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ENDOCRINOLOGICAL DISORDERS IN DOWN SYNDROME: EVALUATION, TREATMENT AND IMPACT ON QUALITY OF LIFE

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Abstract: Goal: Comprehensively analyze the main endocrinological changes that occur in Down Syndrome, offering a detailed approach to assessment, treatment and the impact of these changes on quality of life. Methods: Bibliographic review conducted in the PubMed Central database, resulting in 334 articles. Subsequently, after rigorous application of inclusion and exclusion criteria, only 11 articles were selected to be part of the present study. **Results:** It was observed that among the most recurrent endocrine-metabolic changes in patients with Down Syndrome are hypothyroidism, associated with type 1 diabetes mellitus, with increased risks and prevalence due to specific genetic factors and hormonal dysregulations. Final considerations: The comprehensive review carried out in this article highlights endocrine-metabolic dysfunctions in patients with Down Syndrome, highlighting the importance of an accurate diagnosis to direct necessary therapeutic interventions, ensuring the health and well-being of these individuals.

INTRODUCTION

Down Syndrome (DS), caused by trisomy 21, is the most common chromosomal alteration, affecting a large number of individuals (ALAARAJ N. et al., 2019; CALCATERRA V. et al., 2020; WHOOTEN R. et al., 2018). In addition to the characteristic intellectual disability, DS makes sufferers more susceptible to various clinical conditions (WHOOTEN R. et al., 2018). According to AlAaraj N. et al. (2019) describes, there is an increased risk of developing thyroid disease, with an emphasis on autoimmune conditions. This leads patients to face and treat a series of diseases triggered by the syndrome, negatively impacting their quality of life.

Among the diseases secondary to DS, endocrinopathies stand out, particularly those related to the thyroid. Congenital

hypothyroidism is 28 to 35 times more prevalent in these patients compared to the general population (CALCATERRA V. et al., 2020). However, despite the American Academy of Pediatrics (AAP) recommendation for annual screening for thyroid disease, approximately 25% of patients over one year of age are not adequately screened (WHOOTEN R. et al., 2018). Other thyroid diseases commonly found in people with DS include hyperthyroidism, Hashimoto's disease, and Graves' disease.

Among the metabolic changes in patients with DS, hypothyroidism stands out as a documented condition, with increased prevalence, being more common in women than in men (ALAARAJ N. et al., 2019). Studies indicate that subclinical hypothyroidism (HS) is the most common form, and evidence suggests that L-thyroxine treatment benefits the growth of infants and young children with DS and HS. The improvement in these patients is associated with an increase in free T4 levels after treatment, resulting in an improvement in linear growth (ALAARAJ N. et al., 2019).

Studies also indicate that, in addition to thyroid disorders, diabetes mellitus has an increased prevalence in DS patients. According to Rivelli A. et al. (2022), other endocrine changes more prevalent in individuals with DS include adrenal insufficiency, prolactinoma/hyperprolactinemia, diabetes insipidus and type I diabetes mellitus, compared to individuals of the same age and sex without DS. However, polycystic ovary syndrome and type II diabetes mellitus are less prevalent in this population.

It is important to highlight that the accurate diagnosis of conditions secondary to DS is challenging due to the limitations imposed by the syndrome itself, as well as the possibility of different clinical presentations in this group of patients. However, knowledge of the most prevalent metabolic changes in DS can improve the quality of treatment and quality of life for these people (RIVELLI A., et al., 2022). Therefore, care for individuals with DS must be adapted to their special needs and characteristics.

The central objective of this review article is to analyze the main endocrinological changes that occur in DS, addressing the assessment, treatment and impact of these changes on the quality of life of individuals affected by this genetic syndrome. The analysis aims to provide essential information to improve the management of these conditions, promoting early detection, selection of effective treatments and thus optimizing clinical outcomes and quality of life for affected patients.

METHODOLOGY

This study corresponds to a narrative bibliographic review carried out following the criteria of the PVO strategy, which encompasses the analysis of the Population or Research Problem, the Variables under study and the Outcomes considered. The research was developed based on a central question that guided the study: "What are the main endocrinological changes in Down syndrome, how are they evaluated and treated, and what is the impact of these changes on the quality of life of affected individuals?" Within this context, according to the established criteria, the population or research problem focuses on patients with Down Syndrome, with the aim of evaluating and treating the main endocrinological changes that occur in this condition. The prognosis of these patients is of particular interest for research, as it seeks to understand how these changes affect their quality of life.

Literature searches were carried out in the PubMed Central (PMC) database by combining the descriptors "Down Syndrome AND Endocrine System Diseases" using the Boolean operator "AND". Initially, 334

articles were identified and, subsequently, strict selection criteria were applied. The inclusion criteria covered: articles written in English; published between 2019 and 2023; that addressed the themes relevant to this research, including review studies and meta-analyses; available in full. On the other hand, the exclusion criteria include articles that did not directly address the central proposal of the research and that did not meet the other inclusion criteria. After carefully applying these criteria, a total of 11 articles were selected from the PubMed database to compose the present study. These articles will provide valuable information about the main endocrinological changes in Down Syndrome, as well as their assessment, treatment and impact on the quality of life of those affected.

DISCUSSION

Individuals with DS present a significant range of metabolic changes, attributed to the elevated genetic and immunological risk resulting from trisomy 21 (MORTIMER; GILLESPIE, 2020). Endocrine conditions such as Type 1 Diabetes Mellitus and obesity stand out, influenced by specific genetic factors and hormonal dysregulations.

The prevalence of Type 1 Diabetes Mellitus in DS is four times higher compared to the general population, possibly related to autoimmunity triggered by type 1 interferon responses, since four of the six subunits of the interferon receptor are encoded by chromosome 21 (PERSONA D.M.F. et al., 2021; MORTIMER; GILLESPIE, 2020). Neonates with Trisomy 21 are seven times more likely to develop neonatal diabetes, attributed to the aberrant expression of the AIRE gene associated with autoimmunity in DS (JOHNSON M. et al., 2019).

Early diagnosis of Type 1 Diabetes Mellitus in DS occurs around two years of age, being managed with lower doses of insulin, resulting in more effective glycemic control, possibly due to a simpler and more routine lifestyle (PESSOA D.M.F. et al, 2021).

In addition to diabetes, obesity is common in DS, attributed to lack of physical activity, unbalanced diet and hormonal changes, which lead to an increase in body fat, which in turn stimulates the production of Leptin, which has an important hypothalamic effect on satiety and energy expenditure, and contributing to the risk of type 2 Diabetes Mellitus and cardiovascular diseases (MOREAU M. et al., 2021).

Regarding hormonal changes, adults with DS present an increase in LH and/or FSH levels, indicative of hypergonadotropic hypogonadism, persisting from childhood to adulthood, although it does not compromise normal pubertal development or fertility (WOOTEN R. et al., 2018).

Studies on exercise programs in individuals with DS have revealed benefits such as reduced cardiovascular risk, improved aerobic capacity, improved posture, increased muscle mass and reduced body weight (MOREAU M. et al., 2021). These findings highlight the complexity of endocrine changes in DS, demanding an integrated approach to optimize the quality of life of these individuals.

In the context of DS, thyroid function in children becomes a significant area of study. A case-control study compared the prevalence of thyroid changes in children with DS in relation to the general population. The focus was on subclinical hypothyroidism, manifested by elevated TSH with normal levels of T4 and T3, and manifest hypothyroidism, characterized by elevated TSH and reduced T4 or T3 (ZELAZOWSKA-RUTKOWSKA B. et al., 2020).

The results revealed that thyroid dysfunctions are more common in children with DS, with subclinical hypothyroidism being the predominant comorbidity in the first

years of life of these individuals. Interestingly, the isolated increase in TSH did not prove to be predictive for the development of thyroid diseases, and evident hypothyroidism was less frequent in this group (ZELAZOWSKA-RUTKOWSKA B. et al., 2020).

In resource-limited settings, newborn screening for thyroid function has been shown to be inadequate, especially in developing countries. Subclinical hypothyroidism was the main change identified, while overt hypothyroidism occurred to a lesser extent, with hyperthyroidism being observed later. Notably, the physical signs of hypothyroidism often overlap with those of DS. Cases of congenital and subclinical hypothyroidism showed normalization of thyroid function in follow-up exams, highlighting the importance of monitoring for at least 6 to 8 months when TSH is elevated and T4 is normal (MULU B.; FANTAHUN B., 2022).

Levothyroxine replacement is crucial to prevent intellectual deterioration in DS patients diagnosed with overt hypothyroidism. On the other hand, compensated (subclinical) hypothyroidism, identified through screening tests, not necessarily through signs and symptoms, generates controversy regarding the need for treatment, unless T4 levels reach a critical threshold (YAQOOB M. et al., 2019). These conclusions highlight the importance of accurate diagnosis and careful monitoring of thyroid function in children with DS, aiming to optimize therapeutic interventions when necessary and guarantee the preservation of the health and cognitive development of these individuals.

FINAL CONSIDERATIONS

This review provided a comprehensive analysis of endocrinological changes in Down Syndrome, highlighting the complexity of these conditions and the interconnection between different genetic factors and hormonal dysregulations. The identification of the most recurrent changes, such as hypothyroidism and type 1 diabetes mellitus, highlights the need for an integrated approach in the clinical management of these patients. A detailed understanding of these endocrine-metabolic changes not only expands knowledge about the syndrome, but also strengthens the importance of early detection and the implementation of individualized therapeutic strategies. Recognizing these conditions at an early stage can contribute significantly to the quality of life of affected individuals. Continued research and innovation are crucial to further improve understanding and therapeutic approaches, with the ultimate goal of promoting a better quality of life for individuals affected by this genetic syndrome.

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