Exposure factors in the occurrence and development of melasma (Review)

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Abstract. Melasma is an acquired pigmentation disease that mainly involves the development of symmetrical yellow-brown facial patches. The incidence rate of the disease is increasing yearly. Therefore, actively studying the exposure factors that induce melasma could contribute to the prevention and treatment of this disease. In the present review, the possible exposure factors were summarized.

Contents

1. Introduction

Melasma is an acquired pigmentation disease of the skin that is characterized by the development of symmetrical and irregular pigmented spots, especially on the face, which are common in women and seriously affect the appearance of patients. The diagnosis of melasma includes clinical classification and histopathological classification. According to the location of the skin lesions, they are generally divided into three types: i) The central facial type, in which the lesions are distributed on the forehead, cheek, upper lip, nose and chin, and this type is the most common; ii) the cheek type, in which the lesions are distributed on the cheeks and nose; and iii) the mandibular type, in which the lesions are distributed on the area where the branches of the mandibular nerve are located (1). In addition, in clinical practice, Wood's lamps are used in combination with histopathological analyses to divide melasma into the following types: i) Epidermal type: This type has a strong colour contrast under Wood's lamp, and histopathological analysis found pigment deposition in the basement layer and the upper part of the basement layer (2,3); ii) Dermal type: In this type, the colour contrast between the lesions and the normal skin is not obvious under Wood's lamp, and histopathological analysis revealed that there are melanophages around the upper and middle blood vessels of the dermis; iii) Mixed type: The colour contrast of some parts of the same patient under Wood's lamp is obvious, while that of other parts is not obvious, and histopathological analysis demonstrated that there are pigments in the epidermis and dermis; and iv) The fourth type: This type is found in patients with dark skin. The melasma of these patients cannot be classified under Wood's lamp. Histopathological analysis revealed that pigment deposition is mainly located in the dermis. The occurrence and development of melasma are related to the affected individual's genetics, hormone level and ultraviolet exposure, but the specific mechanism remains to be further explored. The present review analysed the possible exposure factors for melasma, along with the newly identified dermal factors, reactive oxygen species (ROS and microRNAs (miRNAs), as well as the pathogenesis of melasma, providing the basis for its prevention and treatment.

2. Hormones

Melasma usually occurs after puberty, supporting the idea that female hormones are closely related to the development of melasma. Although the incidence of melasma varies by ethnicity

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and skin type, it usually affects women of childbearing age. The use of birth control pills, pregnancy, the use of oestrogen cream and the use of prosexol for prostate cancer can induce melasma or aggravate melisma (4,5). Oestrogen serum levels, especially E2 levels, along with Follicle-Stimulating Hormone (FSH) and luteinizing hormone (LH) levels, are increased in patients with melasma. Comparing the expression levels of oestrogen receptors ER-α and ER-β and progesterone receptors in the melasma lesion area with the surrounding healthy skin, it was found that the expression of these receptor proteins was increased (4). This showed that oestrogen plays an important role in the pathogenesis of melasma. This observation is supported at the cellular level by the expression of oestrogen receptors (oestrogen receptor-β) on melanocytes and at the molecular level by the induction and upregulation of tyrosinase (TYR), the key enzyme in the rate-limiting synthesis of melanin (5). However, Filoni *et al* (6) reported the cases of 4 patients in whom even the use of anti-oestrogen drugs could not prevent the formation of melasma. This finding suggested that other factors affect oestrogen metabolism, such as paracrine regulatory factors, and may be new treatment targets for melasma.

The incidence rate of melasma in men is lower than that in women. The etiopathogenesis of melasma in men is considered to be similar to that in women, with the notable exception of the influence of oestrogen (7). While a number of men appear to develop melasma with normal hormone profiles, two studies found lower testosterone and higher LH levels in small cohorts of Indian men compared with age-matched controls, suggesting that even in men, endocrinopathy may contribute to the pigmented phenotype (8).

Associations between melasma and chronic diseases such as autoimmune thyroid disorders and liver dysfunction have been noted and may be linked via hormonal influence. The relationship between abnormal thyroid hormone levels and the onset of melasma remains controversial. In a meta-analysis by Kheradmand *et al* (9), the serum thyroid-stimulating hormone, anti-thyroid peroxidase and anti-thyroglobulin antibodies in patients with melasma were higher than those in healthy individuals, and the difference was more significant in women with melasma. However, the present review could not determine the causal relationship between thyroid disease and melasma and did not distinguish secondary melasma from primary melasma. As an important endocrine element, zinc maintains normal thyroid function. A previous study reported that the incidence of thyroid dysfunction in patients with melasma was four times higher than that in a control group (10). The zinc deficiency rate was 45.8% in patients with melasma and 23.7% in the control group. Zinc deficiency may affect thyroid function and induce the occurrence of melasma. Interestingly, other case-control studies reported no statistically significant difference between similar groups, weakening the evidence and indicating that there may be confounding factors in the epidemiology of the two diseases in similar populations (11,12). Liver dysfunction was also found in patients with melisma (13). Various enzymes and substrates required for melanogenesis are synthesized in the liver. Abnormal liver function leads to the synthesis or activation of different enzymes, but there is no relevant research at present. In traditional Chinese medicine, it is considered that melasma is a deficiency of the liver and kidneys or a stagnation of the liver and kidney, which leads to a disorder of spleen movement, causing blood stasis, qi obstruction, and difficulty in reaching qi and blood. Lesions accumulate on the face, thus patients with melasma can take a prescription for soothing the liver and relieving depression for treatment, which can play a significant role in improving skin lesions (14). Hypothalamic-pituitary-gonadal axis disorder leads to abnormalities in sex hormone levels, thus pituitary injury may also lead to melasma, but this has not yet been reported (15). To summarize, melasma can be treated clinically by regulating endocrine function (Fig. 1).

3. Ultraviolet radiation (UVR)

UVR is well-known to induce melanin production, acutely and chronically, through multiple, likely interrelated pathways. Since its first noted association with melasma in 1953, UVR has grown to be readily accepted as the most critical factor in the development of melasma and the modulation of its clinical severity (16). The use of light protection measures, such as applying sunscreen, avoiding the sun, and wearing a hat, can effectively treat and prevent melasma, supporting the argument that UVR causes melisma (17). Melasma is common in Singapore, Brazil and India. The incidence rates in these areas are 26.8, 27.2 and 55.1%, respectively. As these countries are close to the equator and have strong UVR, the incidence in these areas is significantly higher than that in other areas (18). The two aforementioned studies found a greater incidence of melasma in higher elevation areas of India and China, respectively, which is postulated to be due to higher exposure to UVR at such altitudes (19). Such geographic predispositions may combine with factors such as skin phototype and ancestral genetics, which are also influenced by geography over several generations of evolution.

Multiple laboratory and clinical studies have demonstrated that UVR triggers and exacerbates melisma (20). It is well-known that UVR induces melanin production, acutely and chronically, through multiple, likely interrelated pathways (17). Although these pathways are still poorly understood, microphthalmia-associated transcription factor (MITF) is known to be a central downstream effector of skin pigmentation after UVR exposure. TYR is the key enzyme for melanogenesis. The combination of MITF and the promoter region of the TYR gene can regulate the expression of other melanin-related enzymes by upregulating the expression of the melanogenesis rate-limiting enzyme TYR, which is also the key factor in maintaining the survival of melanocytes and regulating the distribution of melanin and its transport to keratinocytes (21). MITF regulates melanogenic enzyme activity via the tyrosine biosynthesis pathway, and its modulation is associated with predictable, sometimes even dose-dependent changes in melasma-related melanin production (22,23). A previous study reported MITF-siRNA formulations to be clinically efficacious and safe in a small cohort of melasma patients, acting by suppressing melanin induction of melanocyte apoptosis (23). Tranexamic acid has also recently emerged as a promising modality in melasma treatment. The expression of MITF protein in human epidermal melanocytes treated with Tranexamic acid (TA) was found to be decreased (24). Moreover, TA has been shown to act via the downregulation of MITF, among other mediators, and to activate the autophagy system in melanosomes. Such investigations not only assess

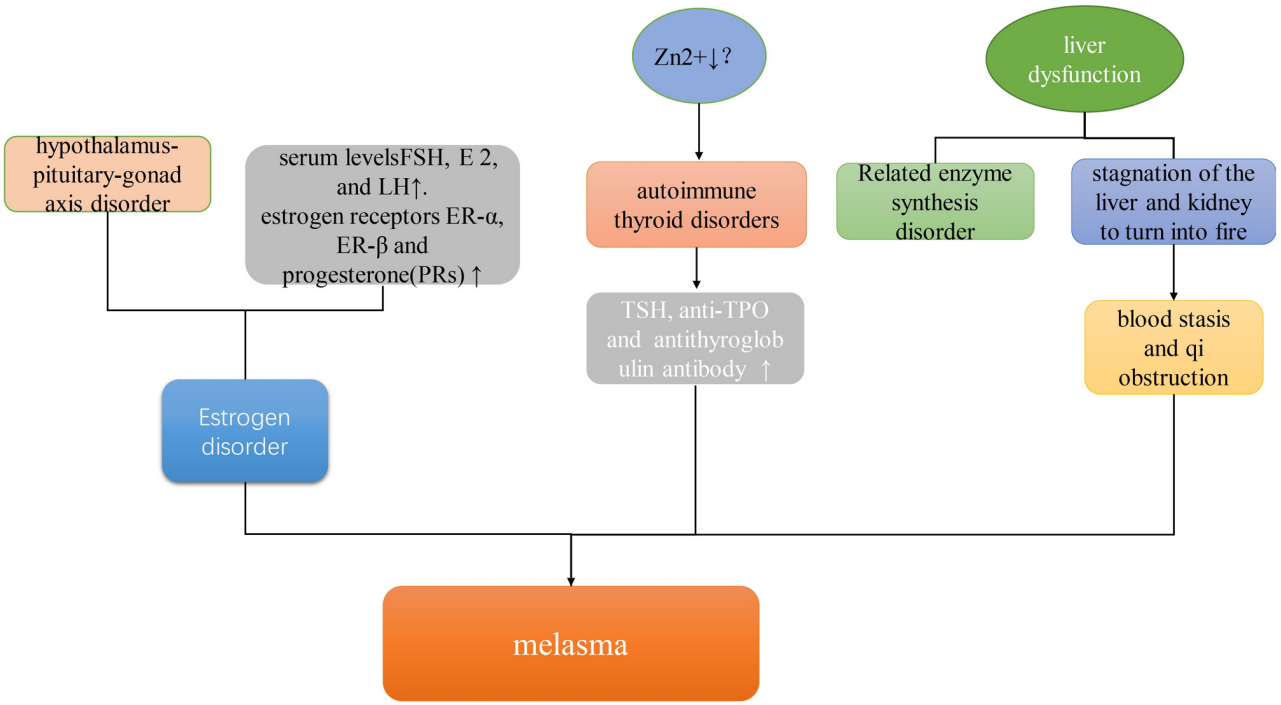

Figure 1. Changes in hormone levels in relation to melasma. FSH, Follicle-Stimulating Hormone; LH, luteinizing hormone; ER, estrogen receptors; PRs, progesterone receptors; TSH, thyroid stimulating hormone; Anti-TPO, anti-thyroid peroxidase.

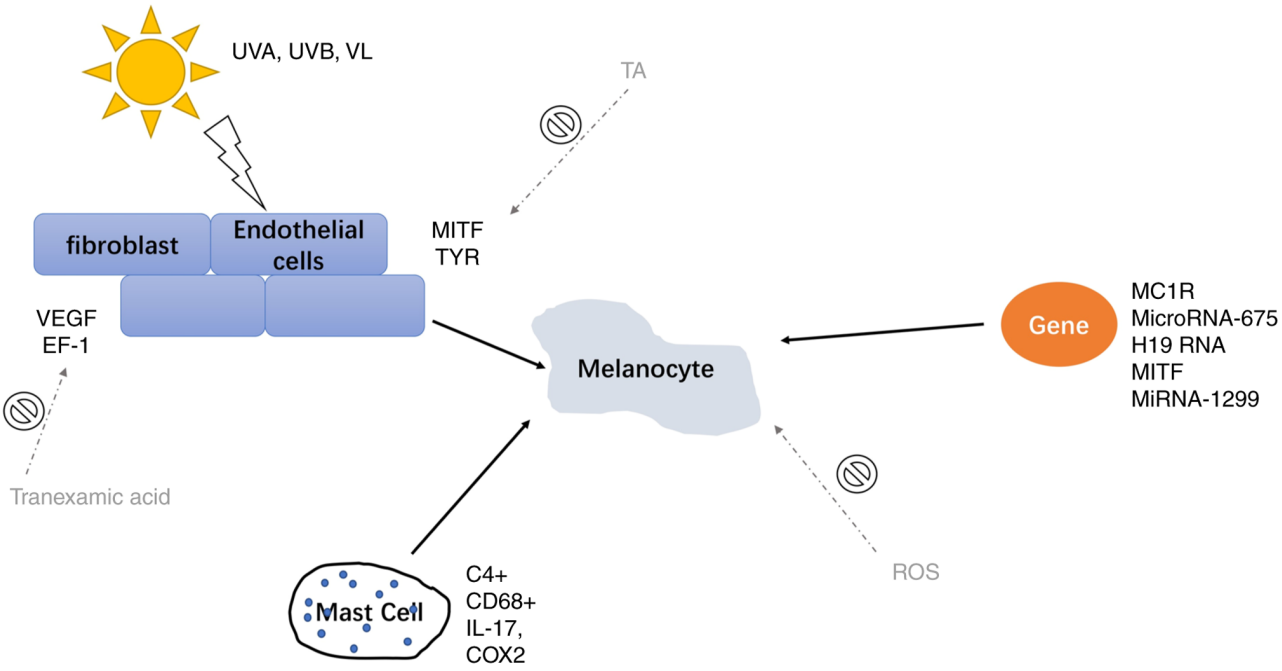

Figure 2. Multiple mechanisms involved in melasma pathogenesis. UV, Ultra violet; MITF, microphthalmia-associated transcription factor; TYR, tyrosinase; MC1R, melanocortin-1 receptor; IL-17, interleukin 17; ROS, reactive oxygen species.

therapeutic options in melasma but also corroborate molecular pathogenesis study findings (Fig. 2).

4. Genetics

Observational studies have found that while individuals of all ethnicities are susceptible to melasma, Asians, Indians, Latin Americans and African Americans are more likely to suffer from melasma than other ethnicities (25). Individuals with a genetic history of melasma are more likely to be affected by high-risk factors. Previous genetic analyses in larger cohorts (>100 patients) have found significant associations between melasma development and African ancestry, family history and overall genetic inheritance (23,26). This genetic

inheritance was found after adjustment for non-genetic risk factors, and in one Brazilian population, it was consistent with dominant segregation (27). Melasma is associated with significant familial susceptibility, with upwards of 41-61% of patients reporting a positive family history in first-degree relatives, including twin sisters; however, the incidence of adult melasma in the same area is 16-28%. A case-control study of 79 patients with melasma vs. 79 controls in an Indonesian population found that patients with melasma were more likely to have a family history, with an odds ratio of 35 (28). In men, data suggested that genetics are the second most contributory factor to disease development after sun exposure, given the reduced influence of oestrogen-receptor compared with their female counterparts (29). The striking familial and racial predisposition at the epidemiologic level provides the greatest evidence of genetic contribution to melasma development.

While no genome-wide study has been conducted to date, to the best of the authors' knowledge, a handful of studies assessing single genes and gene expression have implicated genetic mechanisms related to tyrosine-melanin synthesis, lipid metabolism, H19 modulation, and the Wnt/AKT, PPAR, ERK and cAMP signalling pathways (5,30). The melanocortin-1 receptor (MC1R) is critical in activating the melanin synthesis pathway; it has numerous polymorphisms that may indicate a direct genetic relationship between nucleotide variants and skin colour phenotype. In a previous study, it was identified that the Val92Met variant of MC1R, the variant found in the highest allelic frequency in the south Asian population, was statistically associated with the risk of melisma (29). At the epigenetic level, DNA hypermethylation was reduced in melasma lesions (31). Functional genetic analyses in melasma are limited; a recent study implicated keratinocyte-derived miRNA-675, H19 RNA and MITF in a pathway potentially dependent on exosome-mediated communication (32). In addition, WNT inhibitory factor 1, a secondary signalling molecule involved in melanogenesis in epidermal keratinocytes and dermal fibroblasts, was significantly downregulated in melisma (33). Finally, miRNAs have rapidly been recognized as important in melanocyte biology in previous years, and their direct investigation in melasma has thus far implicated miRNA-675, miR-1299 and H19 miRNA in affecting disease development in the context of multiple different cellular pathways (34). Attention must be given to validating the findings of these preliminary studies, especially in the context of a multifactorial disease with a likely polygenic architecture.

Transcriptomic studies of exosomes and H19 RNA suggested that they may act as markers of disease and phenotypic variability, respectively (35). Levels of DNA methyltransferase-1, the enzyme responsible for DNA hypermethylation that is associated with melasma incidence, were reduced after clinically responsive treatment to niacinamide and retinoic acid (32); this finding implied that such epigenetic changes may predict treatment response or serve as therapeutic targets themselves. Although such conclusions are preliminary, the data of the present review on melasma and the applicable myriad of genetic data on other pigmentary conditions, such as vitiligo, suggested that genetics are a worthy area of investigation.

5. Visible light (VL)

Emerging evidence has also begun to recognize VL as contributing to melasma pigmentation, both individually and synergistically with UV radiation (36). Shortwave VL has been shown to cause persistent pigmentation, possibly through a photo adaptive response, a phenomenon that may explain why numerous melasma patients relapse in summer months despite diligent UVR photoprotection (37). The Severity Index of skin lesions was significantly lower in patients with melasma who used a sunscreen containing iron oxide that protected against both UV and VL than in those who used a sunscreen that protected against only UV light (38). Interestingly, Handel *et al* (39) found an increased incidence of melasma in patients exposed to thermal energy, such as boiler heat and high-intensity lights, who did not appear to benefit from the conventional recommendation of photoprotection. These patients epitomize the multifactorial nature of melasma that contributes to the variable treatment response observed in heterogeneous patient populations, thus highlighting the need for further comparative photoprotection studies.

6. Oxygen free radicals

Exposure to UVR, respiration and air pollution causes the skin to undergo oxidative stress reactions and produce ROS; ROS are produced and subsequently quenched by antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-PX) and glutathione (GSH), which act as scavengers to maintain a homeostatic balance, particularly in the face of increasing free radicals and lipid peroxidation (40). Such peroxidation of biofilms damages cell membranes, increases melanin formation and initiates the formation of melasma. Perspectives have consistently favoured the hypothesis that oxidative stress, mainly induced by UVR, is a crucial contributing factor in creating and maintaining the melasma phenotype (41). Later studies found significantly increased serum levels and enzymatic activities of oxidative scavenger enzymes [SOD, malondialdehyde (MDA), GSH-PX] in the blood of patients with melasma compared with matched controls, highlighting the role of oxidative stress and its homeostasis in melisma (38). GSH is an antioxidant that can clear ROS and protect the integrity of the cell membrane. A recent clinical study revealed that GSH combined with vitamin C can play a role in treating melasma, reducing E2 and FSH levels and increasing P hormone levels to maintain an excellent endocrine environment in the body (42).

Hydrogen (H_2) is a safe, non-toxic potent antioxidant that can selectively eliminate ROS. After hydrogen treatment, the levels of ROS and MDA in the body are reduced, and the expression of SOD, GPX and CAT in the body is increased (43). Some studies (44-46) have confirmed that hydrogen can play a specific role in treating some skin diseases, such as psoriasis, acne, atopic dermatitis and pemphigus. Currently, there is no relevant research, to the best of the authors' knowledge, on the application of hydrogen in the treatment of melasma. Because of the critical role of oxidative stress in melasma, the next step is to observe and study the treatment effect of hydrogen on melasma, opening up a new direction for the treatment of this disease.

7. Vascular factors

Professor He (47) divided melasma into four clinical types: i) The M (pigmented) type, ii) V (vascular) type, iii) M>V (pigmented advantage) type; and iv) V>M (vascular advantage) type, by using Wu's lamp, a capillary microscope, and the fragment pressure diagnostic method. UV-irradiated endothelial cells and fibroblasts contribute to hyperpigmentation in melasma, particularly through the induction of stem cell factor (SCF) (48). SCF has been shown to produce pigmentation via the overactivation of SCF/c-kit signalling (22). Such paracrine effects of melanogenic cytokines highlight a proposed crosstalk between endothelial cells and melanocytes. This theory is bolstered by prior evidence that endothelial cells increase pigmentation through endothelin-1 and reduce pigmentation through TGF-B and clusterin (22,49). Tranexamic acid reduces the number of blood vessels in and around melasma lesions by inhibiting the production of endothelial growth factor (VEGF) and endothelin 1 (50). Evidence of increased vascularity is the basis for pulsed-dye laser (PDL)-based treatments for melasma, the gold standard laser therapy for cutaneous vascular lesions. PDL has exhibited efficacy and tolerability in several studies as monotherapy and in combination with direct pigment-modifying modalities such as Q-switched Nd:YAG laser treatment (51,52).

8. Inflammation

Given the contributions of light, the vasculature and oxidative homeostasis to melasma, inflammation has also been a target of study for its role in melasma. UV-damaged skin commonly manifests with an increased mast cell number, upregulation of melanogenic cytokines, infiltration of leucocytes and augmented vascularity (53). Mast cells, key mediators in acute inflammation, are increased in the pigmented lesional dermis of patients with melisma (54). While not directly studied in melasma, this mast cell induction may be secondary to repetitive UV irradiation and histamine release, which promote melanocyte proliferation and migration. In addition, mast cells may contribute to the observed vascular over proliferation by releasing potent pro-angiogenic factors such as VEGF (55). A previous study that divided 197 women into inflammatory and non-inflammatory groups and utilized immunostaining to compare inflammatory cell populations between the groups represents the most extensive study to date directly assessing inflammation in melisma (56). However, enrolment was limited to patients with the malar variant. The aforementioned study found significant increases in $CD4^+$ T cells, $CD68^+$ macrophages, mast cells, interleukin 17 (IL-17) and COX2 in the lesional skin of the inflammatory group, providing evidence of a Th17/IL-17-mediated chronic inflammatory component to melasma that could explain the persistence of the pigmented phenotype (56).

9. Impairment of the skin barrier

Damage to the skin permeability barrier. Skin serves as the first protective barrier between the human body and the outside world, acting in several ways, including physical protection from external stimuli and trans-epidermal water loss (TEWL). Melasma has long been characterized by barrier disruption, particularly stratum corneum impairment and photodamaged features such as solar elastosis. Histopathologic assessments have bolstered this argument by finding significant epidermal atrophy in lesional skin compared with perilesional skin. The rate of TEWL after barrier perturbation was significantly higher in lesional skin with a delayed barrier recovery rate, further highlighting an impairment in barrier function (57). Li *et al* (58) repeatedly used adhesive tape to damage the skin barrier of mice until TWEL exceeded 40 gr/m2/h and then exposed the mice to ultraviolet irradiation. Compared with the control group, the expression levels of TRP1 and MITF mRNA in the damaged area of the skin barrier increased and the melanin content increased in the experimental group. It was confirmed that the destruction of the skin permeability barrier enhanced the formation of UV-induced melasma. In clinical treatment, skin barrier receptors can be strengthened to achieve an improved effect in treating melasma.

Damage to the microbial skin barrier. The microbial skin barrier is composed of different microorganisms that maintain the balance of the skin microbial population and form the skin barrier. The disturbance of the normal skin microbiota has long been studied and linked to the development of various dermatologic conditions (59), with melasma being one possibility. The abundance of *Propionibacterium* in melasma lesions was found to be decreased, possibly due to the reduction in the abundance of this resident defensive bacterium and increased abundances of foreign pigmented *Micrococcus* and gram-negative bacteria (60). However, recent studies (61,62) showed no significant difference in the diversity and species composition of bacteria and fungi between control groups and melasma groups. The differences in the results between studies may be related to the different methods of bacterial culture or the small sample size of the population; more research is needed in this field to form applicable conclusions.

10. Conclusion

Dissecting the pathogenesis of melasma continues to be a challenge given its multifactorial nature. Most of the new knowledge introduced in the present review results from just a few studies or even a single study, highlighting the need for further research on this topic. With the continuous progress in the development of research methods, further information about the contributions of genetics, ultraviolet rays and hormones to the development of diseases can be obtained. The treatment of melasma by clinicians should not be limited to melanin, and possible pathogenic factors should be considered in individual treatment.

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Availability of data and materials

Not applicable.

Authors' contributions

ZL designed the present study. YC and WK prepared and wrote the manuscript. YC, SS, GV and WK performed a literature search and selected the studies to be included. SS and GV collected literature and analyzed the data. ZL revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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