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Use of pioglitazone in people with type 2 diabetes mellitus with coronavirus disease 2019 (COVID-19): Boon or bane?

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ABSTRACT

Background and aims: People with type 2 diabetes mellitus (T2DM) have increased morbidity and mortality due to coronavirus disease-19(COVID-19). It has been speculated that use of pioglitazone might increase such risk. The aim of our brief commentary is to review the safety of pioglitazone in people with T2DM and mild/moderate COVID-19.

Methods: We searched PubMed database using specific keywords related to our aims till May 15, 2020. Full text of relevant articles published in English language were retrieved and reviewed.

Results: Medications, including pioglitazone, that upregulate tissue expression of angiotensin converting enzyme 2 (ACE2), might have a dual role in COVID-19; on the one hand they might increase risk of infection as SARS-CoV2 uses ACE2 as a coreceptor to enter alveolar cells, but on the other hand, by reducing angiotensin II levels, they can protect against acute lung injury. There is no evidence to date that pioglitazone upregulates ACE2 in the alveolar cells; rather, there is evidence from animal studies of upregulation of ACE2 in insulin sensitive tissues, which might have a protective effect on lung injury. Moreover by moderating the exaggerated host proinflammatory response, pioglitazone can potentially reduce SARS-CoV-2 driven hyperinflammation.

Conclusions: Pioglitazone has more potential for benefit than harm, and can be continued in people with T2DM and mild/moderate COVID-19, unless there are specific contraindications for its use. There is an urgent need to assess clinically relevant outcomes in people with diabetes and COVID-19 based upon baseline antidiabetes therapy, in particular pioglitazone.

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Individuals with diabetes mellitus not only have increased susceptibility to but also higher morbidity and mortality due to coronavirus disease 2019 (COVID-19).The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses angiotensin converting enzyme (ACE)2 as a co-receptor to enter the cell [1]. Among anti-diabetic agents, liraglutide and pioglitazone [2], and among anti-hypertensives, ACE inhibitors (ACEi)/angiotensin receptor blockers (ARB) [3], have been shown in some animal studies to upregulate the tissue expression of ACE2. This has led to the speculation that use of these medications might increase susceptibility to, and severity of, COVID-19. In vitro studies have shown that following initial engagement of SARS-CoV-2 with ACE2 receptor, there is down-regulation of ACE2 [1]. The primary function of ACE2 is to convert angiotensin II to angiotensin-(1–7). There is evidence from animal studies that downregulation of ACE2 might result in unopposed action of angiotensin II, which can mediate acute lung injury in viral infections, including SARS-CoV2 [4]. By increasing ACE2 expression in many tissues, pioglitazone might help ameliorate the harmful effects of excess angiotensin II. Animal studies have also demonstrated that ACE2 has a protective effect on the myocardium [5]. It would thus seem that medications that upregulate tissue expression of ACE2, including pioglitazone, might have a dual action in people with diabetes with COVID-19: increasing the risk and severity of infection with SARS-Cov2 on one hand and reducing the severity of lung injury on the other. A number of recent publications have discussed the possible dual role of ACEi/ARB in COVID-19, but not much has been discussed about pioglitazone. However, it is important to address this question since a significant minority of people with diabetes in the UK are prescribed pioglitazone at onset of diabetes, and it is a common

Table 1
Potential mechanisms by which pioglitazone might be of beneficial in patients with COVID-19[a].

Observation [ref]	Type of study	Potential effects
Increases expression of ACE2 in insulin-sensitive tissues including liver, adipose tissue and skeletal muscle [2]	Animal	Potential to ameliorate the harmful effects of excess angiotensin II, including angiotensin II-mediated lung-injury
Inhibits 3CLPro - a non-structural protein encoded by SARS-CoV2 that is essential for SARS-CoV-2 RNA synthesis and replication [9]	Computer simulation based bioinformatic analysis using virtual ligand screening method	Potential to inhibit SARS-Cov-2 RNA synthesis and replication
Decreases pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6 in monocytes and macrophages [11]	Animal and in-vitro human cell cultures	Potential to reduce SARS-CoV2 driven hyperinflammation
Reduces the expression of CARD 9 in macrophages which inhibits activation of NF-κB and MAPK pathways [12]	Animal	Potential to reduce SARS-CoV2 driven hyperinflammation
Suppresses generation of TNF-α, IL-6 and MCP-1 in adipose tissue [13]	Animal	Potential to reduce SARS-CoV2 driven hyperinflammation

SARS-CoV2: severe acute respiratory syndrome coronavirus 2; ACE: angiotensin converting enzyme; 3CLPro: 3-chymotrypsin-like protease; TNF-α: tumour necrosis factor-α; IL = interleukin; CARD: caspase-recruitment domain-containing protein 9; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1.
[a] Translational value of these potential beneficial mechanisms from animals to humans needs urgent evaluation.

prescription for people with diabetes in many Asian countries; in a study reported in 2016 from India, depending upon the region sampled, 7.9%–13.4% of all antidiabetic drug prescriptions in outpatient departments was pioglitazone [6]. The ADA-EASD 2018 guidelines also recommend using pioglitazone in situations where cost is a factor in decision making. (see Table 1)

Pioglitazone belongs to the thiazolidinedione (TZD) group of medications, and acts as an agonist of the peroxisome proliferator–activated receptor (PPAR)-ɣ. Recent publications have alluded to upregulation of ACE2 by pioglitazone [7]. Indeed, animal studies have shown that pioglitazone increases the expression of ACE2 in the liver, adipose tissue and skeletal muscles [2]. However, pioglitazone was found to have no effect on cardiac ACE2 expression in a study on db/db mice [8]. As such, apart from upregulation of ACE2 in insulin sensitive tissues in animals, unlike ACEi/ARB, there is no evidence that pioglitazone upregulates expression of ACE2 in alveolar cells. On the other hand, Wu et al. have interestingly postulated a possible therapeutic role for pioglitazone in SARS-CoV-2 infection [9]. In their quest for finding a treatment for COVID-19, they embarked on bioinformatic analysis of marketed molecules, using virtual ligand screening method, on various proteins encoded by SARS-CoV-2. The 3-chymotrypsin-like protease (3CLPro) is one such non-structural protein that is essential for SARS-CoV-2 RNA synthesis and replication. Pioglitazone was found to have potential to act as 3CL-Pro inhibitor, which could inhibit SARS-Cov-2 RNA synthesis and replication; however, this nascent concept needs substantiation with further research.

Pioglitazone may also play an important role in people with diabetes with COVID-19 by moderating host inflammatory response at multiple fronts. Subsets of people with diabetes and COVID-19 have SARS-CoV-2 driven hyperinflammation and severe cytokine storm syndrome. A number of immunosuppressive agents, including anakinra [interleukin (IL)-1 blocker] and tocilizumab (IL-6 blocker) are being studied to counter this SARS-CoV-2 driven hyper inflammation [10]. PPAR-ɣ agonists have also been shown to decrease the secretion of various pro-inflammatory cytokines, including tumour-necrosis factor-α (TNF-α), IL-1, and IL-6 in the monocytes and macrophages [11]. PPAR-ɣ agonists in particular has been shown to reduce the expression of caspase-recruitment domain-containing protein 9 (CARD9), which in turn inhibits the activation of nuclear factor kappa-light-chain-enhancer of activated B cells and mitogen-activated protein kinase pathways in macrophages [12]. Adipose tissue is also an active contributor to inflammation, and releases a variety of proinflammatory proteins including TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1). Animal studies have revealed that pioglitazone can

suppress TNF-α and IL-6 generation in adipose tissue [13]. Pioglitazone has been shown in animal studies to decrease mortality from sepsis and lung injury by reducing inflammatory cytokine production in omental tissue [13]. Interestingly, this moderation in cytokine production at multiple fronts by pioglitazone has led researchers to speculate on its role in the treatment of COVID-19 associated cytokine storm. However, lack of parallelism between humans and mice may blunt the translational value of these findings.

In summary, in a rapidly evolving pandemic situation of COVID-19, it is essential to generate evidence quickly to guide management. Pioglitazone is an inexpensive anti-diabetic agent that is used commonly around the globe. It is hence essential to review its safety in people with diabetes with COVID-19. In balance, as argued above, we feel pioglitazone has more potential for benefit than harm, and can be safely continued in people with diabetes and COVID-19 unless there are specific contraindications for use of pioglitazone. More evidence from the laboratory and the clinics are urgently needed to guide the clinician. Among these, retrospective analyses of outcomes in people with diabetes with COVID-19 who were on pioglitazone can serve as a good evidence base. However, most retrospective observational case studies published to date do not have this information. As such, there is an urgent need to assess clinically relevant outcomes, including risk for developing severe disease, risk for hospitalisation and risk of death, among people with diabetes with COVID-19 based on baseline anti-diabetic therapy, in particular pioglitazone.

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Declaration of competing interest

No conflict of interest to declare.

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