Management of endocrinological problems in children on home invasive mechanical ventilation

Zeynep Siklar[1]

[1]Ankara University Faculty of Medicine

July 11, 2023

Abstract

Children with home invasive mechanical ventilation face numerous difficulties, including endocrine problems that can arise as a consequence of their condition. Endocrine problems seen in children treated with HIMV may develop due to the underlying disease, drugs used, or prolonged mechanical ventilation. This manuscript will discuss the most common endocrine problems encountered in children with home invasive mechanical ventilation, including problems in glucose metabolism, thyroid dysfunction, bone metabolism, adrenal dysfunctions, growth and puberty. Close monitoring, multidisciplinary care, and regular assessments are essential to optimize the endocrin system functions of children requiring HMV. By understanding these complications, it can develop effective management strategies to optimize the health and well-being of these vulnerable individuals.

Title: Management of endocrinological problems in children on home invasive mechanical ventilation

Abbreviated title: Endocrinological problems on invasive mechanical ventilation

Zeynep ŞIKLAR

Prof. in Pediatric Endocrinology, Ankara University School of Medicine

E-mail: zeynepsklr@gmail.com

Phone: +90 312 5956635

Fax number: +90 312 3191440

ORCID number: 0000-0003-0921-2694

There is no conflict of interest

Key words: mechanical ventilation, thyroid, glucose metabolism, growth, endocrine,

Abstract:

Children with home invasive mechanical ventilation face numerous difficulties, including endocrine problems that can arise as a consequence of their condition. Endocrine problems seen in children treated with HIMV may develop due to the underlying disease, drugs used, or prolonged mechanical ventilation. This manuscript will discuss the most common endocrine problems encountered in children with home invasive mechanical ventilation, including problems in glucose metabolism, thyroid dysfunction, bone metabolism, adrenal dysfunctions, growth and puberty.

Close monitoring, multidisciplinary care, and regular assessments are essential to optimize the endocrin system functions of children requiring HMV. By understanding these complications, it can develop effective management strategies to optimize the health and well-being of these vulnerable individuals.

Introduction:

Cases who cannot be weaned from mechanical ventilation due to chronic respiratory failure and who are predicted to need mechanical ventilation for a long time are followed up with home-type invasive mechanical ventilation. Invasive mechanical ventilation (HMV) at home is a revolutionary practice in the care of children with chronic respiratory failure such as neuromuscular diseases, congenital anomalies, or chronic lung diseases. The use of HMV in childhood period has become widespread all over the World [1,2].

Although HMV has improved survival and quality of life for many patients, it also brings with it a number of additional problems. In the follow-up of these patients, respiratory problems such as inadequate ventilation, hypoxia, etc. are often at the forefront. Family education, continuing care of patient, maintaining airway clearence etc. are also important situations [3]. As the goal is to improve and maintain respiratory system functions, possible involvement of other systems can be less noticeable. Various endocrinological problems may develop due to both the underlying chronic disease and long-term mechanical ventilation.

There is very limited data in the literature on endocrine problems that may be encountered in cases with HMV. It is notable that especially glucose metabolism disorders and bone tissue are affected in children with HMV. In addition, it is possible to affect the thyroid, growth, adrenal gland and other endocrinological organs. In this article, endocrinological problems that can be seen in HMV cases will be tried to be discussed from a holistic perspective.

Glucose metabolism:

The impact of IMV on glucose metabolism in children can vary depending on several factors, including the underlying condition, duration of IMV, and the management of the patient's nutritional needs. HIMV applied cases are faced with a chronic stress. Glucose metabolism is also easily affected by the stress conditions in the body. Normal blood glucose levels are maintained by factors which control glucose production and glucose utilisation. The key hormones which regulate glucose homoeostasis include insulin and counter-regulatory hormones (glucagon, epinephrine, norepinephrine, cortisol, growth hormone). Counter-regulatory hormones participate in setting the sensitivity of the peripheral tissues to glucagon and insulin [4]. The main effective factors in the deterioration of glucose homestasis and the development of hyperglycemia in critical diseases are "insulin resistance, insulin deficiency, release of counter-regulatory hormones, given drugs" [5].

Especially in critical diseases, gluconeogenesis increases relative to glucose clearance and insulin resistance develops. When respiratory system diseases are accompanied by an inflammatory response, insulin resistance may be even more pronounced [6-8].

In this condition, which is called Stress Hyperglycemia in Critically ill Children, blood sugar is often above 126 mg/dl and over 150 mg/dl according to some authors. Sometimes a threshold value of >200 mg/dl is considered as stress hyperglycemia[5,8].

Both the increase in gluconeogenesis and insulin resistance develop through the increase of the counterregulatory hormones. In addition to the effects of the increase in counterregulatory hormones, inflammatory cytokines can also reduce insulin secretion. This situation goes together with the increase in blood sugar [6,7]. Mechanical ventilation can induce both pulmonary and systemic cytokine release. Hyperglycemia develops in patients who frequently require intensive care and mechanical ventilation and may be an indicator of the severity of the disease [6,8,9]. In turn, stress hyperglycemia can also cause prolongation of the mechanical ventilation period [6].

Chronic obstructive airway disease itself is a risk factor for hyperglycemia [10]. Also, hyperglycemia itself can cause local glucose increase in the airway and increase in airway inflammation[11]. This situation may become an important problem especially for patients with respiratory tract inflammatory diseases or cystic fibrosis followed by HIMV. Children receiving long-term HIMV are likely to develop bacterial colonization of the airways and respiratory infections. Pseudomonas, Stenotrophomonas, Proteus, and Serratia species are frequently identified microorganisms in the airway cultures of these children [3]. Airway inflammation caused by bacterial etc. infections may be more due to the effect of hyperglycemia and the management of patients may be difficult.

There is insufficient data on glucose metabolism in patients who underwent home invasive mechanical ventilation (HIMV). However, hyperglycemia has been reported frequently in children who underwent mechanical ventilation and were followed up in intensive care units. This situation is frequently seen especially in acutely ill children and is related to mortality. [11,12]. The incidence of hyperglycemia was found to be high (99%) in a group of children with bronchiolitis who required mechanical ventilation. In these cases, high glucose levels were associated with high ventilator pressure. The correlation between the severity of pulmonary disease (and/or ventilator-associated lung injury) and hyperglycemia was explained by the systemic and pulmonary effects of hyperglycemia[11]. In addition, prolonged immobility with bed rest and inactivity mediates acquired skeletal muscle insulin resistance in HIMV patients. Insulin resistance contributes to the development of hyperglycemia. In addition, hyperglycemia may directly facilitate the development of neuromuscular failure via mitochondrial dysfunction and apoptosis pathway [8].

Another risk factor is whether patients have a primary disease such as duchenne muscular dystrophy (DMD) that requires steroid use. If steroid use is necessary, glucose metabolism should be monitored more carefully. Steroid increase in gluconeogenesis, increased muscle insulin resistance and impaired pancreatic insulin secretion. Apart from steroids, beta blocking agents, calcineurin inhibitors and some drugs may also cause hyperglycemia [8]. For this reason, the drugs used by the patients treated with HMIV should be carefully reviewed, and if there is a medication that has an effect on glucose metabolism, blood glucose controls should be monitored more closely.

Some of the patients under HIMV may be patients receiving enteral/parenteral nutrition and there is a risk of overfeeding in these cases. Overfeeding can lead to both hyperglycemia and obesity, resulting in increased risk for impaired glucose metabolism [8].

Due to all these reasons, measurement of fasting plasma blood sugar, insulin, c-peptide levels and HbA1c value in terms of glucose metabolism in HIMV applied cases will guide whether the patient requires treatment in this regard. HbA1c values reflect long-term blood glucose levels. If HbA1c is 5.7% to 6.4% and fasting plasma glucose value is 100 to 125 mg/dL, it indicates prediabetes. HbA1c [?]6.5%, fasting glucose [?]126 mg/dL indicates diabetes [13].

If there is persistent hyperglycemia and there is evidence suggestive of pancreatic beta cell damage or failure (low c-peptide), pediatric endocrinological evaluation is required for the necessity of using insulin or other agents. However, strict glycemic control should be balanced with the risk of hypoglycemia, as aggressive insulin therapy may increase the risk of hypoglycemic events. Healthcare professionals should closely monitor blood glucose levels and adjust insulin therapy or nutritional support as needed to achieve target glucose ranges. If there is insulin resistance, since it is the first step in the development of type 2 diabetes, it is essential to regulate the diet in order to reduce insulin resistance.

It is important to note that the impact of IMV on glucose metabolism can vary between individuals, and each case should be evaluated and managed individually.

Bone metabolism:

The physical activities of the cases under HIMV are limited. Physical activity is a very important parameter for bone health[14]. It was stated that bone mineral density (BMD) values were better in those who did intense physical activity in childhood and adolescence, and on the contrary, the BMD value decreased in those who showed excessive sedentary behavior [15].

It has been known for many years that muscle mass and bone mass are closely related. As muscle strength and muscle mass increase, the stimulus on the bone increases and the bone mass also increases. This theory, called the mechanostat theory, is one of the cornerstones of understanding bone physiology and bone health [16]. Dysfunction of the muscle tissue or not using the muscles will cause the bone mass to decrease or not to increase sufficiently. Complications observed in patients receiving HIMV may include muscle weakness, reduced muscle mass, joint contractures, and decreased range of motion. Reduced weight-bearing activities and lack of mechanical stress on the bones contribute to decreased BMD. Bone loss due to inactivity occurs due to impaired osteoblast activity, resulting in decreased bone formation.

During childhood, the skeletal system grows both in size and shape and bone mass increases. Although mineral accumulation in bone differs depending on age and gender, it is in a continuous increase[17]. During the growth and development process, bone formation and resorption go together, resulting in both expansion and elongation of the bone. This so-called bone modeling process lasts from fetal life to the closure of the epiphyses. During puberty, bone mineralization increases with the growth spurt, and by the end of the twentieth years of life, 90% of the peak bone mass is reached[18]. During this critical period, weight-bearing, high-impact, and/or muscle-enhancing physical activity is important for the development of a healthy skeleton. Muscle force is generated during physical activity, and muscle contractions incur high loads on the skeleton [14]. Prolonged periods of inactivity and immobilization can lead to several complications affecting bone tissue in children. Inactivity, such as immobilisation due to medical conditions, coupled with HIMV, can have adverse effects on bone health. Apart from activity, factors such as medications, hormonal changes, nutrition, adequate protein intake, calcium and vitamin D intake are also effective on bone mass gain. [18,19]. Insufficient gain of peak bone mass is a negative condition for bone health and increases the risk of osteoporosis [17].

Osteoporosis is a chronic disease, characterized by low bone mass, microarchitectural bone disruption, and skeletal fragility leading to fracture [20]. BMD measurement and bone formation-resorption markers are guiding tests to determine the degree of negative impact of bone structure and the risk of osteoporosis. BMD is a method used to determine the bone mineral content, indicating the amount of bone mass as well as the bone content [17,21]. In children, an areal BMD z-score of -2 SD or less according to age and gender is defined as “low BMD”. However, the definition of osteoporosis is not based solely on densitometric measurement results. Vertebral compression fractures are helpful in diagnosing osteoporosis. If there is no vertebral compression fracture, osteoporosis is diagnosed with a clinically significant fracture history and a BMD Z score of [?] -2.0. Two or more long bone fractures by the age of ten; three or more long bone fractures at any age up to 19 years of age; determined as a clinically significant fracture history [22].

It is known that there is a loss of bone mass, especially in those with critical illness. Loss of bone mass can lead to an increase in fragility fractures [20]. Among the factors that increase bone loss are activity restriction, inflammation, vitamin D deficiency, malnutrition, use of drugs that have negative effects on bone such as corticosteroids. While bone turnover is increasing, the balance between osteoclasts, which are effective in bone resorption, and osteoblasts, which are involved in bone formation, is disturbed [23].

Patients undergoing HIMV may have more than one problem that may adversely affect bone health. Among these, the characteristics of the underlying primary diseases, inactivity, malnutrition and the drugs they use can be mentioned.

The main source of vitamin D is through sun UVB exposure and foods, food supplements, vitamin preparations. HIMV patients may not be exposed to sufficient sunlight. Therefore, the main source of vitamin D for these patients should be oral preparations. Vitamin D is essential for optimal bone health. At the same time, vitamin D has an important role in the immune system, cardiac functions, lung functions, muscle function and metabolism [24].

Preventing and managing bone-related complications in children on HMV require a multidisciplinary approach. Encouraging physical activity within the limitations of the child’s medical condition is crucial to promoting bone health. In addition, optimal nutrition (containing adequate and high quality protein, trace elements), vitamin D and calcium intake is necessary in terms of bone health in cases. Appropriate physiotherapy, which includes passive exercise that will support the contraction of the muscles, should not be neglected. Regular monitoring of BMD and bone health markers can aid in early detection and intervention. Patients who develop osteoporosis despite preventive measures should be evaluated for treatments such as bisphosphonates to prevent bone loss.

There is no consensus that covers what should be done in terms of bone health in these patients and makes recommendations. Further research is warranted to develop targeted interventions and guidelines specific to children on HMV to mitigate the impact on bone tissue.

Thyroid:

Thyroid hormones released from the thyroid gland are necessary for the normal physiological functioning of the body, growth and development in children. Changes in thyroid hormone synthesis and/or release can be observed, especially during critical illnesses. In patients receiving HIMV, thyroid functions may be affected by various reasons such as individual patient factors and underlying diseases. Under normal conditions, thyroid hormone is controlled by a feedback loop involving the hypothalamus, pituitary gland, and thyroid gland. Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and stimulating synthesis, and release of thyroid-stimulating hormone (TSH) from the pituitary gland. TSH, on the other hand, stimulates the thyroid gland and releases the thyroid hormones thyroxine, T4 and triiodothyronine, T3 [25]. Understanding these thyroid-related problems is crucial for healthcare professionals involved in the care of children on HMV, as early detection and appropriate intervention can help optimize the overall outcomes and well-being of these vulnerable patients. Thyroid dysfunction may present as hypothyroidism, hyperthyroidism or Non-thyroidal illness syndrome (NTIS). NTIS, also known as euthyroid sick syndrome, is a condition commonly seen in critically ill patients, including those on mechanical ventilation. It is characterized by abnormal thyroid functions with no previously diagnosed intrinsic thyroid disease. Critical illness leads to changes in thyroid hormone levels, with the most common abnormality being decreased levels of serum T3. There are normal or low levels of T4 and normal or low levels of TSH, high levels of reverse T3. The exact mechanisms behind NTIS are not fully understood but are believed to involve changes in the hypothalamic-pituitary-thyroid axis and impaired peripheral conversion of thyroid hormones. It is still unclear whether nonthyroidal illness syndrome is a protective adaptation to illness or a maladaptive response to a stressful insult. Likewise, it remains unanswered whether laboratory abnormalities of nonthyroidal illness syndrome should be corrected [26].

NTIS is frequently encountered in both adults and children who have undergone cardiac surgery. In a study conducted in adults, it was reported that a decrease in T3 level is common in patients who have undergone cardiac surgery who receive long-term mechanical ventilation[27].

Cases under HIMV require long-term care support. It is known that the thyroid hormone axis is affected over time in patients who are hospitalized in the intensive care unit for a long time and given life support. T4 and TSH levels decrease over time in those who have low T3 due to the disease. The pituitary TSH pulsatile release pattern is suppressed and a situation similar to central hypothyroidism occurs. As a result, thyroid hormone production and secretion become insufficient in critically long-lasting diseases. The exact cause of this hypothalamic suppression is unknown. One of the possible reasons could be the drugs used. If dopamine or hydrocortisone is used in a critically ill person, these drugs can provoke hypothyroidism [28].

In cases where HIMV is applied, some drugs may be used due to the underlying disease. Drug interactions are likely to affect thyroid function. In addition, the presence of hemodynamic, metabolic and biochemical problems, as well as changes in drug metabolism and clearance may be effective factors. It has been stated that the decrease in cardiac output and glomerular filtration rate in mechanically ventilated patients may affect the drug pharmacokinetics of possible liver dysfunction [29].

Critical illness and systemic inflammation can disrupt the normal regulation of the hypothalamic-pituitary-axis, leading to thyroid dysfunction. Inflammatory cytokines and other mediators released during critical illness can directly affect thyroid hormone axis at multiple levels. synthesis, secretion, and peripheral conversion[25].

The effects of thyroid hormone on the respiratory system are also present. In case of hypothyroidism, it could affect the ventilation function and the reaction of the respiratory center to hypoxia and hypercapnia, leading to sleep apnea or even respiratory arrest[27].

In mechanically ventilated patients, muscle weakness is a problem that can be seen in half of the patients. Patients with thyroid disorders are also associated with neuromuscular abnormalities and may therefore decrease the threshold for developing any type of myopathy. It has been reported that there is a relationship between low fT3 levels and muscle weakness, especially in those with NTIS [30]. Neuromuscular problems are present in a significant portion of HIMV applied cases. For this reason, the control of the cases in terms of the presence of hypothyroidism or the development of NTIS should not be neglected. It is important to perform thyroid hormone replacement in cases with hypothyroidism.

Adrenal:

The adrenal gland is a key organ in coping with the stress situation, containing steroid-producing adrenocortical cells in the cortex and catecholamine-producing chromaffin cells in the medulla. With the activation of the hypothalamo-hypophyseal-adrenal axis as a stress response, corticotropin-releasing hormone (CRH) is secreted from the hypothalamus and stimulates ACTH secretion from the anterior pituitary. ACTH is the main regulator of adrenal glucocorticoid production, stimulating steroidogenesis of adrenal cortex [31].

Adrenal dysfunction may occur in children under HIMV for various reasons, and adrenal function may play a crucial role in HIMV in children. First of all, HIMV can be considered as a sustained physical stress factor. In patients with intact HPA axis, prolonged stress can continuously stimulate the adrenal gland with increased ACTH and is expected to increase cortisol production. It has been stated that although the level of ACTH, which is high in the acute period, decreases later on, cortisol levels can remain high. This situation is also defined as ACTH-cortisol dissociation of critical diseases. Also, adrenal glands showed that ACTH signaling was unaltered during the first week of critical illness, but was severely suppressed in the prolonged phase. Therefore, high plasma cortisol concentrations, accompanying low concentrations of plasma ACTH, and subsequently low ACTH-regulated gene expression in the adrenal cortex during critical illness can be seen. This situation suggests that the adrenal cortex is stimulated by alternative activators other than ACTH [31,32].

In the context of adrenal function, it is important to consider the use of corticosteroids in children on HMV. Corticosteroids, such as hydrocortisone or prednisolone, may be prescribed to children with chronic respiratory failure to improve their lung function and reduce airway inflammation. However, long-term use of pharmacological doses of corticosteroids are well known to suppress the normal function of HPa axis. Prolonged exposure to exogenous corticosteroids can lead to adrenal insufficiency [31-33].

Adrenal insufficiency can have significant implications for children on HMV. During critical conditions, adrenal failure can be present for different reasons: known primary or secondary adrenocortical insufficiency; treatment with systemic glucocorticoids and acquired loss of adrenal function. Cortisol is crucial for maintaining blood pressure, regulating blood sugar levels, and responding to stress. Without sufficient cortisol production, children may be at risk of adrenal crisis, a life-threatening condition characterized by low blood pressure, low blood sugar, electrolyte imbalances, and cardiovascular collapse [31,34].

To mitigate the risk of adrenal insufficiency and adrenal crisis in children on HMV, close monitoring should be performed in terms of adrenal functions. Since basal cortisol levels may not always be reliable, the adrenal glands' response to stress can be evaluated with the ACTH stimulation test in some cases. If adrenal insufficiency is diagnosed, appropriate measures are taken to provide supplemental corticosteroid therapy and prevent adrenal crisis. Children with previous adrenal insufficiency on HIMV may require stress dosing of steroids during illness, surgery, or other stressful situations.

Hipopheseal dysfunction, growth and puberty:

Hypophyseal dysfunctions can affect several aspects of a child's health, including growth, development, metabolism, and hormonal regulation. While there is not extensive research specifically focusing on the interaction between hypophyseal dysfunctions and HIMV in children, it is important to consider the potential implications. The specific impact of hypophyseal dysfunctions on HIMV in children can vary depending on the underlying cause and individual circumstances. The underlying primary diseases in cases using HIMV are predominantly neurological/neuromuscular problems [2]. In cases with intracranial pathology, head trauma, and accompanying structural pituitary anomaly, hypothalamo-pituitary functions may also be expected to be affected. While GH, TSH, ACTH, LH, FSH, prolactin are secreted from the anterior pituitary; ADH is secreted from the posterior pituitary. Hypophyseal dysfunctions can disrupt the normal functioning of these hormones [35]. Investigating whether there is pituitary insufficiency in patients with accompanying CNS problems and using HIMV, monitoring of hormone levels and appropriate hormone replacement therapies may be necessary.

In addition, if there is glucocorticoid use due to the underlying disease, it is inevitable that growth will be adversely affected. Glucocorticoids mainly affect growth through interactions with the GH-IGF-1 axis. It also has "direct actions on chondrocytes at the growth plate" effects [36].

The positive effect of HIMV application on growth should not be ignored. Chronic systemic diseases have a negative effect on growth[37]. Growth retardation is expected, especially in conditions such as cystic fibrosis with chronic inflammation, which is associated with pulmonary functions [36]. HIMV can enhance the respiratory function of children with chronic respiratory conditions. By providing mechanical support to their breathing, it helps alleviate respiratory distress and fatigue, allowing them to maintain adequate oxygenation and ventilation.

Adequate oxygenation and ventilation are crucial for optimal growth and development in children. Clinical observations support "improved nutrition and somatic growth occurring in response to improved oxygenation" [38]. HIMV helps ensure that children receive sufficient oxygen supply and eliminate carbon dioxide efficiently, creating an environment conducive to growth. Improved respiratory function enables children to thrive and reach their growth potential. By stabilizing respiratory function, HMV can help prevent complications associated with chronic respiratory insufficiency, such as recurrent respiratory infections. By reducing the frequency and severity of respiratory illnesses, children may experience fewer interruptions to their growth trajectory.

Close monitoring, multidisciplinary care, and regular assessments are essential to optimize the growth and development of children requiring HIMV. Pediatric pulmonologists, respiratory therapists, and nutritionists often collaborate to ensure the best outcomes for these children.

Puberty describes the transition from childhood to adulthood and is a complex process that involves physical and psychological maturation[39]. Children with chronic illnesses, including those requiring HMV, may experience delayed puberty compared to their healthy peers. Pubertal delay associated with chronic illness is accompanied by a delay in growth and the pubertal growth spurt. The degree of pubertal development are affected in chronic illness depends upon the type of disease and individual factors. Malnutrition is one of the most important mechanism responsible for delayed puberty[40]. Children on HMV often have complex chronic diseases may require specialized nutritional support. Poor nutrition, inadequate caloric intake, or imbalances in essential nutrients can affect the timing and progression of puberty.

The underlying medical condition, severity of illness, and associated treatments can contribute to hormonal imbalances, and potentially impacting pubertal development. Some medications used in the management of chronic respiratory conditions and HIMV can have effects on hormonal regulation and pubertal development. Glococorticoids, commonly used in respiratory diseases, can interfere with the normal secretion of hormones, potentially impacting puberty [39].

To date,there is no specific research on the impact of HMV on puberty in children in the literatüre. Given the complex nature of the relationship between chronic illness, HMV, and puberty, it is crucial to collaborate with specialists in pediatric endocrinology, pulmonology, and nutrition to manage these children comprehensively. Individualized care plans and regular assessments can help mitigate any potential effects on puberty and promote optimal growth and development.

In conclusion, children with HIMV have to deal with not only respiratory challenges but also a range of endocrine problems that can significantly impact their health and development. Diagnose and managing these complications are crucial for providing comprehensive care to this vulnerable population. Further research and collaborative efforts are needed to enhance our knowledge and develop evidence-based guidelines for the optimal management of endocrine issues in children receiving HIMV.

References:

1. Gurbani N, Benscoter D, Torres-Silva C, Huang G, Hossain MM, Simakajornboon N. Utility of polysomnography for management of chronic invasive mechanical ventilation in children. Pediatr Pulmonol. 2022;57(2):560-566.
2. Özcan G, Zirek F, Tekin MN, Bakirarar B, Çobanoğlu N. Risk factors for first nonscheduled hospital admissions of pediatric patients on home mechanical ventilation. Pediatr Pulmonol. 2021;56(10):3374-3379.
3. Kalm B, Lai K, Darro N. Care of children with home mechanical ventilation in the healthcare continuum. Hosp Pract (1995). 2021;49(sup1):456-466.
4. Güemes M, Rahman SA, Hussain K. What is a normal blood glucose? Arch Dis Child. 2016;101(6):569-574.
5. Hacıhamdioğlu B, Kendirli T, Oçal G, Sıklar Z, Savaş Erdeve S, Ince E, Berberoğlu M. Pathophysiology of critical illness hyperglycemia in children. J Pediatr Endocrinol Metab. 2013;26(7-8):715-720.
6. Srinivasan V. Stress hyperglycemia in pediatric critical illness: the intensive care unit adds to the stress! J Diabetes Sci Technol. 2012;6(1):37-47.
7. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity. Pediatr Crit Care Med. 2008;9(4):361-366.
8. Srinivasan V. Glucose Metabolism and Stress Hyperglycemia in Critically Ill Children. Indian J Pediatr. 2023;90(3):272-279.
9. Doola R, Greer RM, Hurford R, Flatley C, Forbes JM, Todd AS, Joyce CJ, Sturgess DJ. Glycaemic variability and its association with enteral and parenteral nutrition in critically ill ventilated patients. Clin Nutr. 2019;38(4):1707-1712.
10. Edriss H, Selvan K, Sigler M, Nugent K. Glucose Levels in Patients With Acute Respiratory Failure Requiring Mechanical Ventilation. J Intensive Care Med. 2017; 32(10):578-584.
11. Branco RG, Tasker RC. Glycemic level in mechanically ventilated children with bronchiolitis. Pediatr Crit Care Med. 2007;8(6):546-550.
12. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. Pediatr Crit Care Med. 2004;5(4):329-336.
13. Wallace AS, Wang D, Shin JI, Selvin E. Screening and Diagnosis of Prediabetes and Diabetes in US Children and Adolescents. Pediatrics. 2020;146(3):e20200265.
14. Tan VP, Macdonald HM, Kim S, Nettlefold L, Gabel L, Ashe MC, McKay HA. Influence of physical activity on bone strength in children and adolescents: a systematic review and narrative synthesis. J Bone Miner Res. 2014;29(10):2161-2181.
15. Christofaro DGD, Tebar WR, Saraiva BTC, da Silva GCR, Dos Santos AB, Mielke GI, Ritti-Dias RM, Mota J. Comparison of bone mineral density according to domains of sedentary behavior in children and adolescents. BMC Pediatr. 2022;22(1):72.
16. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The 'muscle-bone unit' during the pubertal growth spurt. Bone. 2004;34(5):771-5.
17. Di Iorgi N, Maruca K, Patti G, Mora S. Update on bone density measurements and their interpretation in children and adolescents. Best Pract Res Clin Endocrinol Metab. 2018;32(4):477-498.
18. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, O'Karma M, Wallace TC, Zemel BS. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporos Int. 2016;27(4):1281-1386.
19. Adams JE. Bone Densitometry in Children. Semin Musculoskelet Radiol. 2016;20(3):254-268.

20. Orford NR, Pasco JA, Kotowicz MA. Osteoporosis and the Critically Ill Patient. Crit Care Clin. 2019;35(2):301-313.
21. Crabtree N, Ward K. Bone Densitometry: Current Status and Future PerspectiveAllgrove J, Shaw NJ (eds): Calcium and Bone Disorders in Children and Adolescents. 2nd, revised edition. Endocr Dev. Basel, Karger, 2015, vol 28, p 72–83.
22. Weber DR, Boyce A, Gordon C, Högler W, Kecskemethy HH, Misra M, Swolin-Eide D, Tebben P, Ward LM, Wasserman H, et al. The Utility of DXA Assessment at the Forearm, Proximal Femur, and Lateral Distal Femur, and Vertebral Fracture Assessment in the Pediatric Population: 2019 ISCD Official Position. J Clin Densitom. 2019; 22(4):567-589.
23. Cai Y, Kang F, Wang X. Critical illness and bone metabolism: where are we now and what is next? Eur J Med Res. 2022;27(1):177.
24. Amrein K, Papinutti A, Mathew E, Vila G, Parekh D. Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa. Endocr Connect. 2018;7(12):R304-R315.
25. Radman M, Portman MA. Thyroid Hormone in the Pediatric Intensive Care Unit. J Pediatr Intensive Care. 2016;5(4):154-161.
26. Bello G, Spinazzola G, Giammatteo V, Montini L, De Pascale G, Bisanti A, Annetta MG, Troiani E, Bianchi A, Pontecorvi A, et al. Effects of Thyroid Hormone Treatment on Diaphragmatic Efficiency in Mechanically Ventilated Subjects With Nonthyroidal Illness Syndrome. Respir Care. 2019; 64(10):1199-1207.
27. Shen X, Sun J, Hong L, Song X, Zhang C, Liu Y, Liu H, Li G, Mu X. Decreased triiodothyronine (T3) as a predictor for prolonged mechanical ventilation in critically ill patients with cardiac surgery. BMC Anesthesiol. 2022;22(1):66.
28. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid. 2014;24(10):1456-1465.
29. Morales Castro D, Dresser L, Granton J, Fan E. Pharmacokinetic Alterations Associated with Critical Illness. Clin Pharmacokinet. 2023;62(2):209-220.
30. Shabana TS, Anis SG, Ibrahim DM. Association between Thyroid Dysfunction and Intensive Care Unit-Acquired Weakness: A Case-Control Study. Crit Care Res Pract. 2021;2021:8889036. doi: 10.1155/2021/8889036.
31. Boonen E, Bornstein SR, Van den Berghe G. New insights into the controversy of adrenal function during critical illness. Lancet Diabetes Endocrinol. 2015; 3(10):805-815.
32. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. J Clin Endocrinol Metab. 2006;91(10):3725-3745.
33. Schumaker GL, Epstein SK. Managing acute respiratory failure during exacerbation of chronic obstructive pulmonary disease. Respir Care. 2004;49(7):766-782.
34. Uçar A, Baş F, Saka N. Diagnosis and management of pediatric adrenal insufficiency. World J Pediatr. 2016;12(3):261-274.
35. Chung TT, Monson JP. Hypopituitarism. 2022 Nov 27. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–.
36. Le TN, Anabtawi A, Putman MS, Tangpricha V, Stalvey MS. Growth failure and treatment in cystic fibrosis. J Cyst Fibros. 2019;18 Suppl 2(Suppl 2):S82-S87.
37. Rogol AD, Hayden GF. Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr. 2014; 164(5 Suppl):S1-14.e6.
38. Thoracic Society of Australia and New Zealand; Fitzgerald DA, Massie RJ, Nixon GM, Jaffe A, Wilson A, Landau LI, Twiss J, Smith G, Wainwright C, Harris M. Infants with chronic neonatal lung disease: recommendations for the use of home oxygen therapy. Med J Aust. 2008;189(10):578-582.
39. Wood CL, Straub V, Guglieri M, Bushby K, Cheetham T. Short stature and pubertal delay in Duchenne muscular dystrophy. Arch Dis Child. 2016; 101(1):101-106.

40. Pozo J, Argente J. Delayed puberty in chronic illness. Best Pract Res Clin Endocrinol Metab. 2002;16(1):73-90.