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Review Article

EXPLORING THE THERAPEUTIC POTENTIAL OF LOW-DOSE COLCHICINE IN CORONARY ARTERY DISEASE: AN IN-DEPTH ANALYSIS OF INFLAMMATION, SAFETY, AND CLINICAL EFFECTIVENESS

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ABSTRACT

Coronary Artery Disease (CAD) is a prevalent cardiovascular illness that is a primary cause of morbidity and mortality globally. It is distinguished by the constriction or blockage of the coronary arteries, which limits blood circulation to the heart. Inflammation is a driving force in the pathophysiology of CAD. Colchicine is an anti-inflammatory medication that has lately been studied for its potential application in the treatment of CAD. Its multimodal method of action has sparked interest due to its ability to treat inflammation and lower the concentration of critical inflammatory biomarkers. Clinical evidence validates the safe and effective use of Colchicine in CAD. Several recommendations advocate the use of colchicine in the secondary prevention of CAD. This article discusses the use of low-dose colchicine in CAD, its function in inflammation, as well as its safety and therapeutic effectiveness.

Keywords: Coronary artery disease, low-dose colchicine, Inflammation, Cardiovascular events, Pathophysiology, Biomarkers

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INTRODUCTION

Coronary Artery Disease (CAD) is the most common Cardiovascular disorder and has been the leading cause of Mortality and Morbidity worldwide and a significant proportion of Indians suffer from CAD [1, 2]. It is characterized by the formation of an atherosclerotic plaque in the lumen of coronary blood vessels, which leads to an inadequate supply of blood and oxygen to the heart. It can be classified as stable ischemic heart disease and acute coronary syndromes; according to one study, CAD accounts for 2.2% of the worldwide illness burden and 32.7% of cardiovascular diseases [3].

CAD is one of the most prevalent and life-threatening diseases, the search for novel therapeutics to supplement established CAD management techniques are a topic of interest in the medical industry. Among the developing treatment methods, the use of low-dose colchicine has attracted great attention and fascination.

Colchicine is a relatively inexpensive, effective anti-inflammatory drug approved for the treatment of acute gout and other inflammatory conditions like pericarditis [4, 5].

Colchicine's multimodal method of action has sparked interest due to its potential to treat one of the primary driving causes underlying CAD that is inflammation. This inflammatory basis is rapidly becoming seen as a critical component in the pathophysiology of atherosclerosis, which is the main culprit causing CAD formation and progression [5, 6].

Clinical evidence suggests that use of low-dose colchicine as an adjunctive therapy can potentially improve the management of CAD by mitigating inflammation and reducing cardiovascular events. In this article, the use of low-dose colchicine in CAD, its mechanisms of action, and possible advantages are discussed. Low-dose colchicine may improve the prognosis and quality of life for people with CAD.

MATERIALS AND METHODS

A literature search was performed to produce this article using the keywords "low dose colchicine", "Coronary Artery Disease," and "inflammation."
The literature needs to meet the requirements for inclusion, which are the highest number of English-language literature publications from the previous ten years that address the use of low-dose colchicine in CAD. The inclusion criteria were used to reorder the search results. Five articles satisfied the requirements for inclusion. Ten publications were excluded due to their non-compliance with the criteria.

Pathophysiology of cad

The gradual formation of atherosclerotic plaques within the coronary arteries, which results in decreased blood flow to the heart muscle, is the hallmark of CAD, a complicated cardiovascular illness. Atherosclerosis develops and spreads as a result of a number of interconnected mechanisms that make up the pathophysiology of CAD [3].

The major risk factors contributing to the development of CAD can be classified into-

1. Non-modifiable risk factors, including age, male gender, and ethnicity [7].

2. Modifiable risk factors including Diabetes, Smoking, Hyperlipidemia, Hypertension, Poor diet, Sedentary lifestyle, and Obesity [8].

CAD is a common heart condition characterized by the narrowing or blockage of the coronary arteries whose main function is to supply blood to the heart [9].

The cardinal pathophysiologic mechanism begins with the process of atherosclerosis [10]. Endothelial dysfunction and inflammatory dysfunction are the fundamental events in the development and pathophysiology of CAD and are linked to an increased risk of cardiovascular events [11].

The endothelium is a single layer of endothelial cells lining the lumen of vascular beds, which separates the vascular wall from the circulation and blood components [12]. The endothelium modulates the tone of vascular smooth muscle, maintains a non-adhesive luminal surface, and also mediates hemostasis, cellular proliferation, and inflammatory and immune responses in the vascular wall. It also prevents platelet activation and blood clotting by secreting substances like nitric oxide (NO), prostacyclin, t-PA, and Antithrombin III [13, 14].

A prothrombotic state, proinflammatory state, and decreased vasodilation are the hallmarks of endothelial dysfunction [15].

Endothelial dysfunction is marked by changes in the availability and production of endothelial-derived NO, prostacyclin, and endothelin which leads to reduced NO production, oxidative stress, increased vascular permeability, and leukocyte adhesion and inflammatory response [16].

Endothelial dysfunction accompanied by LDL retention and its modification in the intima (composed of endothelium, collagen, and elastic fibers) initiates the process of atherosclerosis [17-20]. The release of reactive oxygen species (ROS) as a result of oxidative stress leads to oxidation of LDL, a key inflammatory component [14]. The oxidized LDL is then captured by differentiated monocytes and vascular smooth muscle cells (VSMC) [19, 20]. These processes ultimately lead to the activation of the endothelium followed by T-cell activation. This causes monocyte recruitment to intima which later differentiate into macrophages [19], which promotes the formation of foam cells, a fatty deposit on the arterial wall that induces the growth of an atherosclerotic lesion [21].

In addition, the differentiated macrophages also cause the release of inflammatory cytokines such as TNF-α, interleukin-1, and interleukin-6 which activate other leukocytes (VCAM, ICAM, and E-Selectin) [22]. It also initiates the release of chemokines, decreases NO, increases ROS production, and increases NF-kβ production in endothelial cells [14]. This promotes monocyte recruitment and inflammatory response propagation which leads to the formation of a sub-endothelial atherosclerotic plaque [19, 23].

The formed atherosclerotic plaque may grow stable over time due to the formation of a fibrous cap or be unstable or vulnerable due to the presence of inflammation caused by neutrophil infiltration, causing plaque rupture in plaques rich in lipid molecules leading to platelet aggregation and vasospasm. This further causes the formation of a thrombus, which leads to partial or complete blockage of the coronary artery, causing CAD [24].

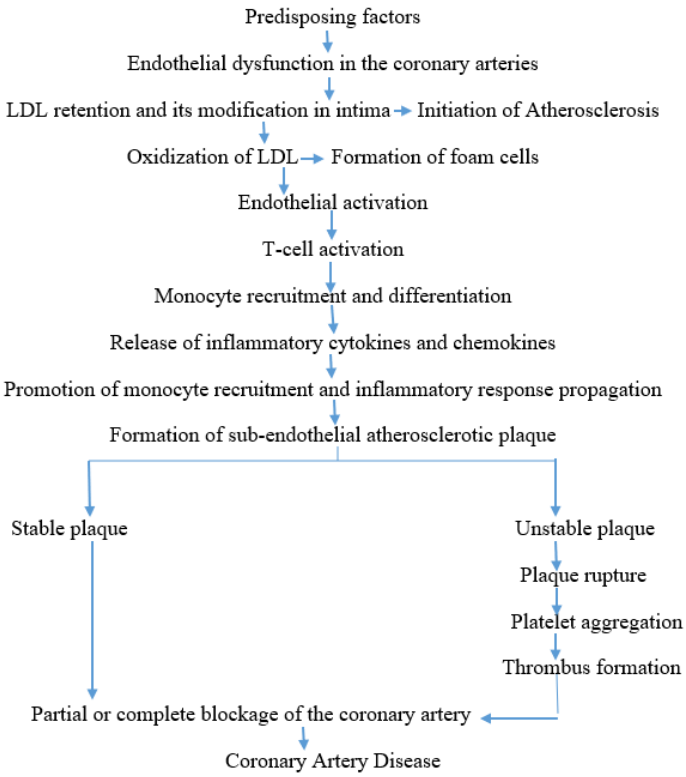

Fig. 1: Flowchart of pathophysiology of CAD. (Designed by Auhtors)

History and background of colchicine

Colchicine is an ancient drug used for various purposes over time. Colchicine is chemically an alkaloid found abundantly in the plant Colchicum autumnale [25].

Colchicine was first isolated in 1820 by a team of French pharmacists, Pierre-Joseph Pelletier and Joseph Bienaimé Caventou. It has been historically used for the treatment of Gout, Pseudogout, and Familial Mediterranean Fever (FMF) [26].

Colchicine was first approved by the FDA in 2009 for its therapeutic uses. It has also found non-FDA-approved uses in the fields of oncology, immunology, cardiology, and dermatology [27]. In view of its significant anti-inflammatory characteristics, colchicine has lately emerged as a viable new therapy option for cardiovascular disease [28].

Role of inflammation in cad

Atherosclerosis is a major event in the pathophysiology of CAD and Inflammation appears to play an important role in atherosclerosis [29]. Inflammation aids atherosclerosis and thrombosis and increases the risk of CAD [30].

The cholesterol crystals within the atherosclerotic plaque and oxidized LDL activate NLRP3 inflammasome in macrophages, leading to the release of pro-inflammatory mediators like interleukins [31]. The oxidized LDL also leads to increased activation of NF-kβ gene, which is a major pathway in the inflammatory process. Expression of this gene leads to the activation of inflammatory mediators like interleukin-1, interleukin-6, E-selectin, VCAM-1, and ICAM [32]. It also leads to reduced NO production, which further contributes to inflammatory response [19].

Biomarkers in the detection of CAD

The extent of inflammation that occurs in CAD is denoted by elevated levels of high-sensitivity C-reactive protein(hs-CRP) [33]. Increased fibrinogen levels were linked to the severity and mortality of CAD [34]. Pro-inflammatory cytokines like TNF-α, IL-6, IL-8, and IL-18 [35]. IL-8 is an effective neutrophil and T

lymphocyte chemoattractant. Several studies have shown that high IL-8 levels might be used as a biomarker for CAD. Studies also suggest Il-8 is a potent biomarker irrespective of hs-CRP values [11]. High levels of Monocytes are also associated with a risk of CAD [36].

Anti-inflammatory effects of colchicine

Anti-inflammatory medication lowers the risk of cardiovascular events in individuals with CAD [37]. The strong evidence that exacerbation of inflammation underlies the instability of atherosclerotic plaques suggests that anti-inflammatory therapy would be of additional benefit to patients already on optimal treatment [38].

Colchicine is an anti-inflammatory drug recently investigated for its use in the treatment of CAD [39].

Colchicine inhibits cytoskeletal microtubule processes like polymerization of β-tubulin at low doses, affecting neutrophil chemotaxis, protein excretion, and phagocytosis. It reduces endothelial selectin family-dependent adhesiveness, affecting E-selectin and L-selectin surface expression, increases leukocyte cyclic adenosine monophosphate levels, inhibits IL-1 production, and downregulates tumor necrosis factor-alpha (TNF-α) receptors in macrophages in addition to prevention of neutrophil migration [27, 40].

It causes a significant reduction in high-sensitivity C-reactive protein(hs-CRP) and IL-6 levels [9].

Colchicine inhibits neutrophil-platelet interaction. It also inhibits neutrophil activation, adhesion, and chemotaxis [41]. It suppresses protein tyrosine phosphorylation in neutrophils following the inhibition of both intracellular mobilization and extracellular release of granular enzymes, such as matrix metalloproteinases, neutrophil elastase, and α-defensins [42]. Colchicine also inhibits NLRP3 inflammasome activation in neutrophils and macrophages in the presence of atherosclerotic plaque-containing cholesterol crystals [5].

It also causes a decrease in the pro-inflammatory mediators [26].

Pharmacokinetic parameters

Colchicine is a medication used in healthy adults with linear pharmacokinetics within a dose range of 0.5 to 1.5 mg.

Absorption

It is absorbed through entero-hepatic recirculation and has a mean absolute bioavailability of 45%.

Distribution

It has a linear distribution, with a mean apparent volume of distribution of approximately 1300 L. Colchicine is found in high concentrations in leucocytes, kidneys, liver, and spleen and can cross the placenta, breast milk, and blood-brain barrier.

Metabolism

It is demethylated into two primary metabolites, 2-O-demethylcolchicine and 3-Odemethylcolchicine (2-and 3-DMC, respectively), and one minor metabolite, 10-Odemethylcolchicine (also known as colchiceine).

Excretion

In healthy volunteers, 40-65% of 1 mg of orally administered colchicine was recovered unchanged in the urine, with enterohepatic recirculation and biliary excretion playing a role in colchicine elimination. The mean effective half-life in healthy volunteers is 19 h. Colchicine is not removed by hemodialysis [27].

Pharmacodynamic parameters

The pharmacodynamic mechanism of colchicine in the intended indication is mostly unclear [27].

Clinical evidence for IT'S use

Over the years, many clinical trials have been conducted to evaluate the safety and efficacy of colchicine. The clinical trial CANTOS which demonstrated the anti-inflammatory effect of the drug Canakinumab in reduced cardiovascular events encouraged researchers to further investigate the effectiveness of anti-inflammatory drugs in cardiovascular diseases [43].

In the past decade, the focus has been 'low-dose' colchicine. Many studies have evaluated the use of low-dose colchicine in CAD. The significant trials among them are-

1. *LoDoCo*-The trial on 'Low Dose Colchicine' was a prospective, randomized observer-blind design whose main objective was to determine whether colchicine 0.5 mg/day can reduce the risk of cardiovascular events in patients with clinically stable coronary disease. 532 patients with stable coronary disease receiving aspirin and/or clopidogrel and statins were randomly assigned to receive either colchicine 0.5 mg/day or no colchicine and followed for a median of 3 y. The study concluded that colchicine 0.5 mg/day when given along with statins and other standard secondary prevention therapies, proved to be effective in the prevention of cardiovascular events in patients with stable coronary disease [44].

2. *LoDoCo2*-This was a randomized, controlled, double-blind trial conducted to evaluate the effect of low-dose colchicine in patients with chronic coronary disease. 5522 patients who participated in the trial were assigned to receive 0.5 mg of colchicine once daily or a matching placebo. The study concluded that the risk of cardiovascular events was significantly lower in the Colchicine group [45].

3. *COLCOT*-This was a randomized, double-blind trial to evaluate the effects of colchicine on cardiovascular outcomes and its long-term safety profile in patients who had recently had a myocardial infarction conducted in 4745 patients with a history of myocardial infarction within a month of recruitment and being treated with standard guidelines. The patients were divided into two groups and each group received colchicine and a placebo drug respectively. It was found that low-dose colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo [29].

4. *COPS*-This was a randomized, multicenter, double-blind study conducted in Australia to determine the potential usefulness of colchicine treatment in patients with ACS. A total of 795 patients with Acute coronary syndrome (ACS) were observed for a period of 12 mo. The study concluded that colchicine as an adjunctive therapy had no effect on cardiovascular outcomes at 12 mo in individuals with ACS and was related to a greater risk of death [28].

5. A study conducted by Akrami M *et al.* (2021), whose primary objective was to evaluate the effect of short-term, low-dose colchicine therapy along with the standard medical therapy in approved ACS patients within a period of six months after a cardiac event says that introducing colchicine to standard medical therapy in ACS patients significantly lowers MACE incidence and increases survival rate over time [43].

6. Various trials have also proven a significant reduction in hs-CRP levels in cardiovascular patients [29, 38, 46].

Other ongoing trials have the potential to determine the efficacy of colchicine in the treatment of cardiovascular diseases like-

- 'COVINCE' Colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke**-**The study was started on December 12, 2016, and is estimated to be completed on 31/12/2023. It is an interventional study with a study population of 3156 patients which aims to determine the effectiveness of low-dose colchicine concerning vascular events [47, 48].

- 'Clear Synergy' is an interventional randomized, blinded, double-dummy, 2x2 factorial design trial of colchicine versus placebo and spironolactone versus placebo in patients with myocardial infarction who have undergone primary percutaneous coronary intervention (PCI). The study started in 2018 and is estimated to end in May of 2024. It has an enrollment of 7063 patients and its main objective is to determine the long-term effect of low-dose colchicine following Percutaneous Coronary Intervention (PCI) to treat MI and monitor the Major Adverse Cardiac Events (MACE) [49].

Safety and efficacy

Colchicine is indicated to reduce the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult

patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease [44].

The recommended dose of colchicine for the secondary prevention of cardiovascular events is 0.5 mg once daily given through oral route [44]. This is contradictory to the available dose of 0.6 mg as the adverse effect of the drug is directly proportional to the adverse effects of the drug [50]. Evidence suggests it has reduced the rate of cardiovascular deaths [44]. Colchicine also prevents the risk of Major Adverse Cardiac Events (MACE) like Myocardial infarction, stroke, and cardiovascular deaths [50].

Colchicine has shown a relative risk reduction of 25% when compared to a placebo group [41].

Colchicine is associated with but a few adverse effects despite being a narrow therapeutic index drug. The major reported adverse events are related to the GIT. Diarrhea was reported in 9.7% of colchicine patients and 8.9% of placebo patients, while pneumonia was reported as a statistically significant serious adverse event in 0.9% of colchicine patients and 0.4% of placebo patients in the COLCOT trial [29]. Other adverse effects include myalgia, myotoxicity, weakness, nausea, vomiting, abdominal pain, rashes, alopecia, myelosuppression, thrombocytopenia, leukopenia, and pancytopenia [27]. However, the occurrence of gastrointestinal symptoms was more prominent in short-term and long-term use of Low-dose Colchicine.

- The drug has been demonstrated to be efficacious in patients with stable coronary conditions while being affordable and safe.

Table 1: Results of RCT on low-dose colchicine

First author	Sample size	Intervention	Results	Conclusion
Nidorf SM [44]	552	Colchicine 0.5 mg/day or no colchicine and followed for a median of 3 y	(15 of 282 patients, or 5.3%), who got colchicine and 40 of 250 patients, or 16.0%, who did not receive colchicine experienced the primary outcome (hazard ratio: 0.33; 95% confidence interval [CI] 0.18 to 0.59; p 0.001; number needed to treat: 11). The primary outcome occurred in 4.5% versus 16.0% (hazard ratio: 0.29;95% CI: 0.15 to 0.56; p 0.001) in a pre-specified secondary on-treatment analysis that excluded 32 patients (11%) assigned to colchicine who withdrew within 30 d due to intestinal intolerance and a further 7 patients (2%) who did not start treatment.	In patients with stable coronary disease, colchicine 0.5 mg/day given in addition to statins and other common secondary prevention treatments, seems to be beneficial in preventing cardiovascular events.
Nidorf SM [45]	5522	0.5 mg of colchicine once daily for one month in a 1:1 ratio to receive 0.5 mg of colchicine once daily or a matching placebo.	The follow-up period was 28.6 mo on average. In the colchicine group, 187 patients (6.8%) experienced a primary end-point incident, while in the placebo group, 264 patients (9.6%) experienced one (incidence, 2.5 vs. 3.6 occurrences per 100 person-years; hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001). 155 patients (4.2%) in the colchicine group and 157 patients (5.7%) in the placebo group experienced a major secondary end-point incident (incidence, 1.5 vs. 2.1 events per 100 person-years; hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P=0.007). The incidence rates of cardiovascular death or spontaneous myocardial infarction (composite endpoint), ischemia-driven coronary revascularization, spontaneous myocardial infarction, and spontaneous myocardial infarction were also significantly lower with colchicine than with placebo. Compared to the placebo group, the colchicine group had a greater incidence of mortality from non-cardiovascular causes (incidence, 0.7 vs. 0.5 occurrences per 100 person-years; hazard ratio, 1.51; 95% CI, 0.99 to 2.31).	Individuals who took 0.5 mg of colchicine once daily had a significantly lower risk of cardiovascular events compared to those who received a placebo.
Tardif JC [29]	4745	low-dose colchicine (0.5 mg once daily) or placebo	The median duration of patient follow-up was 22.6 mo. 5.5% of patients in the colchicine group and 7.1% of patients in the placebo group experienced the primary end point (hazard ratio: 0.77; 95% confidence interval [CI]: 0.61 to 0.96; P=0.02). For cardiovascular-related deaths, the hazard ratios were 0.84 (95% CI, 0.46 to 1.52), 0.83 (95% CI, 0.25 to 2.73), 0.91 (95% CI, 0.68 to 1.21) for myocardial infarction, 0.26 (95% CI, 0.10 to 0.70) for stroke, and 0.50 (95% CI, 0.31 to 0.81) for hospitalization due to angina that required coronary revascularization. 9.7% of patients in the colchicine group and 8.9% of patients in the placebo group reported having diarrhoea (P=0.35). A case of pneumonia was recorded as a major side event (P=0.03) in 0.9% of individuals receiving colchicine and 0.4% of patients receiving a placebo.	Colchicine, administered daily at a dose of 0.5 mg, significantly reduced the incidence of ischemic cardiovascular events in individuals who had recently suffered a myocardial infarction when compared to placebo.
Tong DC [28]	795	0.5 mg oral colchicine twice daily for the first month, followed by 0.5 mg daily for 11 mo; Vs. Placebo.	The colchicine group experienced 24 occurrences during the 12-month follow-up, while the placebo group experienced 38 events (P=0.09, log-rank). In the colchicine group, there was no cardiovascular death (5 against 0; P=0.024, log-rank) and a higher overall mortality rate (8 compared to 1; P=0.017, log-rank). The majority of the reported adverse effects (colchicine, 23.0% versus placebo, 20.8%) were gastrointestinal symptoms, and the rates of adverse effects were not different (colchicine, 23.0% versus placebo, 24.3%). There were two CV deaths, five non-CV deaths, and one CV in Placebo.	Colchicine was linked to a greater death rate in individuals with ACS, but it had no discernible effect on cardiovascular outcomes at 12 mo when added to normal medical care.
Akrami M [43]	361	colchicine at a single dose of 0.5 mg once daily or placebo, plus standard medical therapy or standard medical therapy	There was a significant decrease in MACE events in colchicine group	When ACS patients are prescribed low-dose colchicine, the incidence of significant adverse cardiac events in the six months following a cardiovascular event is reduced. Additionally, compared to the placebo group, the colchicine group's survival rates dramatically improved.

Recommendations for the use of low-dose colchicine in secondary prevention of cad

- The 2021 guidelines of the 'European Society of Cardiology' for the prevention of CVD recommend that low-dose colchicine

0.5 mg daily through oral route be considered for secondary prevention purposes, particularly among individuals with uncontrolled risk factors or recurrent events despite optimal medical therapy.

- National guidelines in Canada and South America advocate broad use of 0.5 mg colchicine daily for the reduction of atherothrombotic events in almost all patients with pre-existing coronary disease, assuming that there are no contraindications [51].

Future research possibilities

- *Studies can be conducted to determine the long-term effects of colchicine in the treatment of CAD*.

- Trials like COPS have indicated an increase in adverse events in the long-term follow-up of patients. Studies to further evaluate the same will be useful in determining the safety of the drug.

- *Researchers can explore the effectiveness of low-dose colchicine in patients with Unstable CAD.* Most of the trials conducted have included patients with Stable CAD. The efficacy of the drug in Unstable CAD is yet to be explored.

- *A sample with variables in ethnicity could be considered.* The role of genetics in CAD can be explored.

- *Exploration of the reno-protective nature of colchicine.* Many studies claim that colchicine has a protective mechanism towards renal function and may be used in the treatment of CKD. Colchicine has the lowest possible nephrotoxicity and its use in CKD is an application that can be explored

- *Effect of low-dose Colchicine on fertility.* This is crucial to determine and prepare the prescribing guidelines for Low-dose Colchicine.

CONCLUSION

Despite the contentious nature of the study results thus far. Colchicine when taken as an adjuvant at a low dose in patients with stable disease on standard medication therapy, including aspirin, other antiplatelets, statins, and/or beta-blockers, is an inexpensive and effective therapeutic option for the secondary prevention of cardiovascular events and improves quality of life in patients with CAD.

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AUTHORS CONTRIBUTIONS

V. S. crafted an article by collecting data from various sources, developing the concept and layout. Following this, the S. S. reviewed and approved the finalized version for publication.

CONFLICTS OF INTERESTS

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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