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REVIEW

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Etiopathophysiological role of the renin–angiotensin–aldosterone system in age-related muscular weakening: RAAS-independent beneficial role of ACE2 in muscle weakness

Shivkanya Fuloria[1] | Vetriselvan Subramaniyan[2] | Dhanalekshmi U. Meenakshi[3] | Mahendran Sekar[4] | Srikumar Chakravarthi[2] | Darnal H. Kumar[5] | Usha Kumari[6] | Venkata G. Vanteddu[7] | Tulsi D. Patel[7] | Kishore Narra[7] | Pradeep K. Sharma[8] | Neeraj K. Fuloria[1,9]

[1]Faculty of Pharmacy, AIMST University, Kedah, Malaysia

[2]Faculty of Medicine, Bioscience and Nursing, Faculty of Medicine, MAHSA University, Jenjarom Selangor, Malaysia

[3]College of Pharmacy, National University of Science and Technology, Muscat, Oman

[4]Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Health Sciences, Royal College of Medicine Perak, Universiti Kuala Lumpur, Ipoh, Perak, Malaysia

[5]Jeffrey Cheah School of Medicine & Health Sciences, Monash University, Johor, Johor Bahru, Malaysia

[6]Faculty of Medicine, AIMST University, Kedah, Malaysia

[7]Synizo Pharmaceuticals Pvt Ltd., Puducherry, India

[8]Accurate College of Pharmacy, Greater Noida, India

[9]Center for Transdisciplinary Research, Department of Pharmacology, Saveetha Institute of Medical and Technical Sciences, Saveetha Dental College and Hospital, Saveetha University, Chennai, India

Correspondence

Neeraj K. Fuloria, Faculty of Pharmacy, AIMST University, Kedah, Malaysia. Center for Transdisciplinary Research, Department of Pharmacology, Saveetha Institute of Medical and Technical Sciences, Saveetha Dental College and Hospital, Saveetha University, Chennai, India.
Email: nfulorias@gmail.com

Abstract

Aging is accompanied by major changes in body composition that can negatively affect functional status in older adults, including a progressive decrease in muscle mass, strength, and quality. The prevalence of sarcopenia has varied considerably, depending on the definition used and the population surveyed—a 2014 meta-analysis across several countries found estimates ranging from 1% to 29% for people aged 60 years or older, who live independently. The potentially relevant studies were retrieved from the ScienceDirect/Medline/PubMed/Public library of science/Mendeley/Springer link and Google Scholar. Multiple keywords were used for the literature search both alone and in combination. Some of the important keywords used for literature search were as follows: "Epidemiology of muscle weakness/muscle disorders," "Pathogenesis of RAAS in muscle weakness," "Role of Angiotensin 1–7/ACE-2/Mas R axis in muscle weakness," and "Correction pathophysiology of muscle weakness via ACE2." The renin–angiotensin system (RAAS), a major blood pressure regulatory system, is a candidate mediator that may promote aging-associated muscle weakness. Previously, studies explored the proof concept for RAAS inhibition as a therapeutic target. Furthermore, in RAAS, angiotensin II, and angiotensin-converting enzyme 2 (ACE2) have been reported to induce endoplasmic reticulum (ER) stress via glucose-regulated protein 78/eukaryotic translation initiation factor 2α (eIF2α)/activating transcription factor 4 (ATF4)/CHOP axis in the liver. In addition, other mitochondria and ER physical interactions contribute to skeletal muscle dysfunction. However, very few studies have investigated the relationship between RAAS and ER stress-associated pathophysiological events and ACE2-mediated biological consequences in muscle weakness. Thus, the study has been

designed to investigate the RAAS-independent beneficial role of ACE2 in muscle weakness.

KEYWORDS
ACE2, angiotensin 1–7, angiotensin 1–7/Mas receptor axis, ER stress, Mas receptor, renin–angiotensin–aldosterone system

1 | INTRODUCTION

Aging is accompanied by major changes in body composition that can negatively affect functional status in older adults, including a progressive decrease in muscle mass, strength, and quality, accompanied by an increase in fat mass. Age-related muscle loss begins in the third to fourth decade of life.[1] Although some loss of muscle and strength, termed sarcopenia, is a normal part of aging, clinically significant sarcopenia associated with functional impairment is thought to be a cornerstone in the process of frailty and disability.[1] Although weakness was initially considered a direct consequence of the loss of muscle mass,[2] it may also be mediated through loss of muscle strength.[2,3] Emerging evidence suggests two distinct subgroups of persons with weakness: one due to low appendicular muscle mass and the other due to reduced strength with intact muscle mass.[4] Lean muscle mass generally contributes up to about 50% of total body weight in young adults but decreases with age to be about 25% of total body weight by age 75–80 years.[5] With aging, declining muscle mass in the lower extremities is most significant to mobility status. The cross-sectional area of the vastus lateralis (quadriceps) muscle decreases by up to 40% between the ages of 20 and 80 years.[6] As a result of skeletal muscle loss, the basal metabolic rate decreases by about 30% between the ages of 20 and 70 years.[7] However, the prevalence of sarcopenia has varied considerably, depending on both the definition used and the population surveyed—a 2014 meta-analysis[8] across several countries found estimates ranging from 1% to 29% for people aged 60 years or older, who live independently. Using the European Working Group on Sarcopenia in Older People guidelines, the prevalence of sarcopenia in a UK population with a mean age of 67 years and comprising people who could live independently was 4.6% for men and 7.9% for women.[8] Such rates are much higher in people in residential care[9] (14%–33%), in those with cancer[8] (15%–50%), and patients in intensive care units[10] (60%–70%).

Although the phenotype is the same, the underlying cellular pathologies and the molecular causes of these pathologies are diverse. One common feature of many muscle disorders is the mispositioning of myonuclei. In unaffected individuals, myonuclei are spaced throughout the periphery of the muscle fiber such that the distance between nuclei is maximized. However, in diseased muscles, the nuclei are often clustered within the center of the muscle cell. Although this phenotype has been acknowledged for several decades, it is often ignored to contribute to muscle weakness.[11] Cellular senescence is another mechanism that leads to cell elimination.

In contrast to apoptosis cells, senescent cells enter a cell cycle arrest and persist in the tissue. Subsequently, they influence neighboring cells by secreting soluble factors, a response collectively known as the senescence-associated secretory phenotype, which activates immune cells to promote clearance of cell debris during tissue remodeling.[12] The tumor suppressor proteins $p16^{INK4A}$, encoded by the *CDKN2A* locus, are often transcriptionally activated in cells undergoing senescence; moreover, these factors are major regulators of the senescence program.[13] Although $p16^{INK4A}$ expression increases with age or chronic inflammation/fibrosis and is a robust senescence marker in multiple human and mouse tissues,[14,15] $p16^{INK4A}$-expressing cells also play essential roles in wound healing.[16,17] The renin–angiotensin system (RAAS), a major blood pressure (BP) regulatory system, is a candidate mediator that may promote aging-associated muscle weakness. Previously, studies explored the proof concept for RAAS inhibition as a therapeutic target.[18–21]

Regarding aging-associated pathological conditions, genetic and pharmacological blockade of angiotensin II (Ang II) type 1 receptor (AT1) improved muscle function in aged mice, suggesting that the physiological level of RAAS activation is associated with a reduction in muscle function due to aging.[22,23] However, few studies have investigated the relationship between RAAS and endoplasmic reticulum (ER) stress-associated pathophysiological events and angiotensin-converting enzyme 2 (ACE2)-mediated biological consequences in muscle weakness. Thus, the study has been designed to investigate the RAAS-independent beneficial role of ACE2 in muscle weakness.

2 | SELECTION OF LITERATURE FOR REVIEW

The potentially relevant studies were retrieved from the ScienceDirect/Medline/PubMed/Public library of science/Mendeley/Springer link and Google Scholar. Some different keywords were used for literature searched in a group or single terms. Inclusion criteria for selecting relevant studies were reporting the role "Epidemiology of muscle weakness/muscle disorders," "Pathogenesis of RAAS in muscle weakness," "Role of Angiotensin 1–7/ACE-2/Mas R axis in muscle weakness," "Correction pathophysiology of muscle weakness via ACE 2," "Effect of apelin in ER stress," "ACE 2 and suppression of muscle weakness," "Relationship of ACE 2/Apelin with ER stress and mitochondria dysfunction" or "Role of RAAS blockers in

muscle weakness," in combination with ER stress. Non-English language studies unpublished studies were excluded from the study. Additional searches were also conducted on the reference collections of the recovered journals to locate articles that were not found by the original research design. This study was performed in the pharmacy department, AIMST University, Malaysia.

3 | PATHOPHYSIOLOGICAL ASPECTS OF MUSCLE WEAKNESS IN THE CONTEXT OF RAAS

Sarcopenia does not have a detailed biological hallmark. There is no single process responsible for the demise of muscle fibers with age. Factors that contribute to the development of sarcopenia include hormonal changes (in particular, falling levels of testosterone, estrogen, or growth hormone), loss of the neurons that stimulate the muscle, infiltration of fat into muscle, insulin resistance, physical inactivity, a vitamin D deficiency, and not eating enough protein, although one of the major associated contributing factors among the misactivation of the classical RAAS signaling pathway begins with binding the RAAS hormone Ang II to the angiotensin I receptor (AT1R) on the cell membrane. Briefly, activation of the AT1R initiates receptor interaction with several heterotrimeric G-proteins that transduce signals to several downstream second messengers, including the mitogen-activated protein kinase (MAPK) family (e.g., p38 MAPK and extracellular signal-regulated kinase 1/2 [ERK1/2]), calcium-dependent protein kinase C, phospholipase C, Janus kinase, and signal transducers and activators of transcription.[24] Moreover, hyperactivity of RAAS activates AT1R-mediated ER stress.[25] Furthermore, in RAAS, Ang II and ACE2 have been reported to induce ER stress via glucose-regulated protein 78 (GRP78)/eIF2α/ATF4/CHOP axis in the liver.[26,27] It demonstrated that alterations in mitochondria and ER physical interactions contribute to skeletal muscle dysfunction. Persistent ER stress/unfolded protein response (UPR), and excessive mitochondrial reactive oxygen species (ROS) production contribute to muscle weakness and atrophy in mice.[28] Similar structures designated sarco reticulum (SR) (mitochondrial-associated membranes (SR-MaMs) are found in the skeletal muscle.[29] They are thought to play a role in matching contraction-associated energy demands with ATP production via Ca^{2+} signaling to mitochondria[30] ER-MaMs are sites of Ca^{2+}, phospholipid, and ROS exchange between the ER and mitochondria,[31,32] and study data suggesting that persistent ER stress drives Ca^{2+} uptake and ROS production by mitochondria at the ER/SR-MaMs.[28] In consequence of ER stress, triggered UPR has three distinct branches of the UPR system that can be initiated by transmembrane effector signal transduction proteins—protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and ATF6—and these signaling branches that are initiated by signals such as the dissociation of BiP(GRP78) from the intracellular receptor domains of the ER. These signals activate combinations of the three stress sensors, protein kinase RNA-like PERK, ATF6, and IRE1α. CHOP is a downstream effector of all three branches of the UPR. Moreover, enhanced CHOP expression has several effects on cells including alteration of the balance of pro- and antiapoptotic proteins that act on the mitochondria.[33] In support of this, we found the following: (a) increased apoptotic nuclei; (b) increased cleaved caspases 3, 9, and 12; (c) increased caspase 3 activity; and (d) marked elevation of the tumor suppressor and proapoptotic protein p53. These findings suggest that the persistent increases in mitochondrial Ca^{2+} and ROS production cause both mitochondrial damage and elevation of proapoptotic pathways, thereby contributing to muscle dysfunction (Figure 1).[28]

4 | INVOLVEMENT OF ANG II IN AGING MUSCLE WASTING

Conversely, the acute administration of Ang II was reported to cause muscle wasting in mice[34–36] via alterations in insulin-like growth factor-1 (IGF-1) signaling, increased apoptosis, and enhanced muscle protein breakdown via the ubiquitin–proteasome system. In addition, decreased appetite resulting from downregulation of hypothalamic orexigenic neuropeptides orexin and neuropeptide Y. Furthermore, Ang II inhibits skeletal muscle stem cell proliferation, leading to lowered muscle regenerative capacity. In addition to that Ang II alters muscle metabolism and energy stores increased mitochondrial-derived superoxide and ROS derived from NADPH oxidase, leading to muscle wasting.[37]

5 | ANGIOTENSIN 1–7/ACE2/MAS RECEPTOR AXIS

Accumulating evidence also suggests that ACE2, which cleaves Ang II to produce angiotensin 1–7 (A1–7), plays a protective role against multiple pathologies by blocking RAAS activation.[38] In addition, A1–7 and its binding to a receptor, Mas, were shown to attenuate muscle dysfunction in animal models of several muscle disorders.[39–42]

ACE2 decreases the generation of Ang II by catalyzing the conversion of Ang II to A1–7. However, A1–7 elicits the opposite effect of Ang II.[43] For example, activation of AT1R results in cellular increases in MAPKs; in contrast, A1–7 binding to the mitochondrial assembly receptor (MASR) (mitochondrial assembly receptor results in a significantly lower activity of both ERK1/2 and p38, and increased phosphorylation of protein kinase B (AKT).[44,45] Importantly, activation of the MASR can also prevent AT1R-mediated activation of NADPH oxidase.[46] Recently, it has been reported that ACE2 regulates mitochondrial function in pancreatic β-cells and ACE2 inhibits the ER stress-associated pathway to preserve hepatic insulin resistance and hepatic steatosis.[26,47] Moreover, the beneficial protection against ER stress in the heart and lung by ACE2 is reported.[48,49] Collectively, these findings indicate that inhibition of the RAAS and activation of the A1–7/Mas pathway may conceivably contribute to the improvement of age-associated muscle disorders in rodents in a similar fashion.

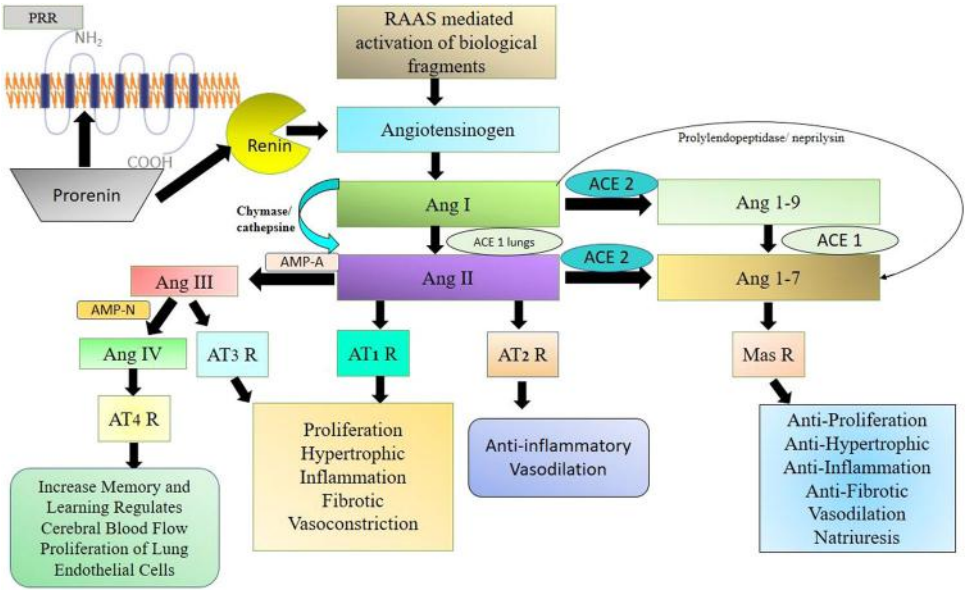

FIGURE 1 Counterbalancing the response of RAAS via biological active fragments in physiology. Abbreviations: ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; AT1R, angiotensin type IA; PRRs, pattern recognition receptors; RAAS, renin–angiotensin–aldosterone system

6 | BIOLOGICAL CONSEQUENCES OF ER STRESS/ACE2 AND APELININ MUSCLE WEAKNESS

A recent study explored the data for *ACE2* gene deletion or RAAS activation caused distinct skeletal muscle phenotypes to reduce muscle strength. Consistent with the study, ACE2KO mice were characterized by the induction of a senescence-associated gene, *p16INK4a*, and increased central nuclei without additional histological alterations in muscle fibers. Furthermore, the BP of ACE2KO mice was normal or only slightly elevated unless treated with Ang II. In addition to that, the muscle Ang II content was increased in Tsukuba hypertensive(TH)mice but not ACE2KO mice. Consistently, the plasma concentration of AII was not altered in ACE2KO mice with normal aging. Thus, it is conceivable that the muscle weakness observed in ACE2KO mice is associated with neither altered BP nor RAAS activation.

A study further exhibits the proof for blocking the AT1 protected against age-associated muscle weakness in mice via downregulation of the aging-promoting complement C1q-Wnt/β-catenin signaling pathway.[23] Burks et al.[50] also reported that an AT1 inhibitor, losartan, improved muscle remodeling and protected against muscle atrophy in old mice by differentially regulating the transforming growth factor-β and IGF-1/Akt/mammalian target of rapamycin signaling cascades. These reports suggested that activation of the RAAS promotes accelerated aging-associated muscle weakness in mammals throughout their life span. Furthermore, a very recent study suggests that the impact of ACE2 on physiological aging does not depend on the endogenous production of A1–7 by ACE2. At the same time, overactivation of the A1–7–Mas pathway could alleviate sarcopenia and osteoporosis in aged mice.[51] Taken together with the data of this study, the accelerated aging phenotypes in ACE2KO mice demonstrate the involvement of RAAS-independent mechanisms of ACE2.

Thus, we need to focus on the different biological potentials of ACE2, which may contribute to protecting muscles from aging. Previously, it has been demonstrated that ER stress-mediated alterations in mitochondria bioenergetics contribute to skeletal muscle dysfunction. Furthermore, ACE2KO mice exhibited smaller body weights than wild-type mice without affecting food consumption and muscle mass in the lower limb at middle age. This implies the possibility that ACE2 deficiency alters metabolic function, leading to a change in body composition.[52] Consistently, a study that explains the differences in GRP78/eIF2α/XBP-1/ATF4/CHOP expression suggested that ACE2 alleviates ER stress in skeletal muscle and liver may go through the same pathway illustrated above. Therefore, the mechanism underlying this process could involve the ability of ACE2 to regulate the GRP78/eIF2α/XBP-1/ATF4/CHOP pathway. Moreover, a recent study reported that the deletion of ACE2 induced the early manifestation of age-associated muscle weakness in mice.[53]

Apelin, an endogenous peptide, is a second catalytic substrate for ACE2 and was downregulated in apelin-deficient mice.[54] Apelin gene (*APLN*) encodes a 77-amino acid pre-pro-apelin in humans, whereas the C-terminal 23 amino acids are 100% conserved among humans, rats, mice, and bovine. Pre-pro-apelin is cleaved into 13-, 17-, and 36 amino acid peptides from the C terminus. Apelin receptor, belonging to the family of G-protein-coupled receptor, is the endogenous receptor of apelin peptides, which mediates signal transduction via G protein.[55] Apelin gene expression is repressed by ATF4 via a p38 MAPK-dependent pathway under endoplasmic

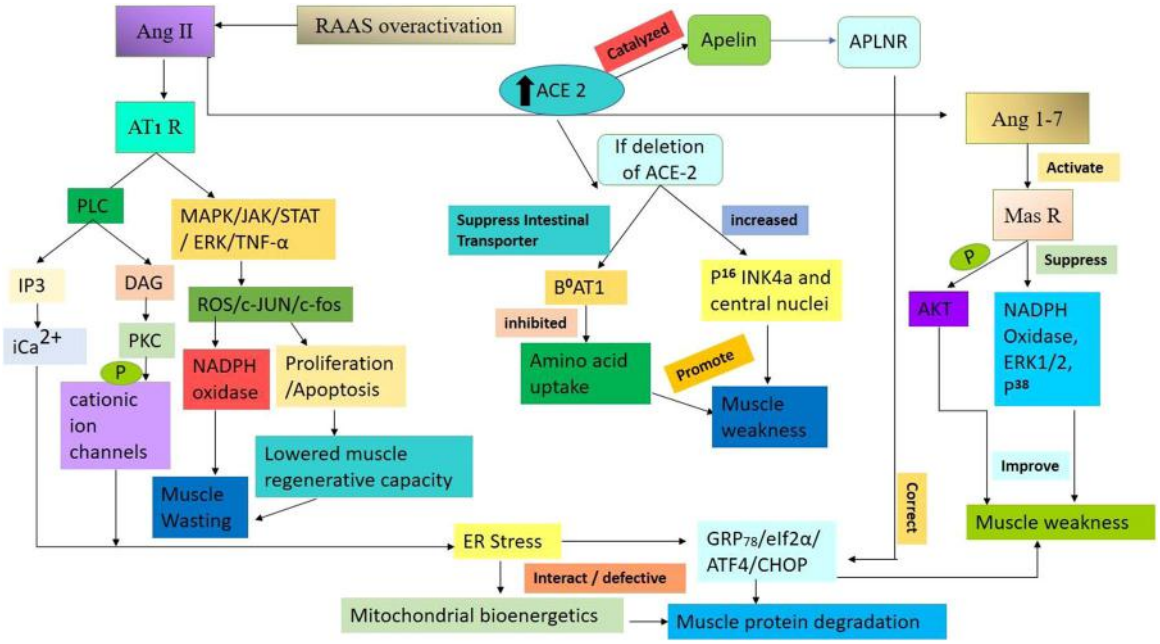

FIGURE 2 Biological consequences of ER stress/ACE2 and apelin in muscle weakness. Abbreviations: ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; APLNR, apelin receptor; AT1R, angiotensin type IA; DAG, diacylglycerol; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; IP3, inositol trisphosphate; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; PLC, phospholipase C; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TNFα, tumor necrosis factor-α

reticulum stress (ERS)[56] A study also showed that apelin inhibited ERS-induced CHOP and GRP78 elevation suppression of eIF2-ATF4-CHOP and protecting cell to dysregulated apoptosis through activating $G\alpha_i/G\alpha_q$-casein kinase 2 signaling.[57,58] Furthermore, apelin has also been reported to upregulate ACE2 messenger RNA expression, suggesting a close relationship between ACE2 and apelin.[59] Interestingly, it was recently reported that apelin expression decreases with aging, and sarcopenia and its restoration in aged mice improved muscle mass and function.[60]

Aging is associated with the overactivation of RAAS and decreases in muscle formation and expression of ACE2. Proteins in ingested food are hydrolyzed to small oligopeptides and amino acids on their way from the oral cavity to the small intestine, where they are absorbed across the mucosa. More precisely, they are transported mostly across epithelial cells by being first imported through their luminal membrane and sequentially exported across their basolateral membrane to be distributed to other body tissues. Most neutral amino acids are transported across the apical brush-border membrane of the small intestine and the proximal renal tubules by the luminal Broad neutral Amino acid Transporter B^0AT1 (Slc6a19), which was first identified in 2004 in mice.[61–64] The expression and function of B^0AT1 have also been shown to depend on the coexpression of members of the RAAS, namely TMEM27 (collectrin) in the kidney and ACE2 in the small intestine.[65,66] Thus, the deletion or low expression of ACE2 and mediated transporter may not capture the amino acid essential for proper muscle growth during aging (Figure 2).

7 | CONCLUSION

Fatigue and weakness may stem from changes within myocytes that affect cross-bridge function or Ca2+ activation to changes within the circulation or function of the nervous system. Myocytes' metabolic products of ATP hydrolysis in the cytoplasm, such as inorganic phosphate, protons (H+ or pH), and ADP, have often been considered agents that could disrupt force generation at the sarcomere level. These effects may be due to direct binding to proteins or a more global alteration of cellular energetics (ΔGATP) in the myocyte. The summary of this study shows for the first time that ACE2 protein levels and augmented activity reveal the RAAS-independent mechanism. The current findings should motivate future studies to determine the underlying mechanisms by which ACE2 loss-of-function promotes aging-associated muscle weakness independent of the classic RAAS- or Mas-dependent pathways.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Neeraj K. Fuloria http://orcid.org/0000-0001-8729-3659

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