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Review article

Bilirubin in metabolic syndrome and associated inflammatory diseases: New perspectives

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ABSTRACT

Diabetes mellitus is one of the major global health issues, which is closely related to metabolic dysfunction and the chronic inflammatory diseases. Multiple studies have demonstrated that serum bilirubin is negatively correlated with metabolic syndrome and associated inflammatory diseases, including atherosclerosis, hypertension, etc. However, the roles of bilirubin in metabolic syndrome and associated inflammatory diseases still remain unclear. Here, we explain the role of bilirubin in metabolic syndrome and chronic inflammatory diseases and its therapeutic potential. Understanding the role of bilirubin activities in diabetes may serve as a therapeutic target for the treatment of chronic inflammatory diseases in diabetic patients.

1. Introduction

Diabetes mellitus is one of the major epidemics of the 21st century [1]. 10–15% of diabetic individuals have type 1 diabetes mellitus (T1DM) characterized by hyperglycemia caused by insulin deficiency due to pancreatic β-cell loss [2]. Most diabetic patients have type 2 diabetes mellitus (T2DM). Individuals with T2DM have a higher risk of developing both microvascular and macrovascular complications, owing to hyperglycemia and individual components of metabolic syndrome (MetS) [3], which is a cluster of abnormalities, such as central adiposity, hypertension, insulin resistance (IR), and dyslipidemias [4].

Multiple studies have demonstrated an inverse association of plasma bilirubin levels, a tetrapyrrole compound (Fig. 1) produced by the heme metabolic pathway, with diabetes and its complications [5,6]. Bilirubin used to be considered as toxic waste product of heme catabolism. However, recent investigations have shown that bilirubin, a tetrapyrrole pigment found in various isoforms in the blood, namely, conjugated with glucuronic acid (direct bilirubin), unconjugated and bound to serum albumin (indirect bilirubin) and unconjugated-unbound (free bilirubin), is highly related to chronic inflammatory diseases development in MetS, including diabetes [7]. Nonetheless, the role of bilirubin in chronic inflammatory diseases and diabetes still remains unclear.

Here, we explain the role of bilirubin in MetS and chronic inflammatory diseases and its herapeutic potential. Understanding the role of bilirubin activities in MetS may serve as a therapeutic target for the treatment of chronic inflammatory diseases in diabetic patients (Table 1).

2. Regulation of bilirubin

The anti-oxidative, anti-inflammatory and anti-adipogenic properties of bilirubin make bilirubin a potential therapeutic target for inflammatory diseases associated with MetS. Strategies to augment bilirubin may yield therapeutic effects for the treatment of MetS-associated inflammatory diseases. Studies have shown that bilirubin can be degraded to form bilirubin oxidation end product (BOX) with propentdyopents as intermediates, which may reduce the effect of bilirubin [8]. The BOX and its isoforms Z-BOX A, B and C appear in serum of healthy individuals, nonetheless, their effects or functions are widely unknown [8,9]. It has been shown that heme oxygenase (HO)-1 and HO-2 mediate bilirubin stability and prevent inflammatory diseases [10,11]. In addition, biliverdin, a metabolite from the catalytic degradation of heme by the isoforms of HO, can be converted to bilirubin which binds to nuclear factor-erythroid 2 (NF-E2) p45-related factor 2, a cytoprotective transcription factor, to mediate cellular protection [10]. In addition, bilirubin administered intravenously with albumin has been found to be stable in islet transplantation for the treatment of

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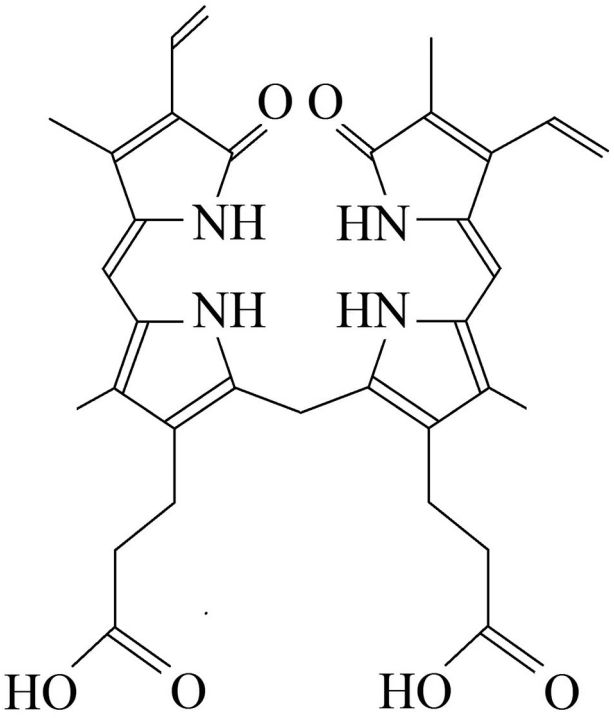

Fig. 1. Bilirubin. Chemical formula.

diabetes [11]. Altogether, bilirubin has been shown to be clinically beneficial in the treatment of inflammatory diseases. The maintenance of its stability and effective production may provide a strategy for the prevention of systemic inflammation and its complications.

3. Bilirubin in diagnostics

Multiple studies examined associations of plasma bilirubin levels in health-related problems, especially hepatocellular diseases, by measuring total plasma bilirubin (unconjugated) and conjugated or direct bilirubin (conjugated bilirubin + delta bilirubin). Recently, bilirubin binding capacity has emerged as a diagnostic technique for diabetes, atherosclerosis, hypertension, peri/endocarditis, etc. [12]. T1DM patients with diabetic retinopathy presented with lower serum total bilirubin (12 U/L) and higher systolic blood pressure (130 mmHg) [13]. A study to investigate the correlation between serum bilirubin and T2DM indicated that lower level of serum bilirubin is inversely correlated with T2DM with the median (interquartile range) of serum total bilirubin, direct bilirubin and indirect bilirubin 13.3 μmol/L, 3.7 μmol/L and 9.5 μmol/L, respectively. It was observed that the mean duration for diagnosis was 4 years which indicated high correlation between the declined level of bilirubin and diabetes incidence [14]. In addition, serum total bilirubin predicted the development of subclinical carotid atherosclerosis in patients with prehypertension and prediabetes by indicating an inverse relationship with carotid intima media thickness (cIMT) and higher systolic blood pressure [15]. Lower bilirubin increased cIMT, blood pressure and blood glucose level with higher inflammatory factors such as high sensitive C-reactive protein expression [15,16]. It has been confirmed that lower serum total bilirubin was an independent predicting factor for atherosclerosis, especially in dyslipidemia patients [17]. In addition, studies have shown that a lower total serum bilirubin and unconjugated bilirubin of 3 mg/dl were associated with a higher systolic blood pressure of 62 mmHg in neonates. Additionally, < 3 mg/dl bilirubin was associated with higher risks of hypertension among preterm infants [69]. Data from the National Health and Nutrition Examination Surveys (NHANES) indicates that systolic blood pressure decreased up to −2.5 mmHg and the prevalence of hypertension was up to 25% lower in patients with bilirubin more than 1.0 mg/dl compared with those with 0.1–0.4 mg/dl [19]. There is an inverse relationship between total serum bilirubin levels and the development of left ventricle hypertrophy (LVH) [20]. Moreover, lower levels of bilirubin highly correlated with the development of pericarditis which can progress to heart failure [20,71]. Interestingly, higher levels of bilirubin have been shown to be more detrimental to cardiac function in postoperative endocarditis. Reports show that higher levels of bilirubin increased long term mortality in patients who underwent infective endocarditis surgery [22]. Collectively, this data shows that lower level of bilirubin is an independent predictive factor for diabetes and associated inflammatory diseases while the opposite is true for endocarditis, suggesting that bilirubin can be a sensitive marker for the diagnosis of atherosclerosis, hypertension, pericarditis and endocarditis.

4. The role of bilirubin in MetS

A meta-analysis has shown that bilirubin level is inversely correlated with hyperglycemia, dyslipidemia, and obesity [5]. Increased total bilirubin was associated with 26% reduction in MetS [23].

It has been shown that bilirubin increases insulin sensitivity and glucose uptake reducing glucose accumulation and the incidence of hyperglycemia [24], revealing that declined bilirubin levels reduce glucose uptake and increase diabetes development. It has been confirmed that reduced bilirubin preceeded the development of MetS [25,26]. Hypobilirubinemia-associated hyperglycemia promoted oxidative stress (OS) [11], while biliverdin administration down-regulated OS enzymes such as NAD(P)H oxidase (NOX) inhibiting OS in diabetic rodents [27]. Biliverdin administration increased insulin sensitivity and decreased adipocytokine expression and systemic inflammation in diet-induced obese (DIO) mice [28]. Biliverdin reductase A knockout in murine adipocytes induces causes increased expansion of visceral fat adipocyte size and inflammation, and reduces insulin signaling and mitochondria number [29].

Bilirubin plays an important role in lipid metabolism. Familial hypercholesterolemia exhibits lower bilirubin levels with excessive increase of systemic inflammation which progresses to atherosclerosis [17], and hypertension [69].

Some roles of bilirubin in MetS can be explained by its effects on PPARs. Their modulation plays a pivotal role in MetS and induces the release of pro-inflammatory cytokines, which account for the symptoms and signs of this syndrome [30] [31]. They could be considered the crossroads of obesity, diabetes, and inflammation [31]. PPARα and PPARβ/δ mainly enable energy combustion, while PPARγ enhances adipogenesis [30].

Bilirubin reduces dyslipidemia by increasing the expression of lipid metabolism transcription factors sterol regulatory element-binding protein-1 (SREBP-1) and PPARγ levels in DIO mice [24]. Bilirubin functions as a signaling molecule (Fig. 2). It binds directly to PPARα, which increases transcriptional activity of carnitine palmitoyltransferase 1 (CPT1) and the fibroblast growth factor 21 (FGF21). This mechanism mediates the protection from adiposity [32]. RNA sequencing revealed that biliverdin-induced transcriptome responses in human HepG2 hepatocytes are predominantly PPARα-dependent (~95%). This transcriptome mediates pathways for oxidation-reduction processes, mitochondrial function, response to nutrients, fatty acid oxidation, and lipid homeostasis [33]. Bilirubin functions as a molecular switch for PPARα. It recruits and dissociates specific coregulators in white adipose tissue, driving the expression of PPARα target genes such as uncoupling protein 1 (Ucp1) and adrenoceptor β 3 (Adrb3). It is a selective ligand for PPARα and does not affect the activities of PPARγ or PPARδ [34].

Obesity reveals combined effects of hyperglycemia and dyslipidemia. Bilirubin prevents obesity by inhibiting lipid accumulation via interacting with PPARα. The treatment of mice with fenofibrate or bilirubin reduces glucose and obesity in mice [32] suggesting that

Table 1
Biomarkers associated with bilirubin. The table focuses on the biomarkers that are also associated with diabetes and related health problems.

Biomarkers	Condition associated with the biomarker	Association with bilirubin
CRP	Chronic vascular inflammation	Inverse relationship among apparently healthy Korean adults [77] Inverse relationship irrespective of the presence of MetS or T2DM [78] Inverse relationship in a large cross-sectional study of middle-aged and elderly Japanese men and women [79]
SAA	Inflammation	Inverse relationship in the subjects without MetS [78] Lower SAA concentrations in GS subjects [80]
IL-6	Inflammation	Lower IL-6 concentrations in GS subjects [80]
GlycA	Systemic inflammation and CVD risk, strongly correlated with CRP	Elevated in MetS coinciding with lower bilirubin levels [81]
Hemoglobin A1C	Hyperglycemia	Inverse relationship in apparently healthy Japanese men and women [82], in T2DM patients [83], in pediatric patients with T1DM [84] and in a large cross-sectional study of middle-aged and elderly Japanese men and women [79]
γ-Glutamyltransferase	Oxidative stress	The simultaneous presence of high total bilirubin and low γ-glutamyltransferase levels may be associated with a lower incidence of MetS [85]
Coronary artery calcium score (CACS)	Preclinical atherosclerosis	Inverse relationship [86]
IGF-1	Decreased in several pathological conditions, including uncontrolled diabetes	Serum bilirubin levels are correlated with circulating IGF-1 levels [87]
Blood total white blood cell count	Inflammation	Higher serum total bilirubin concentrations within the reference range are associated with lower blood total white blood cell count in both adult men and women [88]
Artery intima media thickness	Subclinical atherosclerosis	Relates negatively to bilirubin in subjects without clinically manifested CVD [56]
Neutrophil/lymphocyte ratio	A risk factor for atherosclerosis	Inverse relationship in older men with “severe” obstructive sleep apnea hypopnea syndrome [89]

Abbreviations: CRP: C-reactive protein; CVD: cardiovascular disease; GS: Gilbert's syndrome; IGF-1: insulin-like growth factor 1; IL-6: interleukin-6; MetS: metabolic syndrome; SAA: serum amyloid A.

bilirubin plays a crucial role in the regulation of metabolism. It is obvious that bilirubin could become useful for preventing MetS and its complications.

5. Bilirubin in cellular function

5.1. Endothelial cells (ECs)

The veno-vascular inner lining regulates clotting, thrombosis and homeostasis. Impairment of EC function leads to the development of excessive adhesion process, atherosclerosis, hypertension, etc. Bilirubin prevents these vascular abnormalities by protecting EC function [35]. Reports show that intracellular bilirubin modulates extracellular bilirubin uptake or elevates HO-1, a cellular enzyme related to endogenous bilirubin synthesis, to reduce ectopic OS and increase EC function [35]. Physiologically, HO-1-derived bilirubin acts as an efficient scavenger of reactive oxygen and nitrogen species (RONS) to confer EC protection via the activation of GTP-cyclohydrolase, a cytoprotective protein [36,37]. HO-1 terminates the reactive oxygen species (ROS)-NF-E2-related factor-2 (Nrf2)-ROS-Nrf2 pathway during ammonia intoxication from metabolism which provides adequate cytoprotection and promotes EC survival [38]. In addition, HO-1 abrogates ROS-Nrf2 signaling induced by cytotoxicity of protease inhibitors (PIs), antiretroviral drugs, reducing endothelial adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) which decline monocyte/macrophage adhesion and protect vascular function in HIV patients [39]. Additionally, treatment with biliverdin inhibits ROS-Nrf2 signaling induced by hypochlorous acid (HOCl), a unique oxidant produced by the enzyme myeloperoxidase that promotes EC dysfunction and death in atherosclerosis, in human

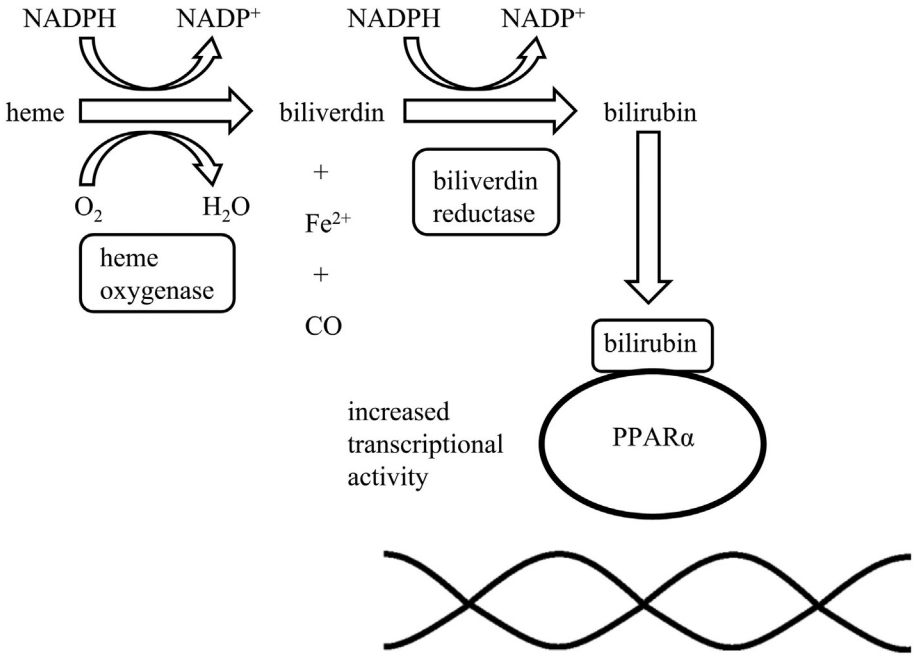

Fig. 2. The heme metabolic pathway and bilirubin binding to PPARα. Heme oxygenase catabolizes free heme into biliverdin, carbon monoxide (CO) and Fe^{2+}. Biliverdin is transformed into bilirubin by biliverdin reductase. Bilirubin binds directly to PPARα, which increases transcriptional activity of genes involved in lipid metabolism. This mechanism explains the role of bilirubin in reducing obesity.

ECs [40]. The data indicate that targeting the elevation of bilirubin may prevent EC dysfunction and inflammatory diseases in MetS individuals.

5.2. Vascular smooth muscle cells (VSMCs)

VSMCs form the underlining layer of ECs which regulate vascular tone by relaxation and contraction. Ectopic proliferation via hyperproliferative or inflammative signaling leads to increased IMT and contributes to the development of atherosclerosis [41]. VSMCs exhibiting impaired contraction due to reduced Ca^{2+} were revived as evidenced by increased uptake of $45Ca^{2+}$ and appropritate contraction upon treatment with bilirubin [42]. Bilirubin prevented hyperproliferation of VSMCs at G1 phase via retinoblastoma tumor suppressor protein phosphorylation and mitogen-activated protein kinase pathways in vitro and lessened balloon injury-induced neointima formation in hyperbilirubinemic Gunn rats [41]. There is a confirmation that bilirubin favors growth arrest which was achieved via interaction with the tRaf/ERK/MAPK pathway, cyclin D1 and Raf content, altered retinoblastoma protein profile of hypophosphorylation, calcium influx, and YY1 proteolysis in human coronary VSMCs [43]. In addition, bilirubin increases the physiological anti-inflammatory function of aryl hydrocarbon receptor (AHR) which reduces OS, generation of oxidized LDL, VSMC foam cell formation, and atherosclerosis [44]. Bilirubin reduced inflammatory response in pigs receiving bilirubin-coated stents or bilirubin/EVL-coated stents [45]. Additionally, HO-1 inhibited heme-induced VSMC concentration-dependent migration and proliferation via abrogating ROS derived from NADPH oxidase (NADPHox) activity or MAPK-NF-κB signaling [46]. However, angiotensin II (Ang II) has been found to effectively inhibit HO-1 which promoted hypertension in rats [47]. Collectively, this data demonstrate that upregulation of bilirubin can serve as a therapeutic target to prevent inflammation, atherosclerosis and hypertension.

5.3. Macrophages

Immune cells play an important role in the regulation of inflammatory diseases. The modulation of immune cells is a vital step to prevent inflammation and its associated diseases. Bilirubin prevents inflammatory mediators emanating from peritoneal macrophages activated by alum causing systemic inflammation in mice. It acts on inflammation through inactivation of Nlrp3 inflammasome [48]. Experiments on lipopolysaccharide-primed murine peritoneal macrophages demonstrated that physiological concentrations of bilirubin inhibit the NF-κB pathway [49]. Elevated bilirubin degrades ATP-binding cassette transporter A1 (ABCA1), a transmembrane cholesterol transporter involved in apolipoprotein A1-mediated cholesterol efflux, in macrophages extracted from Gilbert syndrome patients and Gunn rats [50], reducing foam cell forming potential, systemic inflammation and atherosclerosis or hypertension. In addition, bilirubin declines macrophage secretion of inflammatory mediators, including systemic CCL2, CXCL2, CXCL8, monocyte chemotactic protein-1, and macrophage inflammatory protein 2α levels, reducing pulmonary injury [51], and the risk of pulmonary hypertension.

6. Bilirubin in inflammatory diseases

6.1. Atherosclerosis

Atherosclerosis is the arterial narrowing due to increased inflammation of endothelium, immune cell recruitment and fatty acid and fibrotic protein deposition. MetS plays the central role in atherosclerosis. It has been reported that atherosclerosis accounts for 70% of the morbidity associated with T2DM [52]. A meta-analysis have shown that higher serum total bilirubin significantly improves the prognosis of arterosclerosis [53], and all-cause death in diabetic patients [54]. Prediabetic individuals with lower total bilirubin levels had an increased cMIT and subclinical atherosclerosis [55,56]. Even elderly T2DM people with mildly lower serum bilirubin levels had an increased prevalence of carotid atherosclerosis [57]. Direct and indirect bilirubin levels reduced inflammation, atherosclerosis and arterial calcification in diabetic individuals [58–60]. It has been indicated that bilirubin levels have been constantly lower in MetS, including in individuals with atherogenic dyslipidemia, which allowed the generation of ROS and plasma gamma-glutamyltransferase (GGT) activities and OS [61]. OS is effective in the pathogenesis of atherosclerosis. A study examining the relationship between elevated bilirubin levels, subclinical atherosclerosis and OS in Gilbert syndrome demonstrated that total antioxidant status level is positively correlated with total bilirubin, direct bilirubin, and indirect bilirubin levels [62]. Lowered serum bilirubin levels are associated with oxidant damage of human atherosclerotic plaques and the severity of atherosclerosis. There is an inverse and significant correlation between the levels of serum bilirubin and those of lipoperoxides of human atherosclerotic plaques [63]. Moreover, mild hyperbilirubinemia reduces obesity in T2DM patients [64,65], indicating that enhancing bilirubin production may reduce systemic inflammation.

6.2. Hypertension

Hypertension is the increased arterial pressure due to progressive narrowing of the lumen, calcification and hardening of the arterial walls. The coexistence of MetS and lower bilirubin has been found to be contributing to the development of hypertension. For instance, an observational study indicates that T2DM patients with hypertension show lower serum total bilirubin levels [66]. Moreover, lower serum bilirubin promotes the development of hypertension in patients with both diabetes and dyslipedimia while patients with high serum total bilirubin had normalized blood pressure and sugar and lipid levels [67]. Dyslipidemic patients on lipid lowering drugs showed higher serum bilirubin and reduced serum lipids and glucose in comparison with untreated patients and presented with controlled blood pressure [67,68]. It has been shown that bilirubin prevents hypertension by terminating glucose and lipid accumulation and/or obesity development [32]. However, reports demonstrate that hypertension can occur in individuals with lower serum total bilirubin with/without diabetes, dyslipidemia and obesity. Studies have shown hypertension in preterm and term infants was associated with lower bilirubin but occurred despite the existence of MetS [69]. Here, it is obvious that upregulating bilirubin will be an essential step for the prevention of hypertension in both MetS and patients with normal metabolic function, suggesting that the elevation of bilirubin may serve as a therapeutic target for the treatment of hypertension.

6.3. Myocarditis

Inflammation of the myocardium can progress to hypertrophic cardiomyopathy and heart failure. It is interesting to note that while bilirubin act as anti-inflammatory in atherosclerosis and hypertension, it is highly detrimental in myocarditis. Patients with infective endocarditis caused by Staphylococcus species with prolonged bacteremia ≥ 6 days had elevated bilirubin > 1.5 mg/dL as a strong predictor for mortality [70]. In addition, higher bilirubin increased mortality in patients who underwent pericardectomy for constrictive pericarditis [71]. It was observed that pericardectomy patients had higher levels of inflammatory mediators such as creatinine which increased the mortality rate of the patient [72,73]. However, it is important to note that myocarditis patients who had higher bilirubin had underlying causes such as end-stage liver diseases, cirrhosis and autoimmune chronic active hepatitis [74]. In addition, prolonged bacteremia is an independent factor for hemolysis which increases bilirubin levels and elevates its toxicity [75,76]. Therefore, it is possible that bilirubin toxicity arises from the excessive secretion from abnormal liver or

bacteremia, suggesting that treating the underlying cause may rescue bilirubin anti-inflammatory and anti-toxicity function which may lead to the prevention of inflammatory diseases.

7. Conclusion

Serum bilirubin is negatively correlated with MetS and associated inflammatory diseases. Here we explained anti-oxidative, anti-inflammatory and anti-adipogenic roles of bilirubin in these diseases. It has been clarified that bilirubin provides optimal EC and VSMC protection and reduces immune cell activation which declines systemic inflammation. In addition, it is obvious that bilirubin declines the development of atherosclerosis and hypertension in both human and animals. Bilirubin may serve as a therapeutic target for the treatment of chronic inflammatory diseases in diabetic patients. However, the results of bilirubin research need to be translated into clinical practice.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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