CHAPTER
131

The nutritional status of zinc in children and adolescents with down syndrome: Child development under discussion

https://doi.org/10.56238/alookdevelopv1-131

Cristina Helena de Lima Delambert
Physician - master
UNESP - Faculty of Medicine of Botucatu - Department of Pediatrics
ORCID: 0000-0002-9316-4316

Ingrid da Silva Santos
Nutritionist, specialization in the health area
UNESP - Faculty of Medicine of Botucatu
ORCID: 000-0001-9243-3679

Bruno Zanluqui Moreira
Medical student
UNESP - Faculty of Medicine of Botucatu
ORCID: 0000-0002-4316-8730

Miriam Hashimoto
Prof. Doctor
UNESP - Faculty of Medicine of Botucatu - Department of Pediatrics
ORCID: 0000-0001-6969-9161

Alice Yamashita Prearo
Prof. Doctor
UNESP - Faculty of Medicine of Botucatu - Department of Pediatrics
ORCID: 0000-0002-4356-0599

Lidia Raquel de Carvalho
Prof. Doctor
UNESP – Institute of Biosciences – Department of Statistics
ORCID: 0000-0003-0575-2263

Catia Regina Branco da Fonseca
Associate Professor
UNESP - Faculty of Medicine of Botucatu - Department of Pediatrics
ORCID: 0000-0001-7067-3209

ABSTRACT

Down Syndrome (DS) is a chromosomal disorder. Studies have sought the mechanisms involved in the pathophysiology of diseases associated with DS, as well as the factors that contribute to changes growth and development. Thyroid dysfunctions as well as micronutrient deficiencies have already been evidenced. Zinc is one of the micronutrients involved in the processes of cell differentiation, height growth, neurological development and immune defense, and its deficiency can lead to damage in children with DS. There are no studies in Brazil and the real magnitude of this deficiency is not known in the general population and more specifically among those with DS. The objective of this study was to evaluate the nutritional status of zinc in children and adolescents with and to verify the response to supplementation of this micronutrient, proposing an assistance protocol for this population. A case-control clinical study and a randomized clinical trial, accomplished in 2020 and 2021, in an outpatient service of a University Hospital, with a convenience sample. Case Group: children and adolescents with DS, paired by sex and age with the control group, without the syndrome (1:1), wirh the laboratory analysis of erythrocyte and serum zinc dosages, in addition to assessment of dietary zinc intake. Study approved by the Research Ethics Committee. The results shows differences between groups were significant in relation to birth weight ($p=0.04$), and regarding the level of erythrocyte zinc ($p<0.001$), lower in the control group, despite the fact that the diet of both groups did not show insufficiency in the consumption of this micronutrient. We considerer that with the improvement of care for these children and adolescents will promote better growth and development, impacting their quality of life and that of their caregivers. In opposition to what is described in the literature, children and adolescents with Down syndrome presented better adequacy of the nutritional status of zinc than the control group. The results highlight the relevance of regular follow-up in a health care service, with integral care and multidisciplinary team, from the first months of life.

Keywords: Down Syndrome, Children, Nutrition Assessment, Zinc Deficiency, Promotion of Health.

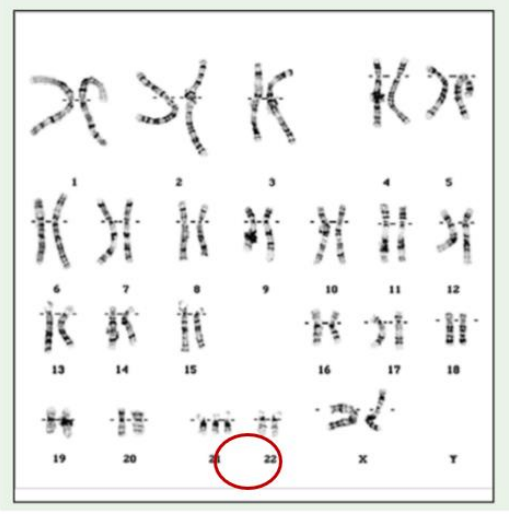
1 INTRODUCTION

1.1 DOWN SYNDROME

Down syndrome (DS) is a genetic alteration present in the human species since its origin. It is a chromosomal disease characterized by the presence and expression of three copies of chromosome 21. Its first description as a clinical picture with its own identity occurred in 1866, by the English pediatrician John Langdon Down (MOREIRA, 2000). In 1958, the French Jérome Lejeune and the English Pat Jacobs independently discover the chromosomal origin, becoming considered a genetic syndrome, naming it Down Syndrome or Trisomy 21, in honor of John Down who initiated the subject in the scientific world (WEFFORT, 2017).

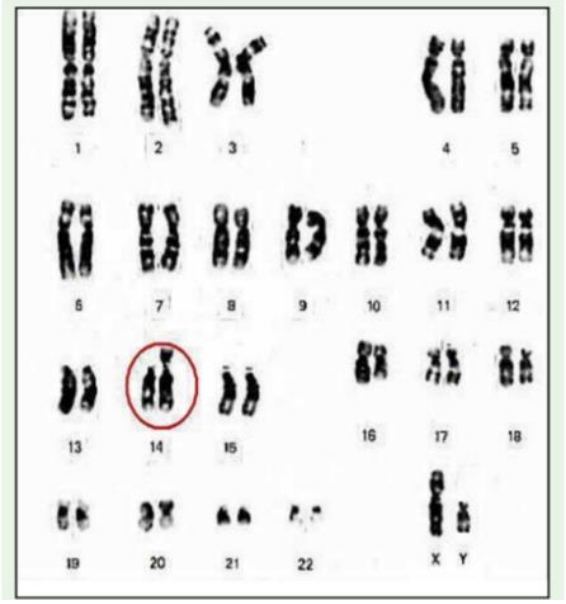
Chromosomal alteration can occur in 3 ways: Simple Trisomy, which occurs during the formation of reproductive cells and depends on chromosomal separation in meiosis, leading to a double chromosome 21 in these cells. Translocation stems from the transfer of one chromosome fragment to another. In the case of DS, this translocation can occur between chromosomes 14 and 21, 21 and 22. The Mosaic is when the extra chromosome 21 is present in some, but not in all the cells of the individual, which, in this way, presents different karyotypes – part with 46 pairs of chromosomes, part with 47 pairs, being a pair of chromosome 21 the additional. Simple Trisomy is the most common, occurring between 90-95% of cases; Translocation, at rates of 5-6%; and Mosaicism, between 2 and 3% (MAZUREK, 2015).

Figure 1 – Female karyotype with Simple Trisomy (Free) 47, XX + 21



Source: BRAZIL, 2012; SBP, 2020.

Figure 2 – Male karyotype with translocation trisomy 46, XY t(14,21) (14q;21q)



Source: BRAZIL, 2012; SBP, 2020.

According to the Brazilian Federation of Down Syndrome Associations, the estimated incidence of the syndrome in the world is 1 in 1,000 live births. The *National Down Syndrome Society* (NDSS) reports that approximately one in every 700 babies in the United States is born with Down syndrome, about 6,000 per year. No different, in Brazil, it is estimated that every 700 births occurs 1 case of trisomy of 21, adding up to around 300 thousand people with the syndrome.

The diagnostic suspicion of DS can be performed before birth, in the gestational period, by ultrasound examination, by observation of phenotypic changes and other typical characteristics (WUO, 2007). After birth, the clinical diagnosis of DS is based on the recognition of the phenotype, characterized by: brachycephaly, flat and round face, upward oblique eyelid folds, epicanthic fold, sinophre, flat nasal base, lingual protrusion, retrognathia, high palate, small pinna, low implantation ears, thin and straight hair, short neck with excess adipose tissue on the back, single palmar fold, clinodactyly of the 5th metacarpal, brachydactyly, flat foot, distance between the 1st and 2nd toes, hypotonia, ligamentous laxity, diastasis of the rectus abdominis muscles and umbilical hernia (MAZUREK, 2015) (BRAZIL, 2012).

Figure 3 – Phenotypic characteristics of Down Syndrome (face, hands and feet)

Source: SBP, 2020.

However, laboratory diagnosis is performed through the study of the karyotype, the representation of the set of chromosomes present in the cell nucleus of the individual. Not mandatory for the diagnosis of DS, but fundamental to guide the genetic counseling of the family, since it is the only way to determine the casual or inherited form of the syndrome (BRASIL, 2012).

Children with DS have a higher incidence of several health conditions that affect quality of life, including prematurity, congenital heart disease, gastrointestinal malformations and disorders, thyroid function disorders, changes in the immune response, among others (MUSTACCHI, 2007) (WEFFORT, 2017) (RIBEIRO, 2003). According to the guidelines of the American Academy of Pediatrics and the Ministry of Health, they also have growth restriction, both intrauterine and postnatal, and overweight.

Life expectancy among people with DS has increased considerably in recent decades. This fact is related to the development of research and service offerings, enabling a better monitoring and

treatment of the comorbidities of the syndrome, also acting in the prevention of complications (BERTAPELLI, 2017) (NISHIHARA, 2006).

Studies have sought to clarify the mechanisms involved in the pathophysiology of diseases associated with the syndrome, as well as the contributing factors for impaired growth and development. Disorders in the function and metabolism of thyroid hormones have already been evidenced, as well as micronutrient deficiency (MARQUES, 2006).

Micronutrients perform complex functions to preserve metabolic balance, iron, zinc, copper, and selenium act as coenzymes, while vitamins A, C, and E act against free radicals. Deficiency or overload can contribute to cell injury (SAGHAZADEH, 2017).

1.2 THE DEVELOPMENT OF THE CHILD WITH DOWN SYNDROME

The *National Down Syndrome Society* (NDSS) reports that approximately one in every 700 babies in the United States is born with Down syndrome, about 6,000 per year (NDSS, 2020). No different, in Brazil, it is estimated that every 700 births occurs 1 case of trisomy of 21, adding up to around 300 thousand people with the syndrome, regardless of ethnicity, gender or social class (MALT *et al*. 2013).

It is, therefore, a significant part of the Brazilian population, consisting of an important portion that may require timely interventions from the earliest childhood, because this chromosomal disease is related to specific organic changes and physical constitution and greater risk for developmental delay.

However, despite the impossibility of predicting the degree of autonomy that a child with DS will have in adult life, it is known that, when adequately attended from birth, receiving adequate guidance and stimulation, they have the potential to present a healthy life and with full social and educational inclusion (BRASIL, 2012). This statement is also valid for all children born with congenital conditions.

The Ministry of Health's Guideline for Attention to People with DS, updated in 2020 by the Brazilian Society of Pediatrics, recommends that care for this population be guided by public policies and that the theoretical assumptions of expanded clinic, integrality and shared care be used. It brings as a proposal for care conducts such as the expanded understanding of the health-disease process; construction shared by the multidisciplinary team of situational diagnosis; and the individual care plan; definition of therapeutic goals and commitment of professionals, family and individual with these goals (BRASIL, 2012; SBP, 2020).

Globally there are about 250 million children under the age of 5 at risk of poor child development due to poverty, most of them in low- and middle-income countries (43% of all children

under 5), despite an 11% decrease between 2004 and 2010. Thus, the identification and early intervention in situations related to developmental delay are fundamental, as they determine the use of the great capacity and brain neuroplasticity of this age group (MIRANDA *et al*., 2003).

It is known that the development of children with DS often occurs with delays, so the importance of following and guiding the family in the first two years of life, also justified by the opportunity of referral to complementary therapies (physiotherapy, occupational therapy, speech therapy, among others), as soon as the need is verified (BONOMO and ROSSETI, 2010; Perera, 2013).

A global delay in the development of the child with DS is expected, affecting the motor, language, personal-social and cognitive domains. In addition, newborns with DS often present several complications, including congenital cardiac malformations, gastrointestinal manifestations, hearing loss, hematological abnormalities, obstructive sleep apnea, ophthalmological disorders, congenital hypothyroidism and hypotonia (BRASIL, 2012; SBP, 2020). Therefore, it is necessary to follow up and multiprofessional and specialized therapy to increase the responsiveness and provide better quality of life and learning of these children and adolescents.

Pioneering studies have shown that children with DS have greater difficulties to evolve in the acquisition of motor skills than those who do not have DS (CARR, 1970; MELYN and WHITE, 1973). According to a study conducted by Pueschel (1990) the following milestones can be observed in relation to motor development in children with DS: sitting independently between 6 and 28 months; standing between 11 and 42 months; and walking between 12 and 65 months.

1.3 ZINC AND ITS RELEVANCE IN CHILD HEALTH

Zinc is an essential component for more than 200 enzymes, participating in the synthesis and degradation of carbohydrates, lipids, proteins and nucleic acids, also important in the metabolism of other micronutrients. Among the functions performed by zinc, its participation in the processes of cell differentiation, height growth, neurological development and immune defense stands out, in addition to having a role in the transcription of polynucleotides and in the process of gene expression (MARQUES, 2006) (PEDRAZA, 2015).

It is widely distributed throughout the body, having its smallest portion found in the blood (KAMBE, 2015). The only source is through food, and the daily recommendation of consumption varies according to age and health condition.

Table 1 – Estimated average daily zinc requirements.

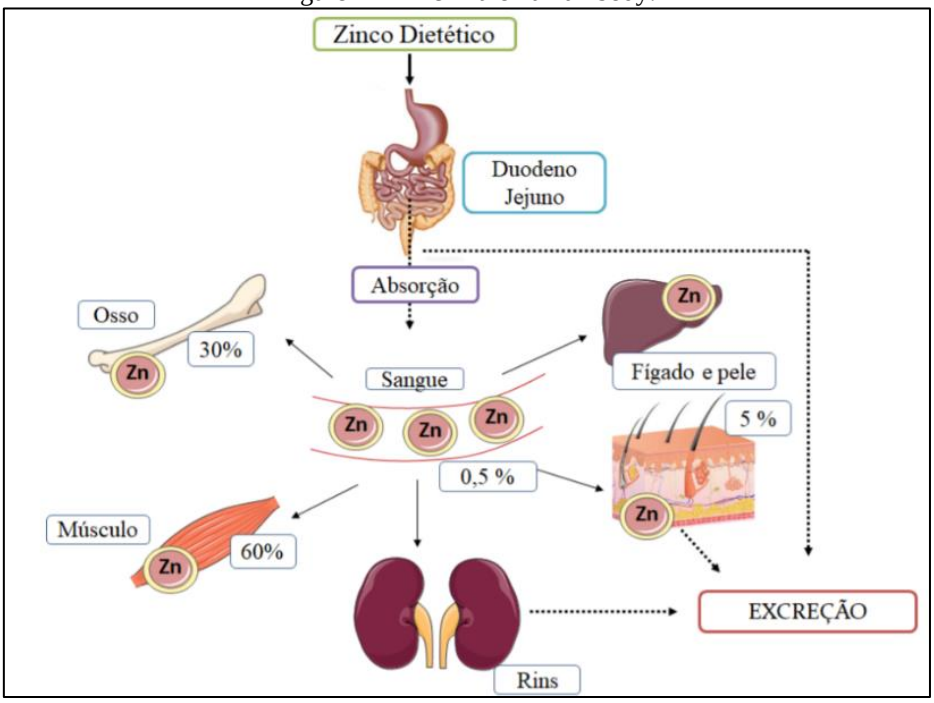
Age group	Zinc (mg/d)
0 to 12 months	2,5
1 to 3 years	2,5
4 to 8 years	4,0
MEN – 9 to 13 years	7,0
14 to 18 years	8,5
WOMEN – 9 to 13 years	7,0
14 to 18 years	7,3

Source: *Institute of Medicine*, 2000.

Of the food sources of zinc, meats (from beef, poultry and fish), milk and derivatives, can provide about 80% of the total diet (CIAMPO, 2014); Other sources are oysters, shrimp, wheat germ, whole grains, nuts, cereals, legumes and tubers.

We know that zinc absorption can occur by diffusion or by transporters, with the jejunum being the site of greatest uptake of this mineral. We have factors that can impair this process, such as the presence of phytates, oxalates, tannins and polyphenols, as well as facilitators, among them the presence of cysteine and histidine, phosphates, organic acids and protein (PEREIRA, 2009).

Figure 4 – Zinc in the human body.



Source: BESERRA, 2018.

Zinc plays an important role in the endocrine system, as well as in other systems of the organism: it participates, for example, as a cofactor of the enzyme deiodinidase type II, in the peripheral conversion of thyroxine (T4) into triiodothyronine (T3), being this reaction diminished, contributes to the manifestation of disorders, such as subclinical hypothyroidism (MARQUES, 2006).

Zinc deficiency is related to increased morbidity and severity of infections, growth deficit, physiological changes (anorexia, hypogonadism, decreased taste, dermatitis, oxidative damage) and impaired cognitive ability (PEDRAZA, 2015).

Considering that Down syndrome already presents alterations in the functions of the immune system, endocrine, among others, often with feeding difficulties (anatomical-structural changes, hypotonia, food selectivity, constipation), we can consider this population as at risk for zinc deficiency.

There are some ways to evaluate the nutritional status of zinc in the body, and serum dosage is the most widely used biochemical indicator. Nevertheless, studies recommend that this parameter not be evaluated in isolation, suggesting three indicators to better estimate the risk of zinc deficiency: I) Laboratory indicator (serum and erythrocyte zinc); II) Dietary indicator (zinc intake); and III) Functional indicator (may be: clinical signs, short stature, prevalence of infections, hormonal response) (WIERINGA, 2015) (PEDRAZA, 2015) (CRUZ, 2011).

Clinical signs suggestive of zinc deficiency are not specific to this mineral and may be due to other causes. In addition, although the laboratory measurement of plasma zinc already has well-established reference values, this parameter may present rapid variation due to stress, infection, diet, catabolism, hormones. Erythrocyte zinc, due to the half-life of the erythrocyte being 120 days, portrays a longer period, therefore more reliable (FERRO, 2010).

In this way, Knowing the nutritional status of children and adolescents with Down syndrome, assessing the need for supplementation, as well as the response to it, is important. However, studies in this population are scarce.

Thus, a study was developed to evaluate the nutritional status of zinc in children with Down syndrome, considering this an important factor for its development.

2 METHOD

This is a case-control study, with a convenience sample, and primary and secondary data collection, clinical and laboratory evaluation.

The Case group was composed of a random sample of children and adolescents diagnosed with Down Syndrome (DS), followed up at the Pediatrics and Genetic Childcare outpatient clinics of the Hospital das Clínicas da Faculdade de Medicina de Botucatu (HCFMB).

2.1 INCLUSION CRITERIA FOR THE CASE GROUP:

- Children and adolescents, of both sexes, from 1 year of age, with confirmed diagnosis of DS (through karyotype examination);

- In follow-up in the outpatient clinics provided and whose guardians agreed to participate in the study with the signing of the Term of Free and Informed Consent, and for adolescents from 12 years of age, the Term of Assent was also requested according to their motor and cognitive capacity for the understanding and signature of the same;

- Those included may have heart disease or other specific changes in DS, which are described and considered in the evaluation of the results.

The Control group was paired by sex and age to the Case group, and the 2:1 ratio was predicted for a better reliability of the outcomes. However, due to the period of the study during the Covid-19 pandemic, with suspension of outpatient care, resumption with very reduced schedules and patients not attending scheduled appointments, it was decided to perform the 1:1 pairing, maintaining the criteria of sex and age.

2.2 INCLUSION CRITERIA FOR THE CONTROL GROUP:

- Children and adolescents, of both sexes, from 1 year of age, without the medical diagnosis of DS or any other genetic/chromosomal abnormality or disease;

- In follow-up at the Childcare Outpatient Clinics of the Hospital das Clínicas de Botucatu, or Adolescent Medicine Outpatient Clinic, whose parents or guardians agreed to participate in the study by signing the Free and Informed Consent Form; for adolescents from 12 years of age, the Term of Assent was also requested.

2.3 EXCLUSION CRITERIA FOR BOTH GROUPS:

- Previous diagnosis of phenylketonuria.

The invitation to be included in the study, the interview for data collection, with food survey and nutritional assessment, were carried out in the outpatient clinics of Pediatrics and Genetic Childcare of the Hospital das Clínicas de Botucatu (HCFMB), for the Case group, and in the Childcare outpatient clinics and in the Adolescent Medicine outpatient clinic of the HCFMB, for the Control group.

The collection of laboratory tests was performed in the laboratory, located in the city of Botucatu/SP, on a date previously scheduled with the study participants, through a 4-hour fast, necessary for the reliability of the results.

2.3.1 The following were carried out:

a) A 24-hour, three-day food recall containing a typical day and a weekend day, occurring in a maximum of two weeks. The most recent recommendations for zinc intake will be

established by the *Food and Nutrition Board* (2002), stipulating the DRI *(Dietary Reference Intakes*) (INSTITUTE OF MEDICINE, 2000) (INSTITUTE OF MEDICINE, 2002) (FISBERG, 2009) (UNICAMP, 2011).

b) Food consumption frequency questionnaire (FFQ) – focusing on food sources of zinc and its interferents, including frequency of consumption and quantity, as well as the way the food is processed (*in natura*, minimally processed, ultra-processed) (MONTEIRO, 2016). To evaluate the zinc supply, the Nutwin® program was used.

c) Serum Zinc Dosage: blood collection in trace tube (without additive and without clot activator). After collection, the clot was awaited for retraction and then centrifuged. Transferred by immersion the serum obtained to another trace tube. The method of analysis was mass spectrometry with inductively coupled plasma – ICP/MS.

d) Erythrocyte Zinc Dosage: blood collection using appropriate material and medium (free of metals) – EDTA trace tube, lithium heparin trace tube or sodium heparin trace tube. The method of analysis was Plasma inductively coupled with mass detector.

3 FINDINGS

As for the pairing of the 42 included in each group, sex was one of the characteristics, the distribution in the groups was 50% female and male. The age of those included ranged from one to 11 years, with a mean age of four years. We included 37 children (88.1%) and five adolescents (11.9%), according to the WHO, considering those over ten years of age (EISENSTEIN, 2005).

There was no statistical difference between the groups regarding the gestation time, and most of them were included at term. Regarding birth weight, low birth weight was more frequent in the Case group (p=0.04). Only one in the Case group (2.4%) and two in the control group (4.8%) were twins (p=1.0). And as for the type of delivery, cesarean section was predominant in both groups, above 50% (p=0.82). There was no difference between the groups regarding malformation at birth (p=0.13).

The laboratory analysis of this micronutrient showed that a percentage of 13.5% had insufficient serum zinc levels in the Case group, while in the Control group we had 24% (p=0.15). On the other hand, considering the erythrocyte zinc values, we do not have any children with DS, while in the control group 60% of deficiency was found.

Table 1 - Nutritional status of zinc, dietary, serum and erythrocyte, according to study groups, Botucatu/SP, 2022.

Variable	Case Group		Control Group		P value
	N	%	N	%	
Dietary zinc1					
Adequate	41	97,6	40	95,2	1,00
Insufficient	1	2,4	2	4,8	
Serum zinc2 (mcg/dL)					
Adequate	29	78,3	7	24,1	0,15
Insufficient	5	13,5	22	75,9	
Elevated	3	8,2	0	0,0	
Erythrocyte zinc3 (mcg/dL)					
Adequate	30	83,3	12	40,0	**<0,0001**
Insufficient	0	0,0	18	60,0	
Elevated	6	16,7	0	0,0	

[1] Case Group: n= 42; Control Group: n= 42; [2]Case Group: n= 37; Control Group: n= 32; [3]Case Group: n= 36; Control Group: n= 30

4 DISCUSSION AND FINAL CONSIDERATIONS

Down syndrome (DS) is the most frequent chromosomal disease in humans, and the leading cause of intellectual disability in the world. Regardless of social class or ethnicity, it is estimated that 1 in every 650 to 1000 pregnancies are born. Early diagnosis and proper conduction are essential due to the neuroplasticity and developmental potential that can present if stimulated from an early age (SBP, 2020).

People with DS who until the mid-twentieth century had reduced life expectancy, and in general in conditions of institutionalization, today can reach 65 years of age and still living with their families (SBP, 2020).

Even though it was initially characterized in 1866, with several contributions in subsequent decades, and is now well defined and widely studied, we still do not have protocols or guidelines established in a way that contemplates all areas of interest or grievances of this population.

In Brazil, in 2012, the Ministry of Health published the first manual on the person with DS, and a new guideline was released only recently, on March 21, 2020, by the Brazilian Society of Pediatrics. Despite the excellent update, issues such as evaluation of micronutrient deficiencies and their supplementation, or the use of supplements on a continuous basis (BRASIL, 2012) (SBP, 2020) are still not contemplated.

The characterization of our population with DS presented data in agreement with those found in the literature when compared to the population without the syndrome: mean shorter gestation duration, with almost 40% of prematurity, and lower mean birth weight and length.

With the beginning of complementary feeding, preferably from six months of life, it is important that the supply of micronutrients through food is able to contemplate the daily needs. Zinc (Zn) is a trace element of importance already demonstrated for the human body, especially for children and adolescents in developing countries, more vulnerable to Zn deficiency due to the characteristics of eating habits (PEREIRA, 2009) (SILVA, 2006).

It is important to remember that the insufficiency of micronutrients, with or without clinical repercussions, can compromise the genetic potential for physical growth and neurological development (CRUZ, 2011).

In Brazil, we can observe that the diet of most of the population has a predominance of sugars, trans and saturated fats, and low fiber content. Among the most deficient micronutrients in the eating habits of our population, we can highlight zinc (CRUZ, 2011).

Given this fact related to the general population, it is necessary to take a closer look at those who are more likely to present functional or metabolic changes, as is the case of people with Down syndrome. Of the pathologies associated with the syndrome and that can interfere in the zinc status, we have gastrointestinal changes with prevalence of 1 to 12% and endocrinological, 1 to 18% (BRAZIL, 2012). Without ignoring, yet, the fact that hypotonia and delayed neuropsychomotor development can also interfere with feeding, and thus in the supply of this mineral.

Zinc deficiency interferes with thyroid metabolism, growth hormone, as well as oxidative stress characteristic and responsible for accelerated cellular aging (WEFFORT, 2017). All these functions that can already be impacted by Down syndrome, therefore, with greater impairment if there is a deficiency.

In contrast to what we have described in the literature, the patients in the Case group presented less deficiency of the micronutrient zinc. As well as, it is reported in scientific publications that an average of 20% of the general population has zinc deficiency, we found values in the Control group above 40% when we consider the erythrocyte zinc dosage, but when we evaluate the serum dosage, the deficiency is present in 19% (PEDRAZA, 2015).

This difference is probably due to the fact that serum zinc is the most used parameter for the diagnosis of deficiency of this micronutrient, but it is quite sensitive to transient variations, such as infection, stress, diet; while erythrocyte zinc portrays the *status of* a longer period of this micronutrient, on average 3 months (which is the half-life of this cell).

Although there may be some influence of the regular use of zinc sulfate on the adequacy of erythrocyte values in the group with DS, some already in use. This recommendation of supplementation in children with DS (LICASTRO *et al*., 1994), has occurred for many years, but without studies on its real influence on blood and erythrocyte levels.

In our study, although many children presented values below the expected in the laboratory investigation (serum), the evaluation of the diet revealed that almost all the research subjects had adequate supply in their diet. This divergence may have occurred due to the fact that zinc is a micronutrient requiring adequate daily intake, and, as previously stated, its serum dosage is more labile than erythrocyte, and may even suffer interference from food.

Thus, it is considered that the results of the present research could contribute to scientific knowledge about the nutritional status of zinc, and about one of the repercussions predicted when oral zinc supplementation, since they are scarce and we do not have current research that deals with this subject, especially on child development, which needs to be well evaluated in these children, with Down syndrome, as well as in the population of children without the syndrome.

The adequate follow-up performed by participants with Down syndrome in the Genetic Pediatrics service may be a contributing factor to the adequate nutritional status of zinc, including erythrocyte zinc, in the face of adequate nutritional guidance to these patients from the beginning of their follow-up, in the first months of life, thus also positively influencing their development.

It is considered that with the improvement of care to these children and adolescents, as well as the adequate nutritional status of micronutrients such as zinc, there will be the promotion of better growth and development of these, impacting on their quality of life and that of their caregivers.

REFERENCES

BERTAPELLI F, MACHADO MR, ROSO RV, GUERRA-JÚNIOR G. Body mass index reference charts for the individuals with Down syndrome aged 2-18 years. J Pediatr, 2017.

BESERRA JB. Zinco como biomarcador da atividade tireoidiana em mulheres obesas [tese]. Teresina: Universidade Federal do Piauí; 2018. Mestrado.

BONOMO LMM, ROSSETTI CB. Aspectos percepto-motores e cognitivos do desenvolvimento de crianças com SD. Rev Bras Cresc Desenv Hum. 2010;20(3):723-34.

BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Diretrizes de atenção à pessoa com Síndrome de Down. Brasília, 2012.

CARR J. Mongolism: telling the parents. Dev Med Child Neurol. 1970;12(2):213-21.

CIAMPO LAD, CIAMPO IRLD. A importância do zinco para a saúde do adolescente. Adolesc. Saude, 2014.

CRUZ JBF, SOARES HF. Uma revisão sobre o zinco. Ensaios e Ciência. Ciências biológicas, agrárias e da saúde [Internet]. 2011;15(1):207-222.

EISENSTEIN E. Adolescência: definições, conceitos e critérios. Adolescência & Saúde, 2015.

FISBERG RM, MARCHIONI DML, COLUCCI ACA. Avaliação do consumo alimentar e da ingestão de nutrientes na prática clínica. Arq Bras Endocrinol Metab, 2009.

INSTITUTE OF MEDICINE. Dietary Reference Intakes: Applications in Dietary assessment. Washington D.C., 2000.

INSTITUTE OF MEDICINE. Food and Nutrition Board. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). The National Academies Press., 2002.

KAMBE, T.; TSUJI, T.; HASHIMOTO, A.; ITSUMURA, N. The physiological, biochemical, and molecular roles of zinc transporters in zinc homeostasis and metabolism. Physiol Rev., v. 95, n. 3, p. 749-84, 2015.

LICASTRO F, CHIRICOLO M, MOCCHEGIANI E, FABRIS N, ZANNOTI M, BELTRANDI E, *et al*. Oral zinc supplementation in Down's syndrome subjects decreased infections and normalized some humoral and cellular immune parameters. J Intellect Disabil Res. 1994 Apr;38 (Pt 2):149-62.

MARQUES RC, MARREIRO DN. Aspectos metabólicos e funcionais do zinco na síndrome de Down. Rev Nutr., 2006.

MALT EA, DAHL RC, HAUGSAND TM, ULVESTAD IH, EMILSEN NM, HANSEN B, *et al*. Health and disease in adults with Down syndrome. Tidsskr Nor Laegeforen. 2013;133(3):290-4.

MAZUREK D, WYKA J. Down Syndrome – Genetic and nutritional aspects of accompanying disorders. Rocz Panstw Zakl Hig, 2015.

MELYN MA, WHITE DT. Mental and developmental milestones of noninstitutionalized Down's syndrome children. Pediatrics. 1973;52(4):542-5.

MIRANDA LP, RESEGUE R, FIGUEIRA ACM. A criança e o adolescente com problemas do desenvolvimento no ambulatório de pediatria. J Pediatr. 2003;79 Supl 1:33-42.

MONTEIRO CA, CANNON G, LEVY RB, MOUBARAC JC, JAIME P, MARTINS AP, *et al.* NOVA. A estrela brilha. [Classificação dos alimentos. Saúde Pública]. World Nutrition, 2016.

MOREIRA LMA, EL-HANI CN, GUSMÃO FAF. A Síndrome de Down e sua patogênese: considerações sobre o determinismo genético. Rev Bras Psiquiatr., 2000.

MUSTACCHI Z. Seguimento da criança com Síndrome de Down. Sociedade Brasileira de Pediatria. Atualizações de conduta em pediatria – recomendações, 2007.

PEDRAZA DF, SALES MC. Deficiência de zinco: diagnóstico, estimativas do Brasil e prevenção. Nutrire, 2015.

PEREIRA TC, HESSEL G. Deficiência de zinco em crianças e adolescentes com doenças hepáticas crônicas. *Rev Paul Pediatr 2009;27(3):322-8.*

PERERA J, FLÓREZ J, RONDAL JA. Rehabilitación cognitiva de las personas con SD: Perspectivas multidisciplinares de normalización. Rev Síndr Down. 2013;30:106-17.

RIBEIRO LMA, JACOB CMA, PASTORINO AC, KIM CAE, FOMIN ABF, CASTRO APBM. Avaliação dos fatores associados a infecções recorrentes e/ou graves em pacientes com síndrome de Down. J Pediatr, 2003.

SAGHAZADEH A, MAHMOUDI M, ASHKEZARI AD, REZAIE NO, REZAEI N. Systematic review and meta-analysis shows a specific micronutrient profile in people with Down Syndrome: Lower blood calcium, selenium and zinc, higher red blood cell copper and zinc, and higher salivar calcium and sodium. Plos one, 2017.

SILVA APR, VITOLO MR, ZARA LF, CASTRO CFS. Effects of zinc supplementation on 1- to 5-year old children. Jornal de Pediatria 2006; 82(3):227-231.

SOCIEDADE BRASILEIRA DE PEDIATRIA (SBP). Diretrizes de atenção à pessoa com Síndrome de Down. São Paulo: Departamento Científico de Genética, 2020.

UNICAMP. Tabela brasileira de composição de alimentos. 4ª edição. Campinas: NEPA- UNICAMP; 2011.

WEFFORT VRS, LAMOUNIER JA. Nutrição em pediatria: da neonatologia à adolescência. 2ª edição. Barueri: Manole, 2017.

WIERINGA, F.T.; DIJKHUIZEN, M.A.; FIORENTINO, M.; LAILLOU, A.; BERGER, J. Determination of zinc status in humans: which indicator should we use? Nutrients, v. 7, n. 5, p. 3252-63, 2015.

WUO AS. A construção social da Síndrome de Down. Cad. Psicopedag. [online], 2007. Disponível em http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S1676-10492007000100002&lng=pt&nrm=iso. ISSN 1676-1049.