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Appetite hormones in children and adolescents with cancer: a systematic review of observational studies

Las hormonas del apetito en niños y adolescentes con cáncer: una revisión sistemática de los estudios observacionales

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ABSTRACT

Introduction: malnutrition in children with cancer is a significant risk factor for negative outcomes, but in the clinical practice setting, it is difficult to pinpoint which factors operate to cause substantial weight loss and malnutrition in a given patient. Appetite-related hormones like ghrelin and leptin are among possible mediators. However, only few studies have examined the role of these hormones in pediatric patients with cancer to date. Thus, the purpose of this study was to systematically review possible changes in the levels of appetite hormones, specially leptin and ghrelin, in pediatric patients with cancer.

Material and methods: we systematically reviewed the literature using PubMed, Lilacs and Scielo, as well as manual bibliographical reference search of the studies. According

to the *Medical Subject Headings of the National Library of Medicine* (MeSH), "childhood cancer", "ghrelin" and "leptin" were used as descriptors.

Results: fifteen studies were included in this systematic review published in English, from 2000 to 2015. A total of 863 patients were evaluated, ages ranging from 0 to 21 years, and most of the studies reported on children and adolescents with acute lymphoblastic leukemia (ALL) survivors. Most studies analyzed leptin levels; only two studies evaluated levels of ghrelin.

Conclusion: this review confirms that changes in the responses of the ghrelin and leptin hormones in children and adolescents with cancer are quite diverse, probably due to the different types of cancer observed, different treatments performed and biological characteristics of this age group.

Key words: Ghrelin. Leptin. Childhood cancer. Nutritional status. Appetite.

RESUMEN

Introducción: la desnutrición en niños con cáncer es un factor de riesgo significativo para resultados negativos, pero en la práctica clínica, es difícil determinar qué factores operan para causar pérdida de peso sustancial y desnutrición en un paciente dado. Entre los posibles mediadores están las hormonas relacionadas con el apetito como la grelina y la leptina. Sin embargo, hasta la fecha, solo unos pocos estudios han examinado el papel de estas hormonas en pacientes pediátricos con cáncer. El propósito de este estudio fue revisar sistemáticamente los posibles cambios en los niveles de hormonas del apetito, especialmente la leptina y la grelina, en pacientes pediátricos con cáncer.

Material y métodos: se llevó a cabo una revisión sistemática de la bibliografía empleando PubMed, Lilacs y Scielo, así como la búsqueda bibliográfica manual de referencia de los estudios. Según los encabezamientos médicos de la Biblioteca Nacional de Medicina (MeSH), "cáncer infantil", "grelina" y "leptina" se utilizaron como descriptores.

Resultados: en esta revisión sistemática, se incluyeron 15 estudios publicados en inglés de 2000 a 2015. Fueron evaluados un total de 863 pacientes, con edades comprendidas entre 0 y 21 años, y la mayoría de los estudios informaron sobre niños y

adolescentes supervivientes de leucemia linfoblástica aguda. La mayoría de los estudios analizaron los niveles de leptina y solo dos estudios evaluaron los niveles de grelina.

Conclusión: esta revisión confirma que los cambios en las respuestas hormonales de la grelina y la leptina en niños y adolescentes con cáncer son muy diversos, probablemente debido a los diferentes tipos de cáncer observado, los diferentes tratamientos realizados y las características biológicas de este grupo de edad.

Palabras clave: Grelina. Leptina. Cáncer infantil. Valor nutricional. Apetito.

INTRODUCTION

Good nutritional status is highly relevant for children with cancer. It enables them to cope better with the intensive cancer treatment regimens (1). The prognosis for childhood cancer has improved in recent decades, with five year survival rates reaching approximately 80% (2). Nonetheless, this improvement in the survival rate in childhood cancer has given rise to a number of treatment-related complications (3). Malnutrition in children with cancer is a significant risk factor for negative outcomes, such as decreased treatment tolerance, increased susceptibility to infections and reduced survival (4). This may occur because the energy intake is diminished, because the energy requirement is increased, or both. Inflammation and alterations in neurotransmitters and neuropeptides (4-6) are relevant factors for malnutrition. However, in the clinical practice setting, it is difficult to pinpoint which factors operate to cause substantial weight loss and malnutrition in a given patient.

Cancer anorexia-cachexia syndrome is multifactorial in origin. Its etiology is gradually being defined. This syndrome is related to malnutrition. Appetite-related hormones (7), like ghrelin and leptin, are among the possible mediators. Ghrelin is a peptide hormone with a potent orexigenic effect, directly related to food intake, and is mainly produced in the stomach (8). Leptin, an adipocyte-derived protein, was identified as a product of the obesity gene (whose autosomal recessive mutation results in profound hyperphagia and obesity) (9). Both hormones are related to the regulation of food intake and, consequently, body weight control, and can play an important role in the occurrence of obesity and metabolic syndrome in healthy children and adults (3,7).

Increased ghrelin levels and decreased leptin levels were reported in patients with a variety of cancers (10,11), and were reported in adult cachectic patients compared with non-cachectic cancer patients (12). However, only very few studies have examined the role of these hormones, or other adipocytokines, in pediatric patients with cancer to date.

Chemotherapeutic agents, in the long term, can also result in changes in leptin secretion, leading to increased plasma levels (13). However, the plasma levels of leptin vary substantially in the available studies on childhood cancer. In the study of Park et al. (14), children with pediatric cancer showed higher plasma concentrations of leptin when compared to healthy children, but lower plasma levels of ghrelin. Moschovi et al. (15) followed nine pediatric ALL patients from the diagnosis to the maintenance phase, and no significant decreases in leptin levels were observed in these patients. In another study, the same authors observed an expressive increase in the levels of ghrelin after the eighth cycle of chemotherapy (16). However, very few studies evaluated alterations of ghrelin and leptin during chemotherapy in different types of cancer, and these discrepant results may be due to the different treatments adopted. Thus, the purpose of this study was to systematically review possible changes in the levels of appetite hormones, specially leptin and ghrelin, in pediatric patients with cancer.

METHODS

Search strategy

We systematically reviewed the literature using a protocol suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to search research databases, screened published studies, applied inclusion and exclusion criteria and selected relevant literature for review (14). An extensive electronic search was carried out in December 2016 to identify the relevant articles. The following databases were used: PubMed, Lilacs and Scielo, as well as manual bibliographical reference search of the studies. According to the *Medical Subject Headings of the National Library of Medicine* (MeSH), “childhood cancer”, “ghrelin” and “leptin” were used as descriptors.

Inclusion/exclusion criteria

Studies (prospective and cross-sectional) with ghrelin and leptin as outcome during follow-up treatment of children and adolescents (age below 20 years) with any type of cancer were included. To be included in this review, articles also had to be peer-reviewed full report, and published either in English or in Portuguese. Book chapters, reviews, letters, abstracts or dissertations, or any clinical trial with an experimental treatment for childhood cancer were excluded.

Study selection and data extraction

We used a spreadsheet to manage screening and selection of studies. Two reviewers (APTF and ADLB) completed an initial, independent screening of all titles and abstracts retrieved from the database searches, and independently reviewed the full texts of the studies. A third reviewer (RF) resolved any conflicts at both stages. In an effort to prevent the false exclusion of a relevant study, among any conflicted decisions in which the third reviewer moved to exclude the study, all three reviewers discussed the article and came to a consensus. Methodological quality was not an inclusion criterion. Furthermore, reported limitations or limitations found during reading were abstracted.

RESULTS

Initially, 76 articles were identified. After removing duplicate articles (03) and reading their title names and abstracts, a total of 23 articles were selected to be read in full. After careful reading, ten articles were excluded of final analyses and two articles were included. A flowchart showing the details of the selection process is shown in figure 1. In the end, 15 studies were included in this systematic review. Table I shows the result of the systematic review.

Characteristics of the population included in the studies

A total of 863 patients were evaluated, ages ranging from 0 to 21 years. Most of the studies reported on children and adolescents with ALL (3,16,18,20-23,26-29), with non-Hodgkin's lymphoma (20,25,27) being the second most prevalent. The studies included a population of both genders, and many of them had completed their

treatment and were considered as cancer survivors. Four studies (16,19,21,28) followed the patients up, including measures before and after treatment.

Hormone concentrations in case-control studies

Most studies analyzed leptin levels; only two studies (16,19) evaluated levels of ghrelin. In one of these studies (16), children with cancer had lower ghrelin concentrations when compared to their controls, but this concentration increased significantly after the maintenance phase of chemotherapy. The studies showed discrepant results in relation to leptin levels when compared to controls. While one study showed that leptin levels were higher in the cancer group (26), others showed that the levels were significantly lower in patients with pediatric cancer (20,27), while still others found no difference between the groups (21,24,25).

Hormone concentrations during treatment or between different conditions of cancer

The studies showed a wide variation in the health conditions of patients, and some studies compared the hormonal levels in different cancer treatment regimens. Srivastava et al. found that leptin levels were slightly higher in obese children with cancer (18), and Kojima et al. found that patients with metabolic syndrome had higher concentrations of leptin (3). As to the impact of treatment on hormonal concentrations, Trivin et al. found that patients with craniopharyngioma and hypothalamic involvement had lower concentrations of ghrelin and higher concentrations of leptin (19). In this same study, after one year of the surgical procedure, ghrelin levels were significantly reduced only in patients with moderate hypothalamic involvement, while leptin levels increased independently of hypothalamic involvement. Treatment with high doses of methylprednisolone during seven days significantly increased leptin levels in patients with leukemia (21), but another study demonstrated a reduction in leptin levels at day 33 of chemotherapy (28).

DISCUSSION

This review confirms that there is a large discrepancy between studies in relation to the concentrations of these hormones in cancer patients compared to controls, and

between different treatment protocols. Many studies evaluated hormones in cancer survivors, not necessarily with active disease, and this may have contributed to the variety of findings. Survival rates after childhood cancer have improved markedly, and, today, more than 80% of patients with a pediatric malignancy will become five-year survivors (30). With the improved survival rates, long-term treatment-related effects are being observed more frequently, and need to be addressed. Obesity is one such late effect, which increases the long-term risk of death from cardiovascular diseases. This condition likely has a significant association with appetite hormones.

An interesting aspect of the studies included in this systematic review is that very few studies have evaluated ghrelin. Ghrelin is a key regulator of nutrient sensing, meal initiation, and appetite (31). Additionally, studies have reported that ghrelin exhibits proliferative properties in cancer (32). Interestingly, the articles that included the evaluation of this hormone dosed total ghrelin, not its fractions (acylated and non-acylated). There is a debate about the usefulness of total ghrelin as a biomarker of appetite. For some authors, total ghrelin measurements do not accurately reflect specific biological actions of ghrelin. Ghrelin circulates in both acylated and unacylated forms; the unacylated form's levels are 2.5 times higher than the acylated form's (33). It is felt that acylation at serine-3 is essential for the biological activity of ghrelin. However, unacylated ghrelin is able to antagonize the metabolic but not the neuroendocrine response elicited by acylated ghrelin (34). More information on the relationships of acylated and unacylated ghrelin in patients with cancer is called for.

Of the studies included in the systematic review, only two evaluated ghrelin concentrations in the pediatric population with cancer (16,19), and both measured total ghrelin. Levels of ghrelin in children with ALL were lower than in controls, and in the maintenance phase of chemotherapy there was a significant increase in the circulating levels of the hormone (16). In acute leukemia, there is inflammation and serum hyperlipidemia, and both may suppress ghrelin at diagnosis (35). Leukemia causes a more intensive inflammatory process than solid tumors; so, gut hormones may behave differently in ALL. Trivin et al. (19) observed that the hypothalamic involvement in patients with craniopharyngioma decreased levels of ghrelin, and this reduction was more significant the greater was the involvement. In the particular setting of craniopharyngioma, the destruction, or functional impairment, of the

hypothalamus is probably responsible for the failure to integrate neuronal, hormonal and metabolic signals from the body, leading to changed feeding behavior (36).

Leptin is proportional to total body fat mass and, communicating primarily with the hypothalamus, has a role in satiety and energy use (18). Recently, leptin has been shown to play a regulatory role for differentiation within the myeloid and erythroid cell lineage, whereas results of its regulatory effects on lymphocytes and related tumor cells have been contradictory (28). Higher serum leptin levels have been associated with body fatness in ALL survivors (37). In the current systematic review, the results in leptin concentrations were quite discrepant between studies. This may be due, in part, to the fact that leptin levels are affected by several variables, including gender, pubertal stage, weight, diet and the analytical method (38). Small variations are expected in the values assayed by different methodology. Large variability is probably due to different pubertal stages and BMIs in the studies (39,40).

Most of the studies included in the review evaluated children and adolescents with ALL or survivors of hematological malignancies. Leukemia is the most common malignancy in children (9,41). It is a heterogeneous group of diseases in which there is a substitution of normal medullary and blood elements by immature cells (blasts), and accumulation of these cells in other tissues (42). Because more than 80% of children with ALL survive to adulthood, the late effects of therapy must be considered (23,43). In survivors, overnutrition may be one of the risk factors for type II diabetes mellitus, hypertension, and cardiovascular disease. This is a particular problem for cancer survivors, who already have the additional risk for cardiovascular disease due to potential cardiotoxic effects of chemotherapy or radiotherapy (44). The role of leptin in hematological malignancies has been explored, not just as an appetite hormone, but also as a stimulus for proinflammatory cytokines, hematopoiesis and lymphopoiesis (25), promoting atherogenesis. It may indeed be an independent risk factor for cardiovascular disease.

According to Srivastava et al. (18), leptin is proportional to total body fat mass and communicates primarily with the hypothalamus, promoting satiety and influencing energy usage. However, studies have failed to find a direct relationship between leptin levels and anthropometric parameters of body fat (45,46). Petridou et al. have shown that elevated serum adiponectin, but not leptin levels, might be independently

associated with both Hodgkin's and non-Hodgkin's lymphoma incidence, as well as with poor prognosis, in children (24,25). In young adult survivors of childhood cancer, adiponectin might be associated with insulin resistance (47). The differences between studies do not allow us to characterize leptin changes in children with cancer in this review. More studies are needed to investigate the role and associations of appetite hormones in children and adolescents with cancer, in order to better understand the pathophysiology of nutritional findings, and even to establish different patterns of response in different types of cancer.

In conclusion, changes in the responses of the ghrelin and leptin hormones in children and adolescents with cancer are quite diverse, probably due to the different types of cancer observed, different treatments performed and biological characteristics of this age group. Because of growing interest in the effectiveness of strategies to minimize cardiometabolic risk in the childhood cancer population, further research is necessary to better understand the behavior of these hormones during the disease and its possible relations with the nutritional status and the prognosis of the patients.

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Table I. Summary of studies and their results

Reference	*Design of study*	*Characteristics of patients*	*Type of cancer*	*Control group*	*Hormone*	*Mean values of hormones: result at diagnostic*	*Mean values hormones: r during treat*
Srivastava et al., 2015 (18)	Cross□sectional	159 (123 boys) acute leukemia survivors aged ≤ 18 years who had completed the treatment at least 1 year before enrollment in this study Mean age: 10.7 ± 4.2 years Patients were stratified according to their nutritional status in obese (26.4%) and non-obese (73.6%)	Acute lymphoblastic leukemia	None	Leptin (pg/ml)	Obese: 3.70 ± 2.27 Non-obese: 2.85 ± 1.91 (p = 0.06 between)	-
Trivin et al., 2009 (19)	Longitudinal	27 patients (15 boys) with craniopharyngioma stratified according to hypothalamic involvement Mean age: 8.3 ± 3.5 (2.8-15.7)	Craniopharyngioma	None	Grhelin (ng/l)	- Without hypothalamic involvement: 2,256 ± 331 - With light hypothalamic involvement: 1,091 ± 251 - With	One year aft surgery: - With light hypothalam involvement 263 - With mode hypothalam involvement

						moderate hypothalamic involvement: 1,083 ± 222 p < 0.05 for hypothalamic involvement between other groups	126
					Leptin (µg/l)	- Without hypothalamic involvement: 5.6 ± 2.6 - With light hypothalamic involvement: 7.7 ± 4.5 - With moderate hypothalamic involvement: 14 ± 9.8	One year aft surgery: - Without hypothalam involvement 14 - With light hypothalam involvement 14 - With mode hypothalam involvement 26 p < 0.05 bet light and mo hypothalam involvement
					Free leptin index	- Without hypothalamic involvement: 12.7 ± 13	One year aft surgery: - With light hypothalam

						- With light hypothalamic involvement: 12.4 ± 9.0 - With moderate hypothalamic involvement: 34 ± 33 p < 0.05 for moderate hypothalamic involvement	involvement 63 - With mode hypothalam involvement 102 p < 0.05 bet light and mo hypothalam involvement
Sawicka-Zkowska et al., 2013 (20)	Cross-sectional	74 Caucasian survivors patients (42 boys) after treatment for acute leukemia (n = 64) and lymphomas (non-Hodgkin lymphoma; n = 10) Mean age: 15.5 ± 2.6.	Acute leukemia and non-Hodgkin lymphoma	51 nonobese patients (34 boys) hospitalized in the department due to reasons other than neoplastic diseases Mean age: 14.8 ± 3.6	Leptin (ng/ml)	Cancer survivors: 6.64 ± 7.70 Controls: 14.48 ± 19.28 p < 0.05	-
Kojima et al., 2013 (3)	Cross-sectional	49 patients (27 boys) survivors of various types of cancer with a	Leukemias, lymphomas and solid tumor	None	Leptin (ng/ml)	Patients were stratified according to	-

		median age at diagnosis of 5.1 years (range: 0.2-14.2 years); the median present age was 10.7 years (range: 6.0-25.3 years)				the number of metabolic syndrome components: 0: 3.6 (1.1-24.8) 1: 4.6 (1.7-19.5) 2-4: 6.2 (1.9-17.6)	
Tavil et al., 2012 (21)	Case-control	72 (39 boys) children with acute leukemia and range of age 1.08-6 years (mean 6.96 ± 4.16, median 6 years) All patients were newly diagnosed and received only high-dose methylprednisolone during the first 7 days of therapy	Acute lymphoblastic leukemia and acute non-lymphoblastic leukemia	70 age- and sex-matched healthy children (41 boys) with an age range of 0.5-16 years (mean 6.76-4.92, median 4 years)	Leptin (ng/ml)	Controls: 5.96 ± 6.76 Cancer: 4.92 ± 3.39 p > 0.05	Cancer 7-da high-dose methylpredn therapy: 7.1 p < 0.001 co with before
Kohler et al., 2011 (22)	Cross-sectional	54 patients (27 male) previously treated with mean of 5.8 years from treatment completion	Acute lymphoblastic leukemia	51 healthy controls (21 male) participated in the study Females mean age	Leptin (ng/ml)	-	Females survivors: 17 18.7 Female cont 7.8 ± 7.4 p < 0.05 Boys survivo

		The mean ages at diagnosis and study entry were 5.8 ± 3.9 years and 14.0 ± 5.0 years, respectively Females mean age was 16.0 ± 4.5 years and boys mean age was 12.1 ± 4.7 years		was 14.3 ± 5.2 years and boys mean age was 13.6 ± 4.5 years			± 2.7 Boys contro ± 5.1 p > 0.05
Chow et al., 2010 (23)	Prospective cross-sectional	Children at age < 22 years Two groups were organized: a) Hematopoietic-cells transplant (HCT) group with 26 (16 boys) patients currently in remission b) Non-hematopoietic-cells transplant (non-HCT) 48 (22 boys) patients in first year complete remission after treatment with conventional chemotherapy	Acute lymphoblastic leukemia	None	Leptin (ng/ml)	-	At least 1 ye HCT: 3.0 (2.2 Non-HCT: 2. 3.5) p > 0.05

		Mean age was 15 (8-21 years) for HCT and , and 14 (8-21y years) for non-HCT					
Petridou et al., 2010 (24)	Case-control	75 patients (0-14 years old) newly diagnosed with histologically confirmed Hodgkin lymphoma Mean age was 11.5 ± 2.97 years	Hodgkin lymphoma	75 controls matched for age (6 months) and gender were recruited among children admitted for other causes in the same hospital at the same time as cases Mean age was 11.2 ± 2.90 years	Leptin (ng/ml)	Cases: 8.2 ± 7.26 Controls: 7.5 ± 8.30 p > 0.05	-
Moschovi et al., 2010 (15)	Case-control	Nine (5 boys) children with newly diagnosed ALL with mean age of 4.3 ± 2.1 years (2.1-7.2) in the	Acute lymphoblastic leukemia	Nine healthy children matched for age and sex were	Leptin (ng/ml)	ALL diagnosis: 27.4 ± 4.2 Controls: 17.8 ± 3.4 p < 0.001	Last measur in maintena phase of chemothera 17.1 ± 3.9 p < 0.001

		diagnosis and 5.6 ± 2.0 years (3.2-8.5) in the last measurement in maintenance phase of chemotherapy		used as controls			
Petridou et al., 2009 (25)	Case-control	121 patients (0-14 years old) newly diagnosed with histologically confirmed non-Hodgkin lymphoma Mean age was 8.8 ± 3.5 years	Non-Hodgkin lymphoma	121 controls matched for age (6 months) and gender were recruited, among children admitted for other causes in the same hospital at the same time as cases Mean age was 8.8 ± 3.5 years	Leptin (ng/ml)	Cancer: 6.0 ± 6.31 Controls: 5.9 ± 7.38 $p > 0.05$	-
Moschovi et al., 2008 (16)	Case-control	Nine (5 boys) children with newly diagnosed ALL with	Acute lymphoblastic leukemia	Nine healthy children	Ghrelin (pg/ml)	ALL diagnosis: 32.6 ± 2.9	Last measur in maintena phase of

		mean age of 4.3 ± 2.1 years (2.1-7.2) in the diagnosis and 5.6 ± 2.0 years (3.2-8.5) in the last measurement in maintenance phase of chemotherapy		matched for age and sex were used as controls		Controls: 97.2 ± 14.4 p < 0.001	chemothera 50.6 ± 16.3 (+57%) p < 0.05
Papadia et al., 2007 (26)	Case-control	27 patients (15 boys) treated for ALL during childhood and in complete remission for at least 2 years They had an average age (± SD) of 14.0 ± 0.8 years (range: 6-21 years)	Acute lymphoblastic leukemia	17 (6 boys) healthy subjects with a comparable mean age (12.8 ± 1 years, range: 8-21 years), selected among relatives of the patients (brothers, sisters, or cousins)	Leptin (ng/ml)	Cases: 15.58 ± Controls: 10.78 ± 2.0 p < 0.05 Obs: expressed in mean ± SD	-
Yaris et al., 2005 (27)	Case-control	20 patients (12 boys, 13 with ALL and seven with non-Hodgkin lymphoma) and mean age 132 ± 45	Acute lymphoblastic leukemia and non-Hodgkin lymphoma	20 (11 male) healthy children aged 68-216 months	Leptin (ng/mL)	Cases: 10.3 ± 5.4 Controls: 15.7 ± 6.6 p < 0.05	-

		(range; 64-218) months The follow-up times from diagnosis and the end of therapy were 60 ± 22 and 25 ± 11 months, respectively		(mean: 134.8 ± 36.5) were selected from the children referred to outpatients clinics of the Department of Pediatrics for suspected disease and were found to be normal			
Wex et al., 2002 (28)	Longitudinal	38 patients were evaluated in the day of diagnosis and in complete hematologic remission at day 33 Median age was 6.0 years; range: 1.2-21.9 years	Acute lymphoblastic leukemia	13 healthy children (median age: 7 years; range: 3-13 years)	Leptin (ng/ml)	Cancer on the day of diagnosis: 0.92 ± 0.79 Healthy donors: 3.01 ± 2.27 ng/ml $p < 0.05$	Average lep concentratio day 33 of chemothera treatment: 2 $p < 0.01$
Mayer et al., 2000	Cross-sectional	Patients were divided in two	Acute lymphoblastic	None	Leptin (ng/ml)	Non-irradiation	-

(29)		groups: - 39 patients (23 boys) who had been treated for non-high risk ALL and who fulfilled the following criteria: a) prolonged first remission for at least 3 years; and b) age between 10 and 20 years at the time of this study - Additionally, 25 patients (15 boys) received comparable chemotherapy and, in addition, fractionated cranial irradiation for prophylaxis	leukemia			group: 0.38 ± 0.53 Irradiation group: 0.48 ± 0.25 p > 0.10	

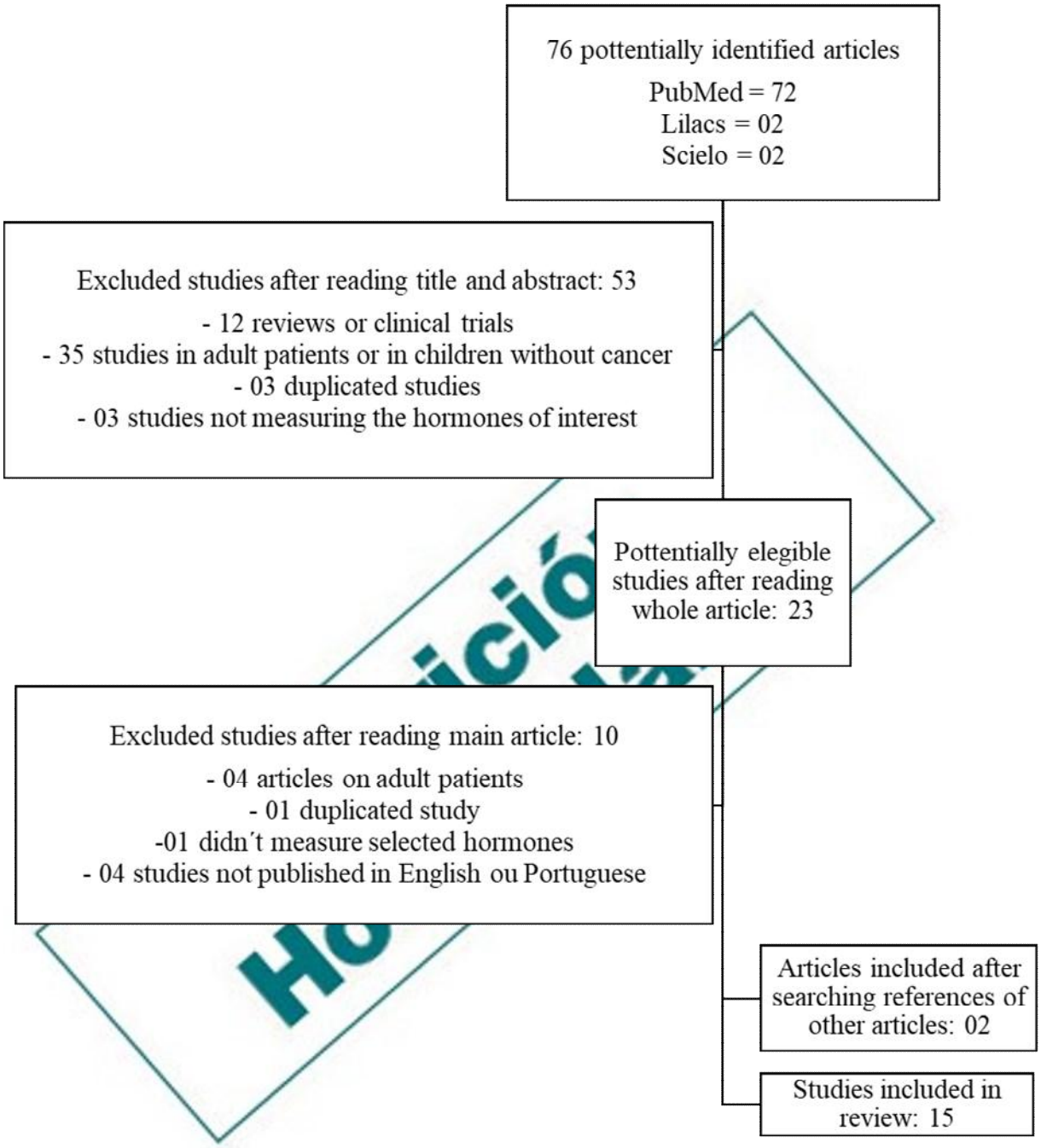

Fig. 1. Detailed flowchart showing the process for studies selection.