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ORIGINAL ARTICLE

Evidence for hyperprolactinemia in migraineurs: a systematic review and meta-analysis

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Abstract

Background One of the hypothalamus-pituitary axis hormones which may play a crucial role in pathophysiology of migraine is prolactin which is secreted from anterior pituitary gland and synthesized by various immune system cells as well. Whether prolactin blood levels can affect the migraine pathogenesis is an open question. Therefore, investigating prolactin circulatory levels in migraineurs may pave the way to underpin the mechanisms of migraine pathophysiology at biochemical levels. In the current investigation, the prolactin blood levels in the migraine subjects were investigated using systematic review and meta-analysis.

Methods Using online and specialized biomedical databases including Google Scholar, Medline, Pubmed, Pubmed Central, Embase, and Scopus, without the beginning date restriction until Feb 2019, the systematic review retrieved 11 publications in this systematic review after fulfilling for the inclusion and exclusion criteria. For heterogeneity, extent calculation statistical testing was applied. In the present study, the levels of circulatory prolactin in migraineurs assessed using standardized mean difference (SMD) as the effect size.

Results Q quantity and I^2% statistic index showed a high heterogeneity in the 13 selected publications (188.370 and 92.568, respectively) and random-effects model was chosen for further analyses. The meta-analysis on a total number of 460 migraineurs and 429 healthy controls found that the weighted pooled SMD for the effects of prolactin blood concentrations on migraine pathogenesis was as follows: SMD = 1.435 (95% confidence interval, 0.854–2.015).

Conclusion The current investigation presents evidence that prolactin blood levels are higher in migraineurs than healthy subjects.

Keywords Prolactin · Migraine · Pain · Pituitary · Aura

Article highlights
- Association between blood prolactin and migraine pathogenesis was investigated using meta-analysis.
- The included studies (systematic review) were heterogeneous and random-effects model was applied.
- The pooled SMD for prolactin blood levels was 1.435 (95% confidence interval, 0.854 - 2.015). *P* value for the *z*-test was 0.000.
- Based on the findings, hyperprolactinemia is associated with migraine pathogenesis.

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Introduction

Migraine is characterized by recurrent headaches that are often throbbing in sensation and frequently unilateral in location and severe in intensity [1, 2]. From the etiology aspects, it is thought that migraine is a form of neuro-vascular headache, i.e., a disorder in which during an attack, the neural abnormality occurs and results in blood vessel dilation, which, in turn, causes pain induction and brain nociceptive activation. Thus, migraine is best understood as a primary disorder of the brain tissue which is triggered by primary brain biochemical homeostasis instabilities and disturbances and vascular tone changes are known as the secondary event [3–6]. Although migraine attacks may occur at any age, it is notable that they are frequently appeared in childhood, especially during puberty periods. It affects women more than men as the 1-year migraine prevalence is nearly threefold higher and the cumulative lifetime incidence is more than twofold higher in comparison with men [7]. The most prevalent subtype is migraine without aura, including menstrual migraine in women [7]. Interestingly, migraine is more prevalent in women during reproductive years and it is well known that there is a strong relationship between headache and endocrine homeostasis, particularly in relation to ovarian hormones. It is thought that hormones acting in the hypothalamus-pituitary-ovaries axis are critically important in the pathophysiology of migraine [7, 8]. Of this axis, prolactin is secreted from anterior pituitary gland and synthesized by a variety of immune system cells [9]. Even though there is a plethora of publications describing prolactin blood concentrations from 1970s to 2010s, however, there is not any meta-analysis in the evidence-based medicine field and actually, whether prolactin circulatory concentrations can be altered during migraine pathogenesis is an open question yet. Therefore, investigating prolactin blood levels in migraineurs may pave the way to underpin our understanding about migraine pathophysiology at biochemical levels. In the current report, the prolactin blood levels in the migraine subjects investigated using meta-analysis under random-effects model and SMD as the effect size.

Materials and methods

Protocol of the systematic review and meta-analysis

To conduct prolactin circulatory levels systematic review and meta-analysis, the PRISMA Checklist 2009 was applied in this study [10].

Information sources and search strategies

A systematic literature search was independently carried out by three of authors (A. N-Z., A. S-N., A. K.) using online specialized biomedical databases of Google Scholar, Medline, Pubmed, Pubmed Central, Embase, and Scopus until Feb 2019 without restriction to the beginning time. The search results were restricted to English language. Published studies using the MeSH and non-MeSH terms "prolactin," "prolactinemia," "hyperprolactinemia," and "hypoprolactinemia" in combination with "migraine," "headache/s," and "migraineur/s" with additional keywords including "hormone," "plasma," "serum," "blood samples," "circulatory," "level/s," and "case-control study" were identified. The publication references were scrutinized for further related references to identify any additional relevant study relevant to prolactin circulatory levels. The review processes were independently limited to case-control study types by three authors, fulfilling the exclusion and inclusion criteria.

Eligibility criteria

Publications were pre-selected if they used standardized biochemical methodology such as enzyme-linked immunosorbent assay (ELISA), chemiluminescent, and radioimmunoassay (RIA) techniques for prolactin blood level determinations. No limitation was applied to the migraine subtype, migraine severity and pain level, race and study participant sex as reported by included publications. Furthermore, studies were excluded if they enrolled individuals other than migraineurs. Only studies describing circulatory prolactin levels in the migraineurs and healthy controls considered for calculating the pooled effect size estimation. The publications which reported the data only by presenting curves and graphs without mentioning the exact mean ± standard deviation (SD)/standard error of the mean (SEM) in the migraineurs and healthy groups were excluded as well. Besides, papers which did not report the number of cases and healthy controls were discarded and not included for meta-analysis processes.

Study selection

Because of describing different protocols used for blood prolactin concentration determination, only publications which evaluated the levels of prolactin in migraineurs in comparison with healthy subjects considered to be included. Moreover, from the pre-included case-control publications for prolactin blood levels, studies providing suitable and enough information were chosen in order to pooled effect size be statistically computable (including mean and standard deviation or standardized error of the mean, number of migraineurs, and healthy controls). Three authors selected the included studies (A. N-Z., A. S-N., and A. K.) and any disagreement has been solved by the fourth author (S. D.).

Data collection process

The first author of the included papers, publication date, the prolactin blood levels in migraineurs and healthy controls, reported criteria for the migraine attack acceptance in patients or rejection in healthy controls, the total number of migraineurs and healthy controls, and other related information were extracted from the finally included publications that have been provided by the systematic review processes in the current study.

Summary measures and synthesis of results

For data analysis in the current meta-analysis, Stata version 14.0 (Stata Corporation, College Station, TX, USA) was considered to be applied. Using the χ^2-based Q test and I^2 index statistics, the between-study heterogeneity was assessed. The Q quantity and I^2 index statistics were used to detect and quantify the extent of inconsistency and heterogeneity among the publication results. A significant Q quantity is a marker for the existence of heterogeneity in the results among published included studies; however, this quantity cannot determine the heterogeneity magnitude. On the other hand, I^2 index statistic estimates the magnitude of result inconsistency among the published studies [11]. For analysis of an estimated pooled effect size (i.e., SMD), the random-effects model was applied. SMD is also known as Cohen's *d* and is the measure of effect and applied when studies report their individual effects in terms of continuous measurement, such as the level of prolactin in the serum. An SMD of zero means that both groups have equivalent effects. The following guidelines were offered by Cohen for interpreting the SMD magnitude: SMD = 0.2, small effect size; SMD = 0.5, medium effect size; and SMD = 0.8, large effect size. (For more information please see reference 12 of the current study [12]). Data were shown as the estimated SMD for each publication SMD and total SMD of all included studies with 95% confidence interval (CI). The significance of the total SMD was determined by the *z*-test and if $P < 0.05$, then the *z*-test was considered statistically significant. The data extracted from each finally included study have been presented in Tables 1 and 2 which were used for calculation of SMD.

Risk of bias across studies

For assessing the risk of bias across published studies, the finally included publications were scrutinized for method validation and data processing. The funnel plot was developed according to the SMD result for each publication and the overall selected studies. For interpretation of any publication bias among the finally included studies, visual inspections of the generated funnel plot were employed to evaluate the plot symmetry. In this plot, the *X* and *Y* axes represent the standard deviation and logarithm of the effect sizes (log of SMD), respectively.

Results

Study selection

In this investigation, the flowchart for the publication selection has been presented in Fig. 1. The initial search for prolactin blood levels in the aforementioned biomedical databases was retrieved a total number of 145 potentially eligible studies. Initial search results were scrutinized for duplicates and 67 records removed as being duplicates. Of the 78 papers, 28 articles were excluded after inaccessibility to the full texts. Moreover, due to insufficient data reported by some publications for SMD and 95% CI calculations and because of poor quality, 37 articles were excluded. Finally, 13 publications (which have been detailed in Tables 1 and 2 and cited in the references part of the current study as [13–22, 39) were included in the meta-analytical processes for prolactin blood levels (Fig. 1). In some of the selected publications, there was more than one case-control study within (here, known as within-article subgroups), which have been presented by letters (a, b, etc.) for discrimination among them, if applicable in further analyses. This systematic review in biomedical databases retrieved 15 case-control studies in overall (Tables 1 and 2).

Study characteristics

For each publication, reported disease characteristics and epidemiological data by the authors were extracted. The age in cases and healthy controls, and criteria for migraine diagnosis, migraine type, and duration of disease have been presented in Table 1. Finally, a total number of 460 migraineurs and 429 healthy controls were retrieved for prolactin serum concentrations in this meta-analysis until Feb 2019.

Risk of bias within studies

The classical measure of heterogeneity among studies' results is calculating Cochran's Q, which is defined as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Q is distributed as a chi-square statistic with *k*-1 degrees of freedom, where *k* is defined as the number of studies. In meta-analytical methodology, calculating the Q quantity is the usual way for evaluating whether a set of single studies are homogeneous versus heterogeneous in terms of studies' results. However, the Q test only reports the presence or absence of results heterogeneity, but it does not refer to its extent. Besides, Q has low power as a comprehensive test

Table 1 The demographic data in migraineurs and healthy controls extracted for each study

Study name	Country	Criteria (as reported by authors)	Mean age in healthy controls, years (SD)	Mean age in migraineurs, years (SD)	Time of testing	Migraine type (with aura/ without aura)	Duration of disease, years (SD)
Eugene M. Cassidy, 2003a [13]	Ireland	International Headache Society (IHS) criteria	41 (15.24)	40 (13.6)	At 9 a.m. following an overnight fasting	0/12	Not reported by authors
Eugene M. Cassidy, 2003b [14]	Ireland	International Headache Society (IHS) criteria (Headache Classification Committee of the International Headache Society, 1988)	42.5 (12.33)	45.6 (12.64)	At 9 a.m. following an overnight fasting	10/0	Not reported by authors
Eugene M. Cassidy, 2003c [14]	Ireland	International Headache Society (IHS) criteria (Headache Classification Committee of the International Headache Society, 1988)	44.8 (13.91)	45.6 (12.64)	At 9 a.m. following an overnight fasting	0/10	Not reported by authors
Eugene M. Cassidy, 2003d [13]	Ireland	International Headache Society (IHS) criteria (Headache Classification Committee of the International Headache Society, 1988)	44.2 (12.33)	45.6 (12.64)	At 9 a.m. following an overnight fasting	Not defined by authors	Not reported by authors
A. Fava, 2014a [15]	Italy	ICHD-3 beta criteria	41.7 (5. 9)	40.2 (6 .8)	After a 10-h overnight fasting	Not defined by authors	24. 7 (6. 8)
A. Fava, 2014b [15]	Italy	ICHD-3 beta criteria	40 (4.7)	40.2 (6 .8)	After a 10-h overnight fasting	11/72	16. 2 (5. 8)
M F P Peres, 2001 [16]	Brazil	Not reported by authors	31(9)	29(6)	On the day of hormonal testing: Blood samples were taken every hour from 19:00 to 07:00	Not defined by authors	8.9 (9.2)
Rachna Parashar, 2014 [17]	India	ICHD-II A1.1.1 (2004) classification	Range 18–35 years	Age-matched	2 h after a light breakfast in the morning of the second day of their menstrual cycle	0/20	Not reported by authors
I. Rainero, 2001 [39]	Italy	International Headache Society (lHS) criteria	41(15.24)	28.3 (3.7)	09:00 h after overnight fasting	6/9	13.5(8.4)
Sibel Guldiken, 2011a [18]	Turkey	International Classification of Headache Disorders-II diagnostic criteria	34.4 (7.8)	38.0 (8.6)	During interictal period-between 08:30 and 09:00 a.m.after overnight fasting	23/0	Not reported by authors
Sibel Guldiken, 2011b [18]	Turkey	International Classification of Headache Disorders-II diagnostic criteria	34.4 (7.8)	38.0 (8.6)	During interictal period-between 08:30 and 09:00 a.m.after overnight fasting	0/27	Not reported by authors
V Solmaz, 2016 [19]	Turkey	diagnosis criteria of International Headache Society	32.43 (7.14)	35.17 (6.40)	Not reported by authors	Not defined by authors	Not reported by authors
Vasfiye Burcu Dogan, 2017 [20]	Turkey	International Headache Society (IHS) International Classification of Headache Disorders-II (ICHD-II) (IHSDII)	34.2 (7.9)	33.9 (6.7)	Not reported by authors	Not defined by authors	Not reported by authors
Etsuko Awaki, 1989 [21]	Japan	Ad Hoc Committee criteria	36.7 (15.1)	36.9 (11.8)	09:00 h after overnight fasting	Not defined by authors	Not reported by authors
Giovanni D'Andrea, 1988 [22]	Italy	Ad Hoc Committee on Classification of Headache	9 (SD not reported by authors)	9 (SD not reported by authors)	Between 8:00 and 9:00 a.m.	Not defined by authors	1–4 years

Table 2 The data in migraineurs and healthy controls extracted for calculating the effect size in each study and pooled effect size as well

Study name	Mean prolactin blood levels in migraineurs (μg/L)	Prolactin standard deviation in migraineurs	Number of migraineurs (male/female)	Mean prolactin blood levels in controls (μg/L)	Prolactin standard deviation in controls	Number of healthy controls (male/female)
Eugene M. Cassidy, 2003a [13]	10.857	0.606	12 (0/12)	13.409	1.066	16 (0/16)
Eugene M. Cassidy, 2003b [14]	14.297	4.187	10 (0/10)	14.518	1.405	10 (0/10)
Eugene M. Cassidy, 2003c [14]	10.311	0.465	10 (0/10)	14.518	1.405	10 (0/10)
Eugene M. Cassidy, 2003d [13]	8.695	0.841	10 (0/10)	14.518	1.405	10 (0/10)
A. Fava, 2014a [15]	16	3.4	83 (0/83)	17	4.2	83 (0/83)
A. Fava, 2014b [15]	18	5.4	83 (0/83)	17	4.2	83 (0/83)
M F P Peres, 2001 [16]	26	11	17 (3/14)	37	17	9 (2/7)
Rachna Parashar, 2014 [17]	7.176	1.431	20 (0/20)	3.575	0.407	20 (0/20)
I. Rainero, 2001 [39]	4	1.8	15 (5/10)	9.2	3.6	10 (4/6)
Sibel Guldiken, 2011a [18]	9.45	4.77	23 (0/23)	10.89	5	25 (0/25)
Sibel Guldiken, 2011b [18]	12.95	10.74	27 (0/27)	10.89	5	25 (0/25)
V Solmaz, 2016 [19]	0.107	0.36	41 (0/41)	11.6	4.5	41 (0/41)
Vasfiye Burcu Dogan, 2017 [20]	0.62	0.343	80 (0/80)	0.893	0.935	62 (0/62)
Etsuko Awaki, 1989 [21]	21.3	9.5	11 (0/11)	14.7	4.7	9 (0/9)
Giovanni D'Andrea, 1988 [22]	5.9	2.8	18 (9/9)	6.1	4	7 (not reported by authors)
			Sum of migraineurs: 460			Sum of healthy controls: 429

for heterogeneity especially when the number of studies is small as it occurs in most meta-analyses [23]. Recently, the I^2 index has been suggested to quantify the degree of homogeneity versus heterogeneity of studies' results. It describes the percentage of variation across studies' results that are due to heterogeneity rather than chance and it is quantified as follows: $I^2\% = 100\% \times$ (Q-degree of freedom)/Q. Unlike Cochran's Q, it does not inherently depend on the number of studies included for the meta-analysis. Thus, I^2 index is a simple and intuitive expression of the inconsistency of studies' results [11, 24]. Because the Q statistic test is only applied for heterogeneity testing among the included articles, but not suitable for calculation of the results heterogeneity extent, a tentative classification of I^2 values with the purpose to interpret heterogeneity extent was developed and the quantities of nearly 25% ($I^2 = 25$), 50% ($I^2 = 50$), and 75% ($I^2 = 75$) for I^2 values would be interpreted as low, medium, and high heterogeneity in studies' results, respectively [11]. The meta-analysis results demonstrated that the finally included articles were not homogeneous and actually, they were inconsistent. Moreover, the Q quantity was calculated as 188.370 for prolactin blood levels across studies. The $I^2\%$ test for prolactin blood levels was calculated as 92.568. It is notable that I^2 quantity and the between-studies variance, known as τ^2, are directly related to each other, meaning that the higher the τ^2, the higher the I^2 index [11], therefore, the random-effects model considered for the presentation of prolactin forest plot of the finally selected publications in the current meta-analysis.

Synthesis of results

The forest plot representation for the included articles and their within-article subgroups in each study have been presented in Fig. 2. In this representation, the mean effect sizes and standard deviations and the SMDs with a 95% of CI for each study and the overall effect size have been demonstrated as well. The meta-analysis calculations found that the weighted overall SMD for the impact of prolactin blood levels in migraineurs was as follows: SMD = 1.435 (95% CI, 0.854–2.015), under random-effects model in the meta-analysis as presented in Fig. 2 for the finally 15 included studies (including their corresponding within-article subgroups in each publication). It is noteworthy that the P value for the significance of the overall SMD was clearly significant ($P = 0.000$) for the average effect size of prolactin blood levels as examined by the z-test.

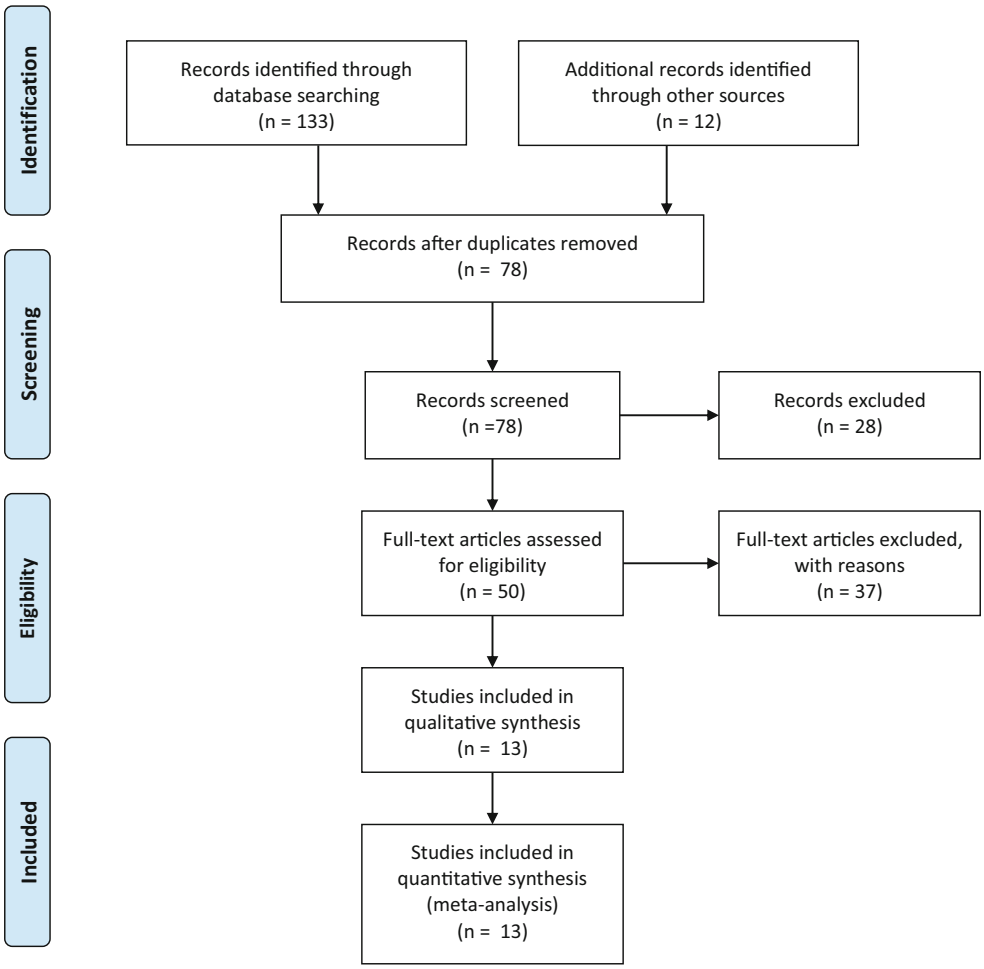

Fig. 1 Searching strategy for systematic review. This flowchart illustrates the processes for identifying relevant studies to be included according to the exclusion and inclusion criteria. 13 included studies fulfilled the inclusion/exclusion criteria. These studies include within-article subgroups. Including these within-article subgroups, the systematic review process retrieved 15 case-control studies

Risk of bias across studies

Notably, the developed funnel plot by the Stata software was considered to be moderately asymmetrical in shape demonstrating the publication bias existence in the finally included articles, including within-article subgroups, for prolactin blood concentrations in migraineurs. For prolactin circulatory levels, this bias mainly visible at the right part of the publication bias plot had been mainly occupied by the articles demonstrating the higher SMD quantities for migraine subjects as compared with corresponding healthy controls (Fig. 3).

Discussion

Investigating prolactin blood levels in migraineurs may pave the way to underpin our understanding about migraine pathophysiology at biochemical levels. Even though there are publications describing prolactin blood concentrations from 1970s to 2010s, however, there was not any meta-analysis in this regard and actually whether prolactin circulatory concentrations could be altered during migraine pathogenesis was an open question. In the current study, the levels of blood prolactin in the migraine subjects were investigated using systematic review and meta-analysis and SMD as the effect size. The primary analysis for the main hypothesis on a total number of 460 migraineurs and 429 healthy controls found that the weighted pooled SMD for the effects of prolactin blood concentrations on migraine pathogenesis was as follows: SMD = 1.435 (95% CI, 0.854–2.015). This systematic review and meta-analysis is the first one providing evidence for hyperprolactinemia in migraineurs in comparison with healthy controls. In this analysis, there was a high heterogeneity in the results of included studies which may originate from the technical aspects and thus random-effects model was applied for further analysis. This phenomenon may stem from the detection methods such as the type of the first antibodies in epitope binding in ELISA technique. As prolactin exists in multiple forms which are known as little prolactin (molecular weight of approximately 22 kDa, predominant form, a single-chain polypeptide of 198 amino acids), big prolactin (approximately 48 kDa, it may be the product of interaction of several prolactin molecules, it appears to have little, if any, biological activity), and big prolactin (approximately 150 kDa, low biological

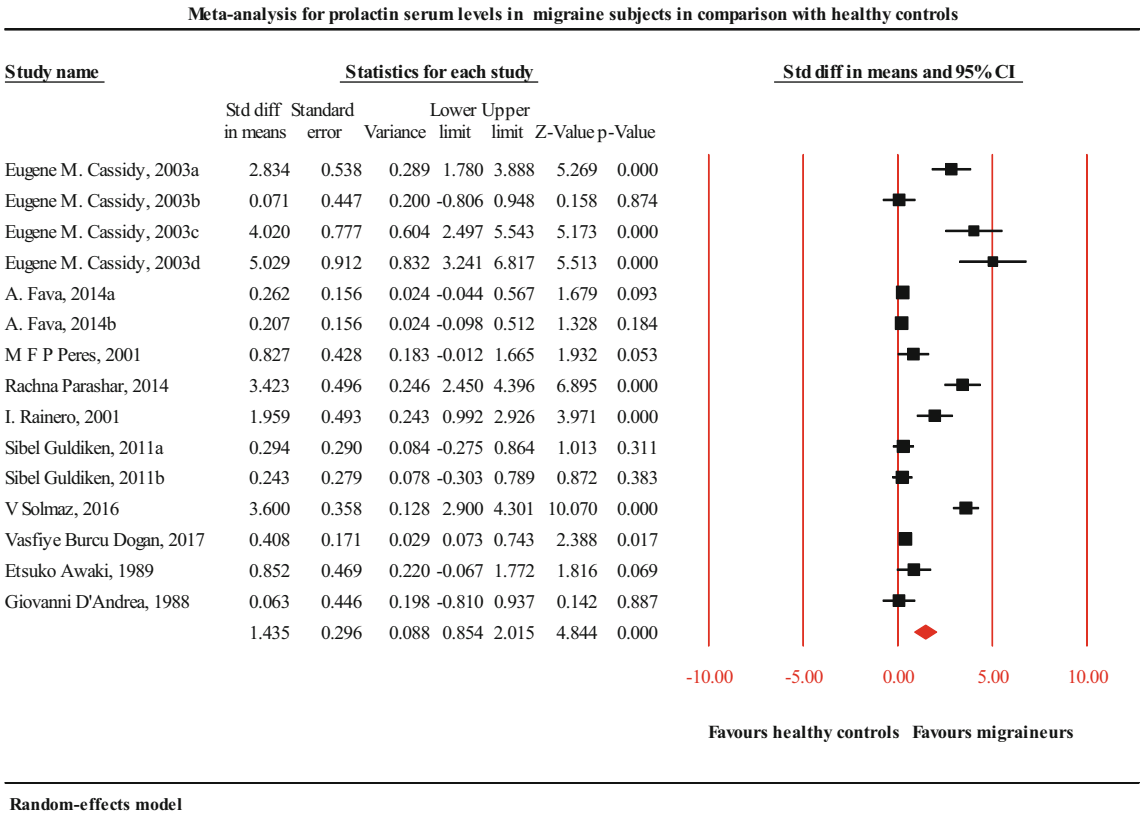

Fig. 2 Forest plot of 13 included studies fulfilled the inclusion/exclusion criteria. These studies include within-article subgroups, which have been presented by letters (a, b, etc.), if applicable. Including these within-article subgroups, the systematic review process retrieved 15 case-control studies. In this presentation, pooled data evaluating the effects of prolactin blood concentrations in migraineurs compared with healthy controls have been demonstrated under random-effects model. The pooled estimate for standardized mean difference (SMD) was calculated as 1.435 (95% confidence interval, 0.854–2.015)

activity) [25, 26] raises questions and provides evidence that the nature and concentrations of the immunoreactive prolactin circulating forms are very important that must be highly considered in the future studies to achieve consolidated results. Besides, as prolactin secretion is influenced by pathologic factors such as primary hypothyroidism, pituitary adenoma, hypothalamic diseases, renal failure, and even physiologic factors such as pregnancy, sleep, stress, intercourse, exercise, nipple stimulation, and also pharmacologic agents (morphine, phenothiazines, reserpine, butyrophenones, estrogens, methyldopa), therefore, such factors may also contribute to heterogeneity among results, even though the majority of included studies, if not all, consider such factors. Prolactin is unique because its secretion is controlled by a central inhibitory mechanism, mediated by dopamine. The current study provides evidence that hyperprolactinemia plays a role at biochemical levels in the migraine patients and neuroendocrine changes may exert a pathological role in migraine or exacerbate the disease severity. It is shown that dopaminergic dysfunction, i.e., the inhibitor of prolactin hormone secretion from the anterior pituitary, is responsible for the development of autonomic symptoms such as nausea and yawning which also predominate in migraineurs [27–29]. Furthermore, it is interesting that hyperprolactinemia induces migraine attacks, and furthermore, prolactin exacerbates other primary headache syndromes as well [30]. Moreover, from the aspects of etiology, hyperprolactinemia can be thought as either the primary or secondary cause or maybe it may be produced as a byproduct in the course of disease pathology. In this regard, there is evidence that hyperprolactinemia induces migraine attacks [30] and thus can be as the primary cause of disease development. On the other hand, other investigations showed that blood estradiol hormonal fluctuations in migraineurs induce migraine attacks developments as well. It is interesting that prolactin secretion is controlled by estrogen levels and indeed the latter induces prolactin secretion from the anterior pituitary by promoting lactotroph cells development in maternal and induction of enzymatic processing of its protein precursor [31, 32] and, in turn, prolactin inhibits estrogen secretion and induces progesterone synthesis [33]. Interestingly, prolactin is associated with hypertension in pregnant women [34, 35] and it may act as a vascular tone modulator, which may possibly occur in migraine subjects. As it is evident, the interplay between prolactin and estrogen is important for migraine attack development. Further experimental evidences are needed to clarify these relationships in migraineurs in

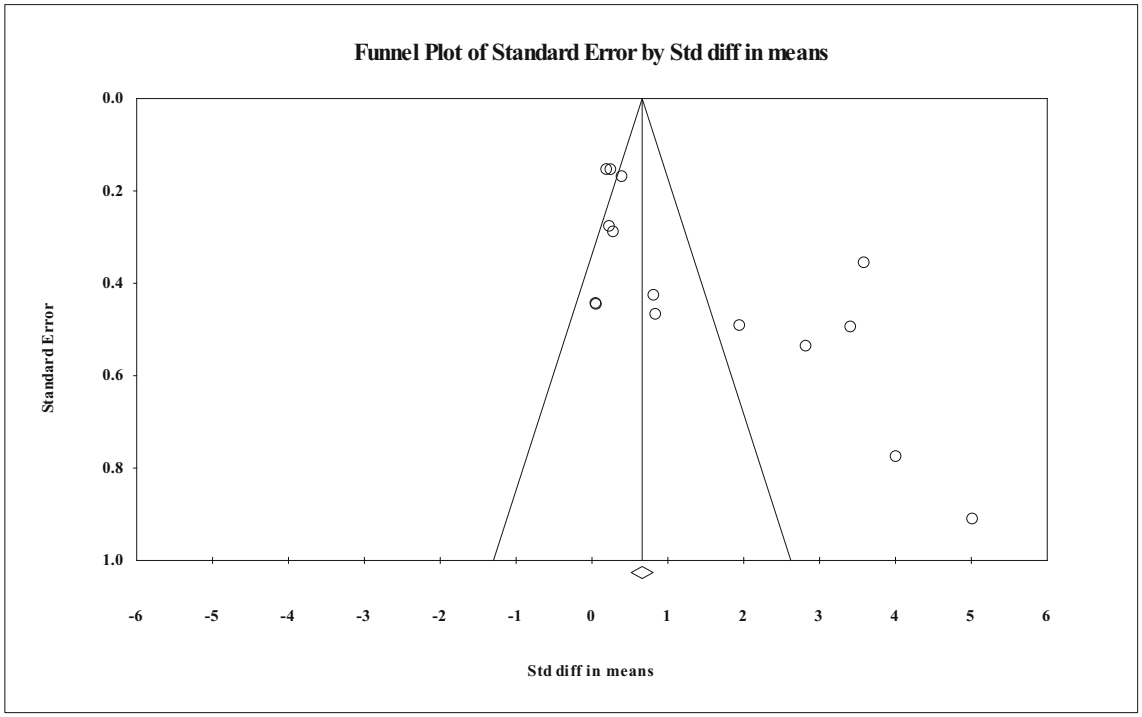

Fig. 3 Funnel plot for 15 case-control studies. For interpretation of any publication bias among studies, visual inspection of the generated funnel plot under random-effects model employed to evaluate the asymmetry. The funnel plot appears asymmetrical and with publication bias toward studies reporting higher prolactin blood levels in migraine patients in comparison with healthy controls. In this plot, the *X* and *Y* axes represent the standardized mean differences (SMDs) and standard errors, respectively

detail. Moreover, the majority of the included studies in this systematic review used female subjects other than males in the case (see Table 2) and controls to compare the serum level of prolactin as migraine is prevalent in females over than males in a ratio of 3:1 [36]. It is noteworthy that recent experimental study demonstrated that meningeal application of prolactin and calcitonin gene-related peptide produces female-specific migraine-related behavior as prolactin caused robust facial and hindpaw hypersensitivity as well as increased grimacing for at least 7 days in females but not male rats [37]. On the other hand, the quantity of the pooled SMD was 1.435 (95% CI, 0.854–2.015) in the current study suggesting the magnitude of the SMD is large [12]. This meta-analysis provides evidence for association between migraine and hyperprolactinema. The Bradford Hill criteria remain one of the most trusted concepts in medical investigations and still provide a valid tool for determining the causality between two factors [38]. One of the Bradford Hill criteria for causality is the strength of association (the effect size) between migraine and hyperprolactinemia which was high in the current meta-analysis. However, all aspects of Bradford Hill criteria must be considered to interpret the causality. These criteria include 9 topics as follows: 1-strength of association, 2-consistency, 3-specificity, 4-temporality, 5-biological gradient, 6-plausibility, 7-coherence, 8-experiment, and 9-analogy [38]. Which one, i.e., migraine or hyperprolactinemia, comes first must be revealed according to Bradford Hill criteria, and thus, further investigations must be considered to determine the existence of this causality relationship. As a matter of fact, pathological and physiological factors that can influence prolactin levels only described in the studies and they were not used to be considered in statistical analysis and future investigations may consider such factors to overcome possible confounders as well.

Conclusions

This meta-analysis presents evidence that prolactin serum levels are higher in migraineurs than healthy subjects.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics The present study was approved by the Ethics Committee of Ilam University of Medical Sciences.

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