Antihyperglycemic properties of hydroxychloroquine in patients with diabetes: Risks and benefits at the time of COVID-19 pandemic

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Abstract
The antimalarial drug hydroxychloroquine (HCQ) has long been used as a disease-modifying antirheumatic drug for the treatment of several inflammatory rheumatic diseases. Over the last three decades, various studies have shown that HCQ also plays a role in the regulation of glucose homeostasis. Although the mechanisms of action underlying the glucose-lowering properties of HCQ are still not entirely clear, evidence suggests that this drug may exert multifaceted effects on glucose regulation, including improvement of insulin sensitivity, increase of insulin secretion, reduction of hepatic insulin clearance, and reduction of systemic inflammation. Preliminary studies have shown the safety and efficacy of HCQ (at a dose ranging from 400 to 600 mg/day) in patients with type 2 diabetes over a short-term period. In 2014, HCQ has been approved in India as an add-on hypoglycemic agent for patients with uncontrolled type 2 diabetes. However, large randomized controlled trials are needed to establish the safety and efficacy profile of HCQ in patients with type 2 diabetes over a long-term period. With regard to the COVID-19 pandemic, several medications (including HCQ) have been used as off-label drugs because of the lack of proven effective therapies. However, emerging evidence shows limited benefit from HCQ use in COVID-19 in general. The aim of this manuscript is to comprehensively summarize the current knowledge on the antihyperglycemic properties of HCQ and to critically evaluate the potential risks and benefits related to HCQ use in patients with diabetes, even in light of the current pandemic scenario.

Keywords
antidiabetic medications, COVID-19, diabetes mellitus, hydroxychloroquine, SARS-CoV-2

Highlights
• Hydroxychloroquine (HCQ) has been shown to exert antihyperglycemic properties by virtue of potential multifaceted effects on glucose homeostasis,
including improvement of insulin sensitivity, increase of insulin secretion, and reduction of systemic inflammation.

- Preliminary studies have shown the safety and efficacy of HCQ as an antihyperglycemic agent in type 2 diabetes over a short-term period.
- A careful risk-benefit assessment of HCQ is critical for a cautious use of this drug in diabetic patients, particularly in light of the current COVID-19 pandemic.

1 HYDROXYCHLOROQUINE AS AN ANTIHYPERGLYCEMIC AGENT

Since the 1940s, the antimalarial drugs chloroquine and hydroxychloroquine (HCQ) have been used as disease-modifying antirheumatic drugs (DMARDs) for the treatment of several inflammatory rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Importantly, HCQ has shown a good safety and tolerability profile in most patients, even during pregnancy and breastfeeding.

Intriguingly, a growing body of evidence coming from studies conducted over the last three decades suggests that HCQ also plays a role in the regulation of glucose homeostasis in individuals with and without diabetes. Although the exact mechanisms of action underlying the glucose-lowering properties of HCQ are still not entirely clear and may differ between patients with and without diabetes, preclinical and clinical data suggest that HCQ could exert multifaceted effects on glucose homeostasis, namely improvement of insulin sensitivity, increase of insulin secretion, reduction of hepatic insulin clearance and intracellular insulin and insulin-receptor complex degradation, increase of adiponectin levels, reduction of systemic inflammation, and/or reduction of inflammation-induced insulin resistance in adipocytes and skeletal muscle cells. In this regard, a randomized study is currently underway at Washington University (MetaHcQ, Metabolic Effects of Hydroxychloroquine; ClinicalTrials.gov Identifier: NCT02026232) to evaluate the effects of 4-week HCQ administration (at a dose of 400 mg/day) on insulin sensitivity (determined by hyperinsulinemic euglycemic clamp), fasting blood glucose, lipid profile, and serum biomarkers of inflammation in subjects with type 2 diabetes mellitus (T2D).

Remarkably, several studies demonstrated that HCQ use is associated with a significantly reduced risk of developing diabetes in nondiabetic subjects with inflammatory rheumatic diseases, including RA, SLE, psoriasis, and Sjögren syndrome.

In the early 1990s, an Italian 6-month randomized, placebo-controlled trial conducted by Quatraro et al. first showed that the addition of HCQ (600 mg/day) to glibenclamide or insulin led to a significant reduction in glycated hemoglobin (HbA1c), accompanied by a 30% reduction in daily insulin dose among patients on insulin therapy. Thereafter, a Canadian randomized, placebo-controlled trial conducted in 135 obese patients with T2D refractory to sulfonylureas showed that the addition of HCQ (up to a maximum of 300 mg bid) reduced HbA1c by an absolute amount of 1.02% more than placebo after 6 months. No significant HCQ-related side effects were reported in these studies, except for a severe hypoglycemic episode that occurred in one patient treated with HCQ in combination with insulin.

More recently, a 24-week prospective randomized trial and two real-world, prospective observational studies of short duration (up to 24-48 weeks) conducted in India have shown that the use of HCQ (400 mg/day) as an add-on treatment in patients with T2D uncontrolled on a combination of two or more oral hypoglycemic agents (including metformin, sulfonylureas, pioglitazone, DPP-4 inhibitors, SGLT2 inhibitors, and alpha-glucosidase inhibitors) was well tolerated and led to a significant improvement of glucose control (assessed by HbA1c, fasting- and postprandial blood glucose) from baseline (without occurrence of severe hypoglycemia).

In India, diabetes has reached epidemic proportions over the last years and newer antidiabetic drugs pose affordability challenges due to their high cost. Based on the aforementioned preliminary results, HCQ (at a dose of 400 mg/day) has been approved in 2014 by the Drug Controller General of India (DCGI) as a third-line (add-on) hypoglycemic agent for patients with inadequately controlled T2D despite lifestyle management associated with sulfonylurea and metformin combination therapy. Thereafter, a vibrant debate about HCQ safety in T2D has arisen within the Indian scientific community.
2 | ANTIHYPERGLYCEMIC PROPERTIES OF HCQ: CURRENT MECHANISTIC EVIDENCE

Animal and human studies support the existence of different molecular mechanisms underlying the antihyperglycemic properties of HCQ (and chloroquine). A study conducted by Halaby et al. in cultured rat muscle cells and in a rat model of insulin resistance demonstrated that chloroquine can promote insulin-mediated glucose uptake and glycogen synthase activity by activating Akt. In 1991, Powrie et al. conducted a randomized, placebo-controlled trial in 20 patients with T2D (referred to as “non-insulin-dependent diabetes mellitus”) who were not receiving any antidiabetic medication and were adopting dietary measures only for diabetes management. The authors performed a hyperinsulinemic euglycemic clamp before and after a 3-day treatment with chloroquine (250 mg administered four times daily) or placebo, using a stable isotopically labeled D-glucose to calculate hepatic glucose production (Ra, rate of glucose appearance) and glucose utilization (Rd, rate of glucose disappearance). Notably, chloroquine led to a significant reduction in fasting plasma glucose and a significant rise in the total amount of exogenous glucose required to maintain euglycemia during the whole experiment, because of an increase in Rd (without changes in Ra). Also, chloroquine administration resulted in a 39% reduction in metabolic clearance rate of insulin at low-dose insulin infusion. More important, fasting C-peptide levels significantly increased throughout the study after chloroquine treatment, despite the initially lower plasma glucose values. A decreased feedback inhibition of C-peptide secretion was also reported during low- and high-dose insulin infusion (by 9.1% and 10.6%, respectively). Overall, these data suggest that chloroquine can improve fasting glucose levels in subjects with T2D by (a) increasing peripheral glucose disposal (as evidenced by the increased overall glucose infusion rate required to maintain euglycemia, associated with an increase in Rd), (b) reducing hepatic insulin clearance, and (c) increasing endogenous insulin secretion both in the fasting state and during hyperinsulinemia. The assumption of the authors that chloroquine has a direct insulinosuppressive effect on pancreatic beta cells is strengthened by the fact that C-peptide has a negligible hepatic clearance and approximately half of the produced C-peptide is metabolized by the kidneys; in particular, the majority of total C-peptide produced is degraded via peritubular uptake and approximately 5% is excreted unchanged in the urine. However, these findings cannot be directly translated to HCQ, even though chloroquine and HCQ display similar pharmacodynamic properties. Thus, further investigation is warranted in this direction.

A study conducted by Emami et al. in diabetic rats showed that HCQ increased circulating insulin levels and reduced blood glucose levels in a concentration-dependent manner. In a subsequent study, the same authors found that HCQ can inhibit cytosolic insulin-metabolizing enzyme and intracellular insulin degradation in rat liver cells.

In 2012, Mercer et al. showed that HCQ therapy (at a dose of 6.5 mg/Kg/day) for 6 weeks was associated with a significantly increase in insulin sensitivity index (ISI)—assessed by a 120-minutes oral glucose tolerance test (OGTT)—along with trends toward reduced insulin resistance (determined by homeostatic model assessment of insulin resistance [HOMA-IR]) in nondiabetic obese subjects without systemic inflammatory conditions. Thereafter, Wasko et al. confirmed similar results in a 13-week randomized, placebo-controlled study, showing that HCQ (400 mg/day) improved both beta-cell function (determined by the disposition index) and ISI (assessed by intravenous glucose tolerance test) in nondiabetic overweight or obese subjects. At variance with these findings, a randomized, placebo-controlled crossover trial conducted by Solomon et al. in nondiabetic subjects with stable RA showed that treatment with HCQ for 8 weeks (at a dose of 6.5 mg/Kg/day and not to exceed 600 mg/day) produced no significant change in ISI (assessed by 120-minutes OGTT) and insulin resistance (assessed by HOMA-IR) compared to placebo. These results may indicate that HCQ can prevent development of diabetes in patients with inflammatory rheumatic diseases—as it has been widely demonstrated—through additional mechanisms other than improvement in insulin sensitivity.

HCQ is a well-known anti-inflammatory and immunomodulatory agent able to reduce the production of pro-inflammatory cytokines and is therefore used as a DMARD for the treatment of several inflammatory rheumatic diseases. With regard to the anti-inflammatory effects of HCQ in T2D, Amit Gupta has recently shown that diabetic patients with higher baseline levels of high-sensitivity C-reactive protein (hs-CRP >3 mg/L) exhibited a more pronounced, although not significant, improvement in glucose control from baseline to 48 weeks after the initiation of HCQ therapy, as compared to patients with lower baseline levels of hs-CRP (≤ 3 mg/L). Furthermore, patients with higher baseline hs-CRP levels also exhibited higher (although not significant) baseline levels of HbA1c and fasting and postprandial glucose levels. The previously mentioned study by Wasko et al. conducted in nondiabetic overweight or obese subjects also found that HCQ (at a dose of 400 mg/day) significantly
increased plasma levels of the adipokine adiponectin, which plays a key role in insulin resistance and metabolic syndrome by exerting anti-inflammatory actions and increasing insulin sensitivity.31-33 Importantly, HCQ use up to 24 weeks (at a dose of up to 600 mg/day) in patients with T2D has also led to an improved lipid profile, which consisted of a significant reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, and non-high-density lipoprotein cholesterol in different studies.12,14,15 A randomized, placebo-controlled crossover trial also found a significant reduction in total cholesterol and LDL-cholesterol after 8 weeks of HCQ therapy (at a dose of 6.5 mg/Kg/day and not to exceed 600 mg/day) in non-diabetic patients with RA.29 Nevertheless, it is still not clear whether the potential lipid-lowering properties of HCQ may depend on its anti-inflammatory actions rather than on other HCQ-related mechanisms.

Interestingly, Type 1 Diabetes (T1D) TrialNet international network is currently investigating the potential ability of HCQ to prevent or delay the progression from normal glucose tolerance to impaired glucose tolerance or symptomatic T1D in subjects with islet autoimmunity, who are at increased risk of developing T1D (ClinicalTrials.gov Identifier: NCT03428945). Therefore, participants enrolled in this study are subjects in stage 1 (islet autoimmunity) of T1D pathophysiology.34 However, the current lack of data on safety and efficacy of HCQ in patients with established T1D does not allow for any conclusion concerning the use of this drug in T1D.

Altogether, these findings suggest that HCQ regulates glucose homeostasis by virtue of multifaceted effects, which may allow for classifying this drug as an antidiabetic medication potentially acting as an insulin-sensitizing agent (insulin sensitizer), an anti-inflammatory agent, and/or an insulinotropic agent (secretagogue) (Figure 1). Since chronic low-grade inflammation and islet inflammation have been linked to insulin resistance and beta-cell dysfunction in T2D, respectively,33,35-37 the anti-inflammatory actions of HCQ may be at the interface between its insulin-sensitizing effects and its insulinotropic properties. On the basis of preclinical data in animals, HCQ appears to have the ability to (a) inhibit intracellular insulin and insulin-receptor complex degradation, (b) increase circulating

![Figure 1](image_url)

**FIGURE 1** Potential molecular mechanisms underlying the hydroxychloroquine-mediated antihyperglycemic effects. Evidence from animal and human studies conducted in subjects with and without diabetes suggests that hydroxychloroquine regulates glucose homeostasis by virtue of multifaceted effects, including increase of insulin secretion, improvement of insulin sensitivity, reduction of hepatic insulin clearance and intracellular insulin and insulin-receptor complex degradation, increase of adiponectin levels, reduction of systemic inflammation, and/or reduction of inflammation-induced insulin resistance in adipocytes and skeletal muscle cells. Altogether, these actions may allow for classifying hydroxychloroquine as an antidiabetic agent which acts as an insulin-sensitizing agent, an anti-inflammatory agent and/or an insulinotropic agent (secretagogue). Since chronic low-grade inflammation and islet inflammation have been linked to insulin resistance and beta-cell dysfunction in type 2 diabetes, respectively, the anti-inflammatory actions of hydroxychloroquine may be at the interface between its insulin-sensitizing actions and its insulinotropic properties. *Effects observed with chloroquine in a rat model of insulin resistance. Abbreviations: CRP, C-reactive protein
insulin levels, (c) reduce blood glucose levels, and (d) promote glucose uptake and glycogen synthase activity in skeletal muscle cells. Thus, it is tempting to speculate that HCQ is able to inhibit glucagon secretion by pancreatic alpha cells and/or glucagon action in the liver. Additionally, it is still not clear whether the putative effect of HCQ on endogenous insulin secretion is mediated by a direct stimulatory effect on beta cells and/or by indirect effects involving the reduction of islet inflammation and/or the reduction of glucotoxicity- and lipotoxicity-related beta-cell dysfunction following the improvement in metabolic control. Moreover, the lack of severe hypoglycemic episodes observed across the studies investigating the use of HCQ as an antidiabetic medication in T2D (even when HCQ was administered in combination with sulfonylureas) may underlie a putative glucose-dependent insulin secretion mechanism mediated by HCQ. Yet, the occurrence of severe hypoglycemic episodes cannot be excluded in these studies, because they did not employ continuous glucose monitoring. Notwithstanding, we believe that all these speculations and unanswered questions may prompt researchers to conduct future mechanistic studies in order to elucidate the exact mechanisms underlying the antihyperglycemic properties of HCQ in both subjects with and without diabetes.

3 | POTENTIAL RISKS OF HCQ USE IN PATIENTS WITH DIABETES

Even though HCQ is considered as one of the safest DMARD and has been widely used for the treatment of RA and SLE,1 data on long-term safety and efficacy of HCQ in diabetes are still lacking. Therefore, the use of HCQ in patients with diabetes should be carefully evaluated, particularly in subjects with established microvascular and/or macrovascular complications.

The most dreaded complication deriving from HCQ use is retinal toxicity.1 However, current evidence suggests that high-dose and long-term (>5 years) use represent the most important predictors of HCQ-induced retinopathy.1 Therefore, the American Academy of Ophthalmology recommends a maximum HCQ dose of ≤5 mg/kg actual body weight per day to markedly minimize the risk of retinopathy.38 Also, HCQ-mediated cardiotoxic effects (including potentially lethal heart rhythm disorders, such as prolonged QT interval, ventricular arrhythmia, and Torsades de Pointes) have been reported.1,39-41 Thus, baseline electrocardiography to evaluate for prolonged QT interval is advisable prior to and following the initiation of HCQ, particularly in high-risk subjects such as hospitalized patients and individuals taking other QT interval-prolonging drugs (eg, macrolides such as azithromycin, quinolones, antihistamines, antiviral and antifungal drugs, anti-arrhythmic medications, etc.).2,42-44 Risk factors for potentially lethal cardiac arrhythmias induced by HCQ include (a) coexisting cardiac conditions such as cardiomyopathy, left ventricular dysfunction, ventricular hypertrophy, coronary artery disease, heart failure, or bradycardia; (b) history of bradycardia, prolonged QT interval, ventricular arrhythmia, or (unexplained) syncope; (c) family history of premature sudden cardiac death or cardiac ion channelopathies; (d) pacemaker and implantable cardioverter-defibrillator use; (e) electrolyte abnormalities such as hypokalemia and hypomagnesemia; (f) genetic and autoimmune channelopathies; (g) systemic inflammation; and (h) concomitant use of azithromycin or other QT interval-prolonging agents.42-51

With regard to the renal function, chronic kidney disease can result in reduced HCQ clearance, increased drug bioavailability and subsequent augmented risk of HCQ-related side effects.1 Furthermore, certain drugs (such as tamoxifen, glycosides, metotrextate, and ciclosporin) can influence the pharmacokinetics of HCQ.1 These drug interactions can increase the risk of HCQ-related side effects and therefore require careful consideration.

Besides the well-known contraindications to HCQ use (including known hypersensitivity to 4-aminoquinoline compounds),2,44 other conditions or circumstances under which HCQ should be contraindicated or used with caution in the context of diabetes include the following:

- Preexisting retinopathy/maculopathy, history or risk for macular edema, and concomitant use of other oculotoxic agents.38,52
- Diabetes complicated by hypoglycemia unawareness, repeated episodes of severe hypoglycemia and/or malnutrition, because of the potential risk for severe hypoglycemic episodes. Although HCQ-induced severe hypoglycemia has mainly been documented in nondiabetic subjects,53-55 there have been a few reports of severe hypoglycemic episodes occurred with the use of HCQ in patients with newly diagnosed T2D56 and established T2D treated with multiple daily injection insulin therapy.11,57
- Preexisting cardiomyopathy or heart failure, because of the possible risk of HCQ-related cardiotoxicity.43
- Preexisting myopathy and/or neuropathy, because of the potential risk of HCQ-induced neuromyotoxicity.58-63
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency, because of the potential increased risk of HCQ-related hemolysis crisis.64 Interestingly,
Heymann et al. found a significantly higher proportion of G6PD-deficient patients among the diabetic population aged 45-64 years. However, a large retrospective study of 275 patients with rheumatic diseases examined the relationship between HCQ use and hemolytic anemia in G6PD-deficient patients, showing that 4% of patients had G6PD deficiency (11 subjects, all African American) and only two of them had episodes of hemolysis that occurred while not taking HCQ. Based on these findings, authors did not support routine measurement of G6PD levels or withholding HCQ therapy in African American patients with G6PD deficiency.

Importantly, a proper risk-benefit assessment of HCQ use in diabetic patients should also be considered in relation to the current coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus SARS-CoV-2 and declared a global pandemic by the World Health Organization on 11 March 2020.

So far, several medications (including HCQ and chloroquine) have been used in hospital settings as off-label drugs for COVID-19 because of the current lack of proven effective therapies. However, a recent observational study conducted on 1376 consecutive hospitalized patients with COVID-19 and moderate-to-severe respiratory illness showed that HCQ did not have a significant impact on the risk of intubation or death over a median follow-up period of 22.5 days. Despite the observational design of this study, these findings do not support HCQ use for treatment of COVID-19 outside randomized, placebo-controlled trials. Indeed, the Food and Drug Administration has recently cautioned against the use of HCQ or chloroquine for COVID-19 outside of hospital- or clinical trial settings due to the risk of potentially lethal cardiac arrhythmias. Nonetheless, several randomized controlled trials are now actively recruiting participants worldwide to assess the safety and efficacy of HCQ (alone or in combination with other drugs) for prophylaxis and treatment of COVID-19.

Importantly, diabetes has reached epidemic proportions over the last years, affecting approximately 463 million people worldwide according to recent estimates. Also, emerging evidence suggests that diabetes represents one of the most prevalent comorbidities in patients with COVID-19, as well as a major risk factor for a worse prognosis of the disease. In light of these remarks, a preemptive and careful evaluation of all the potential risks and benefits related to HCQ is critical for a proper and cautious use of this drug in subjects with diabetes, particularly in the context of COVID-19.

4 | CONCLUSIONS

Over the last decades, several studies have shown that HCQ plays an important role in the regulation of glucose homeostasis through multifaceted effects, including improvement of insulin sensitivity, increase of insulin secretion, reduction of hepatic insulin clearance and intracellular insulin and insulin-receptor complex degradation, and reduction of systemic inflammation, among others (Figure 1). Different studies have shown the safety and efficacy of HCQ use (at a dose ranging from 400 to 600 mg/day) in patients with T2D over a short-term period (up to 18 months). In 2014, HCQ (at a dose of 400 mg/day) has been approved in India as an add-on hypoglycemic agent for patients with inadequately controlled type 2 diabetes despite lifestyle management associated with sulfonylurea and metformin combination therapy. Nevertheless, concerns on long-term safety of HCQ in patients with T2D still persist due to the lack of robust data. Thus, large randomized controlled trials of long duration are warranted to establish the long-term safety and efficacy of this drug in the context of T2D. With regard to the current pandemic scenario, emerging evidence shows that patients with diabetes have a greater risk for adverse outcomes following COVID-19 infection. Although findings from clinical studies have suggested limited benefit from HCQ in COVID-19 in general, several randomized controlled trials are currently investigating the use of HCQ for prophylaxis of COVID-19. Moreover, guidelines from different countries have listed some investigational drugs (including HCQ) as potential adjuvant treatment options, while cautioning to take into account the individual risk of harm. Therefore, a careful risk-benefit assessment of HCQ is required for the most cautious use of this drug in subjects with diabetes.

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DISCLOSURE

None declared.
REFERENCES

1. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16(3):155-166.
2. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020. [Epub ahead of print].
3. Wondafrash DZ, Desalegn TZ, Yimer EM, Tsige AG, Adamu BA, Zewdie KA. Potential effect of hydroxychloroquine in diabetes mellitus: a systematic review on preclinical and clinical trial studies. J Diabetes Res. 2020;2020:5214751.
4. Wasko MC, McClure CK, Kelsey SF, Huber K, Orchard T, Toledo FG. Antidiabetogenic effects of hydroxychloroquine on insulin sensitivity and beta cell function: a randomised trial. Diabetologia. 2015;58(10):2336-2343.
5. Gupta A. Real-world clinical effectiveness and tolerability of hydroxychloroquine 400 mg in uncontrolled type 2 diabetes subjects who are not willing to initiate insulin therapy (HYQ-real-world study). Curr Diabetes Rev. 2019;15(6):510-519.
6. Wasko MC, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. JAMA. 2007;298(2):187-193.
7. Billi A, Sartorius JA, Kirchner HL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol. 2011;17(3):115-120.
8. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying anti-rheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA. 2011;305(24):2525-2531.
9. Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. Rheumatology (Oxford). 2015;54(7):1244-1249.
10. Chen TH, Lai TY, Wang YH, Chiou JY, Hung YM, Wei JC. Hydroxychloroquine was associated with reduced risk of new-onset diabetes mellitus in patients with Sjögren syndrome. QJM. 2019;112(10):757-762.
11. Quatraro A, Consoli G, Magno M, et al. Hydroxychloroquine in uncompensated, treatment-refractory non-insulin-dependent diabetes mellitus. A new job for an old drug? Ann Intern Med. 1990;112(9):678-681.
12. Gerstein HC, Thorpe KE, Taylor DW, Haynes RB. The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas—a randomized trial. Diabetes Res Clin Pract. 2002;55(3):209-219.
13. Rekedal LR, Massarotti E, Garg R, et al. Changes in glycated hemoglobin after initiation of hydroxychloroquine or methotrexate treatment in diabetes patients with rheumatic diseases. Arthritis Rheum. 2010;62(12):3569-3573.
14. Pareek A, Chandurkar N, Thomas N, et al. Efficacy and safety of hydroxychloroquine in the treatment of type 2 diabetes mellitus: a double blind, randomized comparison with placebo. Curr Med Res Opin. 2014;30(7):1257-1266.
15. Purskait I, Pareek A, Panneerselvam SRA, Mukhopadhyay MK, Kumar SRS, Chandratreya SA. 1189-P: effectiveness of hydroxychloroquine (HCQ) 400 mg in uncontrolled T2D patients on dual therapy of metformin and sulfonylurea: a real-world experience in India. Diabetes. 2019;68(Supplement 1):1189.
16. Das AK, Kalra S, Tiwaskar M, et al. Expert group consensus opinion: role of anti-inflammatory agents in the management of type-2 diabetes (T2D). J Assoc Physicians India. 2019;67(12):65-74.
17. Bajaj S. RSDSI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. Int J Diabetes Dev Ctries. 2018;38(Suppl 1):1-115.
18. Sharma M, Kumar M, Dutta D. Hydroxychloroquine in diabetes and dyslipidaemia: primum non nocere. Diabet Med. 2019. [Epub ahead of print].
19. Pareek A, Chandurkar N. Drug approvals in India. Lancet Diabetes Endocrinol. 2016;4(1):19-20.
20. Luthra A, Misra A. Drug approvals in India - authors' reply. Lancet Diabetes Endocrinol. 2016;4(1):20-21.
21. Luthra A, Misra A. The marketing of unproven drugs for diabetes and dyslipidaemia in India. Lancet Diabetes Endocrinol. 2015;3(10):758-760.
22. Halaby MJ, Kastein BK, Yang DQ. Chloroquine stimulates glucose uptake and glycogen synthase in muscle cells through activation of Akt. Biochem Biophys Res Commun. 2013;435(4):708-713.
23. Powrie JK, Smith GD, Shojaei-Moradie F, Sönksen PH, Jones RH. Mode of action of chloroquine in patients with non-insulin-dependent diabetes mellitus. Am J Physiol. 1991;260(6 Pt 1):E897-E904.
24. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013;30(7):803-817.
25. Leighton E, Sainsbury CA, Jones GC. A practical review of C-peptide testing in diabetes. Diabetes Ther. 2017;8(3):475-487.
26. Emami J, Gerstein HC, Pasutto FM, Jamali F. Insulin-sparing effect of hydroxychloroquine in diabetic rats is concentration dependent. Can J Physiol Pharmacol. 1999;77(2):118-123.
27. Emami J, Pasutto FM, Mercer JR, Jamali F. Inhibition of insulin metabolism by hydroxychloroquine and its enantiomers in cytosolic fraction of liver homogenates from healthy and diabetic rats. Life Sci. 1999;64(5):325-335.
28. Mercer E, Rekedal L, Garg R, Lu B, Massarotti EM, Solomon DH. Hydroxychloroquine improves insulin sensitivity in obese non-diabetic individuals. Arthritis Res Ther. 2012;14(3):R135.
29. Solomon DH, Garg R, Lu B, et al. Effect of hydroxychloroquine on insulin sensitivity and lipid parameters in rheumatoid arthritis patients without diabetes mellitus: a randomized, blinded crossover trial. Arthritis Care Res (Hoboken). 2014;66(8):1246-1251.
30. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3(11):722-727.
31. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116(7):1784-1792.
32. Frühbeck G, Catalán V, Rodríguez A, et al. Involvement of the leptin-adiponectin axis in inflammation and oxidative stress in the metabolic syndrome. Sci Rep. 2017;7(1):6619.
33. Calle MC, Fernandez ML. Inflammation and type 2 diabetes. Diabetes Metab. 2012;38(3):183-191.
34. Greenbaum C, VanBuecken D, Lord S. Disease-modifying therapies in type 1 diabetes: a look into the future of diabetes practice. Drugs. 2019;79(9):43-61.
35. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11(2):98-107.
36. Böni-Schnetzler M, Meier DT. Islet inflammation in type 2 diabetes. Semin Immunopathol. 2019;41(4):501-513.
37. Eguchi K, Nagai R. Islet inflammation in type 2 diabetes and physiology. J Clin Invest. 2017;127(1):14-23.
38. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, American Academy of Ophthalmology. Recommendations on screening for choroiditis and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016;123(6):1386-1394.
39. Chen CY, Wang PL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila). 2006;44(2):173-175.
40. Morgan ND, Patel SV, Dvoroka O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. J Clin Rheumatol. 2013;19(5):286-288.
41. O’Laughlin JP, Mehta PH, Wong BC. Life threatening severe QTc prolongation in a patient with systemic lupus erythematosus due to hydroxychloroquine. Case Rep Cardiol. 2016;2016:462679.
42. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for drug interactions on QTc in exploratory COVID-19 (coronavirus disease 2019) treatment. Circulation. 2020.
43. Sapp JL, Alqarawi W, MacIntyre CJ, et al. Guidance on minimizing risk of drug-induced ventricular arrhythmia during treatment of COVID-19: a statement from the Canadian Heart Rhythm Society. Can J Cardiol. 2020. [Epub ahead of print].
44. Kapoor A, Pandurangi U, Arora V, et al. Cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients: a scientific statement from the Indian Heart Rhythm Society. Indian Pacing Electrophysiol J. 2020. [Epub ahead of print].
45. Bloomgarden Z. Is the type of diabetes treatment relevant to outcome of COVID-19? J Diabetes. 2020. [Epub ahead of print].
46. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020. [Epub ahead of print].
47. Bessière F, Roccia H, Delinière A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. JAMA Cardiol. 2020. [Epub ahead of print].
48. Bonow RO, Hernandez AF, Turakhia M. Hydroxychloroquine, coronavirus disease 2019, and QT prolongation. JAMA Cardiol. 2020. [Epub ahead of print].
49. Modell SM, Lehmann MH. The long QT syndrome family of cardiac ion channelopathies: a HuGE review. Genet Med. 2006;8(3):143-155.
50. Lazzerini PE, Capeccchi PL, Laghi-Pasini F, Boutjdir M. Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. Nat Rev Cardiol. 2017;14(9):521-535.
51. Aromolaran AS, Srivastava U, Ali A, et al. Interleukin-6 inhibition of hERG underlies risk for acquired long QT in cardiac and systemic inflammation. PLoS One. 2018;13(12):e0208321. 52. Yusuf IH, Sharma S, Luqmani R, Downes SM. Hydroxychloroquine retinopathy. Eye (Lond). 2017;31(6):828-845.
53. Cansu DUK, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. Rheumatology (Oxford). 2008;47(3):378-379.
54. El-Solia A, Al-Otaibi K, Ai-Hwiesh AK. Hydroxychloroquine-induced hypoglycaemia in non-diabetic renal patient on peritoneal dialysis. BMJ Case Rep. 2018;2018:bcr2017223639.
55. Dai Y, Lin G, Shi D. Hypoglycemia induced by hydroxychloroquine sulfate in a patient treated for connective tissue disease without diabetes mellitus. Clin Ther. 2020;30:149-2918 (20):30176-4.
56. Unübol M, Ayhan M, Güney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. J Clin Rheumatol. 2011;17(1):46-47.
57. Shojania K, Koehler BE, Elliott T. Hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polycythemia. J Rheumatol. 1999;26(1):195-196.
58. Kwon JB, Kleiner A, Ishida K, Godown J, Ciafaloni E, Looney RJ. Hydroxychloroquine-induced myopathy. J Clin Rheumatol. 2010;16(1):28-31.
59. Rothenberg RJ, Suft RL. Drug-induced peripheral neuropathy in a patient with psoriatic arthritis. Arthritis Rheum. 1987;30(2):221-224.
60. Stein M, Bell MJ, Ang LC. Hydroxychloroquine neuromyotoxicity. J Rheumatol. 2000;27(12):2927-2931.
61. Bolaños-Meade J, Zhou L, Hoke A, Corse A, Vogelsang G, Wagner KR. Hydroxychloroquine causes severe vacuolar myopathy in a patient with chronic graft-versus-host disease. Am J Hematol. 2005;78(4):306-309.
62. Casado E, Gratacos J, Tolosa C, et al. Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients. Ann Rheum Dis. 2006;65(3):385-390.
63. Shukla S, Gultekin SH, Saporta M. Pears & Oysters: hydroxychloroquine-induced toxic myopathy mimics Pompe disease: critical role of genetic test. Neurology. 2019;92(7):e742-e745.
64. Beauregard Y, Adam Y, Assouline B, Samii K. COVID-19 infection and treatment with hydroxychloroquine cause severe haemolysis crisis in a patient with glucose-6-phosphate dehydrogenase deficiency. Eur J Haematol. 2020. [Epub ahead of print].
65. Heymann AD, Cohen Y, Chodick G. Glucose-6-phosphate dehydrogenase deficiency and type 2 diabetes. Diabetes Care. 2012;35(8):e58.
66. Mohammad S, Clowse MEB, Eudy AM, Criscione-Schreiber LG. Examination of hydroxychloroquine use and hemolytic anemia in G6PDH-deficient patients. Arthritis Care Res (Hoboken). 2018;70(3):481-485.
67. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.
68. Fauzi AS, Lane HC, Redfield RR. Covid-19 - navigating the uncharted. N Engl J Med. 2020;382(13):1268-1269.
69. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020. [Epub ahead of print].
70. Rubin EJ, Harrington DP, Hogan JW, Gatsonis C, Baden LR, Hamel MB. The urgency of care during the COVID-19
pandemic - learning as we go. *N Engl J Med*. 2020. [Epub ahead of print].

71. FDA Drug Safety Communication. Safety Announcement. https://www.fda.gov/media/137250/download. Accessed April 24, 2020.

72. “Condition or Disease”: COVID; “other terms”: hydroxychloroquine. https://clinicaltrials.gov/. Accessed April 19, 2020.

73. Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 diabetes: demystifying the global epidemic. *Diabetes*. 2017;66(6):1432-1442.

74. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9. *Diabetes Res Clin Pract*. 2019;157:107843.

75. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med*. 2020;382(21):2012-2022.

76. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5):2000547.

77. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.

78. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;e3319. [Epub ahead of print].

79. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest*. 2020;43(6):867-869.

80. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr*. 2020;14(4):395-403.

81. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. *Nat Rev Endocrinol*. 2020;16(6):297-298.

82. Muniyappa R, Gubbi S. COVID-19 pandemic, corona viruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab*. 2020;18(5):E736-E741.

83. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. *Endocr Rev*. 2020;41(3):bmaa011.

84. Hsia SH, Duran P, Lee ML, Davidson MB. Randomized controlled trial comparing hydroxychloroquine with pioglitazone as third-line agents in type 2 diabetic patients failing metformin plus a sulfonylurea: A pilot study. *J Diabetes*. 2020;12(1):91-94.

85. Xu X, Ong YK, Wang Y. Role of adjunctive treatment strategies in COVID-19 and a review of international and national clinical guidelines. *Mil Med Res*. 2020;7(1):22.

86. Lombardy Section Italian Society Infectious and Tropical Diseases. Vademecum for the treatment of people with COVID-19. Edition 2.0, 13 March 2020. *Infez Med*. 2020;28(2):143-152.

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