INTRODUCTION

Chronic periodontitis is a multifactorial infectious disease, which is characterized by progressive loss of attachment and destruction of alveolar bone due to inflammatory processes, which may lead to tooth loss in susceptible individuals if not treated. The putative microorganisms responsible in the development of periodontitis include gram-negative bacteria, which activates innate, inflammatory, and adaptive immune responses. Lowering bacterial load and inhibiting progression of inflammation are the primary therapeutic goals that are achieved by mechanical debridement such as scaling and root planing (SRP), a gold standard treatment for chronic periodontitis.

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This study aimed to evaluate the efficacy of metformin as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis. Electronic searches were conducted in databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials Register databases) up to August 2017. Randomized clinical trials with data in comparison between adjunctive locally delivered metformin use to SRP and placebo in each group and a follow-up period of at least 6 months, were included. Primary outcomes included clinical attachment level, while secondary outcomes were bone defect (BD) fill and reduction in probing depth. The weighted mean differences (WMD) of outcomes and 95% confidence intervals (CI) for each variable were calculated using the random effects model. Five clinical studies were included in the qualitative synthesis and 3 studies were included for meta-analysis. All the included studies showed significant BD fill, probing depth reduction and clinical attachment level gain with adjunctive locally delivered metformin compared to SRP alone. Considering the effects of adjunctive metformin as compared to SRP, a high degree of heterogeneity for BD fill ($Q$ value = 7.03, $P = .02$, $I^2 = 71.55\%$) was noticed among both the groups. Meta-analysis showed a statistically significant clinical attachment level gain (WMD = $-2.83$, 95% CI = $-3.32$ to $-2.34$, $P < .001$), BD fill (WMD = $-2.96$, 95% CI = $-3.99$ to $-1.93$, $P < .001$) and probing depth reduction (WMD = $-3.11$, 95% CI = $-3.63$ to $-2.59$, $P < .001$) for SRP + metformin treatment vs SRP. Adjunctive use of metformin delivery in periodontal treatment appears to be effective in BD fill, reducing probing depth and gain in clinical attachment level. Further multicentered randomized clinical trials are warranted in future to prove additional benefits of metformin as an adjunct to SRP in the treatment of chronic periodontitis.
periodontitis. However, SRP shows physical limitations in certain inaccessible areas such as deep periodontal pockets, furcations and interproximal areas of misaligned teeth, which does not allow complete reduction of anaerobic infection and hence recurrence.

Considering these difficulties, various adjunctive treatments have been investigated and proposed to supplement SRP. These include systemic and localized delivery of antibiotics, bisphosphonates, lasers and photodynamic therapy to reduce bacterial counts and improve clinical periodontal parameters such as probing depth reduction, gaining clinical attachment level and bone defect (BD) fill in periodontitis. Among these compounds, locally delivered metformin have recently been introduced for the treatment of periodontal bone defects in chronic periodontitis.

Metformin is an oral hypoglycemic drug categorized under biguanides and are considered the most efficient agents widely used in the treatment of type 2 diabetes mellitus. The general clinical benefits observed in therapy with metformin seem to be greater than expected. They induce osteoblast cells to promote early bone formation through AMP kinase (AMPK) activity. Moreover, in a recent in vitro study, metformin facilitated in the proliferation of MG63 osteoblast like cells. Thus, their action in stimulating bone formation has justified their use in the treatment of periodontal bone defects in chronic periodontitis.

It is, therefore, the purpose of this systematic review to answer the following PICO question: In patients with moderate to advance periodontitis (Population), what is the effect of locally delivered metformin as adjunct to SRP (Intervention) in comparison to SRP alone (Comparison) on clinical attachment level (Outcome)?

2 | MATERIAL AND METHODS

2.1 | Protocol development and eligibility criteria

This review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO, registration number CRD42017074116). A protocol was developed and followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement.

2.2 | Criteria for considering studies for this review according to PICOS

2.2.1 | Type of studies

Only randomized clinical trials (RCTs) with a duration of ≥6 months were included.

2.2.2 | Types of participants

Studies were included if the participants met the following criteria: (i) had a clinical diagnosis of moderate to advanced chronic periodontitis, and (ii) ≥10 participants per group.

2.2.3 | Types of interventions

The interventions of interest were adjunctive local metformin delivery with SRP, comparing with placebo and SRP.

2.2.4 | Types of outcome measures

Primary. Primary outcome measure included clinical attachment level gain. Secondary. Secondary outcome measures were BD fill and probing depth reduction.

To address the aim of this study comprehensively, parameters such as clinical attachment level gain, probing depth reduction and BD fill in millimeters (mm) were further reported. Studies were excluded if the primary outcome (clinical attachment level gain) was missing. In addition, articles published only in English language were included in the present review. In-vitro studies; case series; animal studies; letters to the editor, abstract; review papers and unpublished articles were excluded.

2.3 | Search strategy

Electronic and manual literature searches were conducted by 2 independent reviewers (ZA and FJ) in the main databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Oral Health Group Trials Register) between January 1, 1978 and August 1, 2017 for articles addressing the focused question. Combinations of following controlled terms (MeSH) and free text words were used: ([Biguanide [MeSH Terms]] OR (metformin)) AND ((periodontitis [MeSH Terms]) OR (chronic periodontitis [MeSH Terms]) OR (periodontal disease [MeSH Terms]) AND (dental scaling [MeSH Terms]) OR [root planing [MeSH Terms]])

The authors independently screened titles and abstracts for eligible papers. If information relevant to the eligibility criteria was not available in the abstract, or if the title was relevant but the abstract was not available, the paper was selected for full reading of the text. Next, full-text papers that fulfilled the eligibility criteria were identified and included in the review. Reference lists of original studies were hand searched to identify articles that could have been missed during the electronic search. The search agreement between the 2 reviewers was evaluated by the Cohen's kappa (κ) test. Manual searching of the following journals was performed from January 1, 1978 to August 1, 2017: Journal of Clinical Periodontology, Journal of Periodontology and Journal of Periodontal Research. Studies that fulfilled the selection criteria were processed for data extraction. Reviewers designed and assessed the proposal for the present project to make sure the PRISMA guideline was followed to minimize risk of bias on the screening process and thus, to provide high level of evidence.

2.4 | Data extraction

Two reviewers (ZA and FJ) performed the data extraction independently. The information from the accepted studies was tabulated.
according to the subject demographics (sample size; mean and age range in years), drop-outs, gender distribution (percentage of females), drug concentration, follow-up period, main outcomes and funding sources in the included studies. Data collected were based on the focused question outlined for the present systematic review. Any disagreement was resolved by discussion until consensus was reached.

2.5 | Risk of bias in individual studies

The risk of bias of RCTs was assessed based on the revised recommendations of the Consolidated Standards of Reporting Trials statement.21 The risk of bias was estimated for each selected RCT based on the Cochrane Handbook for Systematic Reviews of Interventions.22 Briefly, subsequent sections were considered: selection bias (randomization and allocation concealment), performance bias (blinding of study participants and personnel), detection bias (blinding of outcome assessment), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases. Studies were classified as having "high risk of bias" (high), "low risk of bias" (low) or "unclear" (?) for each of these sections. Overall, studies were considered as: (i) low risk of bias if all criteria were met (adequate randomization and allocation concealment; “yes” answer to all questions about the completeness of outcome data and blinding, and “no” answer to selective reporting and other sources of bias); (ii) unclear risk of bias if 1 or more criteria were partly met; or (iii) high risk of bias if 1 or more criteria were not met.

2.6 | Quantitative analysis

In the present review, the primary outcome was clinical attachment level gain in mm while secondary outcomes were BD fill and reduction in probing depth. Meta-analyses were conducted separately for each of the primary and secondary outcomes. Majority of included studies used 1% metformin gel in the test group; therefore, meta-analyses was conducted only for 1% concentration. In addition, heterogeneity among the included studies for each outcome was assessed using the chi-squared test and $I^2$ statistic. For analyses, if the test indicated substantial or considerable heterogeneity ($I^2 > 50\%$), a random effects model would be used. Otherwise ($I^2 \leq 50\%$), a fixed effects model would be applied. $P < .05$ represents significant heterogeneity. Forest plots were computed reporting weighted mean difference (WMD) of outcomes and 95% confidence intervals (CI). The pooled effect was considered significant if $P < .05$. Data unsuitable for quantitative analysis were assessed descriptively. All above statistical analyses were carried out by specialized statistical software (MedCalc Software- B-8400 v 15.11.04, Ostend, Belgium).

3 | RESULTS

3.1 | Study selection

A total of 302 study titles and abstracts were initially identified. After removal of the duplicates ($n = 18$), initial screening of titles and abstracts was performed and 270 articles were excluded as irrelevant to the PICO question ($\kappa$ score for inter-assessor agreement [95% CI]: 0.81 [0.73--0.85]). A total of 14 papers were selected for full-text reading. Of these 14 studies, 9 studies were further excluded. After the final stage of selection, 5 studies were included and processed for data extraction ($\kappa$ score for inter-assessor agreement [95% CI]: 0.96 [0.93--0.99]). All studies were performed at university hospitals. Figure 1 shows the study identification flow
A chart according to PRISMA\textsuperscript{19} with the reasons for exclusion of articles.

### 3.2 General description of included studies

All clinical studies were RCTs.\textsuperscript{13,14,23-25} In all studies, number of subjects ranged between 20 and 70 individuals with age ranging between 25 and 55 years. The number of patients lost at follow-up ranged from 0 to 4 patients in the included studies.\textsuperscript{13,14,23-25} All studies reported the percentage of female participants, which ranged between 0% and 51%. The included studies used different selection criteria for chronic periodontitis based on probing depth $\geq 5$ mm in all studies,\textsuperscript{13,14,23-25} clinical attachment level $\geq 4$ mm in 3 studies\textsuperscript{13,23,25} and bone loss on radiographs in 4 studies.\textsuperscript{13,14,23-25} In all studies,\textsuperscript{13,14,23-25} subjects in the test group received locally delivered metformin + SRP. In 4 studies,\textsuperscript{13,14,23,25} subjects in the control group used SRP with placebo gel, while 1 study\textsuperscript{24} utilized SRP alone. Three studies\textsuperscript{13,14,23} used 1% locally delivered metformin, while 1 study\textsuperscript{25} utilized 0.6% metformin multiple layers film and another\textsuperscript{25} used varying concentrations such as 0.5%, 1% and 1.5% metformin for treating periodontal defects. One study\textsuperscript{24} recruited smokers, while 1\textsuperscript{24} did not mention anything about tobacco users. In all studies, the follow-up period ranged from 24 to 36 weeks. None of the studies reported regarding funding sources (Government or industry; Table 1). All the enrolled participants had complication-free healing period with no side effects related to metformin delivery.

### 3.3 Results of risk of bias assessment

Risk of bias was evaluated by extracting the data for each trial and presented in Table 2. Randomization: All included studies were RCTs\textsuperscript{13,14,23-25} but 2\textsuperscript{13,24} did not report randomization and allocation methods in detail. Three trials\textsuperscript{14,23,25} presented an adequate method

### Table 2 Evaluation of the risk of bias

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Sequence generation</th>
<th>Randomization methods</th>
<th>Allocation concealment</th>
<th>Blinding of study participants and personnel</th>
<th>All patients accounted for at the end of study</th>
<th>Clear explanation of withdrawals</th>
<th>Selective reporting</th>
<th>Over risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradeep et al\textsuperscript{23}</td>
<td>Low</td>
<td>RCTs</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Kassem et al\textsuperscript{24}</td>
<td>Low</td>
<td>RCTs</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Pradeep et al\textsuperscript{13}</td>
<td>Low</td>
<td>RCTs</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Pradeep et al\textsuperscript{25}</td>
<td>Low</td>
<td>RCTs</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Rao et al\textsuperscript{14}</td>
<td>Low</td>
<td>RCTs</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

CAL, clinical attachment level; LDD, local drug delivery; MF, metformin; NA, not available; OFD, open flap debridement; PD, probing depth; RCT, randomized clinical trial; SRP, scaling and root planing.
<table>
<thead>
<tr>
<th>Study groups (n)</th>
<th>Concentration of drug; route of administration; adverse events</th>
<th>Follow-up (wk)</th>
<th>Study outcome</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: 32 SRP + MF Group 2: 32 SRP + placebo</td>
<td>1% MF gel; LDD; None</td>
<td>Up to 36</td>
<td>Group 1 showed significantly greater improvements in all clinical parameters as compared to group 2 at follow-up (<em>P</em> &lt; .001).</td>
<td>Not stated</td>
</tr>
<tr>
<td>Group 1: 10 SRP + MF Group 2: 10 SRP</td>
<td>0.6% MF multiple layer film; None</td>
<td>Up to 24</td>
<td>Group 1 showed significantly greater improvements in all clinical parameters as compared to group 2 at follow-up (<em>P</em> &lt; .05).</td>
<td>Not stated</td>
</tr>
<tr>
<td>Group 1: 30 SRP + MF Group 2: 30 SRP + placebo</td>
<td>1% MF gel; LDD; None</td>
<td>Up to 24</td>
<td>Group 1 showed significantly greater improvements in BD fill (<em>P</em> &lt; .001), CAL (<em>P</em> &lt; .001) and PD (<em>P</em> &lt; .005) as compared to group 2 at follow-up.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Group 1: 9 SRP + 0.5 MF Group 2: 9 SRP + 1 MF Group 3: 11 SRP + 1.5 MF Group 4: 8 SRP + placebo</td>
<td>0.5%, 1%, 1.5% MF gel; LDD; None</td>
<td>Up to 24</td>
<td>MF groups showed significantly greater improvements in all clinical parameters as compared to SRP group at follow-up (<em>P</em> &lt; .001). Furthermore, 1% MF gel showed significantly greater improvement as compared to all the groups at follow-up (<em>P</em> &lt; .001).</td>
<td>Not stated</td>
</tr>
<tr>
<td>Group 1: 22 SRP + MF Group 2: 23 SRP + placebo</td>
<td>1% MF gel; LDD; None</td>
<td>Up to 24</td>
<td>Group 1 showed significantly greater improvements in all clinical parameters as compared to group 2 at follow-up (<em>P</em> &lt; .001).</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

**FIGURE 2** Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies

randomization. Allocation: Only 2 trials presented an adequate method of allocation concealment. All other trials were classified as unclear because the method of allocation was not described. Masking: Examiners were considered masked in 4 studies and unclear in 1 study. Withdrawals and dropouts: All studies reported withdrawals and dropouts either in the text or flow chart. Risk of bias: The risk of bias was considered high in 2 RCTs assessed and low in 2 RCTs and moderate in 1 study (Figure 2).

### 3.4 Clinical periodontal inflammatory parameters of included studies

The results for primary (clinical attachment level gain) and secondary outcomes (BD fill and probing depth reduction) are presented in Table 3. All the studies reported mean probing depth and clinical attachment level, which ranged from 3.2 to 6.77 mm and 2.16 to 5.4 mm at follow-up respectively. All the included studies reported values of BD fill in mm, which ranged from 2.68 to 4.86 mm at follow-up.

### 3.5 Main outcome of the studies

All studies showed that adjunctive metformin delivery was effective in the treatment of periodontal defects in chronic periodontitis at follow-up. In all the included studies, clinical periodontal parameters showed significantly higher improvements in the test group (metformin + SRP) as compared to the control group (SRP + placebo).

For quantitative data assessment, a meta-analysis was performed. Three studies presented data to be included in the meta-analysis considering the effects of adjunctive metformin delivery on clinical attachment level gain, BD fill and probing depth.
reduction. Only data presented for 1% metformin gel were analyzed for clinical periodontal parameters in meta-analysis. One study used 0.6% metformin in the test group; hence, this study was excluded from the meta-analysis. Significant heterogeneity was observed only for BD fill; therefore, a random effects model was employed. A fixed effects model was used for clinical attachment level gain and probing depth reduction.

Three studies were included in the meta-analysis for the effects of adjunctive metformin on clinical attachment level gain, BD fill and probing depth reduction. Considering the effects of adjunctive metformin, no heterogeneity for clinical attachment level gain (Q value = 0.96, P = .61, I² = 0%) and probing depth reduction (Q value = 1.05, P = .58, I² = 0%) was noticed among both the groups. However, a high degree of heterogeneity for only BD fill (Q value = 7.03, P = .02, I² = 71.55%) was noticed between the groups. The overall mean difference for clinical attachment level gain (WMD = −2.83, 95% CI = −3.32 to −2.34, P < .001; Figure 3A), BD fill (WMD = −2.96, 95% CI = −3.99 to −1.93, P < .001; Figure 3B) and probing depth reduction (WMD = −3.11, 95% CI = −3.63 to −2.59, P < .001; Figure 3C) were significant between metformin and SRP groups at follow-up.

### 4 | DISCUSSION

The present systematic review was based on the hypothesis that locally delivered metformin improves clinical periodontal parameters and enhances bone formation in chronic periodontitis. All RCTs included in the present systematic review supported the aforementioned hypothesis.
Chronic periodontitis is a highly prevalent oral disorder, which is associated with several periopathogenic microorganisms, one of which is Porphyromonas gingivalis that contains lipopolysaccharide (LPS), which is the key inflammatory mediator. A recent study investigated the role of metformin on the LPS-influenced inflammatory response and showed that metformin exerts anti-inflammatory effects on various LPS-induced periodontal cells. Moreover, the efficacy of adjunctive metformin in improving periodontal parameters may be explained by their role in stimulating alveolar bone formation. Delivery of metformin in chronic periodontitis facilitates osteoblast differentiation with concomitant gain in the clinical attachment level. It is suggested that metformin significantly decreases the intracellular reactive oxygen species and apoptosis and has a direct osteogenic effect on osteoblasts that could be partially mediated via promotion of Runx2 and insulin-like growth factor-1 expression. Furthermore, in an in vitro study, metformin is found to augment AMPK phosphorylation and can stimulate the AMPK signaling pathway in cells. The role of AMPK in osteoblastic differentiation has been proven and research suggests that AMPK activity is vital for bone nodule formation and maintenance of bone mass, supporting a role for AMPK signaling in bone physiology. These possible bone-sparing and bone-formative effects of metformin may be of considerable interest to the periodontist in managing periodontitis-induced alveolar bone destruction. However, it is important to interpret these findings with caution due to a number of factors.

It is notable that all studies included in the present review used locally delivered metformin gel as an adjunct to SRP and was compared to SRP/placebo in the treatment of periodontal defects. The studies that used local metformin showed significant improvement in all the clinical periodontal parameters as compared to SRP/placebo. A possible elucidation in this regard may lie in the ability of subgingival drug delivery to allow high drug concentrations and have controlled long-term release of the therapeutic agents at target sites (periodontal pockets) avoiding possible systemic side effects. This could prove beneficial over oral/systemic administration due to rapid absorption and low bioavailability in the body. In the present systematic review, the significant reduction in probing depth may be explained by the mechanical debridement (SRP) performed in chronic periodontitis patients to arrest inflammatory disease process, also emphasizing the significant role of SRP in the removal of bacterial deposits.

Several other inconsistencies were noted in the studies included. The different case definitions used for periodontal diagnosis may have masked the treatment outcomes. Pradeep et al showed that metformin gel did not show therapeutic advantage in deep periodontal pockets. Moreover, in the studies included, the follow-up period ranged from 3 to 24 months. Further studies are needed to determine the optimal dosage and duration of treatment for periodontal defects.

### FIGURE 3
Forest plot presenting post-therapy (A) clinical attachment level gain, (B) bone defect fill and (C) probing depth reduction by comparing metformin + SRP vs SRP. SRP: scaling and root planing.
from 24 to 36 weeks only. Outcomes based on such short-term observations are debatable; therefore, long-term clinical trials are needed to appreciate the treatment effect of locally delivered metformin.

The meta-analysis showed significant heterogeneity for probing depth reduction, clinical attachment level gain and BD fill among both the groups. This possibly could be due to the inclusion of patients with different case definition of periodontitis at baseline that ranged from >6 to 8 mm of probing depth. Notably, most of the studies included were from the same study groups that might have produced a bias (Pradeep et al.13,23-25; Rao et al.14). Although calibration was performed for clinical periodontal assessment but accuracy of measurements was not calibrated in BD fill, which might contribute to geometric errors on the conventional radiographs in the included studies. The small number of included studies is another limitation that should be taken into consideration, albeit a small number of patients were lost to follow-up, which may have not significantly affected the outcomes. Moreover, the short follow-up in the included studies may not have produced an actual difference in the periodontal parameters assessed. In addition, the search criteria involved articles only in English. This may have resulted in publication bias with potentially relevant studies published in other languages being missed.34 All these factors may have caused inconsistencies, which make interpretations difficult and such findings should be accepted with caution.

Treatment of periodontitis with adjuncts aims to facilitate manual debridement in reducing further disease progression. Studies7,9,12,35 have shown that SRP when performed with other existing adjunct therapies (such as bisphosphonates, statins, application of lasers and photodynamic therapy) is more effective in reducing periodontal inflammation in systemically healthy individuals compared with SRP alone. Similarly, locally delivered metformin should be used to compare the observed effects in periodontal inflammation. The present study indicates that locally delivery metformin as adjunct to SRP may be a valuable therapeutic option for treating periodontal defects in chronic periodontitis. Owing to its pivotal role in bone formation and immunomodulatory function, the authors suggest periodontal specialists should consider metformin delivery as an important adjunct for local use in treating intrabony periodontal defects in the future.

5 | CONCLUSION

Adjunctive use of metformin delivery in periodontal treatment appears to be effective in BD fill, reducing probing depth and gain in the clinical attachment level. Further multicentered RCTs are warranted in future to prove additional benefits of metformin as an adjunct to SRP in the treatment of chronic periodontitis.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

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