Chapter 12

Alterations of Nutritional Status in Childhood Acute Leukemia

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1. Introduction

Nutritional status is the result of the interaction between environmental and genetic conditions in which a child lives, when these environmental conditions are favorable for life (physical, biological, nutritional and psychosocial), the genetic potential is expressed as an ideal state of nutrition, but when conditions are unfavorable such expression will be diminished, resulting in altered nutritional status, such as malnutrition, overweight and obesity, which among other things would cause the child did not respond to a disease or its treatment suitably at a given time. [1]

In different studies conducted in children with cancer, the authors have evaluated the impact of nutritional status, assuming that if a cancer patient is well nourished, have less toxicity caused by antineoplastic drugs, will have a greater immune resistance to processes serious infectious, and therefore have a better survival and quality of life than the patient who is not well nourished, so in this chapter we will mention the most important conclusions that have been made with respect to this issue. [2]

Malnutrition is the main nutritional disorder that occurs in children with cancer, and has been defined as a state in which a deficiency of energy, protein, and other nutrients, causes measurable adverse effects on the structure and functioning of organs and body

tissues as well as the clinical course of a disease. In order to explain the mechanisms by which it causes malnutrition in children with cancer, three factors have been proposed: a) factors specific to the tumor (tumor growth factors released by the tumor cells as bombesin and adrenocorticotropic hormone) b) factors related to the patient (pediatric age, low socioeconomic status, poor nutrient intake, increased secretion of growth hormone and cytokines that are released by the body in response to tumor growth, among the most important are the tumor necrosis factor, interleukins 1 and 6), and last but not least, c) factors related to the treatment (type / dose of chemotherapy, site / dose of radiotherapy and surgery). It is also suggested that all these factors would cause an alteration in intermediary metabolism, with resultant decrease in appetite, which eventually lead to the patient to lose weight, creating a vicious cycle. [2-6]

1.1. Prevalence of malnutrition in children with cancer

It has been reported that children with cancer will develop signs and symptoms of malnutrition at some point in the disease by up to 50-60% of cases, however, this frequency may vary according to the type of neoplasm, and according to if the study was conducted in developed countries or in developing countries, where there has been an increased frequency of nutritional alterations. It should be mentioned, that the study of the prevalence of malnutrition in children with cancer is mainly determined by whether it is present at diagnosis, this is important because it also could establish their potential impact on the evolution of these patients before treatment started. [7,8]

In this regard, Brinksma A, et al., (2012) reported the prevalence of malnutrition at diagnosis for developed countries, through a systematic review which included patients with different types of childhood cancer, aged from 0-18 years of age for acute leukemias, the prevalence was 10%, 20-50% for neuroblastoma, and those classified as "other malignancies" was 0-30%, these prevalences are low when compared with those that have been estimated for developing countries where they are as high as 50% for all types of childhood cancers. [2,8,9]

2. Nutritional status assessment in children with acute leukemia

There are several clinical, biochemical and physiological indicators to diagnose malnutrition in children with cancer; such as the patient's age, the deficit of specific micronutrients and the presence or absence of infection. The severity of their malnutrition is determined mainly by anthropometric indicators, that are the indexes of weight-for-height (w/h) and weight-for-age (w/a), which indicates acute malnutrition (table 1), height-for-age (h/a) which indicate a delay in growth or chronic malnutrition; and the Body Mass Index (BMI), which is a figure that can diagnose a patient for being underweight, overweight or obesity. [10,11] (table 4)

Percentile	Diagnosis
<5	Malnourished
5-85	Normal
> 85 a < 95	Overweight
≥ 95	Obesity

Table 1. Diagnosis by percentile for the indexes weight-for-height, weight-for-age based on the World Health Organization (WHO) tables.

Waterlow´s Classification:

Denomination	Index	Classification
Wasting	Weight-for-height <5	Acute Malnutrition
Stunting	Height-for-age <5	delay in growth or chronic malnutrition

Table 2. Denomination of wasting and stunting with Waterlow´s classification. [12, 13]

Waterlow´s classifications:

Denomination	Index	Classification
Wasting, no stunting	Weight-for-height <5 , height-for-age Normal	Acute malnutrition
Wasting and stunting	Weight-for-height <5 , height-for-age <5	Exacerbated-chronic malnutrition
Stunting, no wasting	Weight-for-height Normal, height-for-age <5	Chronic malnutrition

Table 3. Combinations of nutritional diagnosis with Waterlow's classification. [12,13]

Percentil	Diagnosis
<5	Underweight - Malnourished
≥5 y <85	Normal
≥85- <94	Overweight
≥95	Obesity

Table 4. Diagnosis by percentile for the Body Mass Index (BMI) based on the World Health Organization (WHO) tables [10]

It's important to consider the body composition in children with cancer, with which we are able to determine the quantity of lean mass and body fat in their bodies, in order to see if there is muscular depletion. The anthropometric measures used to get body composition can be the Mid Upper Arm Circumference (MUAC), triceps (TSF), biceps, subscapularis and suprailiac skinfolds; [14] and in case of having the necessary equipment, the use of electric bioimpedance or D-XA (Dual X-Ray Absorptiometry) is recommendable.

With the mid upper arm circumference and the triceps skinfold, you can calculate the muscle and fat area by using the following formula:

Then comparing the score with the Frisancho tables where:

Percentile	Diagnosis
0 – 5	Wasted
5.1 – 15	Below average
15.1 – 85	Average
85.1 - 95	Above Average
>95	High muscle

Table 5. Diagnosis by percentile for upper arm muscle area based on Frisancho tables. [14]

Aside from those anthropometric indicators, there are biochemical indicators that are used to diagnose protein malnutrition, like albumin and pre-albumin which are the most important due to their hepatic synthesis, and total protein. [15,16]

The half- life of albumin is 20 days, therefore it can assess acute malnutrition and can be used as a morbidity and mortality prognosis factor.

Reference value	Diagnosis
3.5 - 5.5 g/dl	Well-nourished
2.8 - 3.5 g/dl	Malnourished Grade 1
2.1 - 2.7 g/dl	Malnourished Grade2
< 2.1 g/dl	Malnourished Grade 3

Table 6. Albumin reference values and diagnosis [15]

Prealbumin has a 2 days half life wich means it is a very sensible marker for acute malnutrition, but the result may be affected by inflammatory reaction, therefore is not useful to track changes on the nutritional status unlike albumin that can be a better marker for protein malnutrition. [16]

Reference value	Diagnosis
17 - 42 g/dl	Well-nourished
<17 g/dl	Malnourished

Table 7. Prealbumin reference values and diagnosis [17]

It is important to make a full assessment of nutritional status in these children as this can influence the patient's response to the treatment.

3. Impact of malnutrition in Acute Lymphoblastic Leukemia (ALL)

The study of the impact of malnutrition in children with cancer has been conducted primarily in patients with acute leukemia, specifically in (ALL) perhaps because it is the most common type of cancer in children worldwide. [18-21] In two papers published one by Underzo et al., and in another by Reilly J, et al., reported that the prevalence of malnutrition at diagnosis in patients with ALL was 7% for developed countries, and on the contrary, in different studies conducted in developing countries have reported higher prevalence of up to 21-23%, which confirms the statement that in countries with low economic development, malnutrition occurs more frequently, This could be a result of poverty. It is for this reason that for several years, these countries have made efforts to determine the true impact of malnutrition as a prognostic factor in patients with acute leukemia in children at different stages of treatment. [22-25]

3.1. Prognosis

As is known chemotherapy used in the treatment of patients with ALL has some serious effects that may endanger the life of patients at a given time. Among the most common side effects of QT are toxicity to various organs, infection, hemorrhage, tumor lysis syndrome (TLS), among others., which would be the cause of high morbidity and mortality. It is for this reason that the current chemotherapy protocols in children with ALL are based on a risk classification to reduce toxicity in low-risk patients as well as ensure that therapy is adequate and aggressive to those classified as high risk. [26,27]

In the group of patients with ALL who are malnourished at diagnosis, it was found that chemotherapy is more toxic and less effective compared to those found with adequate nutritional status, specifically haematological toxicity is the cause of most complications, such as an increased risk to present infections, bleeding and an increased risk of relapse, the above due to neutropenia, thrombocytopenia, and discontinuation of treatment, respectively.

The main effect of malnutrition on treatment, is due to an alteration of the biodisponibility of antineoplastic drugs, which is achieved through the following mechanisms: a) changes in absorption, eg for drugs like methotrexate and 6 mercaptopurine, b) the decreased drug

transport by the reduction or lack of plasmatic proteins, and c) by decrease in hepatic metabolism of the antineoplastic mainly caused by a lack of enzymatic activity by cytochrome P450. [28-37]

Furthermore. highlight the importance of studying on the subject of how malnutrition affects the prognosis of patients with ALL, because in some of the studies did not allow conclusions to determine whether the association exists in some of these studies were given the limitations by factors such as inadequate sample size, the inconsistency in how to assess the nutritional status between studies, and also have not been studied other possible complications in the evolution of these patients, such as relapse, abandonment in the treatment, among others. [28,38-40]

3.2. Survival

Moreover, since 1980 the rates of event-free survival has improved in patients with ALL, currently reported survival at 5 years is 80% and 10-year survival is 60% in developed countries, however, in developing countries cure rates are less than 35%, so on a quest to determine the factors related to mortality in developed countries, but mainly in developing countries, has been studied by different authors on the role of malnutrition on survival of patients with ALL; remain controversial until now because while on the one hand, some authors have reported that survival rates are lower in malnourished patients compared with patients who are well nourished and of the same risk, in other studies, it has not been possible to confirm this association. [8,29,41] According to Reilly J, et al., There are three mechanisms that explain the direct influence of malnutrition on survival of patients with ALL: The first, means that if there is a greater severity of malnutrition, there will be a greater severity of leukemia this because as we know, malnutrition is a surrogate marker of the disease state, the second mechanism is related to immune system dysfunction that occurs in malnourished patients, which would cause increased susceptibility to potentially serious infections could lead to the death of the patient, and finally, a mechanism related to adipose tissue, which has as one of its main functions being a facilitator to take place the pharmacokinetics of many anticancer drugs, this tissue is functionally and structurally altered in malnutrition, resulting in a lower effective antineoplastic drugs and greater toxicity and that both could be potential factors sufficient to endanger the patient's life, however this mechanism has been studied by other authors who found no such effect. [23-39]

Therefore, it is believed that malnutrition alone is a major factor in poor prognosis and survival of patients with ALL, however, it is noteworthy that most of the studies performed, are from developed countries and / or where it is mainly evaluated the impact of malnutrition on long-term survival, so it is necessary to know whether the association also exists in developing countries, because these populations have certain characteristics, such as frequencies malnutrition and deaths occur primarily during the first year of treatment much higher, and it also has been reported as one of the main obstacles to improved survival rates in patients with ALL. [39,42-45]

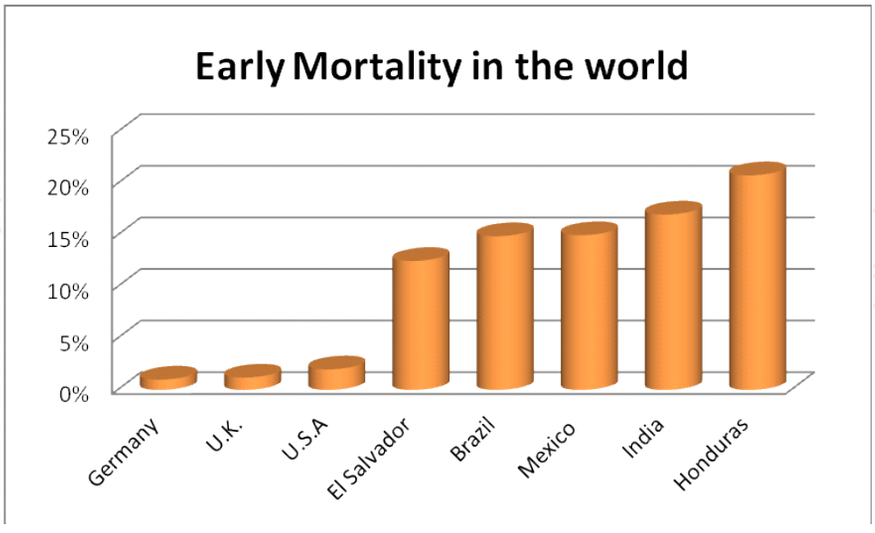
3.3. Malnutrition and early mortality

Early mortality can be defined as death during the first year of treatment, and it includes treatments as chemotherapy of induction to remission, central nervous system prophylaxis and consolidation. In several cases around the globe, the early mortality rate for developed countries is significantly lower than the one presented in developing countries. Main causes for early mortality include complications during chemotherapy treatment, such as infections, hemorrhages and toxicity, since their presence often represent an interruption in the treatment.

A 1999 study conducted by Silverman and collaborators in the Dana-Farber Cancer Institute, United States; a mortality rate of 2% in the first stage of treatment was reported, mainly caused by infections. [46] Another study conducted in the UK in 1997 also measured the rate of early mortality in these patients, reporting a mortality rate of barely 1.2%, with infections still being the main cause of death; however, cases of brain hemorrhage and tumor lysis syndrome (TSL) were also detected. [47]

The country that reports the lowest percentage of mortality in early stages of treatment is Germany, which reported only a 1% death rate in their patients between 1984 and 1996; with most of the deceases caused by hemorrhages and tumor lysis. [41]

While that's the case in developed countries, where very low mortality rates are reported; a study conducted by Rivera Luna and collaborators in Mexico's Instituto Nacional de Pediatría (INP) threw results of a 15% mortality rate during the phases of induction to remission. [37] In other developing countries like Honduras, El Salvador, Brazil, and India mortality also shows a spike in rates compared to developed countries, with an early mortality rate of 20.8%, 12.5%, 14.9% and 17% respectively, as you can see in Graph 1. [48-51]



Germany	U.K.	U.S.A	El Salvador	Brazil	Mexico	India	Honduras
1%	1.20%	2%	12.50%	15%	15%	17%	21%

Graphic 1. Incidence of early mortality in patients with ALL around the world.

A possible explanation for this marked difference might be that malnutrition, poverty and lack of access to public health services are frequent problems in developing countries, unlike developed countries where children with leukemia have lower early mortality rates.

There have been several studies that try to correlate malnutrition with the evolution of patients with ALL. The first one was conducted in Mexico in 1989 by Lobato Mendiazabal et al., where there's a categorization of children with or without malnutrition based on weight-for-height indicators. It was found that, when measuring 5 year survival rate, 80% of children without malnutrition survived, while patients with malnutrition had a survival rate of barely 26% in the same period. [44]

As far as early mortality and relapses during the first year of treatment go, only 4% of children diagnosed with good nutrition suffered any of those events, while 63% of ill nurtured children experienced a relapse or death. This study was conducted in Puebla, with a sample size of 42 children of a single hospital facility (Hospital Universitario de Puebla). [44]

In a case and control study conducted by Mejia Aranguré and collaborators the state of nutrition of several patients with the weight-for-height indicator was tested and compared for diagnosis with the boards of Federico Gómez. For this study 93 cases of 2 hospital sources were taken; Hospital Infantil Federico Gómez and Hospital de Pediatría de Centro Médico Nacional S XXI. [35]

It was found that children with malnutrition at the moment of diagnosis were almost 2.6 times more likely to die in comparison to children without malnutrition. Therefore, it was concluded that malnutrition is a factor that increases the mortality rate of children with ALL, and an association directly proportional to the severity of the nutrition was established. [24]

In a prospective cohort conducted in 63 patients by Khan and collaborators, malnutrition was classified with the index of weight-for-height, and the result was that 46% of children with malnutrition at the moment of ALL diagnose completed their treatment; only 9.8% suffered a relapse and 45% died; meanwhile children without malnutrition experienced a 59% survival to their treatment, a 21% relapse rate and 19% died. Thus, malnutrition was considered as a bad prognosis factor for children with ALL. [36]

One of the most recent studies was conducted in Bangladesh by Hafiz MG and collaborators in 2008. This study only takes a sample of 66 patients from the Indian Pediatric Hospital, the index they used was the weight-for-height measurement, although they don't specify the tables that results were compared to in order to classify the state of nutrition.

They concluded that children that present malnutrition have 2 to 3 times the risk of infection in comparison to children without malnutrition. It was also observed that children with malnutrition needed more time for induction therapy since their dosage has to be lowered, or their treatment was interrupted for toxicity. [28]

Another study realized by Pedrosa F. and collaborators in 2000, took in account indicators as weight-for-height, height-for-age and weight-for-age; comparing them to WHO data. For this study they took in account patients with any type of leukemia and patients with solid tumors. This study was collaboration between two hospitals in El Salvador and Brazil, where they were able to include 443 patients. Of that number, 151 had an ALL diagnosis. At the beginning of the study children were classified as children with malnutrition and children without malnutrition, and children with malnutrition were provided with a dosage of albumin 2 weeks before starting chemotherapy. The study concluded that "malnourishment doesn't have a relevant association with these patients' survival". [38]

The most recent study published on this subject was conducted with patients of Mexico's Instituto Nacional de Pediatría, with 100 patients diagnosed with ALL. Their state of nutrition was determined with indicators of weight-for-height and height-for-age and compared to the NHANES tables of the CDC in the United States. This was a retrospective study where the follow up was done during the phases of induction to remission, and the results were as follow: 14.9% of children without malnourishment died during treatment phase, while 5.1% of patients without malnourishment perished in this stage of treatment Therefore, it was concluded that malnutrition didn't play an important role in early mortality in children with ALL. [37]

In a retrospective cohort done in El Salvador with 469 patients, besides BMI index, triceps skinfolds and Mid Upper Arm Circumference were taken into consideration. This study concluded that malnourishment had no association with mortality during treatment. [49]

A study conducted by Hijiya and collaborators demonstrated with a retrospective cohort of 621 patients of St. Jude's Hospital in United States concluded that BMI didn't affect the evolution of patients with ALL. This study took BMI as the main nutritional indicator and divided children in 3 groups: malnourished, normal and obese. The survival rates in these categories were similar, children with malnutrition presented a survivability rate of 86.1%, children with a normal nutrition state had an 86% survivability rate and in obese children the figure was of 85.9%. [39]

There's controversial information about the relationship between the effects of malnutrition in the evolution of patients with ALL, mostly because even with a wide range of studies, some conclude there's a significant relation between these factors [24,28,44] while others conclude that there's no relation. [37-39, 49]

One of the reasons is the bias in the classification of malnutrition, since in some studies like Pedroza and collaborators [38] the World Health Organization (WHO) charts are used, and in Rivera Luna and collaborators [37] they used the charts of the National Health and Nutrition Examination Survey (NHANES), while in the study conducted by Lobato Mendizabal and collaborators the charts of Ramos Galván were taken into account [44] and at last the study of Mejía Aranguré and collaborators used Federico Gómez' charts. [24]

In the studies mentioned, the sample was taken only from one or two hospital sources, so it's important to conduct a multicentre study that can show a wider panorama of the effects of malnourishment in the evolution of children with ALL.

Autor (Year)	Lobato Mendiazabal et al. (1989)	Mejía Aranguré et al. (1999)	Pedrosa F. et al. (2000)	Rivera Luna et al. (2005)
Country	Mexico	Mexico	El Salvador and Brazil	Mexico
Hospitals	Centro de Hematología Medicina Interna and Hospital Universitario de Puebla	Hospital de Pediatría S. XXI and Hospital Infantil de México Federico Gómez	Hospital de niños Benjamín Bloom and Instituto Materno-Infantil de Pernambuco	Instituto Nacional de Pediatría
Type of study	Prospective cohort	Case- control	Retrospective Cohort	Retrospective Cohort
Sample size	43 patients	93 patients, 17 cases and 76 controls	443 patients 151 with ALL	100 patients
Age	1-15 years	<16 years	0-17.8 years	0-15 years
Parameters used	Weight-for-age	Weight-for-height	Weight-for-age, Height-for-age Weight-for-height	Height-for-age, Weight-for-height
Classification	Ramos- Galvan's Tables	Federico Gómez Tables	WHO`s Tables	National Health and Nutrition examination survey NHANES
Results	5-year survival in well nourished versus malnourished patients: 83% in well nourished Vs 26% in malnourished. Death and relapses: 4% in well nourished vs. 63% malnourished. Reduction of chemotherapy treatment: 75% in well nourished Vs. 56% malnourished.	Children who had malnutrition at the time of diagnosis were 2.6 more likely to die than children without malnutrition; therefore malnutrition increases mortality in children with LLA.	Malnutrition has no association with survival of patients Note: A dose of Albumin was applied to malnourished children 2 weeks before they started treatment.	14.9% of well nourished children died during the induction to remission therapy; 15.1% of malnourished children died during the same stage of treatment, "Malnutrition does not play a role in early mortality in children with ALL".
Country	USA	Pakistan	Bangladesh	El Salvador
Hospitals	St. Jude´s Children Research Hospital	Shaukat Khanum memorial Hospital	Pediatric Hematology and Oncology	Hospital de niños Benjamín Bloom
Type of study	Retrospective cohort	Prospective cohort	Prospective cohort	Prospective Cohort
Sample size	621 patients	163 patients	66 patients	469 patients

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Autor (Year)	Lobato Mendiazabal et al. (1989)	Mejía Aranguré et al. (1999)	Pedrosa F. et al. (2000)	Rivera Luna et al. (2005)
Age	1-16 years	<14 years	1-15 years	0-16 years
Parameters used	BMI	Weight-for-height	Weight for age	BMI, MUAC,(TSF)
Classification	CDC tables	Waterlow`s Classification	Not specified	CDC Tables
Results	Children were divided in 3 categories: <10° malnourished; >ó= 85° well nourished; > 85 < 95° overweight; >95 Obesity; Note: Chemotherapy dosage was not adjusted by BMI. Survival rate: 86.1%, 86.0%, 85.9% and 78.2% respectively BMI has no effect on the survival of LLA children.	Malnourished children: 46% complete treatment and were alive, 9.8% relapse and 45% died. Well nourished children: 59% complete treatment and were alive, 21.3% relapse and 19% died. " Malnutrition is a prognosis factor in LLA children"	Malnourished children are 3 times more likely to present infections tan well nourished ones. Malnourished children need more time of induction to remission treatment due to the dose reduction caused by toxicity.	Malnutrition has no association with early mortality in children with LLA.

Table 8. Studies about the effect of malnutrition at time of diagnosis and early mortality in children with ALL.

4. Overweight and obesity in survivors of childhood acute lymphoblastic leukemia

Concern about children who suffered from ALL is the long-term consequences that therapy may bring after the leukemia has been overcome. Various studies have shown that nutritional abnormalities like obesity and overweight are commonly found in ALL survivors, with a prevalence of 20-34% depending on the country where it has been studied. [52,53]

van Waas et al, conducted a study in 2004 in the Netherlands during the period from 2002 to 2007 in a single-center cohort of 500 survivors of childhood ALL. The ages of these patients at the time of the study ranged from 18 to 59 years, of which 288 were females and 212 were males, measured variables corresponded to the levels of total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, BMI, and the authors finally concluded that patients who had been treated with cranial radiotherapy (CRT) had a higher frequency of overweight (59% versus 34%, P = 0.003) than those who had not received CTR. [54]

Obesity and overweight are defined are the result of varying degrees of abnormal or excessive accumulation of fat. The World Health Organization defines overweight as a BMI of 25 to 29.9, and obesity as a BMI of ≥30. The BMI modifications in survivors of childhood ALL are noteworthy because they are associated with insulin resistance, diabetes mellitus, hypertension, dyslipidemia and with an increased cardiovascular risk. [55]

4.1. Mechanisms involved in the development of overweight and obesity in ALL survivors

Because of this, the processes by which these nutritional abnormalities are developed by ALL survivors are being studied, though the exact mechanisms are still uncertain, nonetheless, there are some hypotheses that would explain metabolic deregulations leading to the development of altered BMI by the excessive accumulation of body fat. Here we will focus on the effects due to radiotherapy and corticosteroids. However, it is important to point out that exist other factors linked to these alterations. For example, long hospitalization periods because of inmunosuppression or vincristine-induced peripheral neuropathy may cause restricted physical activity in these patients. In addition to this, it should not be left out the usual risk factors for developing obesity of each population. [56]

4.1.1. Effects attributed to cranial radiation therapy

In one of the largest studies conducted so far related to the effect of radiotherapy for the development of overweight and obesity in ALL survivors by Oeffinger et al, (2003), reported that the dose and radiation site were the mainly cause. This study was conducted during the period from 1980 to 1994 the study population corresponded to 1765cases and 2588 controls aged 18-42 years old. Considering a radiation dose greater than 20Gy there was a risk factor for obesity in men with an OR 1.86 for ills (95% CI, 1.33 to 2.57, P <.001) and in women with an OR of 2.59 (95% CI, 1.88 to 3.55, P <0.001), without observing this nutritional disorder in patients who had received chemotherapy alone or had received cranial radiation doses of 10 to 19 Gy. [57]

Lackner H et al 1991and subsequently by Janiszewski et al., (2007), reported that the levels of growth hormone (GH), insulin-like factor (IGF1) and leptin levels were significantly lower in CRT than in non-CRT. [58,59]

The mechanism proposed to explain the growth hormone deficiency, holds that cranial radiotherapy (CRT) given at a young age to treat children suffering from ALL, damages the hypothalamus neurons, inducing growth hormone deficiency (GHD). [60] Deficiency in the secretion of growth hormone (GH) has been associated with the augmented percentage of body fat. Evidence that supports these hypothesis are the decreased levels of IGF-1 (also known as somatomedine C), which is a mediator of the GH action in target tissues.

Apart from their individual effects, there is evidence that relates leptin and GH. GH and IGF-1 are decreased in response to fasting. Impaired GH synthesis and secretion occurs along with a leptin deficiency or abnormality on its receptor. Leptin may also regulate GH via somatostatin synthesis inhibition and secretion, allowing GH to yield its actions over the targeted tissues. [61]

Among many other physiological functions of the GH, this hormone promotes utilization of fats as source of energy, inducing the liberation of fatty acids into the bloodstream. At the same time, it has anabolic protein effects which are traduced in an increase of lean body mass. [62]

Moreover, it has been recently suggested that only susceptible individuals will develop obesity when treated with CRT. This susceptibility has been tracked down to a polymorphism in the leptin receptor in the hypothalamus. This polymorphism (Arg/Arg) was found by Ross et al., to be associated to females having a BMI ≥25, treated with CRT. [63] Leptin is a hormone produced by adipocytes and it is involved in feeding behavior regulation and energy balance. Stored energy in adipose tissue is closely watched by the hypothalamus, through this hormone. An increase in adipose tissue will be traduced in increased leptin synthesis by adipocytes, and by negative feedback over the hypothalamus food intake will be inhibited. [64,65]

4.1.2. Corticosteroid therapy

Because corticosteroids are used to treat ALL, it is important to point out that they also promote leptin synthesis. However, conducted studies have only shown short-term effects on increasing body weight. However, these findings strongly suggest doing more research to determine if glucocorticoids induce long-term body weight via leptin synthesis or through other mechanisms. [66]

After it has been released to the blood stream, leptin reaches the central nervous system and binds to its receptors found in the hypothalamic neurons of the arcuate, ventromedial, and dorsomedial nuclei. The activation of the receptors, decreases the production of orexigenic (or appetite stimulant) substances such as neuropeptide Y and agouti-related peptide. It also activates the sympathetic nervous system, increasing the metabolic index and energy consumption. As for the insulin, leptin reduces its secretion, resulting in diminished energy storage. [62]

As it has been shown leptin insensitivity, would have repercussions in the regulation of body weight and metabolism. This leptin resistance can be attributed to abnormal receptors as well as malfunctioning intracellular signaling. [61] Either way, disruption of the leptin signaling, will eventually result in metabolic modifications that would lead to a raised BMI.

Furthermore, ALL survivors with CRT have higher risk of developing other components of the metabolic syndrome. [53] Gurney at al. encountered that ALL survivors who received CRT have increased total cholesterol levels, abnormally low HDL-C, altered triglycerides and LDL-C, compared to those who were not given CRT. [65]

5. Conclusions

As it has been shown, treatment for ALL predisposes patients to suffer from obesity and metabolic alterations, not only after, but also during it. Because of this, physicians should make patients being treated for ALL and those who have overcome ALL, aware of the possi-

bility to develop these changes, and should strongly advise them to develop healthy lifestyles, in order to counteract this increased risk. In addition, strict medical follow-up should be set for the early detection of this alterations, so that adequate medical intervention and/or habit shifts could take place before irreversible damage has occurred.

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