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Kisspeptin Levels in Girls with Precocious Puberty: A Systematic Review and Meta-Analysis

Rafael Guerra Cintra[a, b] Rubens Wajnsztejn[b] Camila Martins Trevisan[a]
Victor Zaia[a] Antonio Simone Laganà[c] Bianca Bianco[d] Erik Montagna[a]

[a]Postgraduate Program in Health Sciences, Faculdade de Medicina do ABC/Centro Universitário Saúde ABC, Santo André, Brazil; [b]Department of Neurosciences, Discipline of Neurology, Faculdade de Medicina do ABC/Centro Universitário Saúde ABC, Santo André, Brazil; [c]Department of Obstetrics and Gynecology, "Filippo Del Ponte" Hospital, University of Insubria, Varese, Italy; [d]Department of Collective Health, Discipline of Sexual and Reproductive Health and Populational Genetics, Faculdade de Medicina do ABC/Centro Universitário Saúde ABC, Santo André, Brazil

Keywords
Central precocious puberty · Kisspeptin · Gonadotropin-releasing hormone · Biomarker

Abstract
Background/Aims: Kisspeptin (KP) is a key player in the regulation of the release of gonadotropin-releasing hormone (GnRH), which increases the secretion of gonadotropin during puberty to establish reproductive function and regulate the hypothalamic-pituitary-gonadal axis. Premature activation of GnRH secretion leads to idiopathic/central gonadotropin-dependent precocious puberty (CPP). We aimed to compare the blood KP concentrations in girls with CPP and healthy controls. ***Methods:*** A systematic review and meta-analysis was performed. We searched MEDLINE, EMBASE, The Cochrane Library, and SciELO. Random-effects model and standardized mean difference (SMD) were used. Heterogeneity was assessed through I^2. Meta-regression considered patient age, KP fraction, and analytical method for KP measurement. ***Results:*** The 11 studies included comprised 316 CPP patients and 251 controls. Higher KP levels in the CPP group were found (SMD 1.53; CI 95% = 0.56–2.51). Subgroup analysis revealed association with patient age (p = 0.048), indicating a positive correlation between elevation in KP concentration and age in CPP group. A group of patients with precocious thelarche (PT) from 5 of the included studies comprising 121 patients showed higher levels of KP (1.10; −0.25–2.45: CI 95%) and high heterogeneity (I^2 = 91%). The CPP/PT ratio for KP level indicates KP 36% higher on CPP than PT patients. ***Conclusions:*** A consistent difference in KP levels between girls with CPP and controls was identified. While there are important limitations in KP assays which argue against its use as a diagnostic tool, the KP levels in CPP versus control and PT children are consistent with the predicted mechanisms and pathophysiology of CPP.

Introduction

Puberty represents a complex biological process of sexual development which leads the individual to attain secondary sexual characteristics and reproductive capac-

karger@karger.com
www.karger.com/hrp

Correspondence to:
Bianca Bianco, bianca.bianco@fmabc.br

ity [1]. Pubertal development results from an increase in impulses and frequency of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which is coordinated by a mechanism involving inhibitory, stimulatory, and permissive factors acting upstream of GnRH neurons [2]. This mechanism is determined by a complex interaction of metabolic, environmental, nutritional, ethnic, and genetic factors [1], although it is far from being fully elucidated. Clinically, the onset of puberty is defined as the first appearance of breast buds in girls, whereas in boys the first pubertal sign is the testicular enlargement. Generally, it occurs between the ages of 8–13 in girls and 9–14 in boys [3].

Precocious puberty is defined as the development of puberty younger than that which is expected for ethnicity and race [4, 5]. Premature activation of GnRH secretion leads to idiopathic gonadotropin-dependent precocious puberty (or CPP) [6].

One of the key players in the initiation of puberty is the kisspeptin (KP), a family of neuropeptides encoded by the *KISS1* gene, mapped at 1q32. KPs act through the binding and subsequent activation of the G protein-coupled receptor, KISS1R, which is encoded by the *KISS1R* gene, mapped at 19p13.3 [7–9]. KPs act on GnRH neurons increasing the secretion of gonadotropin – luteinizing hormone (LH) and follicular stimulating hormone (FSH) – during puberty; as KP levels increase, the amplitude and frequency of GnRH pulsatility is augmented [10–12]. The action of LH and FSH on the gonads also stimulates the production of sex steroids, gametogenesis, sexual maturation, and provides hormonal feedback loops that regulate the release of GnRH, LH, and FSH [13]. Additionally, hypothalamic expression of *KISS1*/*KISS1R* increases during the puberty in rats and monkeys [14]. Activating and inactivating mutations in *KISS1* or *KISS1R* genes cause pubertal failure and precocious puberty in children [15–17]. Concentrations of hypothalamic KP were causally associated with GnRH activation and reproductive maturation in humans [9, 18–21]. Prevalence of CPP has been predicted to be 0.2% in general population [22], and interestingly, females are at least 10 times more likely to develop premature puberty than males [6, 23].

Cases of CPP are particularly interesting to investigate, as uncovering the underlying defect may lead to better understanding of yet unknown or understudied pathways critical for puberty. Furthermore, KP is considered a novel biochemical marker of pubertal activation that may help to diagnose and/or manage children with pubertal disorder, for which many studies have been proposed. Even though, there are no comparative studies that examined the magnitude of circulating concentrations of KP in children with precocious puberty. Considering this, we performed a systematic review and meta-analysis aiming to compare the concentrations of blood KP in girls with precocious puberty and controls.

Material and Methods

Search Strategy

A systematic review and meta-analysis was registered in PROSPERO (CRD: 42020147473) and developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24]. We searched the electronic databases MEDLINE, EMBASE, the Cochrane Library, and SciELO. The search strategy included only terms relating to or describing the main features, adapted for each bibliographic database ("kisspeptin" OR "metastin") AND ("precocious puberty") and correlate terms in order to obtain the largest number of articles involving KP dosage. The search included articles in any language from the inception of the abovementioned databases to April 2020.

Selection of Studies

Titles and/or abstracts of studies retrieved were independently screened by 2 review authors. The full text was retrieved and independently assessed for eligibility by 3 reviewers, with disagreements resolved through discussion with an external collaborator. We have included studies enrolling girls diagnosed with CPP confirmed by Tunner criteria for pubertal development, or breast bud started before the age of 8 , or LH and FSH baseline/peak levels, or bone age analysis that were compared with a healthy control group and that performed blood KP dosage.

The exclusion criteria were CPP caused by neurological disorders such as tumors, trauma, malformations, or genetic syndromes. We also excluded incomplete report or pooled data without the possibility of data extraction for subgroups, reviews, case-reports, animal models, in vitro, or in silico studies.

Data Extraction

A standardized form was used for data extraction, assessment, and evidence synthesis by 3 authors independently, with discrepancies resolved through discussion. Missing data were requested to authors when needed.

The primary data retrieved were the first author, publication year, sample sizes, and KP concentrations for case and control groups. Secondary information included age, body mass index, diagnostic criteria for CPP, KP fraction identified, pre-analytical, and analytical procedures, and kit manufacturer. KP serum concentrations were converted to pmol/mL^{-1} in order to provide the number of active molecules *per* volumetric unity. We considered the molar mass of the KP fraction according to the PubChem Compound Database (National Center for Biotechnology Information). Measures reported were transformed to mean and standard deviation if reported otherwise according to previous studies [25].

Risk of Bias Assessment

We used a modified version of the Newcastle-Ottawa Scale (NOS) [26] in order to include parameters which could interfere with KP measurement. It was considered the patient selection cri-

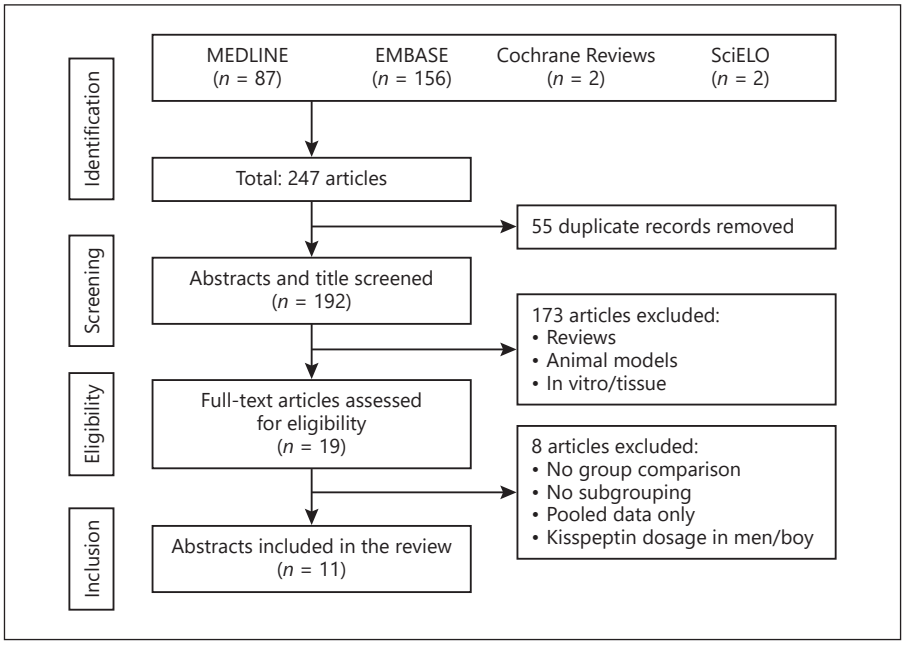

Fig. 1. Flow diagram of study selection. SciELO, scientific electronic library online; KP, kisspeptin

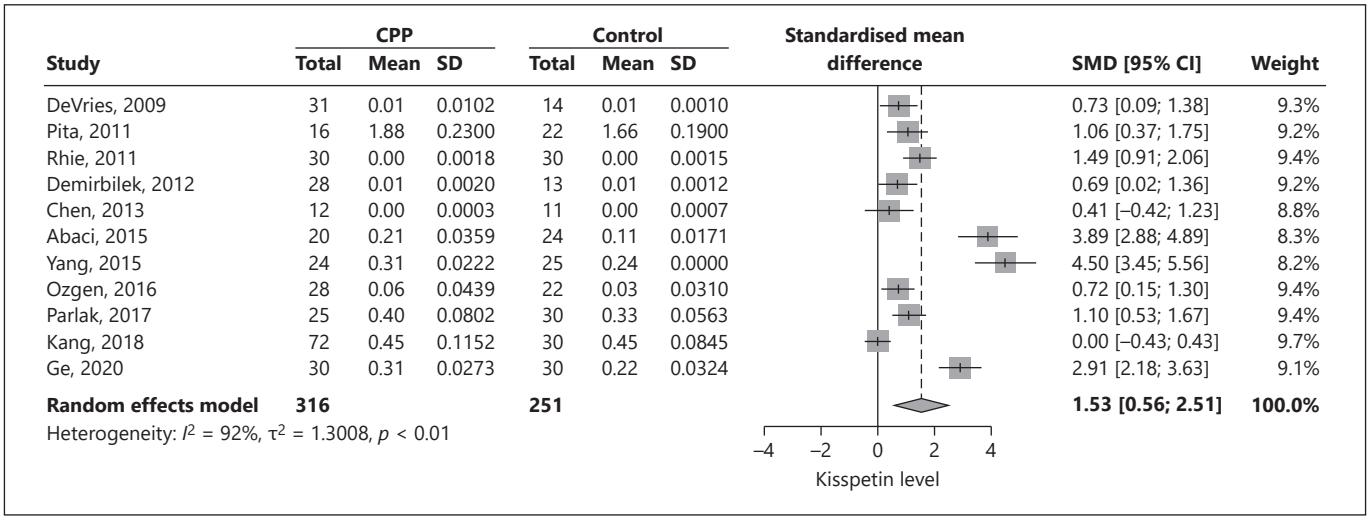

Fig. 2. Forest plot of KP levels in patients with CPP versus healthy controls. KP, kisspeptin; CPP, central gonadotropin-dependent precocious puberty; SD, standard deviation; SMD, standardized mean difference

teria presented in the original articles, the description of data collection and timeframe between the data collection and patients' CPP diagnostic. Pre-analytical parameters consider the description of the sample treatment before analysis, description of tube for sample collection (e.g., EDTA or protease inhibitor), time lapse between the sample collection and processing, sample temperature maintenance until processing, processing protocol (e.g., centrifugation, separation, and fraction obtained), and protein purification techniques for KP fraction isolation. Analytical parameter comprises technique (e.g., Enzyme-Linked Immunosorbent Assay [ELISA] or radioimmunoassay [RIA]), dosage protocol, parameters (calibration curve, sensitivity, and ROC curve), and interferents. Three authors assessed the studies considering low, medium, or high risk of bias, with discrepancies resolved through discussion.

Statistical Analysis

The meta-analysis was performed using a random-effect model. The bias-corrected standardized mean difference (SMD) was adopted [27] for pooling estimates due to the large variations in the KP concentrations observed in the studies. Heterogeneity was tested with τ^2 and I^2 statistics [28], considering values between 50 and 75% moderate, and high if >75%. In addition, a meta-analysis of studies which also presented precocious thelarche (PT) com-

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Table 1. Summary of evidence of the included studies

Authors	Country	Study design	Studied group	Age at diagnosis, years	Tunner criteria	Breast bud started <8 years	Bone age >2 SD	Peak LH test	Kisspeptin fraction	Main findings	NOS
De Vries et al. [34]	Israel	Case-control	31 girls with CPP 14 prepubertal age-matched healthy controls	6.98±0.93	Yes	Yes	No	Yes	KP-10	KP levels were significantly higher in the girls with CPP than in the controls: 14.62±10.2 pmol/L versus 8.35±2.98 pmol/L	9
Pita et al. [20]	Spain	Cross-sectional	16 girls with CPP 22 pubertal females 34 prepubertal females	7.42 (6.94–7.9)	Yes	Yes	Yes	No	KP-54	An increase in KP levels was observed in prepubertal obese girls compared to healthy prepubertal girls and girls with idiopathic CPP. In prepubertal and idiopathic CCP girls, they found a relationship between leptin, BMI, and kisspeptin	7
Rhie et al. [35]	Korea	Cross-sectional	30 girls with CPP 30 age-matched healthy prepubertal controls	6–9	Yes	Yes	Yes	No	KP-10	Serum KP levels were significantly higher in CPP group than in the control group (4.61±1.78 vs. 2.15±1: 52 pmol/L)	9
Demirbilek et al. [36]	Turkey	Cohort	28 girls with CPP 13 girls age-matched prepubertal controls	7.9±0.7	Yes	Yes	Yes	No	KP-10/54	KP levels of girls with CPP (10.2±2.6 pg/mL) were higher than those in controls (8.6±1.5 pg/mL)	3
Chen et al. [37]	Taiwan	Case-control	CPP/PT 12 girls with CPP 11 prepubertal controls	8.9 (7.7–10.6)	Yes	Yes	Yes	No	KP-54	Serum KP levels were higher in the CPP group than control and were still significantly higher after adjusting for age	11
Abaci et al. [38]	Turkey	Cross-sectional	20 girls with CPP 22 girls with PT 24 age-matched healthy prepubertal girls	7.05 (4.8–8)	Yes	Yes	Yes	No	KP-54	Serum KP levels were significantly higher in CPP and PT groups than control	11
Yang et al. [39]	China	Case-control	24 girls with CPP 21 girls with PT 25 normal girls	7.53±0.71	Yes	Yes	Yes	No	ni	The KP level of the CPP group (1.80±0.13 ng/mL) was significantly higher than those of the other 2 groups	10
Özgen et al. [40]	Turkey	Case-control	28 girls with CPP 28 girls with PT 22 prepubertal girls	6.38–8.4	Yes	Yes	Yes	No	KP-54	Serum KP levels were higher in CPP group than control	4
Parlak et al. [41]	Turkey	Case-control	25 girls with CPP 35 girls with PT 30 healthy prepubertal controls	7.0±0.8	No	Yes	Yes	No	ni	KP levels were higher in the CPP and PT groups than control	5
Kang et al. [42]	Korea	Case-control	72 girls with CPP with normal-weight 56 girls with CPP with overweight/obese 30 age-matched normal controls	7.0–8.9	No	Yes	Yes	No	KP-10/54	Serum KP levels were lower in CPP girls with normal-weight (0.59 ng/mL) than in CPP girls with overweight/obese (0.66 ng/mL). However, KP levels were not different among CPP girls (normal-weight or overweight/obese) and controls (0.59 ng/mL)	5
Ge et al. [43]	China	Case-control	30 girls with CPP 30 girls wit PT 30 age-matched healthy control girls	7.20±0.41	Yes	Yes	No	Yes	ni	Lower KP concentrations in controls than in CPP and PT, and negative correlations among KP and peak LH/Peak FSH concentration	11

CPP, central precocious puberty; KP, kisspeptin; ni, Not informed by the study; NOS, Newcastle-Ottawa Scale; PT, precocious thelarche; RIA, radioimmunoassay; yr, years old; BMI, body mass index; LH, luteinizing hormone; FSH, follicular stimulating hormone.

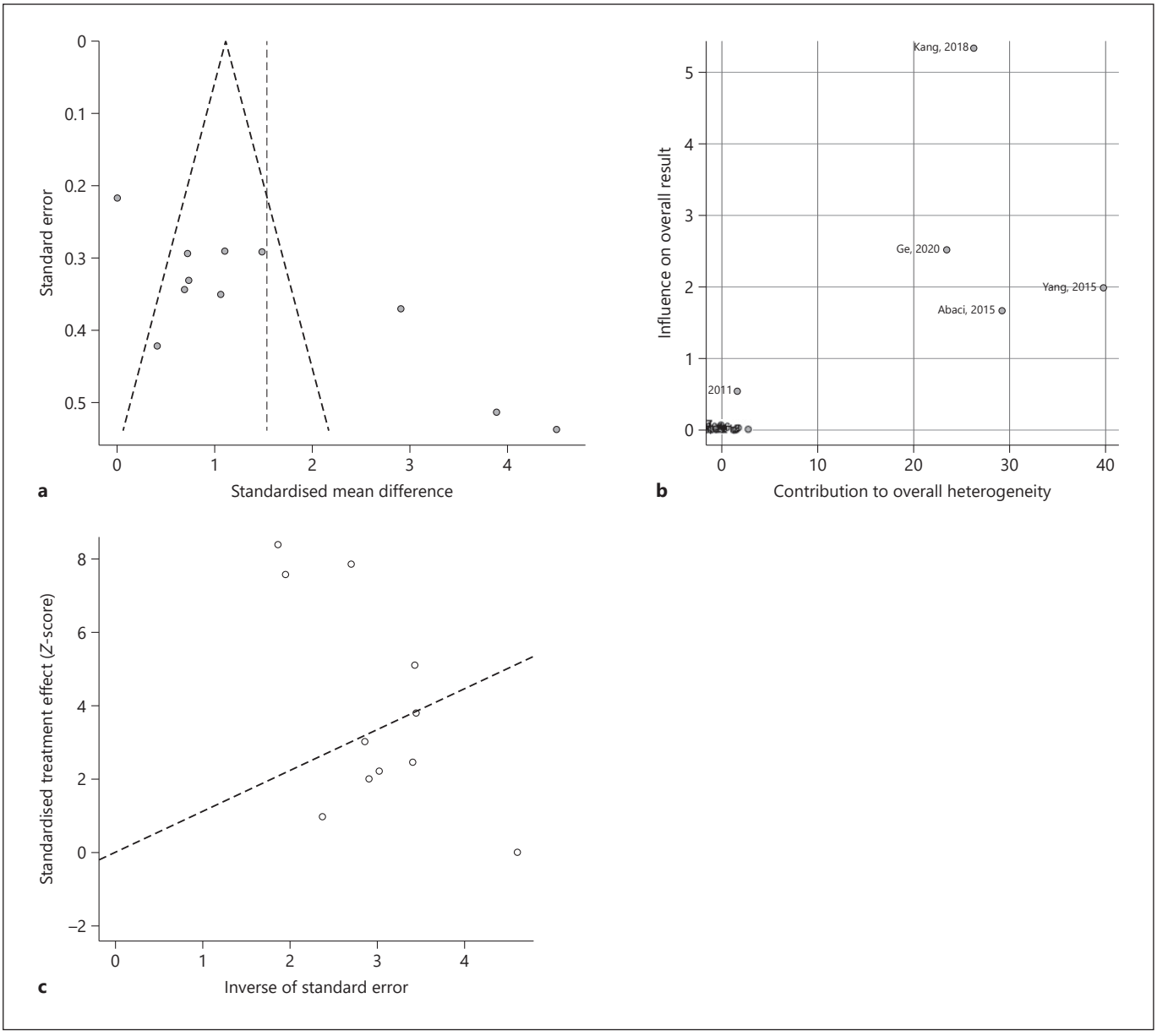

Fig. 3. Analysis of publication bias. Publication bias is presented as funnel plots considering the SMD (**a**), as a Baujat plot considering the publication bias and general contribution of each study (**b**), and the radial plot (**c**). The Baujat plot shows the contribution of each study to the overall Q-test statistic for heterogeneity. SMD, standardized mean difference

pared to CPP was performed, and the KP level related to patient age as previously reported [29]. The Egger test [30], the Baujat plot [31], and the radial plot [27] were used to detect sources of heterogeneity. Results are displayed as forest plots showing SMD and 95% CIs.

Meta-regression analysis was conducted with mixed-effects model and the DerSimonian-Laird estimator. Parameters tested were patient age, disease staging, and analytical procedures when possible. The results of the meta-regression analysis are given as regression coefficients with 95% CIs. Post hoc analyses for patients with PT were considered after data extraction for subgroup analysis.

Data imputation was performed when the KP fraction was not described. We checked the manufacturer reported in the methods section, and if unavailable, we assumed that the KP fraction used was the KP-54 considering that commercial kits commonly use such fraction. Statistical analyses were performed with RStudio (version 1.1.383), using the meta [32] and the metafor packages [33].

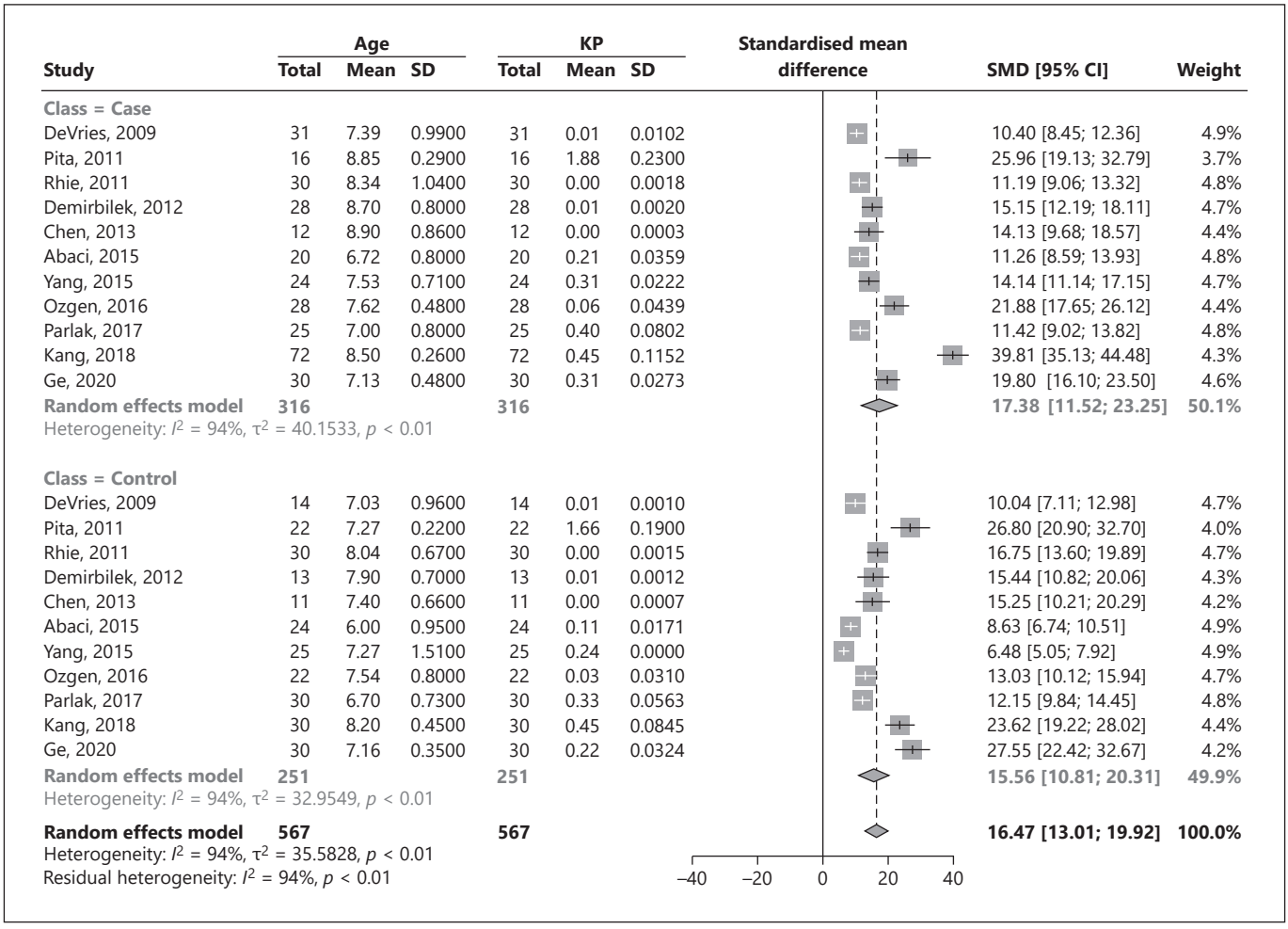

Fig. 4. Forest plot of patient age versus KP levels for CPP and control groups. KP, kisspeptin; CPP, central gonadotropin-dependent precocious puberty; SD, standard deviation; SMD, standardized mean difference

Findings

Systematic Review and Summary of Evidence

A total of 11 studies [20, 34–43] were included, comprising 316 CPP patients and 251 controls. Figure 1 outlines study selection process in a PRISMA flowchart. The summary of evidence is presented in Table 1.

Results of the Meta-Analyses

The Kisspeptin levels were higher in the CPP group than the control group (SMD = 1.53; CI 95% = 0.56–2.51). The heterogeneity was I^2 = 92%, considered high (Fig. 2).

Risk of Bias

Figure 3a, b, and c present the funnel plot, Baujat plot, and radial plot, respectively. The linear regression test of the funnel plot reveals asymmetry (p = 0.004). The Baujat plot confirms that the 3 studies [38, 39, 43] were strong sources of heterogeneity.

Quality Assessment

The NOS scale presented variations among the studies (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000515660). Four studies presented high risk of bias [19, 36, 40, 41], and the remaining varied from mild [20] to low risk. Studies showed poor descriptions of the sample collection and pre-analytical procedures. The description of the healthy controls presented mixed results with 5 studies presenting limited descriptions [20, 34, 36, 40, 41]. However, the case group characteristics, description, and diagnostic criteria presented generally better descriptions.

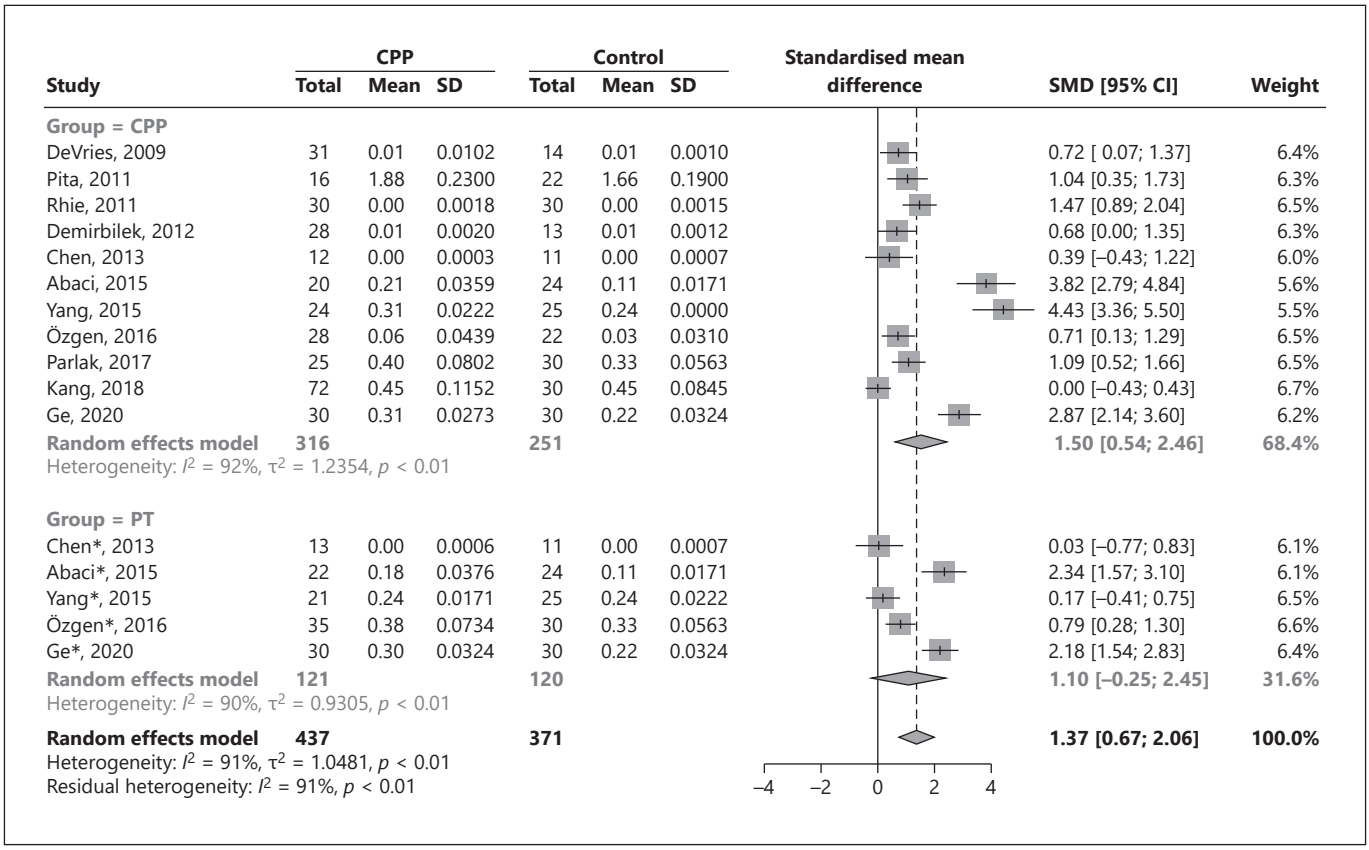

Fig. 5. Forest plot of subgroup analysis comparing CPP and PT patients from studies. CPP, central gonadotropin-dependent precocious puberty; SD, standard deviation; SMD, standardized mean difference; PT, precocious thelarche

Subgroup Analysis

Meta-regression tests considered analytical techniques (ELISA vs. RIA), KP fraction (KP-54 vs. KP-10), and patient age (case vs. control groups). No significant contribution of analytical technique ($p = 0.1728$) or the KP fraction used ($p = 0.2415$) was observed. However, it was significant for the age of patients ($p = 0.048$), with a residual heterogeneity of $R^2 = 21.91\%$. This finding indicates a positive correlation between the elevation in KP concentration and age in the CPP group. In this sense, 2 forest plots were produced in order to obtain further details about the aspects relevant to age and disease progression (Fig. 4, 5).

The first subgroup analysis consisted of a within-group evaluation of the relationship between patient age and KP levels (Fig. 4). The meta-analysis was performed comparing age versus KP levels in CPP group and age versus KP levels in control group. The result for each comparison allows the estimation of the difference of KP level between the groups by the standpoint of the patient age. The result of age versus KP in the case group (CPP patients) was 17.38 (11.52–23.25; 95% CI) comprising 50.1% of the weighted sample and for the control group was 15.56 (10.81–20.31; 95% CI) comprising 49.9% of the weighted sample. The age versus KP for the case/control ratio estimate was 1.12 and indicates a KP level approximately 12% higher on CPP patients regardless of the age differences among the groups and studies.

The second subgroup analysis was performed comparing CPP patients versus control group with PT patients versus the control group (Fig. 5). The analysis of PT patients included data from 5 of the included studies [37, 38, 39, 40, 43] comprising 121 patients with PT and 120 patients in the control group, respectively, also with higher levels of KP in the PT group (1.10; –0.25–2.45: CI 95%) and high heterogeneity ($I^2 = 91\%$). The CPP/PT ratio for KP level is 1.36 and indicates a KP level approximately 36% higher on CPP patients than PT patients.

Discussion

The exact cause of puberty initiation is still poorly understood [44, 45] and approximately 90% of girls with CPP have an idiopathic cause [46]. KP has been identified as one of the key players to pubertal initiation [5, 47]. *KISS1* encodes a 138-amino-acid peptide precursor of KP, which is proteolytically processed into a 54-amino-acid protein, and can be further cleaved to 14, 13, and 10 amino-acid peptides widely referred to as "kisspeptins." KPs have recently been identified as vital upstream regulators that integrate both central and peripheral signals with GnRH release [9]. Evidences have shown that systemic or central administration of KP in immature female rats and in a gonadal juvenile male monkeys induced precocious activation of the gonadotropic axis, by provoking GnRH secretion from hypothalamic GnRH neurons expressing KISS1R [48, 49]. It was showed that KP levels are higher in girls with CPP than in age-matched healthy prepubertal girls [23] and also suggested that this parameter may be useful as an adjunctive tool in the diagnosis of the CPP [34].

Using a systematic review and meta-analysis, we compared the KP levels between 316 girls with CPP and 251 controls from 11 studies (Table 1) [20, 34–43]. In all studies, the values of KP concentration were higher in CPP girls than in controls (SMD = 1.53; CI 95% = 0.56–2.51), except in 1 study [42] which found no difference in KP levels. However, the presence of an overlap between KP levels of girls with CPP and the control group suggests that KP levels alone cannot be strong criteria for CPP diagnosis.

There is a comparative paucity of data examining the circulating concentrations of KP during human reproductive development. This is mainly attributable to the technical challenge of measuring plasma KP in blood samples. Rapid centrifugation and separation are required in order to avoid substantial degradation of KP in the blood samples [50]. Regarding the adoption of preanalytical procedures to improve KP detection, 4 articles reported the use of tubes with protease inhibitor to prevent KP degradation [20, 34, 39, 43] and 1 reported the use of protein purification column [35]. However, this observation alone does not explain the differences observed in the KP concentration. Moreover, some analytical factors were different among the studies, despite the fact that meta-regression revealed that KP fraction measured (KP-54 vs. KP-10), and the analytical procedure (ELISA or RIA) did not significantly contribute to the heterogeneity observed. Three studies presented even higher difference for KP concentration between the case and controls [38, 39, 43] than the other studies. However, no common characteristics were observed to explain such differences.

On the other hand, the meta-regression analysis showed positive correlation between the patient age and KP concentration. These data indicate that the KP levels rise with patient age in CPP, although the KP level was approximately 12% higher on CPP patients regardless of the age differences among the groups and studies. Activation of GnRH neurons is the key to triggering the initiation of the puberty as KP neurons are connected to GnRH neurons. Studies in animal models and humans showed that the central or peripheral administration of KP was able to induce precocious activation of the gonadotropic axis and precocious pubertal development, besides to exert a potent stimulatory effect on gonadotropins secretion [21, 51–55].

In addition to age, the subgroup analysis showed an association between KP levels and PT. The levels of KP in PT group were above the observed in healthy patients and below the observed in CPP patients. PT is defined as the isolated breast development without the development of other sexual characteristics [56], often occurs in toddler girls, and usually regresses over several months [23]. The possible causes of PT include increased FSH secretion, but not LH, excessive dietary intake of estrogens and phytoestrogens, obesity, and endocrine-disrupting chemicals [57, 58]. Therefore, early breast development is not always manifestations of CPP. The differential diagnosis between the early stages of CPP and PT is challenging and requires clinical and laboratory investigation, with long-term follow-up.

As puberty is metabolically gated, obesity has been shown to impact the timing of puberty [59]. KP has a close relationship with leptin, suggesting a link between the metabolism and reproduction [42, 60, 61]. There is evidence for changes in central KP expression both in response to food restriction (negative energy balance) or in genetic or diet-induced models of obesity (positive energy balance), without firm consensus [46].

The limitations of the present study rely on the high heterogeneity, the quality of clinical data provided in the articles, and the huge variation in KP levels observed even after the normalization of concentration unity. In addition, possible variants in the *KISS1* and *KISS1R* genes that could interfere in the KP levels were not evaluated. Also, the technical challenges of KP assays are evident in the studies reviewed. Finally, our study is based on observational studies, which are more subject to biases.

Conclusion

To the best of our knowledge, this is the first meta-analysis to compare KP levels in girls with CPP and controls, showing consistently higher levels in CPP patients. The meta-regression indicated that the KP levels are positively correlated with patient age. Also, the level of KP is higher in CPP than in PT. These findings are coherent with the pathophysiology of the condition. Finally, important limitations in KP dosage strongly advise against its use as a regular diagnostic tool even in face of its undeniable value as a biomarker in this complex scenario.

Acknowledgments

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Statement of Ethics

The research was conducted and developed according to the PRISMA statement. This systematic review and meta-analysis was registered in PROSPERO (CRD: 42020147473). A study approval statement was not required for this study type; no human or animal subjects were used.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The authors did not receive any funding.

Author Contributions

R.G.C., B.B., and E.M. conceived the study. B.B. and E.M. designed the research. R.G.C., C.M.T., V.Z., and E.M. extracted the data. All the authors analyzed the data. R.G.C., B.B., and E.M. wrote the manuscript. All the authors critically reviewed the manuscript and approved the final version of the manuscript.

Availability of Data and Materials

The datasets used in this study are available from the corresponding author on reasonable request.

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