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REVIEW ARTICLE

DISRUPTED ARGININE–NITRIC OXIDE SIGNALING IN SICKLE CELL DISEASE: MOLECULAR MECHANISMS, PATHOPHYSIOLOGICAL CONSEQUENCES AND EMERGING THERAPEUTIC TARGETS

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Abstract

Sickle cell disease (SCD) is marked by ongoing hemolysis and blood vessel dysfunction, with the arginine–nitric oxide (NO) pathway being crucial to its pathophysiology. This review examines the molecular mechanisms that contribute to the disruption of the arginine–NO axis in SCD, emphasizing how hemolysis-mediated arginase release reduces L-arginine, the precursor for NO production, while cell-free hemoglobin captures bioactive NO. Moreover, increased concentrations of natural NOS inhibitors like asymmetric dimethylarginine (ADMA) and oxidative stress play a role in the uncoupling of nitric oxide synthase (NOS), which further diminishes NO bioavailability. Impaired citrulline–arginine recycling worsens substrate shortage, together resulting in endothelial dysfunction, vasoconstriction, and inflammation. Therapeutic strategies aimed at this pathway, such as arginine and citrulline supplementation, arginase inhibition, antioxidants, and NO donors, are examined, highlighting their ability to restore vascular balance.
Keywords: Nitric oxide, nitrogen metabolism, sickle cell disease, therapeutic strategies, vascular dysfunction.

INTRODUCTION

Sickle cell disease (SCD) is a genetic hemoglobin disorder marked by the existence of abnormal hemoglobin S, which clumps together in low oxygen situations, resulting in red blood cell (RBC) distortion, ongoing hemolysis, and blood vessel blockage. These abnormal characteristics lead to a wide range of clinical issues, such as painful episodes, acute chest syndrome, stroke, and ongoing organ impairment. Even with progress in comprehending the genetic foundations of SCD, the complex molecular processes that lead to vascular problems and inflammation continue to be a focus of ongoing research. At the core of these mechanisms lies the dysregulation of the arginine–nitric oxide (NO) pathway, which is essential for regulating vascular tone and homeostasis[1-3]. Nitric oxide is a gaseous signaling molecule produced from L-arginine by nitric oxide synthase (NOS) enzymes, notably endothelial NOS (eNOS) in the vascular endothelium. NO produces strong vasodilatory, anti-inflammatory, and anti-thrombotic effects, preserving endothelial integrity and inhibiting abnormal vessel constriction. In individuals without health issues, this pathway rigorously regulates blood circulation and restricts vascular damage. In SCD, the availability of NO is significantly diminished, leading to endothelial dysfunction and the prothrombotic condition characteristic of the disease[4-6].

The disturbance of NO balance in SCD arises from several interrelated molecular irregularities. Hemolysis, a characteristic of SCD, causes the release of intracellular substances like arginase-1 and free hemoglobin into the plasma. Arginase-1 facilitates the breakdown of L-arginine into urea and ornithine, reducing the substrate needed for NO synthesis. Simultaneously, free hemoglobin eagerly captures NO, producing inert nitrate and methemoglobin, thus diminishing NO's ability to induce vasodilation. These two processes result in a significant functional deficiency of arginine and a swift reduction in NO availability. Additionally, increased levels of endogenous inhibitors like asymmetric dimethyl-arginine (ADMA) further suppress NOS activity in patients with SCD. Oxidative stress, caused by

repeated ischemia reperfusion injury and ongoing inflammation, facilitates the uncoupling of NOS. In this uncoupled condition, NOS generates reactive oxygen species instead of NO, worsening oxidative harm and impairing endothelial function[7-10].

The downstream effects of arginine–NO pathway dysfunction is significant. Decreased NO signaling promotes vasoconstriction, platelet clumping, leukocyte sticking, and smooth muscle growth, resulting in a vascular environment susceptible to blockage, inflammation, and remodeling. These pathological alterations are associated with numerous serious complications observed in SCD, such as pulmonary hypertension, stroke, and chronic organ ischemia[11,12]. Recent years have seen significant interest in therapeutic strategies that focus on the arginine–NO axis. L-arginine or L-citrulline supplementation seeks to enhance substrate availability, while arginase inhibitors aim to maintain natural arginine levels by blocking its breakdown. Antioxidants and NOS cofactors, including tetrahydrobiopterin (BH_4), are investigated to lessen oxidative stress and reestablish NOS coupling[13,14]. Moreover, inhaled nitric oxide and novel gene-targeted therapies indicate pioneering methods to directly enhance NO bioactivity or address fundamental genetic issues

The primary aim of this review is to comprehensively examine the role of NO and nitrogen metabolism in the pathophysiology of SCD and to explore current and emerging therapeutic strategies targeting these pathways.

An overview of the arginine–nitric oxide pathway

The arginine–nitric oxide (NO) pathway is central to many physiological processes, controlling vascular tone, immune responses, neurotransmission, and cellular signaling. At the heart of it is the amino acid L-arginine, a semi-essential compound that acts as the main substrate for NOS enzymes, which facilitate the transformation of arginine into nitric oxide and L-citrulline. This enzymatic process is fundamental to endothelial wellness and overall vascular balance. In the vascular endothelium, endothelial eNOS is crucial. In response to shear stress or different agonists (such as acetylcholine, bradykinin), eNOS is activated through a calcium-calmodulin–dependent mechanism. With vital cofactors like tetrahydrobiopterin (BH_4), oxygen, and NADPH, eNOS facilitates the oxidation of L-arginine, generating nitric oxide, a gaseous signaling molecule, along with L-citrulline[15,16].

In addition to vasodilation, NO has anti-inflammatory, antithrombotic, and anti-proliferative effects. It prevents platelet adhesion, decreases leukocyte-endothelial interactions, and regulates oxidative stress by opposing reactive oxygen species (ROS). These defensive functions are particularly important in conditions marked by vascular damage and inflammation[17]. Nevertheless, the supply of L-arginine is closely controlled and affected by competing processes. A significant rival is arginase, which breaks down arginine into ornithine and urea, redirecting it from NO synthesis. This competitive interaction is especially significant in pathological states like sickle cell disease, where hemolysis driven release of arginase-1 reduces arginine levels, hindering NO synthesis and facilitating vascular issues[18]. Additionally, there is another regulatory layer from endogenous inhibitors like asymmetric dimethylarginine (ADMA), which competes with L-arginine for NOS binding, further limiting NO production. Additionally, in situations of oxidative stress or lack of cofactors, NOS may become uncoupled, resulting in the production of superoxide rather than NO-thereby increasing vascular harm. The arginine-NO pathway is consequently a delicate, well-regulated system. Any disruption in its components such as arginine availability, NOS function, cofactor integrity, or competing metabolic pathways can shift the balance toward endothelial dysfunction, a key feature of numerous cardiovascular and hemolytic diseases[19].

Mechanisms of arginine–nitric oxide pathway impairment in sickle cell disease

The arginine–nitric oxide pathway, essential for maintaining vascular integrity and regulating the immune system, is significantly altered in SCD, leading to the endothelial dysfunction, vasculopathy, and inflammation characteristic of this hemoglobin-pathy. Nitric oxide synthesis is crucial for physiological functions, yet its dysfunction in SCD arises from a mix of biochemical, oxidative, and inflammatory factors that limit substrate availability, impede enzymatic activity, and promote NO degradation[20]. This disruption primarily involves L-arginine, the precursor substrate for NOS. In people with SCD, hemolysis significantly contributes to the reduction of systemic arginine levels. When red blood cells break apart, they discharge arginase-1 into the plasma. This enzyme quickly converts L-arginine into ornithine and urea, thereby decreasing the arginine accessible for NO production. Increased plasma arginase activity has consistently been linked to reduced vasodilation, heightened pulmonary pressures, and worse clinical outcomes in SCD. Besides substrate depletion, SCD also creates conditions for NO scavenging. Hemoglobin released into the bloodstream during intravascular hemolysis interacts with and deactivates NO in a stoichiometric reaction, resulting in the formation of methemoglobin and nitrate[21,22].

A significant factor in disrupting the arginine–NO pathway is the buildup of natural NOS inhibitors, especially ADMA. In SCD patients, elevated ADMA competes with arginine for binding to NOS, thereby inhibiting NO production. Concurrently, oxidative stress common in SCD due to ongoing inflammation, ischemia reperfusion damage, and ROS production may cause NOS uncoupling. In its uncoupled condition, NOS stops producing NO and instead produces superoxide anions, which interact with any leftover NO to create peroxynitrite, a strong and harmful oxidant. Moreover, citrulline recycling the mechanism by which L-citrulline, a byproduct of NO synthesis, is reverted to L-arginine is similarly impaired in SCD. This recycling relies on the coordinated function of argininosuccinate synthase

and argininosuccinate lyase, enzymes that are frequently downregulated in inflammatory or hypoxic conditions typical in SCD. The inability to convert citrulline back to arginine further restricts NO synthesis and continues vascular dysfunction[23,24].

These interconnected processes arginase mediated substrate depletion, hemoglobin's NO scavenging, ADMA-induced inhibition, oxidative stress related NOS uncoupling, and disrupted citrulline recycling collaborate to establish a condition of nitric oxide resistance in SCD. The resulting impacts are clinically relevant: heightened vascular tone, platelet clumping, leukocyte sticking, and smooth muscle growth all factors that lead to the vaso-occlusive episodes, pulmonary hypertension, and organ impairment observed in this condition[25]. Treatment approaches like arginine supplementation, arginase blockers, citrulline treatment, and NO donors are being studied to reestablish NO equilibrium. Nonetheless, addressing this intricate metabolic dysfunction necessitates a comprehensive strategy focused on the fundamental hemolysis, oxidative stress, and enzymatic dysregulation that hinder the arginine–NO axis in sickle cell disease[26].

A molecular perspective

The pathophysiology of SCD is deeply rooted in molecular disturbances that extend beyond the well known hemoglobin S polymerization. Central among these is the dysregulation of the arginine–nitric oxide pathway a biochemical axis crucial for maintaining vascular tone, endothelial health, and immune balance. A detailed molecular perspective reveals a cascade of interrelated mechanisms that converge to impair NO bioavailability and drive the complex clinical phenotype of SCD[27]. At the core of this dysfunction is arginine metabolism. Under physiological conditions, L-arginine serves as the principal substrate for NOS, which catalyzes the conversion of arginine into NO and L-citrulline. In SCD, however, chronic intravascular hemolysis leads to the release of erythrocyte contents, notably arginase-1, into the plasma. This enzyme competes with NOS by converting arginine into ornithine and urea, thereby depleting circulating and intracellular arginine pools. The consequence is a "functional arginine deficiency" that restricts NO synthesis at the endothelial interface[28].

In parallel, the release of cell free hemoglobin into the bloodstream represents a potent NO scavenger. Free hemoglobin binds NO with high affinity, leading to the formation of inactive nitrate and methemoglobin, and diminishing NO's vasodilatory effects. This mechanism exacerbates vasoconstriction and contributes to the development of pulmonary hyper-tension and vaso-occlusive crises, key complications in SCD[29]. The molecular environment is further destabilized by elevated levels of ADMA, an endogenous NOS inhibitor. ADMA interferes with NOS activity, reducing NO output and promoting endothelial dysfunction. Compounding this, oxidative stress, a hallmark of SCD due to recurrent ischemia-reperfusion injury and chronic inflammation, leads to NOS uncoupling. In this uncoupled state, NOS generates superoxide anions instead of NO, which not only fails to fulfill NO's vasoprotective functions but also reacts with residual NO to form peroxynitrite a highly reactive and damaging oxidant[30]. Moreover, the citrulline–arginine recycling pathway, mediated by argininosuccinate synthase (ASS) and arginino-succinate lyase (ASL), becomes compromised in SCD due to oxidative and inflammatory signaling. This disruption impairs the regeneration of arginine from citrulline, weakening intracellular arginine replenish-ment and further suppressing NO production in endothelial and immune cells[31].

The downstream effects of these molecular events are far reaching. Impaired NO signaling contributes to leukocyte adhesion, platelet activation, smooth muscle proliferation, and vascular remodeling, all of which foster a pro-inflammatory and pro-thrombotic milieu. This biochemical cascade links molecular dysfunction to clinical manifestations such as stroke, acute chest syndrome, priapism, and chronic organ damage.[32] Importantly, this molecular understanding has guided the development of targeted therapies. Agents such as L-arginine, L-citrulline, and arginase inhibitors aim to replenish substrate availability and reduce enzymatic competition. Concurrently, antioxidants and NOS cofactors such as tetrahydrobiopterin (BH_4) are being explored to restore NOS coupling and enhance NO production. Inhaled NO and gene based therapies further reflect the shift toward precision medicine rooted in molecular insight[33].

Pathophysiological role of nitric oxide in sickle cell disease

NO plays a central role in maintaining vascular integrity, modulating inflammation, and preventing thrombotic complications. In SCD, the dysregulation of NO bioavailability is a major contributor to disease pathology, exacerbating vascular dysfunction, oxidative stress, and inflammatory processes[19].

1. NO bioavailability and hemolysis

In SCD, chronic hemolysis releases large amounts of free hemoglobin into the plasma. This cell-free hemoglobin avidly scavenges NO, converting it to inactive nitrate and reducing its availability. Additionally, hemolysis releases arginase, an enzyme that depletes L-arginine, the substrate required for NO synthesis. The combined effects of NO scavenging and L-arginine depletion create a state of NO deficiency, impairing vascular function and promoting disease complications[20].

2. Endothelial dysfunction

NO is essential for maintaining endothelial homeo-stasis by promoting vasodilation and inhibiting endothelial activation. In SCD, reduced NO levels lead to endothelial dysfunction, characterized by the upregulation of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin. These molecules enhance the adhesion of sickled erythrocytes and leukocytes to the vascular endothelium, initiating vaso-occlusion and microvascular ischemia. The dysfunctional endothelium also becomes a source of pro-inflamm-atory cytokines, amplifying vascular inflammation and further impairing blood flow[21].

3. Vaso-occlusion and ischemia

The interaction between sickled erythrocytes, leukocytes, and the endothelium is central to VOCs. NO deficiency exacerbates these interactions by promoting vasoconstriction, increasing vascular resistance, and reducing blood flow. The resultant ischemia contributes to severe pain episodes, tissue damage, and organ dysfunction. The role of NO in preventing such events underscores its importance in the pathophysiology of SCD[22].

4. Oxidative stress and reactive oxygen species

In SCD, the chronic inflammatory state and hemolysis generate ROS, which further deplete NO and impair its signaling. NO reacts with superoxide, forming peroxynitrite, a reactive nitrogen species that damages cellular components and exacerbates oxidative stress. This creates a vicious cycle where oxidative stress and NO deficiency perpetuate endothelial damage and vascular dysfunction[23].

5. Pulmonary hypertension and cardiovascular complications

Pulmonary hypertension (PH) is a severe complication of SCD associated with high mortality rates. NO deficiency contributes to PH by promoting vasoconstriction, vascular remodeling, and increased pulmonary arterial pressure. Chronic NO depletion also predisposes patients to cardiovascular complications, such as stroke and heart failure, by impairing vascular elasticity and increasing systemic vascular resistance[24].

6. Immune dysregulation

NO plays an immunomodulatory role by regulating leukocyte activity and suppressing excessive inflammation. In SCD, reduced NO levels impair immune regulation, leading to heightened leukocyte activation and increased production of pro-inflammatory cytokines. This inflammatory milieu exacerbates vascular damage and promotes VOCs, further complicating the disease course.[25]

7. Renal and neurological implications

The kidneys and brain are particularly vulnerable to the effects of NO deficiency in SCD. In the renal vasculature, reduced NO bioavailability leads to vasoconstriction, glomerular injury, and progression to chronic kidney disease (CKD). Similarly, in the cerebral vasculature, NO dysregulation contributes to ischemic strokes, a common complication in pediatric SCD patients[26].

Clinical implications of NO deficiency in sickle cell disease

NO deficiency in SCD has profound clinical consequences that underpin many of the disease's most debilitating complications. NO's critical role in maintaining vascular homeostasis means that its depletion contributes directly to the widespread endothelial dysfunction, vasoconstriction, and inflammation observed in SCD patients. These pathophysiological changes translate into a clinical phenotype marked by recurrent vaso-occlusive episodes, progressive organ damage, and increased morbidity[34,35]. One of the most prominent clinical manifestations linked to NO deficiency is vaso-occlusive crisis (VOC), characterized by episodes of severe pain due to microvascular occlusion and ischemia. NO deficiency exacerbates vasoconstriction by impairing endothelial relaxation, reducing blood flow through already compromised microcirculation. This creates a vicious cycle where ischemia and reperfusion injury further elevate oxidative stress, fueling more NO depletion and endothelial injury. As a result, patients experience frequent painful crises, which significantly impact quality of life and increase healthcare utilization[36,37]. Beyond VOC, NO deficiency is implicated in the development of pulmonary hypertension (PH), a severe and life-threatening complication of SCD. Reduced NO bioavailability impairs pulmonary vasodilation, leading to increased vascular resistance and right ventricular strain. PH in SCD patients is associated with increased mortality, emphasizing the critical need for therapeutic strategies that restore NO signaling to improve pulmonary vascular function[38,39]. Another critical clinical consequence of impaired NO metabolism is end-organ damage. The kidneys, brain, and heart are particularly vulnerable to ischemia driven by microvascular dysfunction. NO deficiency contributes to a prothrombotic state, promoting platelet aggregation and leukocyte adhesion, which can precipitate strokes and chronic kidney disease. In the brain, endothelial dysfunction compromises cerebral blood flow, increasing the risk of silent cerebral infarcts and overt stroke, particularly in pediatric populations[40]. Chronic NO depletion also affects immune regulation and inflammation, further complicating disease progression. NO possesses anti-inflammatory properties; its deficiency facilitates leukocyte activation and endothelial adhesion molecule expression, amplifying systemic inflammation. This heightened inflammatory state exacerbates vascular injury and contributes to the chronic pain and fatigue experienced by many SCD patients[41]. Importantly, the clinical implications of NO deficiency extend to therapeutic considerations. Conventional treatments, such as hydroxyurea, indirectly modulate NO pathways by reducing hemolysis and inflammation. Meanwhile, emerging therapies directly targeting NO bioavailability-through supplementation with arginine or citrulline, arginase inhibitors, and inhaled NO aim to correct the underlying biochemical defects. Understanding the clinical ramifications of NO deficiency is vital for optimizing these interventions and tailoring treatment to individual patient needs[42].

Therapeutic strategies targeting the arginine–NO axis in sickle cell disease

The disruption of the arginine–nitric oxide axis in SCD has emerged as a pivotal mechanism driving vascular dysfunction, inflammation, and end-organ damage. As research uncovers the biochemical underpinnings of this impaired pathway—marked by reduced arginine availability, NO scavenging, and endothelial injury several therapeutic strategies have been developed or proposed to restore NO bio-availability and reestablish vascular homeostasis. These interventions aim to correct substrate deficiencies, modulate enzymatic activity, and prevent

NO inactivation, offering new hope in the management of SCD related complications[43,44]. One of the most extensively studied approaches is L-arginine supplementation. By replenishing systemic arginine levels, this strategy seeks to overcome substrate depletion caused by hemolysis induced arginase release. Clinical studies have shown that oral or intravenous L-arginine can improve endothelial function, reduce pulmonary pressures, and potentially alleviate the severity of vaso-occlusive crises. However, the effectiveness of arginine therapy is influenced by concurrent arginase activity and the presence of endogenous inhibitors such as ADMA, which may limit its clinical impact[45,46].

Recognizing the competitive consumption of arginine by arginase, arginase inhibitors have been developed as a complementary or alternative therapeutic strategy. These agents block the enzymatic conversion of arginine to ornithine and urea, preserving arginine for NO synthesis. Preclinical models of SCD have demonstrated that arginase inhibition enhances NO production, improves vascular reactivity, and reduces inflammation. Early phase clinical trials are underway to evaluate their safety and efficacy in human subjects[47,48]. Another promising intervention is L-citrulline supplementation, which leverages the citrulline–arginine recycling pathway. Unlike arginine, citrulline is not a substrate for arginase and is more efficiently taken up by cells. Once inside, citrulline is converted to arginine by argininosuccinate synthase and lyase, providing a sustained intracellular source of arginine for NOS-mediated NO production. This strategy not only circumvents extracellular arginase activity but also enhances the local availability of NO where it is most needed within the vascular endothelium[49]. Inhaled nitric oxide (iNO) has also been explored for acute vaso-occlusive episodes. As a direct NO donor, inhaled NO offers the potential to rapidly dilate constricted blood vessels and mitigate pain. While some studies have shown short term hemodynamic benefits, larger clinical trials have yielded mixed results, highlighting the challenges of delivering NO effectively in a systemically deficient and inflamed vascular environment[50].

Beyond these direct approaches, antioxidant therapies such as N-acetylcysteine and tetrahydrobiopterin (BH_4) aim to prevent NOS uncoupling and reduce the oxidative inactivation of NO. These agents stabilize NOS function and scavenge reactive oxygen species, indirectly enhancing NO bioavailability and endothelial protection. Furthermore, statins, traditionnally used for lipid management, have shown pleiotropic effects, including upregulation of endothelial NOS and improvement of endothelial function in SCD models[51]. By addressing the root cause of NO pathway deregulation, these approaches represent a paradigm shift toward curative strategies in SCD[52].

Emerging therapeutic targets

The increasing recognition of nitric oxide (NO) deficiency as a central contributor to sickle cell disease (SCD) pathology has catalyzed the development of targeted therapies aimed at restoring NO bioavailability and improving vascular function. Therapeutic interventions now extend beyond symptom management to focus on correcting the molecular imbalances driving disease progression. These emerging strategies aim to address the specific disruptions in the arginine–NO pathway, offering hope for more effective and personalized treatments.[53]

One of the most direct approaches involves arginine supplementation, intended to replenish the substrate necessary for NO synthesis. Clinical studies have demonstrated that intravenous or oral L-arginine can improve endothelial function, reduce pulmonary pressures, and shorten the duration of vaso-occlusive crises (VOC). However, systemic arginase activity remains a significant barrier, rapidly metabolizing administered arginine and limiting its therapeutic impact. To overcome this, researchers are increasingly exploring arginase inhibitors as a complementary or alternative strategy. By blocking the activity of arginase particularly arginase-1 released during hemolysis these agents preserve endogenous arginine levels, promoting sustained NO production[54].

In addition to arginine based therapies, L-citrulline supplementation offers another promising route. Citrulline, a precursor to arginine in the urea cycle, bypasses arginase degradation and is efficiently converted into arginine intracellularly. This not only supports NO generation but may also have a longer lasting effect on plasma arginine levels. Combined citrulline and arginine therapy is currently being investigated to determine whether it provides synergistic benefits in restoring vascular NO signaling[55]. Another important area of exploration involves targeting oxidative stress, a key factor in nitric oxide synthase (NOS) uncoupling and vascular injury. Agents such as N-acetylcysteine (NAC) and vitamin C have been evaluated for their ability to scavenge reactive oxygen species and stabilize NOS function. Additionally, supplementation with tetrahydrobiopterin (BH_4), an essential cofactor for NOS activity, has shown potential in reducing NOS uncoupling and enhancing NO production. These antioxidant based approaches aim to improve NO bioefficacy by correcting the redox imbalances that impair enzyme function[56].

Inhaled nitric oxide (iNO) represents a more direct intervention, delivering exogenous NO to the pulmonary vasculature to alleviate hypoxia and pulmonary hypertension. While iNO has demonstrated benefits in acute settings, particularly during VOC or acute chest syndrome, its utility as a long term therapy remains under investigation. Advances in NO delivery systems, including sustained release formulations and NO donors with longer half lives, may expand its role in chronic SCD management[57].

CONCLUSIONS

The disruption of the arginine–nitric oxide pathway in sickle cell disease serves as a key mechanism connecting hemolysis, vascular issues, and organ damage. Persistent arginine scarcity, increased arginase activity, nitric oxide depletion by free

hemoglobin, and oxidative stress come together to disturb endothelial balance and sustain the pathophysiological features of SCD, such as vaso-occlusion, inflammation, and pulmonary hypertension. Grasping these molecular disruptions not only clarifies disease mechanisms but also paves the way for targeted therapeutic approaches focused on reinstating NO bioavailability and vascular function.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey. **Ezeala CC:** formal analysis, critical review. Final manuscript was checked and approved by the both authors.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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