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Enhanced endocytosis elevated virulence and severity of SARS-CoV-2 due to hyperglycemia in type 2 diabetic patients

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ABSTRACT

Diabetes mellitus is a metabolic disease that causes hyperglycemia. In COVID-19 patients the severity of the disease depends on myriad factors but diabetes mellitus is the most important comorbidity. The current review was conducted to investigate the virulence of SARS-CoV-2 and disease severity of COVID-19 in type 2 diabetes mellitus patients and relevant treatment. The literature published in PubMed, Scopus, Web of Science, and Google Scholar was reviewed up to September 2021. The keywords including SARS-CoV-2, type 2 diabetes mellitus in COVID-19, hyperglycemia in COVID-19, opportunistic infections in type 2 diabetes mellitus and COVID-19 were used in different combinations. Hyperglycemic individuals over-express ACE-2 receptors in the lungs thus increasing the SARS-CoV-2 susceptibility and replication. Although dipeptidyl peptidase-4 plays an important role in glucose homeostasis, additionally it also stimulates the production of proinflammatory cytokines such as IL-6 and TNF-α creating a cytokine storm. Cytokine storm might be responsible for respiratory insufficiency in severe COVID-19 patients. Type 2 diabetes mellitus is associated with immunosuppression and the patients are prone to get many opportunistic infections. Type 2 diabetes mellitus patients with severe COVID-19 have lymphopenia. Moreover, in type 2 diabetes mellitus patients the neutrophils exhibit decreased chemotaxis, hydrogen peroxide production, and phagocytosis. Reduction in lymphocyte count and defective neutrophil capacity renders them with COVID-19 susceptible to opportunistic bacterial and fungal infections increasing the mortality rate. The opportunistic bacterial infections in COVID-19 patients were due to *Staphylococcus aureus*, *Streptococcus* pneumonia, and coagulase-negative Staphylococci, *E. coli*, *Pseudomonas aeruginosa*, and *Klebsiella* sp. In COVID-19 patients with type 2 diabetes mellitus, mucormycosis was found to be the most common fungal infection with a higher predilection to males. Hyperglycemia in COVID-19 patients with type 2 diabetes mellitus enhances the SARS-CoV-2 replication with an adverse outcome. A strong correlation exists between the poor prognosis of COVID-19 and type 2 diabetes mellitus. Proper glycemic control in COVID-19 patients with diabetes mellitus might lessen the severity of the disease.

1. Introduction

Coronaviruses are diverse, spherical and enveloped RNA viruses with 80–120 nm in size. These viruses are associated with different types of clinical syndromes like severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and coronavirus disease – 2019 (COVID-19). Coronaviruses are known to cause diseases in both human as well as in animals (Li et al., 2020). The etiological agent of COVID-19 was identified as SARS-CoV-2, first reported from Wuhan, China, on 31 December 2019. The World Health Organization (WHO) declared COVID-19 as a pandemic on March 11, 2020 (Kannan et al., 2020).

Type 2 diabetes mellitus (T2DM) is a metabolic disease with increased levels of blood glucose, and its persistence over a period of time leads to severe damage of eyes, blood vessels, heart, nerves and kidneys. The untreated, uncontrolled and poorly managed diabetic

Abbreviations: SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; COVID-19, Coronavirus disease 2019; T2DM, Type 2 diabetes mellitus; MERS, Middle East respiratory syndrome; SARS, Severe acute respiratory syndrome; WHO, World Health Organization; ATP, Adenosine tri phosphate; ACE-2, Angiotensin-converting enzyme 2; TMPRSS2, Transmembrane Serine Protease 2; IFN-1, Interferon-1; ARDS, Acute respiratory distress syndrome; CLR, C-lectin type receptors; GRP78, non-immune receptor glucose regulated protein 78; TLR, toll-like receptors; NRP1, neuropilin-1.

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patients may have severe health consequences (Chatterjee et al., 2017). Due to the presence of high glucose levels in the body, the normal metabolic activities are affected or may occur in abnormal way, leading to severe damage to the tissues. In addition, hyperglycemia might contribute to reduced mitochondrial metabolism and ATP synthesis due to metabolic changes in β-cells (Haythorne et al., 2019). Hyperglycemic environment in diabetes patients leads to immune dysfunction specifically neutrophils such as reduced chemotaxis and phagocytosis. On the other hand, it also causes angiopathies, neuropathy and gangrenous cholecystitis affecting many organs and tissues (Alves et al., 2012). When compared to normal individuals, T2DM patients have been reported with severe and chronic infections. COVID-19 patients with preexisting T2DM have a higher susceptibility to SARS-CoV-2 infection, bacterial and fungal opportunistic infections, severe COVID-19 disease with poor prognosis and high mortality (Abu-Farha et al., 2020; Erener, 2020).

This review is focused on COVID-19 patients with T2DM as a comorbid condition. We reviewed if the T2DM patients have higher susceptibility to SARS-CoV-2 and influence of hyperglycemia on replication of the virus. Additionally, other associated factors like effect of hyperglycemia on angiotensin-converting enzyme 2 (ACE-2) receptor expression, proinflammatory cytokines leading to cytokine storm and opportunistic infections leading to severe disease outcome as well as treatment options were reviewed. Further focus was laid if the hyperglycemic patients showed any aggravated form of COVID-19.

The aim of this review was to investigate the relationship between hyperglycemia and virulence of SARS-CoV-2, severity of COVID-19 disease in type 2 diabetes mellitus patients as well as the available treatment options.

2. Material and methods

A systematic review was conducted on the following databases: MEDLINE/PubMed, SCOPUS, Web of Science, ScienceDirect, and Google Scholar. Medical Subject Headings (MeSH) terms such as “COVID-19”, “SARS-CoV-2”, “type 2 diabetes mellitus in COVID-19”, “hyperglycemia in COVID-19”, “opportunistic infections in type 2 diabetes mellitus and COVID-19” and “treatment for COVID-19 in type 2 diabetes mellitus” were used. This review included the published scientific articles with COVID-19 and T2DM from 1/1/2020 to 30/09/2021.

3. Results

3.1. Role of T2DM in COVID-19 patients

T2DM affects the glucose metabolism and results in hyperglycemia. Many studies have indicated that there is notably increased severity of COVID-19 in diabetes patients (Jin and Hu, 2021; Roberts et al., 2021). Lack of adequate insulin hormone and presence of high blood glucose in the body may play a significant role in the mortality of COVID-19 patients. Diabetes induced immunosuppression play an inevitable role in the severity of COVID-19 disease. Many studies revealed that diabetic patients possess excess free glucose molecules that may indirectly enhance the susceptibility to SARS-CoV-2 and enhance the severity of COVID-19 (Fathi and Rezaei, 2020; Dowey et al., 2021). Recently reported variant of SARS-CoV-2, delta variant expressed strong affinity in diabetic patients. In India the delta variant has caused a huge mortality especially among uncontrolled diabetic patients (Kannan et al., 2021). We speculate that there may be a strong relationship exist between hyperglycemia in T2DM and emergence of variants of SARS-CoV-2 from different parts of the world. So, we suggest that further detailed researches need to be conducted on this aspect.

3.2. Molecular association between hyperglycemia and replication of SARS-CoV-2

The replication of SARS-CoV-2 is initiated by the viral attachment of spike proteins to host receptors. In a normal host with optimal levels of insulin secretion and blood glucose levels, the initiation of viral replication by attachment is affected. In hyperglycemic individuals, it has been noted that expression and glycosylation of ACE-2 receptors is enhanced that might increase the susceptibility to SARS-CoV-2 entry (Fig. 1) (Ceriello, 2020). There is a link between hyperglycemia and oncogenesis and tumor progression (Gerstein, 2010; Nagy et al., 2019). Similarly, hyperglycemic state might increase the viral replication. Many studies revealed that the cells infected with the virus increases the glycolytic metabolism to secure the precursors for the virus production and assembly (Thai et al., 2014; Heiden et al., 2009). A study hypothesized that the human cells infected by SARS-CoV-2 leads to an excess of glucose utilization to synthesize the precursors for viral assembly (Thaker et al., 2019). In T2DM patients the total and glycosylated ACE-2 receptor overexpression could favor the SARS-CoV-2 entry into host cells thus increasing the infectivity with SARS-CoV-2 in these patients (D'Onofrio et al., 2021). High blood glucose increases the exposure of SARS-CoV-2 host receptors like ACE-2 and TMPRSS2 (Transmembrane Serine Protease 2) (D'Onofrio et al., 2021). In these categories of patients, hyperglycemic condition might enhance the affinity between the virus and the host cell. At normal glucose levels the absence of glycosylated ACE-2 and over expression of ACE-2 may lead to lesser SARS-CoV-2 infectivity. Following the binding of SARS-CoV-2 to ACE-2 the events like endocytosis, activation of proteolytic cleavage and processing takes place (Gheblawi et al., 2020). In the tissues lacking ACE-2, the SARS-CoV-2 utilizes other important innate immune receptors like, CLR (C-lectin type receptors), GRP78 (non-immune receptor glucose regulated protein 78), TLR (toll-like receptors) and NRP1 (neuropilin-1) (Mourad et al., 2021). NRP1 acts as a cofactor when co-expressed with SARS-CoV-2 to enhance the SARS-CoV-2 entry. In T2DM, NRP1 is over expressed and may rise the infection risk (Cantuti-Castelvetri et al., 2020). Collectively, the over expression of receptors may enhance the viral endocytosis and subsequent steps of SARS-CoV-2 replication.

Many researches revealed that COVID-19 patients with normal blood glucose levels exhibited poor SARS-CoV-2 endocytic activity. A recent study demonstrated that fasting plasma glucose levels were higher in SARS-CoV-2 positive patients in comparison to patients with no-SARS pneumonia. In patients who had died from COVID-19 disease the glycemic levels were even higher (Mazucanti and Egan, 2020). This indirectly states that glucose concentration might favor the entry and replication of SARS-CoV-2. An in vitro study demonstrated that under increasing glucose concentrations elevated SARS-CoV-2 viral load was observed in monocytes (Varghese et al., 2021). The symptomatic COVID-19 patients with elevated blood sugar may enhance the viral budding and release because of the enhanced endocytosis. This could be contrary in patients with normal glucose levels.

Diabetes mellitus in conjunction with chronic inflammation and other comorbidities along with the low levels of IFN-1 might facilitate unhindered replication of SARS-CoV-2. This leads to increased levels of inflammation, exaggerated immune reactions worsening the response to SARS-CoV-2 (Rajpal et al., 2020).

3.3. Relationship between hyperglycemia and severity of COVID-19

Majority of asymptomatic COVID-19 patients with normal blood glucose levels exhibited mild symptoms of COVID-19 disease. RT-PCR positive patients for SARS-CoV-2 with normal blood sugar showed less severe symptoms or no symptoms at all. In COVID-19 with T2DM the acute pulmonary and severe exaggerated inflammation is very frequent and common (Hussain et al., 2020; Singh et al., 2020). Many COVID-19 patients with high blood glucose levels have exhibited cardiac dysfunction, renal and hepatic malfunction, in addition to respiratory

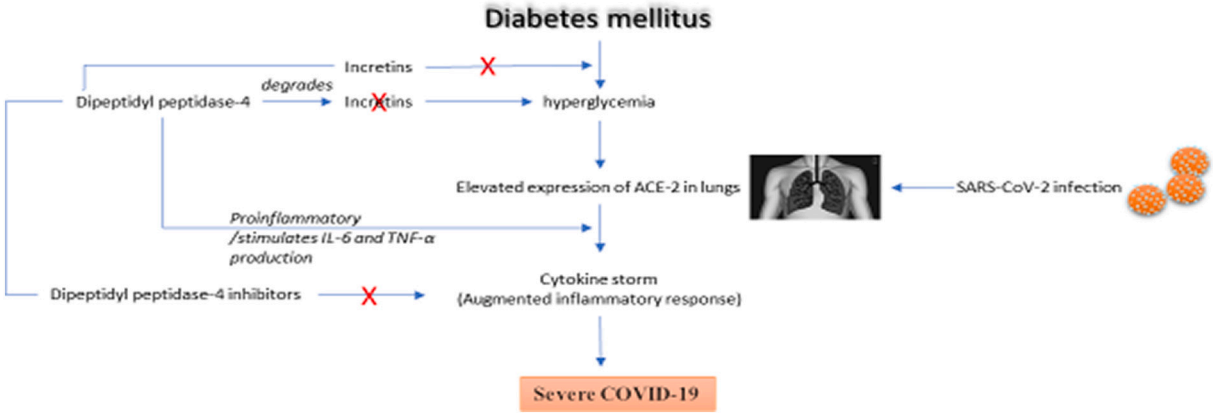

Fig. 1. Factors influencing the severity of COVID-19 in diabetes mellitus.

problems (D'Marco et al., 2020; Bansal, 2020; Kumar et al., 2020). Mortality rate was observed to be very high in COVID-19 patients with high blood glucose levels. A retrospective study was conducted with subjects involving well controlled diabetes with COVID-19 and poorly controlled diabetes with COVID-19. The study demonstrated that in poorly controlled diabetes patients the acute respiratory distress syndrome (ARDS) was approximately 3% and death was 4.4%. Whereas, in the case of poorly controlled diabetes the ARDS was 6% and the mortality rate was 18.5% (Raoufi et al., 2020).

Apart from other factors, cytokine storm is another important factor that can cause respiratory insufficiency in COVID-19 patients. In COVID-19 patients with diabetes, dipeptidyl-peptidase 4 (DPP4) is suggested to be responsible for cytokine storm (Fig. 1) (Shi et al., 2020). DPP4, an enzyme found throughout the body, rapidly inactivates glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), decreases the secretion of insulin. GLP-1 and GIP are incretins, which are gastrointestinal peptides released after meals and augment the secretion of insulin by a glucose-dependent mechanism (Fig. 1). DPP4 other than glucose metabolism might have proinflammatory action. It stimulates the production of IL-6 and TNF-α in monocytes, as well as exert a possible modulating function in the immune system (Shao et al., 2020). DPP4/CD26 is directly involved in various immune or inflammatory diseases. DPP4/CD26 is mainly present on type I and II alveolar cells, alveolar macrophages, vascular endothelium, and pleural mesothelium in the lungs of healthy subjects. In pulmonary diseases, such as asthma, chronic obstructive pulmonary disease, and lung fibrosis, there is a direct functional role of DPP4/CD26 (Pantanetti et al., 2020). It was observed that excess glucose molecules circulating in the blood will not allow the immune cells to act on SARS-CoV-2 in the process of eviction of viruses (Fathi and Rezaei, 2020). This may be the reason that the rapid replication of SARS-CoV-2 leads to increased severity of fatal COVID-19 symptoms in diabetic patients.

3.4. Association of hyperglycemia and opportunistic bacterial infections

Several studies demonstrated the presence of bacterial coinfection among COVID-19 patients. The predominant Gram-positive bacteria was found to be *Staphylococcus aureus*, *Streptococcus pneumoniae* and coagulase negative Staphylococci. Among the Gram-negative bacteria *E. coli*, *Pseudomonas aeruginosa* and *Klebsiella* sp. were present (Fig. 2) (Garcia-Vidal et al., 2021; Cox et al., 2020). Independent studies showed that nearly 7.2% - 12.7% of the COVID-19 patients were diagnosed with bacterial coinfection. A myriad of factors were associated with bacterial coinfection in COVID-19 patients such as intensive care unit (ICU) hospitalization, severity of illness, ventilation treatment, glucocorticoids therapy and T2DM (Garcia-Vidal et al., 2021; He et al., 2021).

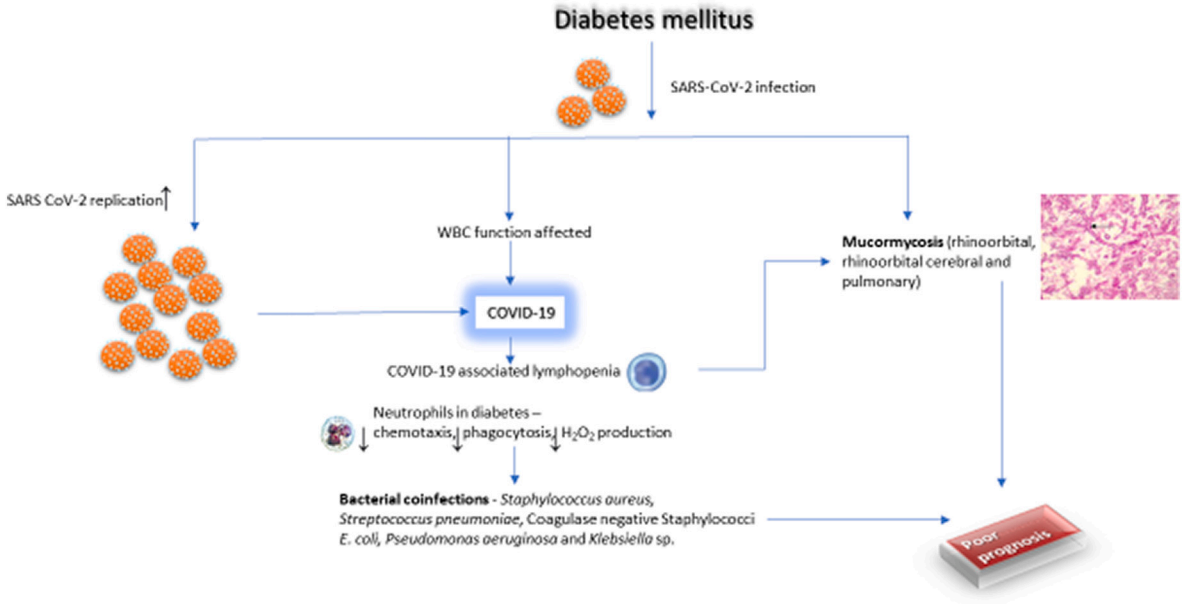

Fig. 2. Interplay between white blood cell (WBC) function and opportunistic infections in COVID-19 patients with diabetes mellitus.

Among them T2DM was found to be one of the predominant comorbidities (Chen et al., 2021; Senok et al., 2021). In COVID-19 patients, 85% of the patients showed lymphopenia (Fig. 2) (Fathi and Rezaei, 2020). A lower lymphocyte count and a higher neutrophil count was noted in COVID-19 patients with diabetes compared to COVID-19 patients without diabetes. A recent study by Guo et al (2020) showed that individuals with diabetes and COVID-19 had a lower lymphocyte count, higher absolute neutrophil count, and high levels of IL-6, ferritin, ESR, and CRP compared to patients with COVID-19 without diabetes. The reduced numbers of B/T-cells might increase the susceptibility to bacterial infections (Guo et al., 2020). It has been shown previously that neutrophils in T2DM patients exhibited decreased phagocytosis, chemotaxis that resulted in poor bacterial killing. Additionally, diabetic monocytes demonstrated decreased chemotaxis to bacteria and reduced hydrogen peroxide production (Gan, 2013). These factors in diabetic COVID-19 patients in addition to lymphopenia might have increased the susceptibility to bacterial coinfections.

3.5. Relationship between T2DM and opportunistic fungal infections

Although a myriad of factors contributes to the mortality and morbidity of COVID-19 patients, another factor that should be accounted for is opportunistic fungal infections. Opportunistic fungal infections are common among influenza patients with majority of the cases reported to be an invasive Aspergillosis due to *Aspergillus fumigatus* (Verweij et al., *2020a*). Similarly, several cases of opportunistic fungal infections in COVID-19 patients have been reported globally from various countries including USA, Western European countries, India and China (Cafardi et al., 2021; Gangneux et al., 2020; Verweij et al., 2020b; Alanio et al., 2020). In severe cases of COVID-19 sustained lymphopenia has been demonstrated. Lymphopenia dents the adaptive immunity ability and thus compromises the immune system (Liu et al., 2020; Zhu et al., 2020; Lin et al., 2020). Among the opportunistic fungal infections in COVID-19 patients, majority of the infections were due to *Aspergillus* sp., *Mucor* sp. and *Candida* sp. However, a few cases of histoplasmosis, cryptococcosis and *Pneumocystis jiroveci* pneumonia (PCP) have also been reported (Cafardi et al., 2021; Ezeokoli and Pohl, 2020).

Mucormycosis is a fungal infection caused by moulds i.e., mucormycetes. These fungal etiologic agents include *Mucor* sp., *Rhizopus oryzae*, *Lichtheimia*, *Saksenaea*, *Apophysomyces*, *Cunninghamella* and *Mortierella*. Mucormycosis is rare but generally occurs in immunocompromised patients such as uncontrolled DM and haematological malignancies (Lin et al., 2017; Peng et al., 2019). The most common risk factor for mucormycosis among the COVID-19 patients was found to be DM or glucocorticoids therapy. Pre-existing DM was present in 80% of COVID-19 patients with mucormycosis (Fig. 2). Nearly, 76.3% of mucoymycosis occurred in COVID-19 patients under the influence of corticosteroids (Singh et al., 2021). However, mucormycosis occurred in higher frequency in males (78.9%). Mucormycosis in COVID-19 patients manifested in the form of rhinoorbital, rhinoorbitalcerebral and pulmonary mucormycosis. Rhinoorbital mucromycosis was the most common followed by rhino orbital, cerebral and pulmonary mucormycosis (Pal et al., 2021). Lymphopenia among COVID-19 patients could be an additional contributing factor since Mucorales-specific T-cells (CD4+ and CD8+) that could directly damage the mucorales hyphae were demonstrated in patients with invasive mucormycosis (Potenza et al., 2011). Therefore, pre-existing diabetes in COVID-19 patients along with lymphopenia might increase the susceptibility to mucormycosis.

3.6. Therapeutic strategies and prognosis for COVID-19 patients with T2DM

Preexisting diabetes is associated with poor outcome in COVID-19 patients. COVID-19 patients admitted to the ICU were more likely to have preexisting diabetes compared to the patients not requiring ICU hospitalization (Wang et al., 2020). Moreover, studies demonstrated that COVID-19 patients with diabetes more commonly developed ARDS (Wu et al., 2020). COVID-19 patients with diabetes tend to develop severe illness, higher incidence of organ damage and higher mortality rate (Blanke, 2020; Zhou et al., 2020).

Sufficient glycemic control in COVID-19 patients with diabetes should be ensured. The COVID-19 patients with diabetes were treated with insulin and metformin. But the patients treated with insulin had a poor clinical outcome compared to metformin (Bornstein et al., 2020; Chen et al., 2020). Sodium-glucose transporter 2 inhibitors and glucagon-like receptor-1 analogue should be used with caution because of their side effects (Hsia et al., 2017; Filippatos et al., 2014). DPP4 inhibitors were suggested to have beneficial effects and may improve the mortality of COVID-19 with T2DM (Fig. 1) (Yang et al., 2021). Treatment of COVID-19 patients with Remdesivir demonstrated different outcomes between the diabetic and non-diabetic patients. Nondiabetic patients treated with Remdesivir recovered from COVID-19 within 10 days, whereas the diabetics recovered after 15 days (Qureshi et al., 2021). The delayed recovery in diabetics treated with Remdesivir is not fully understood.

4. Conclusions

Hyperglycemia in COVID-19 patients with type 2 diabetes mellitus induces over expression of ACE-2 receptors on the lungs thereby increasing the chance and susceptibility to SARS-CoV-2. This leads to fatal symptoms like ARDS and severe pneumonia, thus increasing mortality. High glucose level in COVID-19 patients with diabetes also generate cytokine storm ensuing a vulnerable environment in the body for the suitable replication of SARS-CoV-2. In type 2 diabetes mellitus patients, hyperglycemia creates enhanced endocytosis of SARS-CoV-2. It was also observed that SARS-CoV-2 also utilize the excess sugar available in the blood of hyperglycemic individuals, thereby increasing the severity of COVID-19. Hyperglycemic type 2 diabetes mellitus patients with COVID-19 were more prone to opportunistic bacterial and fungal infections. A strong correlation exists between the poor prognosis of COVID-19 and type 2 diabetes mellitus. Proper glycemic control in COVID-19 patients with diabetes mellitus might lessen the severity of the disease.

Ethical approval

All authors read and approved the final manuscript.

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CRediT authorship contribution statement

SK: conceptualization; project development. SSA: critical discussion; manuscript writing. SA: critical discussion; manuscript writing; data analysis. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interests.

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