Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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International Diabetes Federation

Commentary

Metformin, neutrophils and COVID-19 infection

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In recent commentaries, possible mechanisms of action of metformin which may have conflicting effects in COVID-19 has been proposed [1–3]. In this commentary, a possible role of metformin in COVID-19 on neutrophils, the first line of defense against microbial, fungal and viral infections is proposed. Although a controlled neutrophilic response is needed to combat infection, uncontrolled neutrophilic response can be deleterious [4].

A longitudinal study in 548 patients from China reported that a progressive increase in neutrophil count or neutrophil lymphocyte ratio was associated with a fatal outcome [5] and a similar report have been published from Poland [6]. In an autopsy study of COVID-19 patients, neutrophil infiltration in pulmonary capillaries, extravasation of neutrophils into the alveolar space, and neutrophilic mucositis has been reported [7].

Neutrophil extracellular traps (NETs) first described in 2004 [8], are extracellular chromatic webs released from neutrophils and contains deoxyribonucleic acid (DNA), histones, microbicidal proteins, (neutrophil elastase and myeloperoxidase) [9]. Recent reports have shown that that sera from patients with COVID-19 have elevated levels of NETS such as cell-free DNA, myeloperoxidase (MPO)-DNA, and citrullinated histone H3 (Cit-H3), highly specific markers of NETs and these were associated with markers of inflammation [10]. If controlled, NETs are beneficial in the host defence against pathogens [10]. However, if excessive NET formation occurs it has the potential to trigger inflammatory cascade that has been associated with cytokine storm [10], ARDS [11] and microthrombosis [12] all causes of fatality in COVID-19.

Metformin has been shown to reduce neutrophil count in polycystic ovarian disease [13] and reduce neutrophil lymphocyte ratio in patients with diabetes [14]. It has also been shown to ameliorate NETosis in patients with diabetes [15] and pre-diabetes independent of glucose control [16]. Metformin has been associated with a decrease in neutrophil gelatinase-associated lipocalin (NGAL), an acute phase protein released by neutrophils and is known to be elevated in patients with diabetes [17]. Animal studies have shown that metformin reduces post myocardial infarction injuries by reducing cardiac remodelling and myocardial neutrophil activity [18]. Metformin has also been seen to reduce neutrophil and macrophage infiltration in hyperoxia induced lung injury in neonatal rats [19].

While beneficial mechanistic links through neutrophils can be suggested with the use of metformin, it is important to realise that a relatively high rate of mortality in patients with co-existing diabetes has been reported in COVID-19 [20]. A vast majority of these patients would have been on metformin. Until we have real world data on the effects of metformin use in COVID-19 patients with diabetes, no conclusive judgement with regards to its overall usefulness, neutral or detrimental effects can be made.

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Declaration of Competing Interest

The author declare that there is no conflict of interest.

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