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Calcium silicate as a graft material for bone fractures: a systematic review

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Abstract

Objective: The goal of this review was to determine whether calcium silicate (wollastonite) as a bone graft material is a viable alternative to autogenous bone or whether the evidence base for its use is weak.

Methods: In this systematic review, electronic databases (MEDLINE/PubMed and BVS) were searched for relevant articles in indexed journals. Articles published in a 10-year period were identified (n = 48). After initial selection, 17 articles were assessed for eligibility; subsequently, seven articles were excluded and 10 articles were included.

Results: Among the studies included, 20% emphasized the importance of randomization, which adds reliability to the study, minimizing the risk of bias. High variability was observed in the material used, such as additives, amounts, dosage, and chemical alterations, rendering direct comparison among these studies impossible. The experimental periods varied considerably; one of the studies did not include statistical analysis, weakening the evaluation. Nonetheless, the true potential of wollastonite as a graft material conducive to new bone formation was reported in all studies.

Conclusion: The results support the use of wollastonite as a bone graft material. The initial research question was answered despite the significant variability observed among these preclinical studies, which hindered the precision of this analysis.

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Introduction

The current gold standard in the treatment of pathological, degenerative, esthetic, or traumatic conditions is autogenous bone. However, there is a need to replace autogenous bone with a new biocompatible natural or synthetic bone substitute for tissue regeneration, to minimize postoperative trauma.[1,2]

The ideal material should mimic bone in shape, size, texture, and performance, promoting an adequate response in the biological system.[3] Synthetic materials have emerged as a relevant option because there is no risk of disease transmission and because these materials are available in potentially unlimited quantities.

Bone repair materials currently in use are either bioinert, bioresorbable, or biodegradable, depending on the characteristics of the treatment site or the subsequent treatments planned. Bioinert materials remain in the treated site and interact with the medium without inducing rejection by surrounding bone. Biodegradable materials ideally should promote bone formation as they are resorbed, and both the material and its degradation products must be well accepted by the organism. Degradation of bone biomaterials should be gradual and proportional to new bone formation: neither too fast, nor too slow. If too fast, the healing process can leave gaps that may result in voids or fibrosis in the newly formed bone. If degradation is slower than new bone formation, bone repair may be delayed.

Calcium silicate, also known as wollastonite, is capable of inducing *in vivo* osseointegration. The bioactivity of wollastonite is attributed to the nucleation of hydroxyapatite (HA), activated by the dissolution of calcium and silicate ions. This material is regarded as osteoinductive and has the added advantage of not being cytotoxic.[4–7]

Considering the limitations of wollastonite as a bone graft material,[8] the aim of this systematic review was to seek greater evidence in the scientific literature to support the utilization of this biomaterial, which is still not widely applied in clinical practice.[9]

Methods

Protocol and search strategy

The methodology used was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org) and on the Population, Intervention, Comparison, Outcome (PICO) model to frame the theme and the search strategy (Table 1).[10–14]

A literature search of the MEDLINE/PubMed and BVS electronic databases was conducted between 23 February 2016 and 23 December 2016; relevant articles published in indexed journals in the previous 10 years were included. Prospective studies were evaluated for possible inclusion.

Table 1. Systematic search strategy (PICO model).

Population	#1	Wollastonite OR Calcium silicate (All Fields)
Intervention	#2	Bone defect (All Fields)
Comparison	—	Not applicable
Outcome	#3	Bone repair OR Bone healing OR Bone regeneration OR Bone formation OR Bone neoformation (All Fields)
Search combination		#1 and #2 and #3
Language		English, Spanish, Portuguese
Electronic Databases		MEDLINE/PubMed, BVS

Focused question and study objective

The focused question in this systematic review was, "Can wollastonite ($CaSiO_3$) be used to effectively aid the bone repair process?"

Screening and selection

Review articles, *in vivo* tests in animals, clinical trials, randomized controlled trials, and controlled clinical trials in English, Portuguese, and Spanish investigating the use of wollastonite in bone fractures were included. Case reports on the use of wollastonite, studies involving only *in vitro* tests on the use of wollastonite, and articles describing the use of wollastonite in patients with pre-existing systemic conditions were excluded. The articles were selected by two evaluators (AMO and GVOF) working independently, and selection was based on the titles and the abstracts. Articles that were included in the study were evaluated in their entirety. Duplicate articles were excluded.

Data collection process

The formulations used; characteristics of the bone defects; types of treatment performed; clinical, histological, and radiographic results; and statistical analyses performed in the articles retrieved were systematically recorded.

Risk of bias assessment

The methodological quality of the studies included was evaluated both independently and jointly by two evaluators (AMO, GVOF), using the Cochrane collaboration tool for assessing risk of bias, and the PRISMA and the CONSORT statements.[13,15,16] The risk of bias was assessed based on the following quality criteria: randomization, standardization of the study execution, use of test and control groups, standardization of the bone defects, statistical analysis, and results obtained. All of these criteria were established as adequate, inadequate, unclear, or not described.[16]

Articles were deemed as presenting low risk of bias when all the criteria were identified and accepted (low likelihood of bias affecting the results), moderate risk of bias when one of the criteria was not found or when there were doubts about the results, and high risk of bias when two or more criteria did not match the parameters selected.

Any discrepancies between the two evaluators were resolved through discussion; when no consensus was reached, a third evaluator was consulted (MSA).

Data analysis

The quality of the studies included in the review was assessed, focusing on the similarities (homogeneity) and differences (heterogeneity) among the studies. GraphPad

Prism 7.0c for Mac (GraphPad Software, La Jolla, CA, USA) was used for data analysis.

Results

After application of the inclusion and exclusion criteria, 48 articles were selected initially.

Specifically, the search using the PICO model, as described in Table 1, yielded 26 articles from MEDLINE/PubMed and 22 articles from BVS published within the past 10 years. After preliminary analysis of the abstracts, 17 articles were selected for full analysis and evaluation, after which seven articles were excluded and 10 articles were selected for detailed analysis (Figure 1).

Only data from *in vivo* studies were analyzed. Results concerning evaluations of the biomaterial itself (preparation, characteristics, and *in vitro* analyses) were not included. The main data from the articles selected are shown in Table 2. The articles excluded, along with the reasons for exclusion, are listed in Table 3.

Study characteristics

Among the studies analyzed, wollastonite was used in animal model studies (parietal, femoral, tibial, and radial bones), usually in association with other biomaterials or growth factors, as well as in adapted formulations. Standardized creation of bone defects was performed in nine studies, and in only one study wollastonite was used as an implant coating. No clinical studies were found.

All studies included histological and/or histomorphometric analyses of the samples

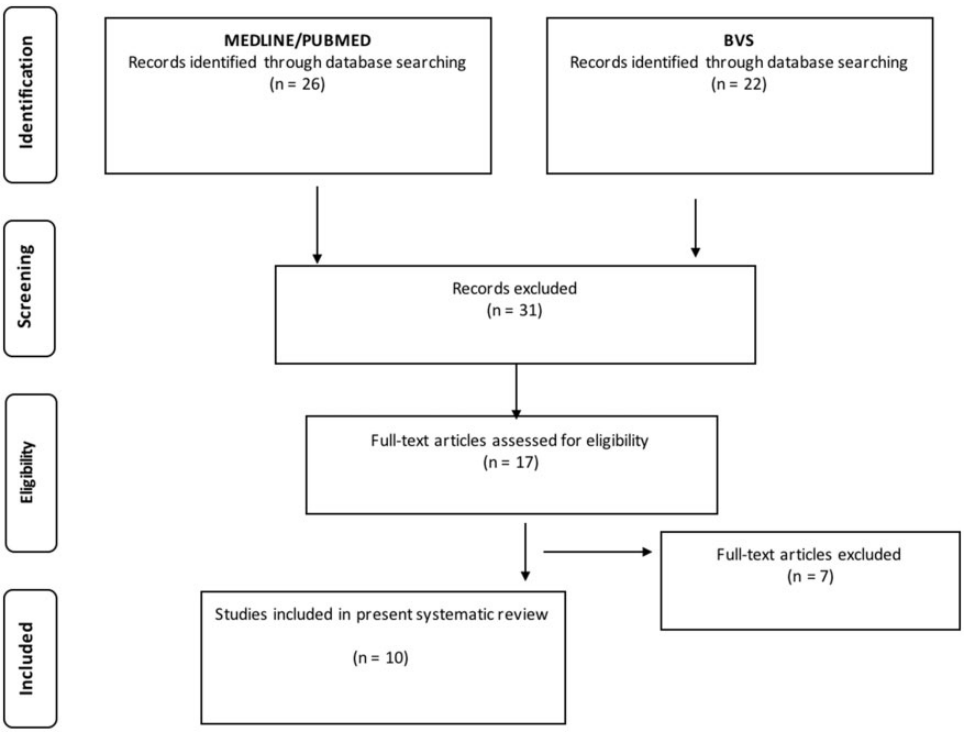

Figure 1. Flow diagram of the screening and selection process

Table 2. Main data from the studies selected.

Authors, year	Formulation/scaffold	Objectives	Study design	Population	Analyses	Outcomes	Conclusions
Xu et al., 2008	Porous β-calcium silicate (β-CS) and β-tricalcium phosphate (β-TCP)	Investigate and compare osteogenic property and degradability of β-CS and β-TCP	Two separate circular bone defects (10 mm) in parietal bone randomly filled with porous β-CS and β-TCP ceramics 4, 8, and 16 weeks to euthanasia	12 adult New Zealand white rabbits (n = 4 for each time period)	Micro computed tomography (CT), histomorphometry, scanning electron microscopy (SEM), energy-dispersive x-ray spectroscopy (EDS)	Micro CT: Decrease in areas and volumes of porous β-CS remarkably higher than porous β-TCP Histomorphometry: Bioresorption rate two times higher in β-CS group and percent of newly formed bone of β-CS remarkably higher than β-TCP SEM and EDS: Bone did not bond to β-CS directly, but through bone-like apatite layer	Quantitative analysis results showed that porous β-CS had a much higher resorption rate and better bone regenerative capacity than β-TCP
Sharma et al., 2009	Coating of apatite-wollastonite (AW)/chitosan	Compare bone response in coated and uncoated titanium implants	Two groups (coated and uncoated implants); tibial defect 14, 21, 35, and 42 days to euthanasia	Rabbits (n = 12)	Radiography, scintigraphy, histopathology, fluorescence labeling, hematology	Radiography: Coated implants suggested expedited healing Scintigraphy: Coated implant sites showed faster bone metabolism Histopathology and fluorescence labeling: Higher osteoblastic activity and faster mineralization on coated implants Hematology: No significant differences	AW/chitosan-coated implants have advantages of faster bone healing, increased mechanical strength, and good bone-implant bonding
Guo et al., 2012	Bioactive cement by incorporation of wollastonite nanofibers (WNFs) into calcium phosphate cement (CPC)	Study cell and tissue responses to WNF-CPC and CPC	Femur defect (6 mm) Two groups (WNF-CPC and CPC, randomized) 3, 6, and 12 weeks to euthanasia	24 New Zealand white rabbits (n = 4 for each material and time period)	Histology	WNF-CPC showed excellent biocompatibility, degradability, and osteogenesis, with greater bone-forming efficiency than CPC	WNF-CPC exhibited improved efficiency of bone regeneration
Zhang et al., 2013	Calcium silicate/CPC scaffold (CSPC) with macropores and micropores	Assay osteoinductive properties and bone regeneration efficacy of CPC, CPC/recombinant human bone morphogenetic protein-2 (rhBMP-2) and CSPC scaffolds	Study 1: Insertion in muscle pocket to examine ectopic bone formation of CSPC/rhBMP-2 scaffold Four groups (CPC, CPC/rhBMP-2, CSPC, CSPC/rhBMP-2 scaffolds) 2 and 4 weeks to euthanasia Study 2: Femur defects (5 × 10 mm)	Study 1: 48 male C57BL/6 mice (n = 6 for each material and time period) Study 2: 24 female New Zealand rabbits (n = 12 per group)	Study 1: Synchrotron radiation–based micro CT, histology Study 2: Micro CT, histology	Study 1: Bone formation in rhBMP-2–loaded groups at 2 weeks and 4 weeks, while no bone formation was observed in either CPC or CSPC group; CSPC/rhBMP-2 induced significantly more new bone formation than CPC/rhBMP-2 in 2 weeks Study 2: New ingrowth of bone in	Compared with CPC, CPC/rhBMP-2 and CSPC scaffolds, rhBMP-2-loaded CSPC scaffold significantly promoted ectopic bone formation and bone regeneration These observations indicate that porous CSPC/rhBMP-

(continued)

Table 2. Continued

Authors, year	Formulation/scaffold	Objectives	Study design	Population	Analyses	Outcomes	Conclusions
			Four groups (CPC, CPC/rhBMP-2, CSPC, and CSPC/rhBMP-2) 8 weeks to euthanasia			groups with rhBMP-2. Extensive ingrowth of bone throughout entire volume of implants in CSPC/rhBMP-2 scaffolds CSPC and CSPC/rhBMP-2 groups showed more extensive degradation and more trabecular appearance with osteoid deposition at surface of material Newly formed bone percentages in CSPC and CSPC/rhBMP-2 groups were higher; amount of bone matrix deposition in CSPC/rhBMP-2 group was significantly higher than in other groups	2 scaffold system may be promising
Lin et al., 2013	Calcium silicate (CS) and porous Sr-substituted calcium silicate (SrCS) ceramic scaffolds	Compare CS and combination of SrCS scaffolds in osteoporotic bone regeneration	Two bilateral calvarial defects (5 mm each) Randomly filled with CS and SrCS ceramic scaffolds, respectively 4 weeks to euthanasia	6 ovariectomized Fisher female rats (n = 6)	Sequential fluorescence labeling, Microfil perfusion, Micro CT, histology/histomorphometry	For all analyses, newly formed bone area was bigger with greater density in SrCS ceramic scaffolds than in CS group	CS and SrCS showed inhibitory effects on osteoclastogenesis; SrCS presented better results in osteoinductive activity and angiogenesis
Lee et al., 2014	Synthetic bone scaffold based on hydroxyapatite-gelatin-calcium silicate (HGCS), decellularized bone matrix (DECBM), and multipotent adult progenitor cells (MAPCs)	Evaluate potential of HGCS scaffold in bone formation *in vivo*	Calvarial critical-sized defect Four groups randomized: control (defect only), DECBM, HGCS with and without MAPCs 12 weeks to euthanasia	12 Sprague-Dawley rats (n = 3 per group)	Micro CT, mineral apposition rate (MAR) by fluorescence microscopy, histology	Micro CT: Better results in HGCS + MAPCs group MAR: Interface between host tissue and scaffold of HGCS + MAPCs and HGCS groups with higher MAR values Histology: Bone regeneration prominently better in HGCS + MAPCs group	HGCS had osteoinductive properties and seeding it with MAPCs yielded a synergic effect to enhance bone regeneration in critical-sized defects
Li et al., 2014	Apatite-wollastonite-magnetic glass ceramic/chitosan (A-W-MGC/CS)	Investigate biocompatibility and *in vivo* osteogenic capability of A-W-MGC/CS with and without bone	Radial bone defects Group 1: A-W-MGC/CS with BMSCs Group 2: A-W-MGC/CS without BMSCs	18 Japanese white rabbits (n = 2 for each material and time period)	SEM, radiography, histology	SEM: Good attachment and growth of BMSCs on A-W-MGC/CS; rate of ossification 90% with A-W-MGC/CS groups versus 40% with	A-W-MGC/CS combined with adenovirus–human bone morphogenetic protein-2-green fluorescent protein-transfected

(continued)

Table 2. Continued

Authors, year	Formulation/scaffold	Objectives	Study design	Population	Analyses	Outcomes	Conclusions
		marrow stromal cells (BMSCs)	Blank group: BMSCs without any scaffold Randomized 4, 8, and 12 weeks to euthanasia			BMSCs and in control group Radiography: Greater bone formation in A-W-MGC/CS groups Histology: Better and more mature bone tissues were formed in A-W-MGC/CS groups	BMSCs exhibited better osteogenic repairing, with good biocompatibility, bone conductibility, bone inducibility, and mechanical strength
Lin et al., 2015	Calcium silicate (CS) and β-tricalcium phosphate (β-TCP)	Investigate biodegradation of CS during bone regeneration; Si excretion from CS and distribution of Si in animal body were also traced	Femur defect (5 mm x 6 mm) Two groups (CS and β-TCP) 4, 8, and 12 weeks to euthanasia	18 adult male New Zealand white rabbits (n = 3 for each material and time period)	Histology, silica excretion and distribution	Histology: Compared with CS group, much less newly formed bone in β-TCP group; both samples showed higher resorption Silica excretion and distribution: Only significant difference between CS and β-TCP implant groups was found in urine	CS was safe, bioactive, and biodegradable; CS significantly stimulated bone regeneration compared with β-TCP
Sun et al., 2016	Magnesium (Mg) doping into calcium silicate (CSi), CSi-Mg*x* (*x* = 6, 10, 14)	Study effect of dilute Mg doping into CSi on osteogenic capacity and mechanical strength of 3D printed CSi-Mg*x* (*x* = 6, 10, 14)	Four skull defects (8 mm diameter); CSi, CSi-Mg*x* (*x* = 6, 10, 14); 6 or 12 weeks to euthanasia	16 New Zealand white rabbits (8 male and 8 female)	Characterization of CSi-Mg*x* ceramic powders and scaffolds, compressive strength evaluation, *in vivo* skull defect repair evaluation (micro CT, mechanical testing of retrieved samples, histology)	Micro CT: Residual biomaterials decreased and new bone areas increased over time. Highest bone to total volume ratio was in CSi-Mg14 group at week 12 Histomorphometry: Results consistent with micro CT Mechanical testing: Elastoplastic response in CSi-Mg groups at 6 weeks	3D printed diluted magnesium doping wollastonite porous scaffolds have superiority of both bone regeneration potential and mechanical evolution in repairing thin-wall bone defects
Saravanan and Selvamurugan, 2016	Mesoporous $CaSiO_3$ or wollastonite (m-WS)	Investigate bone-forming ability of m-WS particles	Three groups (n = 6/group/period); group 1: control (left unfilled), group 2: carbopol, and group 3: carbopol + m-WS were maintained for 2 and 4 weeks with critical-sized tibial defect (3 mm diameter)	36 male Albino-Wistar rats	Histology, SEM, and EDS	Histology: New bone growth in defect with bone regeneration and integration with host bone tissue were higher at 4 weeks in response to m-WS particles SEM: Drill hole almost filled at 4 weeks in rats treated with m-WS EDS: Confirmed presence of hydroxycarbonate apatite layer in implanted region	Particles promoted deposition of collagen and phosphate, enhancing new bone formation at 4 weeks after implantation

obtained, and five studies used micro computed tomography as a tool for analysis.[17–20] Additional methods used in the analyses were scanning electron microscopy and energy-dispersive x-ray spectroscopy,[17] radiography,[21,22] scintigraphy,[21] fluorescence labeling,[18,21] Microfil injection compound perfusion (Flow Tech, Inc., Carver, MA, USA),[18] mineral apposition rate,[19] and scanning electron microscopy.[22,23] All analytic methods rendered useful information. Hematological and urinary excretion analyses did not show relevant changes.

Use of wollastonite was associated with better tissue biocompatibility,[24–26] faster biomaterial resorption rate,[17,21] and improved bone repair,[17–19,21,24–26] especially in the adapted formulations.

Table 3. Excluded studies.

Reason for rejection	Authors, year
Importance of calcium silicate (wollastonite) was not evaluated	Nair et al., 2009 Nair et al., 2010 Yu et al., 2013 Ali-Saghiri et al. 2015
In vitro only study	Wang et al., 2014
Large variations of spacer and confusing evaluation method	Ito et al., 2005
No standardization of defects	Balabumar et al., 2014

Quality assessment

Results from the quality assessment of the studies selected for detailed analysis are

Table 4. Quality assessment of studies analyzed.

Authors, year	Randomization	Execution standardization	Test group x control group	Standardization of bone defects	Statistical analysis
Xu et al., 2008	ND	Y	Y	Y	Mean ± SD ANOVA
Sharma et al., 2009	ND	Y	Y	Y	Mean ± SD ANOVA
Guo et al., 2012	ND	Y	Y	Y	Mean ± SD Student's t-test
Zhang et al., 2013	ND	Y	Y	Y	Mean ± SD ANOVA
Lin et al., 2013	Y	Y	Y	Y	Mean ± SD ANOVA Equal variance assumption test
Lee et al., 2014	Y	Y	Y	Y	Mean ± SD
Li et al. 2014	ND	Y	Y	Y	Mean ± SD ANOVA
Lin et al., 2015	ND	Y	Y	Y	Mean ± SD ANOVA
Sun et al., 2016	ND	Y	Y	Y	Mean ± SD ANOVA
Saravanan and Selvamurugan, 2016	ND	Y	Y	Y	N

Y, yes; N, no; ND, not described; SD, standard deviation; ANOVA, analysis of variance.

shown in Table 4. This systematic review followed the CONSORT statement guidelines.[15]

Discussion

Wollastonite has been studied mainly in preclinical studies aiming to validate this material for clinical applications. Accordingly, in the present systematic review, only animal model studies were found. Wollastonite does not show evidence of carcinogenicity and has been evaluated as a bone substitute because of its biocompatibility, high mechanical resistance, and excellent bioactivity compared with calcium phosphate bioceramics.[27] Evidence for these qualities has been previously assessed through various tools, such as micro computed tomography, histomorphometric analysis, scanning electronic microscopy, and others. This was corroborated by the articles included in the present review, which also aimed to verify the osteogenic potential of wollastonite particles.[17,21,22]

New techniques have been developed for the synthesis of wollastonite, including the use of additives and processing at lower temperatures in order to improve its physical, chemical, and biological properties.[18,22,24] Analysis of all the procedures employed to improve the performance of this material underscores the fact that great effort has been placed to this end, as demonstrated in the literature. In addition, structural changes and experiments have been performed to test the full potential of this material; favorable results were observed for the association of wollastonite with recombinant human bone morphogenetic protein-2[28] and for magnesium-doped wollastonite, both in terms of bone regeneration potential and for improved mechanical properties.[19] Moreover, the ability of wollastonite to stimulate the bone regeneration process was compared with β-tricalcium phosphate, a well-known and widely used material.[29]

De Aza *et al.*[30] verified that materials containing wollastonite (α-$CaSiO_3$) and pseudowollastonite (β-$CaSiO_3$) are capable of developing *in situ* porosity when in contact with physiological fluids, inducing adhesion of osteoblasts and osseointegration *in vivo*. Synthetic wollastonite displays a greater degree of purity compared to natural wollastonite, which may present other chemical elements in its composition (Ca [Mg, Al][Si, Al]$_2O_6$). The association of natural or synthetic wollastonite and HA with chemical elements that act as bone turnover cofactors, such as magnesium or zinc, may be worthy of further study with respect to the tissue repair process.[2,31] Silica ion deficiency leads to bone malformation. In contrast, during osteogenesis, proliferation of osteoblasts is increased because of the presence of silica ions. Therefore, silica has been proven to be an essential element for bone cell activity.[32]

Among the studies included in this review ($n = 10$), we verified that only two (20%) emphasized the importance of randomization,[18,19] a procedure that adds reliability to the study and minimizes the risk of bias. Nonetheless, analysis of each study showed that in all of them the execution, research model, and type of defect were standardized. Still, great variability was observed with regard to the characterization of the material used, its association with wollastonite and additives, as well as the amounts, dosage, and chemical changes, rendering the direct comparison among these studies impossible. Moreover, the experimental periods varied greatly; one of the studies did not include statistical analysis, weakening the validity of its findings.[23]

Greater standardization of the research models, duration of treatment, and materials employed would help to better demonstrate the true potential of wollastonite as a graft material conducive to new bone

formation, despite the fact that all the articles reviewed have reported excellent results in this regard.

Clinical studies should be able to confirm the clinical viability of wollastonite, and verify its association with calcium phosphate ceramics in proportions yet to be established, aiming to improve bone repair. Associations with other bone turnover ion cofactors might also be studied, with the same goal.

Conclusion

The preclinical studies included in this systematic review demonstrate that wollastonite ($CaSiO_3$) can be used to effectively aid the bone repair process, thus answering the focused question affirmatively. However, great variability was observed among the studies, hindering the precision of this analysis and highlighting the importance of conducting standardized studies.

Ethical approval and patient consent

Not required (human subjects were not involved).

Authors' contributions

AMO and GVOF developed the systematic review. MSA contributed to the introduction and discussion, in addition to serving as the third reviewer. JMG corrected the manuscript and provided the necessary guidance to ensure the logical sequence of this article.

Availability of data and materials

The datasets generated and/or analyzed in the present study are available from the corresponding author on reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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