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Commentary

COVID-19 and diabetes management: What should be considered?

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Management of diabetes today has been addressed as an exciting confusion [1]. Considering the fast spread of the "Corona Virus Disease 2019 (COVID-19)" due to the "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)", there is currently a considerable debate on several important topics related to the most appropriate way to manage people with diabetes during this pandemic, including the susceptibility to this new infection, the severity of the complications, as well as the role of the drugs to use for the glycemic control [2].

Even epidemiological data available so far on COVID-19 do not support the hypothesis that diabetic patients are at increased risk than the general population for SARS-CoV-2 [3], it seems clear that diabetes, particularly when not well controlled, exposes people to be more complicated and prone to die [4,5].

An important element is the molecule that has the role of receptor for SARS-CoV-2, which has been identified in the Converting-Enzyme-2 (ACE2) [6]. Recently, it has been hypothesized that the Sodium-Glucose-Transporter-2 inhibitors

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(SGLT-2i), the Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1RAs), the Pioglitazone and even the Insulin might induce an over-expression of the ACE2 receptor [2], therefore increasing the risk of people with diabetes to have more serious consequences if infected.

The issue is of great relevance, because, on the other hand, is today claimed that, never as before, an optimal glycemic control is needed in diabetes [7]. When the same issue about a possible induction of the ACE2 was raised about the use of Angiotensin-Converting-Enzyme inhibitors (ACEi) or Angiotensin-Renin-Blockers (ARBs), several Scientific Societies and also the European Medical Agency (EMA) clarified that until this is just an hypothesis coming from some in vitro studies and not yet confirmed by any clinical evidence in people affected by COVID-19, it is absolutely not justified to stop the use of such drugs, which have been shown to be very effective in saving the life of people [8].

We believe that something similar is urgently needed also for the anti-hyperglycemic therapy.

Meanwhile, it is worth to be remembered what some anti-hyperglycemic drugs can do when used [9]. The usefulness of both GLP-1Ra and SGLT-2i for the prevention of cardiovascular and kidney disease is well know [10], and we must consider how important is to preserve the cardiovascular system and the kidney, particularly during this pandemic. People with the presence of a cardiovascular or kidney disease show a worse prognosis during the COVID-19 [11], therefore it seems to be mandatory to preserve the integrity of kidney and of the cardiovascular system in people who could be affected by the SARS-CoV-2.

However, there are other aspects worth to mention.

Inflammation plays a key role during the SARS-CoV-2 infection [12]. The Dipeptidyl Peptidase 4 (DPP4) is expressed ubiquitously in many tissues, including those in the respiratory tract, thus representing a potential target to reduce the severity of the COVID-19 [13]. At the same time, the DPP4 is the target of incretin-based therapies, and this opened the discussion whether DPP4-inhibitors, currently used for the treatment of people with type-2 diabetes (T2DM) may be effective against SARS-CoV-2. Yet, the scientific community is cautious about this hypothesis, since this speculation is based on preclinical data, and clinical data is therefore needed. In addition, it has to be highlighted that GLP-1 receptor analogues have shown over the years significant anti-inflammatory and anti-adipogenic effects, thus decreasing insulin resistance [14,15]. The effect of reducing the inflammatory stress and the peripheral insulin resistance by lowering the infiltrate with macrophage, via GLP-1 dependent signaling by regulating M1/M2 macrophage polarization, have been described with DPP4 inhibition and GLP-1 activation [16]. Similar evidence on the effect on inflammation is also available for the SGLT-2i [17] and pioglitazone [18]. Therefore, waiting for specific clinical data, certainly it is the case to balance between the potential dangerous effects of some drugs, supported mainly by experimental data, and the proven effects of the drugs on the cardiovascular system and the kidney, as well as their potential anti-inflammatory action.

Regarding current management of people with diabetes during this pandemic, Pal and Bhadada [2] have recently highlighted that the anti-malaria hydroxychloroquine (HCQ) has been used in the last weeks as a prophylaxis against COVID-19 in many countries; yet, in case of co-administration of HCQ together with other anti-diabetic drugs, the dosages of concomitant therapies may be reassessed, particularly in patients at higher hypoglycemic risk. Indeed, it is known since more than 30 years that HCQ has hypoglycemic effects that may precipitate severe episodes of hypoglycemia. Smith et al. in 1987 described a significant improvement of glycemic values in few patients with non-insulin dependent diabetes mellitus treated with HCQ [19]. This finding was then reinforced by Quatraro et al. in a study published in 1990 in T2DM treated with insulin or glibenclamide associated to HCQ for six months, where the authors found a significant decrease in HbA1c by 3.3% compared to placebo, and a reduction in insulin dosages by 30% [20]. Therefore, the anti-glycemic effect of HCQ is worth of investigation in clinical studies on COVID-19 in people with diabetes; HCQ, if safely used, may also contribute to an improvement of diabetes control.

In summary, our knowledge on the new SARS-CoV-2 is increasing day by day, and the lessons learnt from this pandemic in different countries are very precious to establish the best approach to manage the disease [21,22]. People with diabetes are particularly exposed to a worse prognosis if infected [4,5]. Therefore, it is a scientific and clinical need to obtain data on the antidiabetic treatments used so far in T2DM affected by COVID-19, and particularly to clarify whether the use of the new therapies in such people is correlated, or not, to a better prognosis and less severe forms of the disease.

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