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REVIEW

PCOS and vitamin D: a clinical appraisal

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Abstract

Purpose Polycystic ovary syndrome (PCOS) is the most common endocrine-reproductive disease linked not just to infertility but also to serious comorbidities. There is a reported association between low vitamin D levels and multiple health conditions including PCOS. This narrative review aims to analyze the role of vitamin D in PCOS development, use of the vitamin D in the treatment of PCOS, and the molecular basis of these observations.

Methods A Medline and PubMed research was performed, during the years 1990–2023, using a combination of keywords on such topic. According to the author's evaluation and target, papers were identified and included for a narrative review.

Results There are associations between lower levels of vitamin D and PCOS, as well as with insulin resistance, metabolic syndrome, hyperandrogenemia, metabolic and endocrine disorders as well as the onset of oxidative stress and pro-inflammatory milieu, in PCOS women.

Conclusion Vitamin D has a role in pathologic changes linked to PCOS. Molecular and clinical investigations which give new information about the role of vitamin D in the development of PCOS and related endocrine and metabolic disturbance are further needed.

Keywords PCOS · Vitamin D · Metabolic syndrome · Endocrine disorders · Insulin resistance

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine-reproductive disease that affects many women in the reproductive period of life [1]. It is estimated that about 1 in 10 women before women is diagnosed with PCOS and have some complications of this disease [2]. PCOS is associated not just with reproductive troubles, but also with numerous comorbidities such as insulin resistance, metabolic syndrome, obesity, diabetes mellitus type 2, higher risk for cardiovascular diseases and cancers, anxiety, and depression [3–5]. Although the central role in PCOS development has a high ratio of the luteinizing hormone (LH) to follicle-stimulating hormone (FSH) as well as the increased frequency of gonadotropin-releasing hormone (GnRH), the true mechanism of PCOS development is not well-known [1, 6].

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According to the current comprehensions PCOS is defined as polygenic, multifactorial conditions caused by different internal and external factors, environmental factors, genetic, and epigenetics factors which result in hyperandrogenemia (HA), hyperinsulinemia/insulin resistance (IR), increased estrone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) ratio imbalance [1, 3]. Even though PCOS is one of the most common endocrine gynecological diseases there is yet not a specific medical therapy for this condition. There are physical activity and specific fat and sugar-free diets recommended to women with PCOS. Also, there are the medicines such as oral contraceptives, insulin sensitizers antiandrogen agents, and ovulation inducers for the treatment of the different conditions in PCOS women, but all of these therapies are used off-label [1, 6, 7].

Vitamin D is a fat-soluble vitamin that is available from sun exposure and food. In the human body, Vitamin D receptors are present in different cells and in this way vitamin D has the role of hormone involved in different physiological processes [8, 9]. It is reported the association between low vitamin D levels and multiple health conditions [8]. Also, it is presumed that vitamin D has a role in the different processes in the female reproductive tract influencing the expression of the genes in ovaries, endometrium, and placenta [10–12]. The studies in animals and humans found an association between vitamin D levels and different conditions such as preeclampsia, in vitro fertilization pregnancy outcomes after assisted reproductive techniques, PCOS, etc. [13–15].

Considering that PCOS is a growing female health issue worldwide associated with numerous complications and on the other hand the lack of effective therapy, this narrative review aims to summarize the data about the potential role of the vitamin D in PCOS development and use of the vitamin D in the treatment of the PCOS and related conditions and molecular basis of these observations.

Material and methods

The authors searched the available data on vitamin D and its association to PCOS. Authors conducted a MEDLINE, Scopus, and PubMed research, during the years 1990–2022, using a combination of keywords, such as "PCOS", "vitamin D", "vitamin D receptor", "ovary", “insulin resistance”, “hyperandrogenism”, “metabolic syndrome”, “supplementation”, “molecular”. Peer-reviewed articles concerning the role of vitamin D in PCOS development were included in this paper. Additional articles were identified from the references of relevant papers. Comprehensive database search was conducted by two independent authors (A.T. and R.S.), and disagreements were discussed and resolved by consensus or arbitration with a third author (M.A.). Finally, the discussion points of the literature to be included in the narrative review were divided among the various authors and discussed and analyzed all together for the completion of the manuscript (D.V., A.Ma., G.M.B., O.D’O., A.Mo.). By this method, way we assumed that study selection bias was substantially reduced. The results of the research have been divided into different paragraphs, with which we have illustrated what has been reported in the scientific literature.

Results

Possible association of vitamin D with PCOS and its endocrine and metabolic components

There is some evidence about the association between vitamin D and different components and characteristics of PCOS. Ozyurt et al. [16] reported that vitamin D levels in serum, as well as I follicular fluid, are similar in women with and without PCOS who underwent oocyte retrieval for procedures of assisted reproductive technology. On the other hand, they revealed that the vitamin D levels in follicular fluid correlate with total and MII oocyte counts, clinical pregnancy rate, and positive pregnancy test [16]. Güngör et al. [17] reported that vitamin D levels do not correlate with the ovarian reserve in PCOS women. Bindayel et al. [15] conducted a case–control study aimed to determine the difference in vitamin D serum levels between women diagnosed with PCOS and healthy women. The authors showed lower levels of vitamin D serum levels in women affected by PCOS. Gokosmanoglu et al. [18] reported that lower levels of vitamin D are at risk for PCOS development. The same authors also reported a significant association between vitamin D levels and body mass index, serum testosterone, and dehydroepiandrosterone-sulfate levels in women with PCOS. Dawood et al. [19] reported similar results. They observed significantly lower levels in lean PCOS women than in the control group. Simpsons et al. [20] reported lower vitamin D levels in adolescents with PCOS and suggest the vitamin D3 level as a surrogate marker for PCOS risk in the adolescent population.

On the other hand, there are controversial results that showed there is no significant association between vitamin D levels and PCOS. Bostanci et al. [21] conducted a case–control study to compare vitamin D levels between girls with PCOS defined using the Rotterdam criteria and non-PCOS girls. The authors reported no differences in the serum level of vitamin D between the two groups as well as no significant correlations between vitamin D and metabolic or endocrine parameters in PCOS girls and non-PCOS girls. Similar results were observed by Arslan et al. [22]. They reported no difference in the serum vitamin D as well as AMH levels between patients with and women without PCOS. Also,

there was no correlation between vitamin D levels and AMH in the PCOS group or controls.

Studies observed the link between vitamin D and metabolic syndrome and /or metabolic syndrome components in PCOS women. Nandi et al. [23] conducted a cross-sectional study which includes aimed to evaluate the association between serum vitamin D levels and metabolic syndrome in PCOS. This cross-sectional study included 170 patients diagnosed with PCOS of which 85 have metabolic syndrome and 85 patients without metabolic syndrome. The authors revealed statistically significant lower vitamin D levels in PCOS women who have metabolic syndrome than in women without metabolic syndrome. In both groups of patients, the vitamin D levels correlated negatively with the Waist: hip ratio, waist circumference, and diastolic blood pressure.

Krul-Poel et al. [24] compared the vitamin D status between PCOS women and fertile women as well as the possible link between the vitamin D status and metabolic disturbances in PCOS women. The authors observed significantly lower levels of vitamin D in PCOS women than in fertile women. The lower vitamin D level was associated with higher HOMA-IR and an unfavorable lipid profile in PCOS women. Wang et al. [25] reported similar results. They observed significantly lower vitamin D levels in PCOS women than in healthy women. The authors also observed a significantly higher prevalence of vitamin D deficiency and insufficiency in women with PCOS than in controls, especially in PCOS women with obesity or insulin resistance. They reported a significant negative correlation between vitamin D level and body mass index, waist-to-hip ratio, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein, and significantly positive correlation between vitamin D level with high-density lipoprotein cholesterol.

He et al. [26] conducted meta-analysis which aimed to investigate the possible relationship between vitamin D levels and PCOS. They included the 30 studies with the total 3182 patients. They showed that lower serum levels of vitamin D are associated to the metabolic and hormonal disorders in PCOS women such as dysglycemia. In addition, they observed no significant association between vitamin D supplementation and reduction in the metabolic and/or hormonal disorders in PCOS women.

Łagowska et al. [27] conducted the meta-analysis to evaluate the effect of the vitamin D supplementation (alone or with co-supplementation) on the insulin resistance in the women diagnosed with the PCOS. They included in theri meta-analysis all reports of randomized controlled trials published prior to April 2018. In their meta-analysis, 11 studies with the 601 women with PCOS were included. The authors reported that vitamin D co-supplementation leads to the significant decrease in the fasting glucose concentration and the HOMA insulin resistance. Interestingly, the vitamin D supplementation lower than 4000 IU/day leads also to the declining in the HOMA-IR.

Fang et al. [28] performed a meta-analysis to explore the effect of the vitamin D supplementation on the patients affected by PCOS. They included the randomized control trials which compared the influence of the vitamin D supplementation wit placebo or metformin in PCOS women. In this meta-analysis 9 studies with 502 women diagnosed for PCOCS were included. The authors observed that the vitamin D supplementation improve the follicular development in PCOS women. The supplementation of the combination of vitamin D and metformin is better option than metformin alone in the regulation of the irregular menstrual cycles in PCOS women.

Yazadi et al. [29] conducted meta-analysis to evaluate the influence of vitamin D supplementation on the androgen profile in women with PCOS. They included 6 clinical studies with 183 patients which were follow up for the 3–24 weeks. The authors revealed that the vitamin D supplementation decreases the total testosterone levels but, on the other hand, it does not lead to the decrease in the serum free testosterone or sex hormone binding globulin levels.

Conversely to the observed results in the previous meta-analysis, Pergialotis et al. [30] and Jia et al. [31] didn't observe any beneficial effects of the vitamin D in the PCOS women.

Also, some studies investigated the role of vitamin D receptor polymorphisms in PCOS development and their correlation with some endocrine and metabolic components of PCOS. Santos et al. [32] assumed the genotype and haplotype distribution of the Bsm-I (rs1544410), Apa-I (rs7975232), and Taq-I (rs731236) vitamin D receptor gene polymorphisms in PCOS and non-hirsute women and their associations with the PCOS as well as vitamin D levels, and metabolic abnormalities in PCOS women. The authors observed that the CC genotype of Apa-I is associated with a higher risk of metabolic syndrome in PCOS women. Also, this polymorphism was associated with higher systolic blood pressure, total cholesterol, and LDL-cholesterol in PCOS and control groups. Xavier et al. [33] analyzed the association between vitamin D levels, polymorphisms in the vitamin D receptor gene (ApaI, BsmI, FokI, and TaqI), and PCOS. They reported that there is no significant association between vitamin D serum and PCOS, but the TaqI and BsmI polymorphisms are associated with PCOS.

The meta-analysis reported the associations between some genetic polymorphisms especially Apa1 polymorphism, with PCOS development, with the difference in the polymorphisms in dependence on the regions, where the included studies were performed [34–37].

Moreover, the vitamin D deficiency is related to the infertility, and it has possible key role in the PCOS-related

infertility and the pregnancy-related complications. It is considered that the vitamin D supplementation could improve the PCOS-related reproductive health issues [38]. It has been observed the lower ovulation and 40% lower chance of live birth in PCOS women with the vitamin D deficiency than PCOS women with normal vitamin D status which need ovulation stimulation. Also, the pregnant women with PCOS vitamin D deficiency are associated with the higher risk of early pregnancy loss [39].

Clinical studies about the influence of vitamin D on the endocrine and metabolic characteristics of PCOS patients

There are clinical studies that assumed the influence of vitamin D supplementation on the characteristics of women diagnosed with PCOS. Dastorani et al. [40] estimated the effects of vitamin D supplementation on the levels of the anti-Müllerian hormone, metabolic profiles, and expression of a gene involved in insulin and lipid metabolism in infertile women with PCOS. The study involved 40 infertile PCOS women, aged 18–40 years. Participants were randomly divided into two intervention groups for receiving either 50,000 IU vitamin D or a placebo every other week for 8 weeks. It has been observed that the Vitamin D supplementation led to a significant reduction in serum insulin and AMH levels, serum total and LDL-cholesterol levels, homeostatic model of assessment for insulin resistance, and a significant increase in quantitative insulin sensitivity check index compared with the placebo. Maktabi et al. [41] conducted a randomized double-blind, placebo-controlled trial that included 70 vitamin D-deficient (serum concentrations < 20 ng/ml) PCOS phenotype B-diagnosed women to estimate the influence of vitamin D supplementation on the metabolic, endocrine, inflammation, and oxidative stress biomarkers. The included participants were divided into groups, the study group received 50 000 IU vitamin D and the control group received a placebo every 2 weeks for 12 weeks. According to the results observed in this study, vitamin D supplementation leads to a decrease in the fasting plasma glucose, insulin, homeostasis model of assessment-estimated insulin resistance, homeostasis model of assessment-estimated B cell function, serum high-sensitivity C-reactive protein, plasma malondialdehyde levels and increase in the quantitative insulin sensitivity check index. Similar beneficial effects of vitamin D supplementation on insulin sensitivity in PCOS women were observed by Javad et al. [42]. Contrasting results were observed by Trummer et al. [43] and Figurová et al. [44] who reported that supplementation with vitamin D does not influence the metabolic parameters in PCOS women.

There is also a beneficial effect of vitamin D supplementation on the androgen milieu in PCOS women. Razavi et al. [45] conducted a randomized double-blind, placebo-controlled trial that included 60 vitamin D-deficient women diagnosed with PCOS aged 18–40 years old. Participants were randomly divided into 2 groups of which groups received a combination of 200 IU vitamin D, 90 µg vitamin K plus, and 500 mg calcium, and the second group received a placebo twice a day for 8 weeks. The authors reported that the combination of vitamin D-K-calcium co-supplementation led to a significant reduction in serum-free testosterone and dehydroepiandrosterone sulfate (DHEAS) levels, and on the other hand in a significant increase in plasma total antioxidant capacity compared with the placebo. Also, the trend of a greater decrease in luteinizing hormone was observed in patients who received vitamin D-K-calcium co-supplement than in patients who received a placebo.

Miao et al. [46] settled the meta-analysis which included 11 studies with 483 participants, aimed to determine the influence of the vitamin D supplementation on the clinical characteristics of the PCOS women. They observed that the supplementation with the vitamin D leads to the improvement in the homeostasis model assessment of insulin resistance [WMD = − 0.44, 95% CI (− 0.86, − 0.03)], levels of total testosterone [weighted mean differences (WMD) = − 0.10, 95% CI (− 0.18, − 0.02)] and homeostasis model assessment of β-cell function [WMD = − 16.65, 95% CI (− 19.49, − 13.80)]. It has been observed that the supplementation with vitamin D is linked to the improvement in the lipid profile of the women with PCOS, and that vitamin D supplement intake led to the decrease in the total cholesterol [WMD = − 11.90, 95% CI (− 15.67, − 8.13)] and low-density lipoprotein-cholesterol [WMD = − 4.54; 95% CI (− 7.29, − 1.80)]. On the other hand, this meta-analysis does not show a beneficial effect of vitamin D supplementation on the body mass index, dehydroepiandrosterone sulfate, triglyceride levels or high-density lipoprotein-cholesterol.

Discussion

The PCOS is one of the most common endocrine disorders in women in reproductive age. This is a polygenic, polyfactorial and systemic disorder, characterized by an inflammatory and dysregulated steroid state. The PCOS is linked to the numerous health issues, such as infertility, insulin resistance, obesity, and cardiovascular problems, which lead to the significant morbidity in PCOS population. Although there are pharmacological treatments for PCOS management, including as oral contraceptives, metformin, and hormone therapy, changing one's lifestyle, particularly one's diet and level of physical activity, is essential for both PCOS prevention and treatment [3]. There is evidence that the specific diet such as meat–egg and shellfish–shrimp–dairy and the higher dietary inflammation potential increase the risk for the PCOS

development, and that Mediterranean diet decrease the risk for the PCOS development [47]. Also, it has been observed that the Dietary Approaches to Stop Hypertension diet and calorie-restricted diets have possible beneficial effect in the reducing IR and improving body composition in the PCOS women. Interestingly, it has been reported that beneficial effect was greater, the longer duration of the diet was and that the diet has adventurous effect on the weight loss in comparison to the metformin [48].

Although the molecular mechanisms link vitamin D and PCOS pathophysiology as well as vitamin D and components of the PCOS, some possible mechanisms could explain these associations observed in the clinical studies. Vitamin D achieves its activity via the vitamin D receptor, a nuclear receptor that activates the second messenger and regulates DNA transcription [49]. Since, the vitamin D response element region is identified in the promoter of the insulin receptor gene, it has been presumed that vitamin D has a possible role in the transcriptional control of insulin activity [50, 51]. It has been also suggested the potential role of the interaction between vitamin D receptor, retinoid X receptors, and their ligand in the link between vitamin D and insulin resistance considering their role in the regulation of expression of genes involved in energy homeostasis [50]. Considering that the secretion of insulin is a calcium-dependent process, vitamin D could influence insulin secretion by regulating the calcium channels [52]. Also, one of the possible mechanisms of regulating insulin sensitivity is stimulating the expression of insulin receptors and activating peroxisome proliferator-activated receptor delta by vitamin D [53].

It has been observed in human as well as mouse islets culture that the vitamin D receptor mRNA and vitamin D receptor expression is glucose responsive [54]. The vitamin D increases the glucose-stimulated calcium influx in pancreas inlets and the treatment of the human and mouse islets with vitamin D led to the glucose stimulated insulin secretion. It is presumed that the vitamin D upregulates the expression of the variant of the R-type voltage-gated calcium channel gene, Cacna1e, which has role in the calcium influx and consequently insulin secretion in islets cells [54].

Although the oxidative and inflammatory status varies between an individual with PCOS, one of the explanations for the beneficial effect of the vitamin D on PCOS is its ability to control oxidative stress, mitochondrial respiratory function, and systemic inflammation in human beings [55, 56]. Vitamin D activates the expression of the nuclear factor-E2-related factor 2 which translocate from the cytoplasm to the nucleus, and further increase the expression of several genes involved in antioxidant activity [55, 56]. Also, the β cell dysfunction due to inflammatory stress and insulin resistance in PCOS is possible linked to the role of the vitamin D receptor as a significant modulator of inflammation and β cell survival. It is presumed that VDR association with PBAF, chromatin remodeling complexes lead to the genome-wide changes in chromatin accessibility and enhancer landscape, resulting in an anti-inflammatory response in β cell [57].

In addition, the elevated pro-inflammatory advanced glycation end-products and increased accumulation of this product in ovarian granulosa and theca layers in women with PCOS could explain the role of these inflammatory mediators in PCOS pathogenesis and negative reproductive and metabolic role of advanced glycation end-products in PCOS women [58]. Vitamin D deficiency is linked with a decrease in soluble receptors for advanced glycation end-products (which reduces the accumulation of the advanced glycation end-products [59]. This explains vitamin D's pivotal role in providing the optimal conditions for normal ovary function [47, 60].

Finally, vitamin D has a possible role in follicular development and luteinization via the regulation ofanti-Mullerian hormone signaling, follicle-stimulating hormone sensitivity, and progesterone production [61, 62]. Also, vitamin D regulates the expression of the enzymes involved in estrogen and androgen biosynthesis [63–66].

The possible mechanisms of the influence of the vitamin D on PCOS-related pathological conditions are shown in Fig. 1.

Special attention must be directed to the heterogeneity of the patients which are included in the research study about association of vitamin D and PCOS as well as the different factors which could affect vitamin D levels in women diagnosed with PCOS. Also, the new information about mechanisms which explain the relationship of the different aspects of the PCOS, and vitamin D and vitamin D receptor are needed, because it seems that the supplementation with vitamin D leads to the improvement in the PCOS aspects as well as body mass index, lipid profile, insulin resistance, cardiovascular risk, infertility, menstrual irregularity, and bone health.

The strength of this narrative review is the giving of the clinical understanding of the vitamin D role in the PCOS, taking into account complex pathogenesis of the PCOS and pleiotropic role of the vitamin D. In our opinion, a narrative approach should be more suitable for the analysis of significant results obtained from representative studies. The news in this manuscript, if compared to the former literature, is the review of the molecular pathways which could explain possible role of vitamin D in the PCOS. A limitation is a lack of detailed information on association of the vitamin D and PCOS-related pathologies, which could explain of the mechanisms of the vitamin D role in PCOS pathogenesis and give any etiological role of the vitamin D in the PCOS.

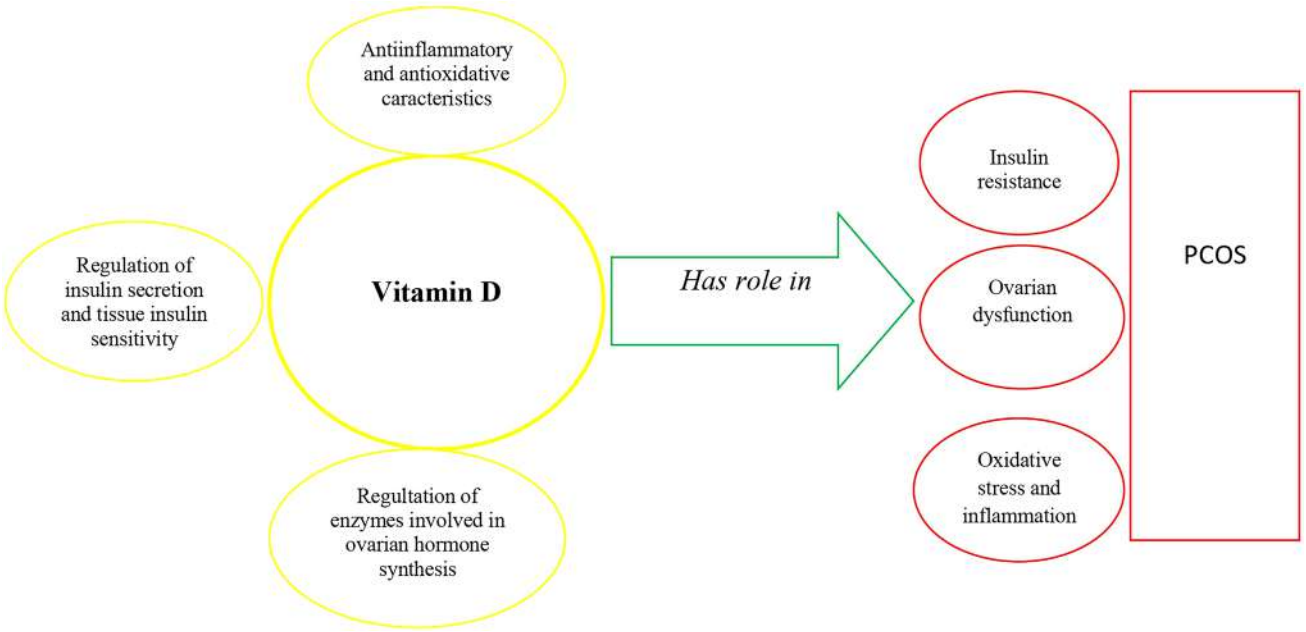

Fig. 1 The possible mechanisms of influence of vitamin D on PCOS-related pathological processes

Conclusions

Most observational and interventional studies' reported findings indicated that possible vitamin D contributes to the etiology of PCOS, and the endocrine, inflammatory, and metabolic abnormalities connected to PCOS. Additionally, women with PCOS benefit from taking vitamin D supplements, either on their own or in combination with other supplements. Future research must determine whether vitamin D plays a crucial role in the development of PCOS or if it is merely a cofactor in the pathogenesis of POCS and related comorbidities given that PCOS is a multifactorial disease that is related to numerous morbidities including metabolic, cardiovascular, and infertility diseases. In addition, the future investigations could include the pharmacogenomic research considering that the vitamin D receptor polymorphism is related to PCOS development. In women with the risk factors for the PCOS development, the supplementation with the vitamin D is potential preventive strategy. More research is required to learn more about the processes through which vitamin D affects PCOS women's metabolic, inflammatory, and endocrine environments.

Author contributions RS: conceptualization, writing—original draft preparation, manuscript supervision, data collection. MA: manuscript review and editing, methodology, data analysis, supervision. DV: data analysis, methodology, writing—original draft preparation. AM: data analysis, methodology, writing—original draft preparation. OD: formal analysis, data curation. GMB: formal analysis, data curation. AM: formal analysis, data curation. AT: conceptualization, manuscript review and editing, manuscript supervision, data collection.

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Data availability It is not feasible for a review, as all the data belong to papers alreadypublished and included in the review.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval Not applicable.

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