalence with combined rates of 740 cases per 100,000 person and 1539/100,000 population respectively for the year 2016. The regions with the lowest incidence of TBI were Oceania, South East Asia and East Asia with incidence rates of 282,283 and 312 cases per 100,000 persons respectively.[2]

In Africa and North America, the incidence of TBI was 801 and 1299 cases per 100,000 people respectively.[10]

There is a gender difference in the prevalence of TBI with men suffering more head injuries as compared to

women[6,15] However, in patients older than 75 years this gender difference is negligible.[16] Based on the age, people aged 15 to 24 years constitute the most at risk group for head injuries.[17]

Globally, half of the TBI cases were resulting from RTIs and falls, while conflicts and terrorism caused more TBI in some regions like North Africa and Middle East.[2] When compared to overall cases of TBI, RTIs-related TBI varied between countries with North America and Southern Asia recording 25% and 56% respectively. [10] Klose *et al.* documented that RTIs and falls affected 94% of the 46 cases included in a prospective study in Denmark with the rest resulting from assault.[18] According to US 2002-2006 analyzed data, TBI resulting from RTIs were estimated as 17.3% and from falls were above 35%.[14]

A systematic review and meta-analysis by Emelifeonwu and colleagues revealed that RTIs are the culprit in 53% of the cases of chronic post-TBI NED followed by falls at 28%.[33]

The three-quarters rule has been suggested by some authors. This refers to the fact that three-quarters of the patients with TBI are male less than 40-years of age, three-quarters of the cases are due to RTIs while three-quarters of patients present within the first year post TBI.[14]

In a qualitative review of 30 articles (*n*=165,000) in five continents (excluding South America), Dewan et al. found that the global incidence of TBI was in the range of 47 and 280 cases per every 100,000 children.[19] In this review, children less than two years and adolescents between 15-18 years were more at risk of TBI. However, more than 80% of pediatric TBI cases were mild in nature and regardless of their country of origin; the majority of children with TBI had favorable outcomes.[19]

Falls were the commonest cause of TBI amongst children below 4 years of age and adults above 65 years old.[17]

Selassie and colleagues in a retrospective cohort study of 10 years duration that included 26,681 children up to 5 years of age, stated that 1.8% of all TBI in children may be the result of abusive head trauma (AHT) with an incidence of around 4% among 5 years old children and 28.9% among infants.[20]

According to the GBD 2016 study, the global prevalence of TBI ranged between 53-58 million (average 55 million) cases with an age-standardized prevalence rate of 759 cases per 100,000 persons.[2]

Subdural hematomas (SDH) and diffuse brain injuries were the most prevalent types of injuries in more than 50% of the TBI cases as was demonstrated by Nemes and colleagues in a prospective study (*n*=126).[12]

### *Incidence and prevalence of post-TBI hypopituitarism*

Recently, a significant difference in the prevalence of TBI-related neuroendocrine dysfunction has been demonstrated ranging between 6% to 69%.[9,12,18,21-25,32,33]

Table-I is generated by referring to references[9,12,18,21-25,32,33] and it summarizes literature review of research on prevalence of PTHP.

This wide variation in TBI-related NED prevalence could possibly be due to variations in times of assessment during the acute and chronic phases of TBI, inter-laboratory assay variations, test panels and different cut-offs.[6,21,26] In addition to this, using or not using body mass index (BMI)-related thresholds for growth hormone (GH) axis assessment,[27] age of patients, trauma severity,[28] and single as opposed to repeating tests, contribute to the diversity of prevalence rates.[29]

Other factors contributing to this variability in prevalence are: severity of injury, injury type, population under study, the study design applied and diagnostic criteria used to diagnose the hormone deficiency as documented in a literature review undertaken by Kokshoorn and colleagues. In this review, the frequency GHD was in the range of 2% to 39%. However, when using different diagnostic tests, there was a variation of this frequency as follows; 8% to 20% when GHRH-Arginine Test was used, 11% to 39% when glucagon stimulation test (GST) was used, while it was between 15% and 18% when insulin tolerance test (ITT) was used.[30]

Klose and colleagues studied 439 post TBI patients and 124 healthy control in a consecutive cohort study with precise focus on the prevalence of GHD influenced by bias.[29] The study found difference in data by local versus guideline cut-offs and difference in testing by ITT versus pyridostigmine-GHRH/Arginine-GHRH testing.[29] Authors connected the high false-positive rate of GHD in their study to non-using BMI-related cut-offs for obese patients.[29]

Schneider and colleagues in a systematic review reported, that PTHP was more prevalent in those with severe TBI (35.3%) as compared with those with moderate (10.9%) and mild TBI (16.8%).[21] This means that TBI of any severity may lead to hypopituitarism. Klose and colleagues[32] reported that the risk of PTHP is higher among patients with severe TBI than among those with mild TBI. Moreover, TBI victims with increased intracranial pressure have a higher prevalence of hypopituitarism. Contrary to this, Niederland and colleagues[25]

in a study in children failed to find a link between severity of TBI and the occurrence of PTHP which was observed to appear without clear symptoms suggesting screening for pituitary dysfunction in all children hospitalized for TBI.

According to the time elapsed since TBI, Alavi and colleagues reported a 10.3% prevalence rate of acute PTHP occurring less than seven days post TBI and a 21.3% prevalence rate of chronic PTHP occurring 6-12 months after trauma.[24] Kopczak and colleagues found that 28.5% of the cases of TBI had at least, an isolated anterior pituitary hormone dysfunction within two weeks post trauma and 4.5% of the patients had partial hypopituitarism.[22]

A study by Kozlowski-Moreau and colleagues (*n*=55) of cases with mild to severe TBI, found that 69% of this cohort had isolated hypopituitarism by one year post trauma.[23]

Post-TBI pituitary dysfunction is usually transient in nature with patients recovering their functional abilities

Table-I: Review of Research on the Prevalence of PTHP.

| *Authors, year* | *Study Design/ Number of participants (n)* | *TBI severity, time elapsed post TBI* | *Prevalence of PTHP (%)* |
|---|---|---|---|
| Emelifeonwu *et al.* (2020) [33] | Systematic review and meta-analysis, 29 studies, *n*=2756 (67% men) | ≥12 months post injury, mild – severe TBI | 31.86% |
| Tanriverdi *et al.* (2015) [9] | Systematic review, 16 studies, *n*=1291 | ≥3 months after TBI, mild – severe TBI | Pooled prevalence: isolated deficiency - 28%, multiple deficiency - 6% |
| Schneider *et al.* (2007) [21] | A systematic review, 14 studies (10 cross-sectional and 4 prospective), *n*=1015 | patients in chronic phase, mild – severe TBI | Pooled prevalence: 27.5% (15-68%) |
| Kopczak *et al.* (2014) [22] | Cross-sectional, observational, single-center study, *n*=340 (18-65 years) | 2 weeks after trauma | 28.5% |
| Klose *et al.* (2007) [32] | Cross-sectional cohort study, control group, *n*=104, 30 controls (78 men, 26 women) (18-64 years) | 10–27 months post injury; mild TBI (*n*=44), moderate (*n*=20), severe (*n*=40) | Cross-sectional: 15% |
| Klose *et al.* (2007) [18] | Prospective study, consecutive patients, *n*=46 | 0–12 days after injury, 3,6 and 12 months after trauma; mild TBI (*n*=22), moderate (*n*=9), severe (*n*=15) | Prospective: 11% |
| Kozlowski Moreau *et al.* (2012) [23] | Cohort study, *n*=55 (46 men, 9 women), (mean age 36 years) | >1 year after trauma, mild – severe TBI | 69% |
| Alavi *et al.* (2016) [24] | Prospective study from a neurosurgical center, *n*=105 (58 serial cohort, 47 cross-sectional late cohort) | Acute phase: ≤ 7days post TBI<br>Chronic phase: 6 months to 12 months | Serial cohort: 10.3%<br>Cross-sectional late cohort: 21.3% |
| Niederland *et al.* (2007) [25] | Cohort study, control group, *n*=26 children, 21 controls (17 boys, 9 girls), (mean age 11 years) | 30.6 ± 8.3 months post injury; mild – severe TBI | 61% |
| Nemes *et al.* (2015) [12] | Prospective study, *n*=126 (103 men, 23 women) | 1 month-5.75 years; moderate TBI (*n*=50), severe (*n*=76) | 57.1% |

within 12 to 36 months. Nevertheless, PTHP may clinically manifest many years after TBI.[6]

***Prevalence of PTHP based on the affected hormone axes in acute and chronic phases of TBI***

The time lapse since trauma occurred influences the hormone axes affected. Generally, the commonly encountered hormone deficiency amongst TBI survivors is GHD.[5,28,31-34] This deficiency also contributes to majority of isolated hypopituitarism cases, i.e., isolated growth hormone deficiency (IGHD).[32]

It seems that children are the most vulnerable to GHD than other axes deficiency[11,36,37] with boys affected more than girls.[25] According to Niederland and colleagues, GHD was diagnosed in 42% of all children with TBI using L-dopa stimulation test.[25] Recent data.[11,38] Using various dynamic tests like, betaxolol+glucagon, arginine-insulin test, glucagon-propranolol also showed high rate of GHD in children (27.8-36.7%).

Patients' hemodynamics can be affected by acute anterior pituitary hormone dysfunction, which subsequently influences the long-term convalescence. Adrenal insufficiency (AI) and central diabetes insipidus (CDI) are more prevalent in the acute phase and tend to resolve. Prolactin (PRL) levels may rise due to lack of inhibitory effect of dopamine, which is lost due to pituitary stalk injury resulting in mild hyperprolactinemia. Following acute injury, acute adaptive responses to stress result in elevation of the stress hormones levels. Stress hormones include cortisol, GH, PRL and vasopressin.[13,18]

TBI presents as an acute and critical illness triggering physiological responses, which may mimic central hypogonadism and hypothyroidism. In a hospital-based

prospective study by Klose and colleagues hormonal assays from days 1-12 after TBI and revealed a high prevalence of thyroid stimulation hormone (TSH) of 67% and gonadotrophin follicle-stimulating hormone (FSH)/ luteinizing hormone (LH) deficiencies reported in 33% of the TBI cases when compared to the healthy controls. However, T4 and insulin-like growth factor 1 forty-six cases studied [18] In these patients, four hormones (TSH, Triiodothyronine (T3), LH and testosterone) were notably low in comparison to the healthy controls, indicating a central pathology. On the other hand, cortisol and copeptin levels showed significant elevation in the (IGF-1) were similar in the two arms. The prolactin level was elevated in 39% of the cases. These were predominantly young patients whose mean age was 38 years with a male preponderance (72%).[18]

Testosterone levels were low during critical illnesses in males on the background of normal gonadotrophin hormones due to the high cytokine levels. This confers a survival advantage, as there is reduction of anabolism. If the critical illness is prolonged, the gonadotrophins will fall due to the hyperprolactinemia further worsening the testosterone deficiency.[39]

Also,a prospective study of severe TBI cases by Olivecrona et al.[40] documented a significantly suppressed hypothalamo-pituitary gonadal axis in those admitted within 24 hours of head injury. On day 1, the testosterone levels were low in 82.1% of these patients. This percentage rose to 100% on day 4 when all the patients recorded low testosterone levels. This was on the background of a normal mean serum sex hormone binding globulin (SHBG) level.[40]

Assessment and interpretation of plasma cortisol levels in the acute phase following TBI is oftentimes challenging as the levels can be inappropriately low on a background of a stressful event. These levels are affected by the cortisol binding globulin (CBG) levels, which can vary acutely and hence affect plasma cortisol level. There is no clear relationship between free and total plasma cortisol following acute TBI. Moreover, old studies underestimated the incidence of hypocortisolism (4%-53%) in the acute phase post-TBI, as they were based on a one-time assay of serum cortisol level ignoring the fact that plasma cortisol levels are highly dynamic.[41] Recently, hypocortisolism was noted to be very common (78%) amongst cases of acute moderate-severe TBI in a cohort study of 100 patients and 15 controls of previously healthy individuals admitted after major surgeries.[41] Bensalah and colleagues found that 20 out of 66 patients (30.3%) with initially acceptable levels of cortisol in the acute phase, who were diagnosed later (at 3 months) with hypocortisolism[42]

Table-II[41-45] shows the results of the above mentioned studies in addition to other studies on the prevalence of hypopituitarism during the acute phase of TBI. It is generated by referencing to references.[41-45]

In the chronic phase after TBI, the hormonal profile picture differs from that of the acute phase and again with progression of time since occurrence of TBI i.e., at three, six, and twelve months as well as at one year and beyond. This is because some of the hormonal deficiencies recover spontaneously with time while some new deficiencies may appear much later.[11,18,35,46] This knowledge is important as it guides in determining the follow-up period after TBI.

Various studies have captured the hormonal profiles at differing times of the chronic phase. Klose et al.[18] extended the follow-up period to three, six and twelve months after the TBI and documented different hormonal axes deficiencies as compared to the ones in the acute phase. These authors repeated the hormonal assays at 3 months for 41 out of the 46 patients studied, at six months for 36 patients of these patients and at twelve months for all of the 46 patients. They found that there was a significant drop in the overall prevalence of PTHP from 76% noted in the acute phase to 13% at three months. GHD was the most prevalent NED observed in 10.8% of the cases under study followed by ACTH deficiency reported in 6.5%. TSH, gonadotrophin and anti-diuretic hormone (ADH) deficiencies were noted in 2.1% of the patients per hormone.[18] At one year, the prevalence of PTHP was at 11% with majority having GHD; one patient had multiple deficiencies. One female patient was reported to have high prolactin level and deficiencies of gonadotropin and TSH in the acute phase of TBI. She additionally developed a GHD at 3 months post-TBI, and she had complete recovery of her hypopituiatrism at 12 months follow-up.[18]

Dassa et al.[11] prospectively studied children over more than 5 years' time and found that out of 17 children with registered GHD at 1 year, 12 children resolved it later at 3.5-4.5 years follow-up, while one child with no GHD deficiency at 1-year follow-up has developed GHD at 6.5 years post trauma follow-up.

Prospective long-term follow-up studies beyond one year after TBI are lacking. Tanriverdi and collaeuges.[35] followed up 30 TBI survivors and assessed their pituitary hormone profiles in one year and again in the third year after head trauma. GHD remained the most prevalent pituitary hormone deficiency in these two times. Interestingly, above 50% of the cases who had GHD in one year had full spontaneous recovery by the third year without use of GH replacement therapy. Those who recovered mainly had mild to moderate TBI. New onset GHD was reported in one patient (3.2%) in the third year of follow-up period.[35]

Another notable observation is that 83.3% of the patients, who were ACTH-deficient in the first year, had recovered spontaneously twenty-four months later. Another patient who previously had adequate ACTH levels, became ACTH-deficient in the third year.[35]

However, in a study by Tanriverdi and colleagues, there were no notable differences in the hormonal profiles of the thyroid, gonadal, prolactin, GH, IGF-1 and cortisol axes at the two times these (12 months and 24 months). An exception to this observation were the concentrations of ACTH, total testosterone and free testosterone which had significantly decreased and increased respectively.[35]

Table-II: Frequencies of Specific Hormone Deficiency during the Acute Phase of TBI.

| *Authors* | *Study design, severity* | *GH/ IGF-1* | *ACTH/ Cortisol/* | *FSH/LH/ Estrogen/Testosterone/ Total Testosterone (TT)* | *Total/fT4/ T3/TSH* | *PRL* | *CDI or ADH/ Copeptin* |
|---|---|---|---|---|---|---|---|
| Hannon et al. (2013) [41] | Cohort study, control group; n=100, controls n=15 (after major surgery); moderate-severe TBI; D1, D3, D5, D7, and D10 | - | Low cortisol (<300 nmol/l): 78% | - | - | - | Acute CDI: 51%; Acute SIADH: 15% |
| Olivecrona et al. (2013)[40] | Prospective study, consecutive patients; n=45; severe TBI; Day 1 | Low IGF-1: 30.2%; High IGF-1: 0% | Low cortisol (<276 nmol/l) Morning: 54.5%, Evening: 52.3%; High cortisol (>800 nmol/l) Morning: 0% | Men: Low LH: 55.2%; High LH: 6.9%; Low TT: 82.1%; Low FSH: 10.3%; High FSH: 6.9% | Low fT4: 5.5%; High fT4: 9.1%; Low TSH: 4.5%; High TSH: 0% | High PRL Men: 48.3%; Women: 66.7%; Low PRL Men: 6.7%; Women: 0% | - |
| | Day 4 | Low IGF-1: 2.3%; High IGF-1: 7% | Low cortisol (<276 nmol/l) Morning: 70.5%; Evening: 59.1%; High cortisol (>800 nmol/l), Morning: 6.8% | Men: Low LH: 58.6%; High LH: 6.9%; Low TT: 100% Low FSH: 37.9%; High FSH: 3.4% | Low fT4: 27.3%; High fT4: 0%; Low TSH: 15.9%; High TSH: 9.1% | High PRL: Men: 72.4%; Women: 86.7% | - |
| Hadjizacharia et al. (2008)43 | Prospective study; n=436; severe TBI | - | - | - | - | - | 15.4% Blunt injury: 12.5%; Penetrating injury: 40.9% |
| Dalwadi et al. (2017) [44] | Cross-sectional study, consecutive patients; n=49; within 24 hr of admission; mild-severe TBI | Low IGF-1: 46.9% | Low cortisol (<7mcg/dl): 12.24% | 63.5% | Low fT4: 6.1% | High PRL: 4% | - |
| Mirzaie et al. (2013) [45] | Multicenter, cross-sectional study; n=50; D0-D10; moderate-severe TBI | --- | 18% and 28% | - | - | - | - |
| Bensalah et al. (2018) [42] | Prospective study; n=277, male 93%; moderate-severe TBI; severe AI: S. cortisol ≤83 nmol/L, moderate ≤276 nmol/L, registered ≤414 nmol/L; D1-D7, | - | Severe: 2.9%, moderate: 20.2%, registered: 35.4% | - | - | - | DI: 2.8% |

Tanriverdi and colleagues further followed up 25 patients up to the fifth year and provided more insight on long-term effects of TBI on the pituitary hormones.[46] GHD remained the most prevalent pituitary hormone defects even on long-term follow-up period of sixty months. 28% of the patients under study had isolated hormone deficiency (24% IGHD and 4% isolated ACTH deficiency) while multiple hormonal axes involvement was documented in only 4% with no case of panhypopituitarism. The more severe the TBI was, the higher the risk of persistent hormonal deficiency at three and five years post TBI.[46]

A systematic review by Kokshoorn, *et al.* which included 931 patients presenting at one year or more following TBI, showed a high variability in the prevalence rates of the various pituitary hormone deficiencies.[30] This was due to inter-laboratory differences in the analytical methods as well as differing cut-off values used for definition of hypopituitarism as well as the reversibility of intracranial insults like intracranial hypoperfusion and hypertension following TBI.[35]

Kopczak and colleagues undertook a cross-sectional observational study during which they observed individuals undergoing neurorehabilitation after TBI ($n$=340) or subarachnoid hemorrhage (SAH) ($n$=169) in post-acute phase <1 month and up to 39 years following trauma. Testosterone deficiency was the commonest abnormality amongst these patients with a low level documented in 40.7% of the patients of which 30.1% did not have concomitant hyperprolactinemia. The other hormone deficiencies were all less than 10% (fT4 5.9%, IGF-1 5.8%, cortisol 1.4% and prolactin 0.2%). 28.0% of these patients had one axis affected while 4.5% had two or more axes involved.[22]

Frequencies of PTHP based on the axis affected during the chronic phase are shown in Table-III.[32,33,11,18,23,25,30,35-38,42,46,59.]

### *Pathophysiology and pathogenesis of post-TBI hypopituitarism*

The pathophysiology of traumatic brain injury is an unquestionably intricate topic to comprehend owing to the vastness of contributing factors like severity and mechanisms of the injuries and patterns of brain injury across all ages. Nevertheless, in the recent past, it is becoming clearer with better clinical appreciation of the process. This clarity has played a significant role in the advancement of the current treatment model that emphasizes on urgent management of primary brain injury while circumventing secondary brain injuries and maintaining cerebral blood flow and enhancing metabolism.[47]

### *Mechanisms of pituitary dysfunction following TBI:*

The pathogenesis of hormonal dysfunction post-TBI is multifaceted and includes several mechanisms as discussed by different authors.[5,6,47-50]

### *Primary mechanism:*

The pituitary gland is located in a saddle-shaped depression at the base of the skull called the sella turcica. It has two lobes, anterior and posterior, which are attached to the hypothalamus by the infundibular stalk. Direct impact on the base of the skull can cause primary damage to the gland and other related structures. Furthermore, hypothalamus, the infundibulum stalk and the pituitary gland can be damaged by whirling and shearing forces during the injury. In addition, the hemorrhaging blood within the sella turcica can compress on the gland causing further damage.[6,47,51] Vascular injury involving the long hypophyseal portal veins can result in ischemia or infarction of the pituitary gland as noted by Gray and colleagues.[13] Infarction of adenohypophysis was confirmed in 43% of autopsies (13/30 patients with PTHP), injured during road traffic incidents.[52] Pituitary changes were confirmed on magnetic resonance imaging (MRI) in 93% of PTHP patients.[6]

### *Secondary mechanism:*

Secondary mechanisms can further cause ischemic damage to the pituitary gland. These are as a result of low blood pressure, low oxygen saturation, brain swelling with subsequent elevation of intracranial pressure, alterations in blood flow to the brain, and altered metabolism.[13,51] Necrosis of the pituitary also could occur secondary to the effect of generalized hypovolemia and the pressure effect of raised intracranial pressure (ICP) which could also lead to dissection or displacement of the pituitary stalk.[6] This impaired vascular supply hypothesis seems a plausible mechanism since it explains the order of hormonal loss in PTHP which follows the distribution of vascular damage in TBI. The somatotrophs and gonadotrophs are located in the lateral part of the anterior pituitary and pars tuberalis respectively and secrete GH and gonadotrophin hormones (LH/FSH) sequentially. These two areas are prone to vascular damage following TBI. Therefore, the first hormonal deficiencies to appear post TBI involves these hormones. The central area harbors the corticotrophs and thyrotrophs and secretes ACTH and TSH respectively. It is less vulnerable to vascular damage, thus these two hormonal deficiencies occur later on.[6]

The most affected axes, GH and FSH/LH, are provided blood supply only by the long hypophyseal portal pathway and are susceptible to ischemia. On the other hand, the less affected axes, ACTH and TSH are provided blood supply by two pathways; the long and short hypophyseal portal supplies thus less susceptibility to ischemia and subsequent hormone deficiencies.[28]

### *Critical illness-induced stress, post-TBI inflammation and drug effects:*

Cytotoxicity and inflammation following TBI may contribute to pituitary hormone deficiency.[5] Damaged and dying cells within few minutes post trauma initiate release of damage-associated molecular patterns (DAMPs). DAMPs, through activation of pattern recognition receptors (PRR), consequently induce the release of cytokines and chemokines.[48]

Both primary and secondary insults can activate the complement system with further release of proinflammatory cytokines including tumor necrosis

Table-III: Frequencies of Specific Hormone Deficiency during the Chronic Phase of TBI.

| *Author/ Year* | *Study Design/ Sample size* | *Hormone Deficiencies* | *Prevalence* | | | | |
|---|---|---|---|---|---|---|---|
| | | | *Short term follow-up* | | | *Long term follow-up* | |
| | | | *≥3months* | *≥6months* | *≥1 year* | *≥3 years* | *≥5 Years* |
| Tanriverdi *et al.* (2008) [35] | Prospective study; *n*=30; one and three years postinjury; mild-severe | GH | - | - | 43.3% | 23.3% | - |
| | | ACTH | - | - | 20% | 6.6% | - |
| | | TSH | - | - | 6.6% | 0% | - |
| | | FSH/LH | - | - | 3.3% | 0% | - |
| Klose *et al.* (2007) [59] | Cross-sectional, cohort study control group; *n*=104, 30 controls (78 men, 26 women) (18-64 years); 10–27 months postinjury; mild-severe | GH | - | - | 15% | - | - |
| | | ACTH | - | - | 5% | - | - |
| | | FSH/LH | - | - | 2% | - | - |
| | | TSH | - | - | 2% | - | - |
| | | PRL | - | - | 6% | - | - |
| Klose *et al.* (2007) [18] | Prospective study, consecutive patients; *n*=46; 3,6 and 12 months after trauma; mild-severe | GH | 13% | 13% | 10.8% | - | - |
| | | ACTH | 6.5% | - | 6.5% | - | - |
| | | FSH/LH | 4.3% | - | 2.1% | - | - |
| | | TSH | 4.3% | - | 2.1% | - | - |
| | | PRL | 2.1% (high) | - | 2.1% (high) | - | - |
| Tanriverdi *et al.* (2013) [46] | 5 year prospective follow-up study; 1st yr *n*=25; 3rd yr *n*=17; 5th yr *n*=25; mild-severe | GH | - | - | 44% | 23% | 28% |
| | | ACTH | - | - | 16% | 0% (3 recovered, one not tested) | 4% (new onset) |
| | | FSH/LH | - | - | 8% | 0% | 4% |
| | | TSH | - | - | 4% | 0% | 0% |
| Emelifeonwu *et al.* (2020) [7] | Systematic review and meta-analysis 29 studies, *n*=2756 (67% men); ≥12 months postinjury; mild-severe | GH | - | - | 22.1% | - | - |
| | | ACTH | - | - | 9.9% | - | - |
| | | FHS/LH | - | - | 10.2% | - | - |
| | | TSH | - | - | 6.2% | - | - |
| | | PRL | - | - | 3.6% | - | - |
| Niederland *et al.* (2007) [25] | Cohort study in children, *n*=26 children, 21 controls (17 boys, 9 girls) (mean age 11 years); 30.6 ± 8.3 months postinjury; mild-severe | GH | - | - | - | 42% (L-dopa) | - |
| Kozlowski Moreau *et al.* (2012) [23] | Cohort study; *n*=55 (46 men, 9 women), (mean age 36 years); >1 year after trauma; mild-severe | GH | - | - | 63.6% (40% severe, 23.6% partial) | - | - |
| | | ACTH | - | - | 27.3% | - | - |
| | | TSH | - | - | 21.8% | - | - |
| | | ADH | - | - | 1.8% (SI-ADH) | - | - |
| | | FSH/LH | - | - | 3.6% | - | - |
| | | PRL | - | - | 7.3% (high PRL) | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Norwood *et al.* (2010) [37] | Cohort study; *n*=32 (8-21 years old); 6-7 months after the TBI; moderate-severe | GH | 16%: deficiency 19%: insufficency | - | - | - | - |
| Kokshoorn *et al.* (2010) [30] | Systematic review. *n*=931; ≥1 year post TBI; mild-severe | GH | - | - | 2-39% | - | - |
| | | ACTH/ Cortisol | - | - | 0-60% | - | - |
| | | TSH | - | - | 0-19% | - | - |
| | | FSH/LH | - | - | 0-29% | - | - |
| | | PRL | - | - | 0-16% | - | - |
| Bensalah *et al.* (2018) [42] | Prospective study; *n*=133, three months after the TBI; moderate-severe | GH | 18% | - | - | - | - |
| | | ACTH/ Cortisol | 29.3% | - | - | - | - |
| | | TSH | 1.5% | - | - | - | - |
| | | FSH/LH | 6.8% | - | - | - | - |
| | | PRL | 6.8% (high), 3.8% (low) | - | - | - | - |
| Casano-Sancho *et al.* (2013) [36] | Prospective study; *n*=37 (23 patients ≥ 6 years old, 14 patients <6 years old); three and twelve months after the TBI; mild-severe | GH | ≥6 years old: 47.8% (glucagon and clonidine); <6 years old: 0% | - | ≥6 years old: 34.7% (glucagon and clonidine) | - | - |
| | | ACTH/ Cortisol | ≥6 years 43.4% (223–436 nmol/l); <6 years 0% | - | 13% (low normal); 0% | - | - |
| | | TSH | <6 years 0% | - | 0%; 0% | - | - |
| | | FSH/LH | <6 years 0% | - | 0%; 0% | - | - |
| | | PRL | - | - | 0%; 0% | - | - |
| Dassa *et al.* (2019) [11] | Prospective longitudinal study; *n*=66 (*n*=61 with follow-up), children, below 15 years old; severe TBI | GH | - | - | 27.8% (17/61) IGF-1, Arg-insulin test, glucagon-propranolol test | 8.19% (5/61) | 9.83% (6/61: 1 new, 5 remaining) |
| | | ACTH | - | - | ACTH 1.63% (1/61) | - | - |
| | | TSH | - | - | 3.27% (2/61) | 3.27% (2/61) | 3.27% (2/61) |
| | | PRL | - | - | 0% | - | - |
| Personnier *et al.* (2014) [38] | Prospective longitudinal study, *n*=87, median age 6.7 years old, 9 > months after the TBI; severe TBI | GH | - | 36.7% (betaxolol +glucagon/glucagon); 31% (Arg) | - | - | - |

factor alpha (TNF-α), interleukin-1 (IL-1),[28] interleukin-6 (IL-6),[53] chemokines (growth-related oncogene (GRO), macrophage inflammatory protein-2 and protein-1 beta (MIP-2 and MIP-1 beta), monocyte chemotactic protein-1 (MCP-1), prostaglandins, and free radicals, as well as nitric oxide (NO).[50,53]

Cerebral inflammation following trauma is characterized by neutrophils, monocytes, and lymphocytes infiltration which results in glial activation.[48]

***Role of autoimmunity:***

Anti-pituitary antibodies (APA) and anti-hypothalamic antibodies (AHA) associated with a more drastic and/or prolonged pituitary dysfunction after TBI. This implies an involvement of the immune system.[6,9,47] A 5-year prospective study by Tanriverdi and colleagues revealed that higher levels of the antibodies were associated with increased frequency of PTHP, whereas absence of these antibodies was linked to recovery of the pituitary function.[46] APA and AHA can be detected in post-TBI survivors for up to five years after the trauma. The mechanism by which autoantibodies influence PTHP is unclear, suggesting a need for research to ascertain the relevance of these autoantibodies to PTHP. Knowledge of autoimmunity has the potential role of categorizing patients at risk of PTHP.[6]

***Genetic predisposition/polymorphism:***

A genetic component is part of the intricate pathophysiology of PTHP.[6] Genetics have been implicated in the evolution of post-concussion clinical outcomes. A recent multicenter prospective cohort study by Terrell and colleagues in 2018 involving 1056 college athletes, genotyping was done for various genetic biomarkers and results were analyzed using a self-reported history of concussion and clinical outcomes.[49] IL-6R CC was linked to concussion risk while presence of apolipoprotein E 4 (ApoE4) was found to be protective against concussion. This latter finding was surprisingly the opposite of what other researchers had observed both in the past and in recent times when they documented poor outcomes of TBI with ApoE4 positivity.[49]

Many genes associated with TBI susceptibility is under investigation, and currently the gene encoding apolipoprotein E (ApoE) has taken more attention.[54] ApoE is a lipoprotein with documented neuronal anti-inflammatory properties and eminent response to growth and repair of neurons.[6, 54] Several alleles (3 alleles formed 6 genotypes) have different actions. ApoE3 stimulates neuron growth, while ApoE4 inhibits its growth.[54] ApoE genetic polymorphism revealed poor outcome for ApoE4 positivity, and better outcome for ApoE3 genotype in TBI.[54]

A meta-analysis performed by Zhou and colleagues revealed that presence ApoE4 allele was not related to severity of primary injury in TBI, however ApoE4 is associated with an adverse outcome in the extended duration of 6 months post-TBI.[55] Meta-analysis of pediatric patients revealed similar data, with more than a double risk of poor outcome in children with ApoE4 allele.[56] Cases with ApoE4 genotype not only have a poor outcome comparing to non-ApoE4 carriers, but also have impaired neuropsychological outcome and higher possibility for developing dementia and Alzheimer's disease.[54] Cases with ApoE3 genotype have a low risk of developing PTHP.[54] However, further research is required to ethically justify genetic screening of those at risk of concussion.[49]

Another possible genetic component is the circulating microRNAs (miRNAs); as patients with PTHP have been reported to have altered miRNA expression. Several miRNAs have been detected in the serum of patients with PTHP on the 1st, 7th, 28th days and at 5 years post TBI. This is a potential area where patients at risk of PTHP can be identified if microRNAs related genes have been identified.[6]

***Necrosis and apoptosis:***

TBI can be as result of two types of cell deaths: necrosis and apoptosis. Autopsy reports showed that up to 80% of dead patients had necrotic pituitary changes. [27] While necrosis occurs as a result of immediate physical damage to the neurons, apoptosis on the other hand occurs over a few hours to days following the primary insult in a programmed manner. In this latter process, the neurons are intact.[50]

The pituitary gland, the hypothalamus, and the hippocampus are indirectly affected by the apoptosis secondary to raised intracranial pressure.[30]

***Medications:***

Excessive use of medications including opioids, barbiturates, high dose heparin amongst others drugs, in the intensive care unit (ICU) set-up may further complicate the clinical picture of TBI by their mechanism of action or adverse effects.[47]

## Clinical Features

TBI presents with a vast range of clinical manifestations spanning from an asymptomatic picture apparent only on biochemical evaluation to a severe clinical picture due to varying numbers of hormone deficiencies from a single hormone to all of the anterior pituitary hormones. The onset could be sudden and severe requiring urgent care in the intensive care unit or may take many years after the brain injury to manifest.[9]

It is imperative therefore, to consider TBI as a chronic disease process and not an event as commonly assumed taking note of its contribution to considerable morbidity and mortality.[57]

Chronic morbidity in TBI survivors usually presents with a range of physical, neurological, cognitive and psychological symptoms. Brain injury may present with mental fatigue and impaired cognitive function months later and this cluster of symptoms is termed brain injury associated fatigue and altered cognition (BIAFAC) which can impact negatively on the individual's quality of life. These symptoms can overlap with subtle signs of existing PTHP, which results in difficulty with the differential diagnosis

Table-IV: Clinical Features.

| *Hormone Deficiency/ Insufficiency* | *Clinical Features of Hormone Insufficiency/Deficiency* |
|---|---|
| ACTH | Acute: Fatigue, weakness, dizziness, nausea, vomiting, diarrhea, circulatory failure (62), hypoglycemia, hyponatremia, hypotension (26, 61-63).<br>Chronic: Tiredness, pallor, dry skin, anorexia, nausea, weight loss, myalgia, hypoglycemia, hypotension (61-63). |
| FSH/LH (Males) | Impaired fertility, impotence, testicular hypotrophy, reduced libido, decreased muscle mass and strength, decreased bone mass, decreased erythropoiesis, and decreased hair growth, fine wrinkles (62, 63). |
| FSH/LH (Females) | Amenorrhea, oligomenorrhoea, infertility, loss of libido, dyspareunia, fine wrinkles, breast atrophy, osteoporosis, premature atherosclerosis (62, 63). |
| TSH | Fatigue, cold intolerance, constipation, weight gain, dry skin, slow-relaxing reflexes, bradycardia, shortness of breath, cognitive changes (short-term memory), depression (9, 61-63). |
| GH | Reduced exercise capacity and muscle power, impaired psychological wellbeing, low QoL, depression (34), endothelial dysfunction and atherosclerosis (associated with increased cardiovascular risk and early CV deaths), increased central obesity, weight gain in children (37), dyslipidemia, insulin resistance, decreased muscle mass, increased fractures, cognitive changes (including verbal memory, attention changes), fatigue (64) and mood alterations (13, 23, 47,64). |
| PROLACTIN | Failure of lactation (63), hyperprolactinemia, menstrual alteration and sexual dysfunction (28, 62). |
| ADH | Polyuria, polydipsia (including nocturnal), thirst (62, 63), electrolytes abnormality (43), severe hypernatremia (60). |

without laboratory assay. On the other hand, PTHP may aggravate the course of TBI itself.[3,5,51,58] Such changes include depression, irritability, fatigue, low attention, anxiety, sleep disturbances and low memory capacity.[9,58] Patients with PTHP presented with poor quality of life (QoL) and self-social isolation.[59] On the contrary, Gray and colleagues in 2019 documented that, intracerebral bleeding was responsible for the cognitive dysfunction and the subsequent poor quality of life and did not attribute them to hypopituitarism.[13]

Some hormone deficiencies are transient and self-limited with most cases with acute ACTH deficiency recovering within 6 months. However, some patients may experience new hormone deficiencies appearing beyond this time.[41,21]

Diabetes insipidus (DI) can start suddenly within an average period of 1-2 days after head trauma.[43] Some patients may experience an abrupt onset of transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[43] while others can develop a classic triphasic response where DI present initially, then few days later transient SIADH, followed by a second DI which can either be transient or permanent.[60]

In a prospective study by Klose and colleagues, 60% of GHD patients were overweight or obese. However, dyslipidemia was unrelated to GHD scores, and a high mean BMI compared with patients without GHD.[59] Norwood and colleagues noted prevalence of overweight in young adults who have GHD compared to patients without GHD.[37]

Age and gender of the patient as well as the phase of TBI i.e., acute vs. chronic will influence the clinical picture manifesting in a TBI survivor.[61]

The clinical features of pituitary hormonal insufficiency are listed in Table-IV which is generated by referencing to.[5,9,13, 23,26,28,34,37,43,47,60-64]

Those patients with PTHP who develop ACTH deficiency rarely suffer from Addisonian crisis as the secretion of aldosterone via the Renin-Angiotensin-Aldosterone System (RAAS) takes over, producing just enough aldosterone for the normal body requirements except in the presence of acute stress. Again, skin hyperpigmentation is absent in these patients, unlike in those with primary ACTH deficiency.[63] Females with ACTH deficiency may experience hyposexuality together with pubic and axillary hair loss as ACTH is necessary for adrenal androgen production. However, men do not have this complaint as they have sufficient testosterone from the testes.[63]

In adults, GHD manifests mostly with non-specific signs and symptoms. Moderate obesity along with dyslipidemia with subsequent increase in cardiovascular

APPENDIX-A: Glasgow Coma Scale Adapted from Jain et al.[65]

*Glasgow Coma Scale*

| *Activity* | *Best Response* | *Score* |
|---|---|---|
| EYE OPENING(E) | Spontaneous | 4 |
| | To Speech | 3 |
| | To Pain | 2 |
| | None | 1 |
| VERBAL (V) | Appropriate Speech | 5 |
| | Confused Speech | 4 |
| | Inappropriate Words | 3 |
| | Incomprehensible Words or Non-specific Sounds | 2 |
| | None | 1 |
| Motor (M) | Obeys Commands | 6 |
| | Localizes Pain | 5 |
| | Withdraws to Pain | 4 |
| | Decorticate to Pain | 3 |
| | Decerebrate to Pain | 2 |
| | None | 1 |

(CV) risk are associated features.[6, 37, 63] Patients with GHD are usually more debilitated compared to those without GHD. There is connection between severe GHD and low cortisol as well as testosterone levels.[34]

Growth hormone and thyroid hormone deficiencies post TBI may present with growth retardation; a feature not observed in adults. In addition, children may also experience a sudden increase in weight in the presence of GHD.[37]

Casano-Sancho and colleagues in 2013 studied children with GHD after TBI and reported that 10 of the 11 children studied were significantly overweight at one-year follow-up compared to children without GHD.[36] Furthermore, those with GHD had lower FSH levels and the boys had lower testosterone levels compared to those without GHD.[37]

## CONCLUSION

Incidence and prevalence of PTHP are widely variable amongst researchers. Possible reasons of this variability include variations in times of assessment during the acute and chronic phases of TBI, single or multiple tests, kind of laboratory test and different cut-off level for these tests. Age of patients and trauma severity of assessed patients also may influence the diversity of incidence and prevalence rates.

TBI of any severity may lead to hypopituitarism with higher risk of PTHP encountered in patients with severe TBI. Hormonal deficiencies can manifest at any time after head trauma. It is important to appreciate that, hormonal deficiencies during this time can be transient.

Frontline physicians in A&E departments should improve their awareness of PTHP especially on adrenal insufficiency in the immediate period following head trauma.

## ACKNOWLEDGMENTS

The authors would like to thank Dr. Aisha Sheikh; our tutor while we were students in the 20S group of Post Graduate Diploma in Endocrinology from the University of South Wales (USW) in 2020.We acknowledged that she supported us much while we were students and she encouraged us to publish this work in one of the esteemed journals of endocrinology. Also we would like to thank the members of 20S group of Post Graduate Diploma in Endocrinology from the University of South Wales (USW) in 2020, who participated in the initial literature review for this work when it began as a project for partial completion of requirements of being awarded Post Graduate Diploma-Endocrinology from the University of South Wales (USW) in 2020.

***Statements and Declarations:*** All authors read, approved and gave consent to submit this manuscript. No potential conflict of interest relevant to this article was reported.

***Disclosure Summary:*** The authors have nothing to disclose.

***Ethical Approval and Consent to participate:*** Not applicable.

***Human and Animal Ethics (IRB):*** Not applicable.

***Consent for publication:*** Not applicable.

*Availability of supporting data:* Not applicable.

*Disclosure Summary:* The authors have nothing to disclose.

*Ethical Approval and Consent to participate:* Not applicable.

*Human and Animal Ethics (IRB):* Not applicable.

*Consent for publication:* Not applicable.

*Availability of supporting data:* Not applicable.

*Funding:* The authors declare that no funds, grants or other support were received during the preparation of this manuscript.

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### *Author's Contribution:*

All authors contributed equally in reviewing relevant online articles, collecting as well as editing literature relevant to this topic. The Corresponding author drew the algorithms and the tables. The author and first co-author corrected the spelling and grammar mistakes. The first author organized the whole manuscript according to the guidelines provided by the JPES, wrote the covering letter, title page, abstract, objectives, methodology and results, and the introduction. In addition, she put the references in Vancouver style and inserted them in text and references list.


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