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Treating diabetes with combination of phosphodiesterase 5 inhibitors and hydroxychloroquine—a possible prevention strategy for COVID-19?

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Abstract

Type 2 diabetes (T2D) is one of the major risk factors for developing cardiovascular disease and the resultant devastating morbidity and mortality. The key features of T2D are hyperglycemia, hyperlipidemia, insulin resistance, and impaired insulin secretion. Patients with diabetes and myocardial infarction have worse prognosis than those without T2D. Moreover, obesity and T2D are recognized risk factors in developing severe form of COVID-19 with higher mortality rate. The current lines of drug therapy are insufficient to control T2D and its serious cardiovascular complications. Phosphodiesterase 5 (PDE5) is a cGMP specific enzyme, which is the target of erectile dysfunction drugs including sildenafil, vardenafil, and tadalafil. Cardioprotective effects of PDE5 inhibitors against ischemia/reperfusion (I/R) injury were reported in normal and diabetic animals. Hydroxychloroquine (HCQ) is a widely used antimalarial and anti-inflammatory drug and its hyperglycemia-controlling effect in diabetic patients is also under investigation. This review provides our perspective of a potential use of combination therapy of PDE5 inhibitor with HCQ to reduce cardiovascular risk factors and myocardial I/R injury in T2D. We previously observed that diabetic mice treated with tadalafil and HCQ had significantly reduced fasting blood glucose and lipid levels, increased plasma insulin and insulin-like growth factor-1 levels, and improved insulin sensitivity, along with smaller myocardial infarct size following I/R. The combination treatment activated Akt/mTOR cellular survival pathway, which was likely responsible for the salutary effects. Therefore, pretreatment with PDE5 inhibitor and HCQ may be a potentially useful therapy not only for controlling T2D but also reducing the rate and severity of COVID-19 infection in the vulnerable population of diabetics.

Keywords Cardioprotection · Diabetes · Chloroquine · Inflammation · Myocardial infarction · Phosphodiesterase inhibitors

Introduction

Type 2 diabetes (T2D) is one of the major risk factors for developing cardiovascular (CV) disease and the resultant devastating morbidity and mortality in the world [1, 2]. The main features of T2D are hyperglycemia, hyperlipidemia, insulin resistance and reduced insulin production in the late stages of the disease. Patients with diabetes and myocardial infarction (MI) have worse prognosis than those without diabetic co-morbidity [3]. Moreover, individuals with diabetes are resistant to most of the cardioprotective modalities that are normally beneficial in the non-diabetic people [4, 5]. In the diabetic heart, reduced glucose uptake and increased circulating free fatty acids lead to shift of energy substrate from carbohydrates to fatty acids, resulting in less ATP production with more oxygen consumption, which makes cells more susceptible to myocardial ischemia [6]. It has been suggested that diabetic hearts retain metabolic flexibility to adapt to hypoxia and become more dependent on oxidative metabolism following hypoxia with 30% lower glycolytic rates and 36% higher fatty acid oxidation than non-diabetic controls, which lead to functional deficit in response to

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ischemic stress [7]. Thus, normalization of circulating glucose and lipid levels is an important therapeutic strategy for management of diabetic patients [2, 8, 9].

The pathology of myocardial ischemia/reperfusion (I/R) injury involves multiple pathways, which include calcium overload, pH paradox, generation of reactive oxygen species (ROS), inflammation, endothelial dysfunction, and altered myocardial metabolism [10]. Numerous therapeutic strategies targeting single mechanistic pathway have limited effect on human and animal models, indicating that myocardial I/R injury is a complex confluence of divergent biological signaling. Due to the pathogenic complexity, the current lines of drug therapy are insufficient to control diabetes and its serious cardiovascular complications. There is an ongoing search for new and more effective therapies for management of T2D and its CV consequences.

Phosphodiesterase 5 inhibitors and diabetes

Phosphodiesterases (PDEs) belong to a class of phosphohydrolytic enzymes that modulate the intensity of intracellular second messenger signaling by catalyzing the degradation of 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′cyclic guanosine monophosphate (cGMP) molecules to their inactive 5′ AMP and 5′ GMP forms, respectively. PDEs are divided into 11 different families, which include 21 different genes and comprises more than 100 enzyme variants that are generated from multiple promoters and products of alternative splicing [11, 12]. Phosphodiesterase 5 (PDE5) inhibitors are a class of drugs widely used to treat erectile dysfunction (ED). Two of the PDE5 inhibitors sildenafil and tadalafil (TAD) are also approved by FDA for the treatment of pulmonary arterial hypertension [13–15]. Tadalafil is a long-acting drug with the average half-life of 17.5 h whereas the duration of actions of sildenafil and vardenafil is generally 4–8 h [16]. Tadalafil has the advantage of being more than 10,000-fold selective for PDE5 over PDE1 to PDE4 and nearly 600-selectivity over PDE6. Moreover, the activity of tadalafil is unaffected by food and has short time (nearly 16–17 min) to onset of action as compared to other PDE5 inhibitors. Several studies from our laboratory have shown that PDE5 inhibitors protect against myocardial I/R injury in both healthy and diabetic animals [17]. The underlying molecular mechanism of cardioprotection with PDE5 inhibitors involves induction of nitric oxide (NO) synthase [18, 19], which leads to subsequent NO-cGMP-protein kinase G (PKG) signaling cascade with promotion of hydrogen sulfide production [20], activation of extracellular signal-regulated kinase 1/2 (Erk1/2) pathway [21], and opening of mitochondrial K_{ATP} channels [22].

Metabolic syndrome is a complex systemic disorder, which is comprised of multiple inter-related factors including abdominal obesity, abnormal glucose metabolism, hypertension, insulin resistance, endothelial dysfunction, and inflammatory reaction [23, 24], and may lead to the development of CV diseases [25]. Long-term treatment with sildenafil reduced body weight gain and visceral fat in high fat-fed mice and rats by preventing diet-induced energy balance [26, 27]. In fact, PDE5 is involved in adipocyte physiology and it has been suggested that its inhibition may affect adipogenesis and ameliorate white adipose tissue quality. Chronic treatment with sildenafil had beneficial effects on subcutaneous adipose tissue plasticity in type 2 diabetic mice. Therefore, treatment with PDE5 inhibitors may reduce weight gain by different mechanisms than fat cell lipolysis. Clinical studies suggest a potential protective role of PDE5 inhibitors on endothelial function in short- and long-term assessments [28–30]. Diabetic patients with ED are at increased risk for silent coronary artery disease and ED is also is powerful predictor of CV morbidity and mortality [31]. TAD treatment in men with ED showed improved endothelial function, increased insulin levels and a robust decrease in the inflammatory marker, high sensitivity C-reactive protein (hs-CRP) [32]. Furthermore, both acute and chronic administration of sildenafil improved endothelial function in patients with T2D as shown by improved flow-mediated dilatation of the brachial artery [32, 33]. PDE5 inhibitors may have potentially reduced CV events in high risk populations such as men with T2D [34–36].

As indicated before, the diabetic myocardium is vulnerable to I/R injury, which has been confirmed in diabetic animal models with hyperinsulinemia [37, 38]. We first demonstrated that chronic treatment of db/db diabetic mice with TAD ameliorated circulating inflammatory cytokines and chemokines while improving fasting glucose levels and reduced infarct size following myocardial I/R injury [39]. Also, chronic treatment with TAD reduced blood glucose and triglyceride levels [39], indicating beneficial effects in maintaining homeostasis of whole body metabolism under conditions of T2D. Likewise, long-term treatment with TAD improved LV diastolic dysfunction (E/A ratio) in C57BL/6NCrl-Lepr^{db-lb}/Crl strain mice, a model which fulfills all the criteria of metabolic syndrome (MetS) [40]. Also, TAD had positive effect on the metabolic health status by improving insulin sensitivity, lowering circulating lipids, and protecting against I/R injury via enhanced NO production in MetS mice. This study was particularly important since the favorable effects of TAD treatment in these mice could clinically benefit MetS patients who are at high risk for CV disease. While the mechanism of these antidiabetic effects is not fully clear, our studies showed that TAD treatment upregulated myocardial SIRT1, PGC-1α expression, and increased phosphorylation of Akt as well as AMPK in the diabetic hearts. In addition, TAD treatment normalized oxidative phosphorylation and attenuated reactive oxygen

species production from complex I in the diabetic heart [41]. Using proteomic approaches, we further demonstrated increased expression of antioxidant mitochondrial enzyme glutathione S-transferase Kappa-1 (GSKT-1) and downregulation of redox regulatory chaperones like heat shock protein 8 (HSPA8), and 75 kD glucose regulatory protein (75GRP). Thus, it appears that chronic treatment with TAD in db/db mice modulates proteins involved in cytoskeletal rearrangement and redox signaling of the heart, which may explain the beneficial effects of PDE5 inhibition in diabetes [42, 43]. More recently, a relationship between PDE5 and β2 adrenergic receptor (β2AR) has been suggested which could be a mechanistic axis by which sildenafil improves symptoms of diabetic cardiomyopathy [44]. It was shown that PDE5 inhibition enhanced β2AR stimulation of cGMP and cAMP signals, as well as PKG-dependent excitation–contractile coupling in myocytes derived from high fat diet-fed mice (Fig. 1).

In a clinical study, chronic treatment with sildenafil in diabetic men with non-ischemic, nonfailing diabetic cardiomyopathy had an anti-remodeling effect, resulting in improved cardiac kinetics and circulating markers [45]. This effect was reported to be independent of any other vasodilatory or endothelial effects and is apparently exerted through a direct intramyocardial action. More recently, TAD was shown to improve maladaptive cardiac kinetic changes in diabetic men as compared to women [46]. However, TAD treatment reduced hsa-miR-199-5p with increased α-Klotho and improved low-grade inflammation thereby halting renal disease progression in both sexes. Intriguingly, this trial uncovered new molecular pathways targeted by PDE5 inhibition, which may have a role in prevention of cardiac remodeling and renal complication in T2D [46]. Table 1 summarizes a series of completed and ongoing clinical trials using PDE5 inhibitors in management of T2D patients and may be referred for further information.

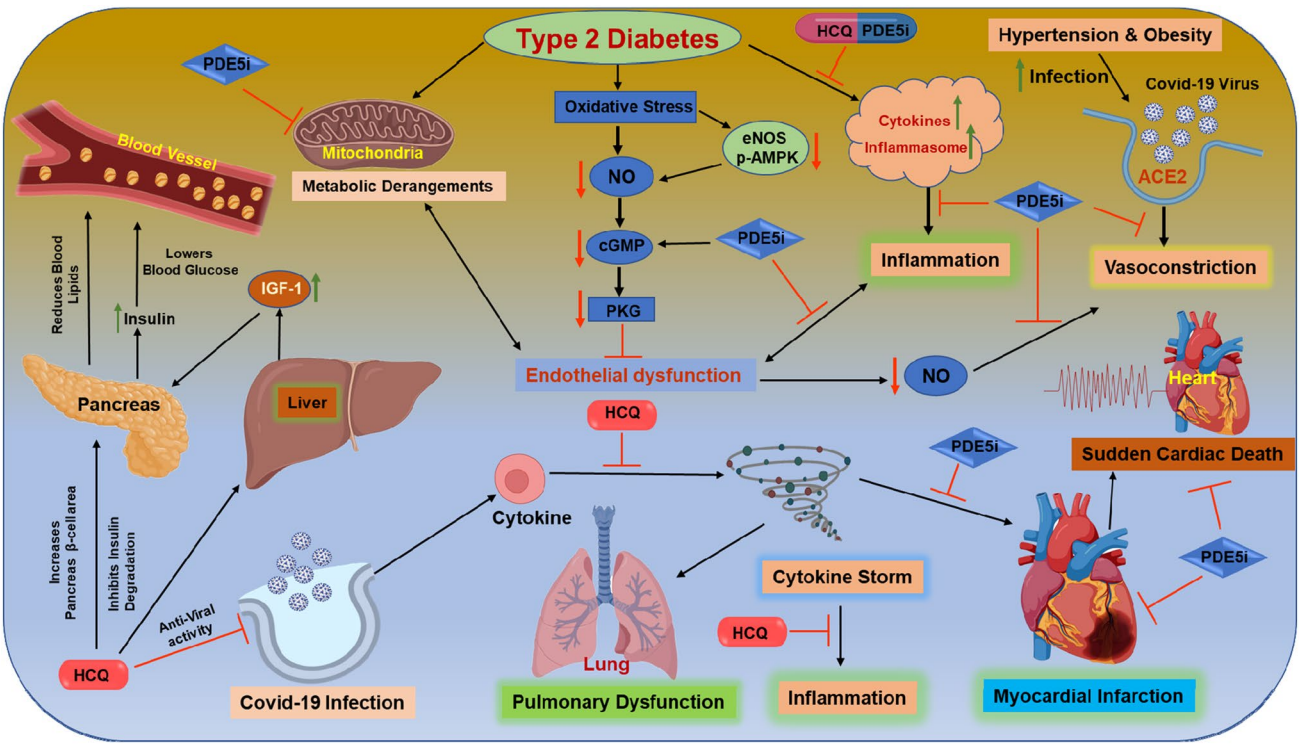

Fig. 1 Protective mechanisms of phosphodiesterase 5 (PDE5) inhibitors and hydroxychloroquine (HCQ) against Type II diabetes and pathophysiology of COVID-19 infection. Type II diabetes leads to oxidative stress, inflammation, metabolic derangement, downregulation of NO/cGMP/PKG signaling resulting in endothelial dysfunction and vasoconstriction. These conditions predispose diabetic individuals extremely vulnerable to severe COVID-19 infection and "cytokine storm", which may lead to high risk of vascular hyperpermeability, pulmonary dysfunction, increased risk of myocardial infarction, and sudden cardiac death. PDE5 inhibitors are known to activate NO/cGMP/PKG signaling pathway, which may improve pulmonary function and exert cardioprotective effect. HCQ can exert anti-diabetes actions via inhibiting insulin degradation as well as enhancing pancreatic insulin secretion, along with its well-known anti-inflammatory effects. Furthermore, PDE5 inhibitors and HCQ may also suppress SARS-CoV-2 cell entry/viral proliferation and alleviate the pathological events (e.g., cytokine storm) of COVID-19 in the vital organs, such as heart and lungs. *eNOS* endothelial nitric oxide synthase, *HCQ* hydroxychloroquine, *NO* nitric oxide, *cGMP* cyclic guanosine monophosphate, *PKG* protein kinase G, *COVID-19* coronavirus disease 2019, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *ACE2* angiotensin-converting enzyme 2. The authors would like to acknowledge the use of software of BioRender.com for drawing this figure

Table 1 Representative completed or ongoing clinical trials and/or published clinical studies concerning the therapeutic effects of phosphodiesterase 5 (PDE5) inhibitors on type 2 diabetes (T2D)

Trial ID and other information	Number of T2D patients and their health conditions	HCQ dosage, protocol, endpoints	Key clinical and basic research findings	Current status
1 Randomized, double-blind, placebo-controlled, cross-over trial NCT00527995 *Acute Effects of Sildenafil on Flow Mediated Dilatation and Cardiovascular Autonomic Nerve Function in Type 2 Diabetic Patients* PI: Stirban, A., German Diabetes Center Duesseldorf, Germany Started: August 2001 Completed: June 2003	40 male 35–70 years old patients with T2D as well as impotence, with and without hypertension and hypercholesteremia	Sildenafil 100 mg or placebo p.o. once; *Primary Endpoints:* Improvement of flow mediated dilatation of the brachial artery following a single dose of 100 mg Sildenafil. Time Frame: 60 min; *Secondary Endpoints:* Change in hemodynamics and cardiovascular parasympathetic and sympathetic nerve function using heart rate variability (HRV), baroreflex sensitivity (BRS) following a single dose of 100 mg Sildenafil. Time Frame: 60 min	60 min after administration of sildenafil but not placebo, a fall of supine systolic blood pressure (SBP) (-5.41 ± 1.87 vs. $+0.54 \pm 1.71$ mmHg) and diastolic blood pressure (DBP) (-4.46 ± 1.13 vs. $+0.89 \pm 0.94$ mmHg), as well as standing SBP (-7.41 ± 2.35 vs. $+0.94 \pm 2.06$ mmHg) and DBP (-5.65 ± 1.45 vs. $+1.76 \pm 1.00$ mmHg), accompanied by an increase in heart rate ($+1.98 \pm 0.69$ vs -2.42 ± 0.59 beats/min), $p < 0.01$ vs. placebo. HRV and BRS were comparable between sildenafil and placebo	Completed and results published in Stirban A et al. 2009 [30]
2 Randomized, double-blind, placebo-controlled trial of 4 weeks of oral drug treatment NCT00645268 *A Multicenter, Double-blind Study to Evaluate the Effect of Pretreatment With a Daily Dose of Sildenafil on the As-Needed Efficacy of Viagra in Men With Erectile Dysfunction and Type 2 Diabetes* PI: Pfizer, USA Started: December 2002 Completed: January 2004	300 male 35–70 years old T2D patients with HbAlc < 10 and erectile dysfunction, currently on insulin or combination therapy with another oral hypoglycemic agent	Sildenafil 50 mg once daily during Week 1 (7 doses), followed by a daily dose of sildenafil 100 mg during the next 3 weeks *Primary Endpoints:* Measures The IIEF Erectile Function (EF) Domain score, Time Frame: Week 4 *Secondary Endpoints:* Flow mediated brachial artery dilation (FMD) as an index of generalized endothelial function, Time Frame: Week 4, 6, and 16	Results not available	Completed, but results have not published yet

Table 1 (continued)

Trial ID and other information	Number of T2D patients and their health conditions	HCQ dosage, protocol, endpoints	Key clinical and basic research findings	Current status
3 Randomized, double-blind, parallel-arm trial NCT00692237 *Cardiovascular Effects of Chronic Sildenafil in Men With Type 2 Diabetes (CECSID)* PI: Lenzi, A., University of Roma La Sapienza, Italy Started: January 2008 Completed: December 2009	59 male T2D patients (age 60.3 ± 7.4 years), 30 received Sildenafil 100 mg and 29 received placebo	Sildenafil (100 mg/day) were orally taken 3 capsules per day (25 mg at 8.00 a.m. + 25 mg at 4.00 p.m. + 50 mg at 10.00 p.m.); Identical-looking placebo capsules were treated for the same duration; *Primary Endpoints:* Changes of cardiac performance, measured by MRI analysis of left ventricular torsion, before and after 3 months of 100 mg Sildenafil daily treatment. Time Frame: 0 and 3 months	After 3 months of treatment, sildenafil significantly improved left ventricular torsion (sildenafil, − 3.89 ± 3.11° versus placebo, 2.13 ± 2.35°; $p < 0.001$) and strain (sildenafil, − 3.30 ± 1.86 versus placebo, 1.22 ± 1.84; $p < 0.001$). Sildenafil improved ventricular chamber geometry and performance with a improvement in mass-to-volume ratio over placebo ($p < 0.05$). No changes in endothelial function, afterload, and metabolism occurred In conclusion, chronic PDE5 inhibition has anti-remodeling effect, resulting in improved cardiac kinetics and circulating markers. This effect is direct to myocardium and seems to be independent of vasodilatory or endothelial effects Sildenafil significantly decreased P-selectin, post-prandial glycemia, HbA1c, low-density lipoprotein cholesterol, and increased high-density lipoprotein	Completed and results published in 1. Giannetta E et al. 2012 [45] 2. Mandosi E et al. 2015 [134] 3. Venneri MA et al. 2019 [135] 4. Pofi R et al. 2020 [136]
4 Randomized, quadruple-blind, placebo-control trial NCT01238224 *Effects of PDE-5 Inhibition on Post-prandial Hyperglycemia in Type 2 Diabetes* PI: Jansson, P.A Sahlgrenska University Hospital at University of Göteborg, Sweden Started November 2009 Completed November 2011	7 postmenopausal women with T2D (age 55 to 65 years; BMI 27 to 35 kg/m^2; HbA1c 5% to 7.5%) and 10 age-matched healthy female controls (BMI 18 to 25 kg/m^2)	A single dose of Tadalafil 20 mg or placebo; *Primary Endpoints:* Capillary recruit-ment and glucose uptake in forearm muscle as well as circulating glucose levels following acute administration of tadalafil or placebo. Time Frame: 5 h after a mixed meal *Secondary Endpoints:* Arterial stiffness as measured by pulse wave velocity and circulating biomarkers of metabolic variables	In female T2D patients, but not in the healthy control females, tadalafil increases the incremental area under curve (AUC) for permeability surface area for glucose PS(glu) (tadalafil vs placebo 41 ± 11 vs 4 ± 2 ml/100 g/min ($p < 0.05$) and forearm glucose uptake (46 ± 9 vs 8 ± 4 µmol/100 g/min, $p < 0.05$). Fasting glucose and insulin concentrations were similar between placebo and tadalafil treatment	Completed and results published in Jansson PA et al. 2010 [137]

Table 1 (continued)

Trial ID and other information	Number of T2D patients and their health conditions	HCQ dosage, protocol, endpoints	Key clinical and basic research findings	Current status
5 Randomized, multicenter, double-blind, placebo-control trial NCT01200394 *A Phase 2, Placebo-Controlled Study To Evaluate The Efficacy And Safety Of PF-00489791 In Patients With Type 2 Diabetes And Overt Nephropathy* PI: Pfizer, USA Started December 2010 Completed August 2013	256 T2D patients of either gender with an eGFR between 25 and 60 ml/min per 1.73 m^2 and macro-albuminuria (urinary albumin-to-creatinine ratio > 300 mg/g)	PDE5 inhibitor, PF-00489791 tablet, 20 mg once daily or placebo for 12 weeks; *Primary Endpoints:* Change from baseline in urinary albumin creatinine ratio (UACR) at Week 12; Time Frame: Baseline, Week 12 (Day 5, 6, 7)	12-week treatment with PF-00489791 led to a significant reduction in urinary albumin-to-creatinine ratio of 15.7% (ratio 0.843) as compared with placebo. PF-00489791 was safe and generally well tolerated in the T2D patient population, suggesting that PF-00489791 may improve renal outcomes in diabetic nephropathy	Completed and results published in Scheele W et al 2016 [138]
6 Randomized, double-blind, placebo-controlled trial NCT02219646 *Diabetes & Vardenafil (DiVa)* PI: Simoni, M., Azienda USL of Modena, Italy Started March 2010 Competed February 2013	54 male T2D patients with erectile dysfunction, among them, 26 patients received Vardenafil and 28 patients received placebo	Vardenafil 10 mg twice daily or placebo two tablets per day for six months; *Primary Endpoints:* Change in serum endothelin 1 concentration; Time Frame: 6 months; *Secondary Endpoints:* Flow mediated dilation (FMD)	IIEF-15 erectile function improved during vardenafil treatment ($p < 0.001$). At the end of the treatment both FMD and IL6 significantly improved. Testosterone increased significantly under vardenafil treatment and returned in the eugonadal range only in hypogonadal men (n = 13), without affecting gonadotropin Chronic vardenafil improves endothelial parameters and hypogonadism in male T2D patients	Completed and results published in Santi D et al. 2016 [139]
7 Randomized, quadruple-blind, placebo-controlled trial NCT02601989 *Effects on Insulin Resistance With Tadalafil in Type 2 Diabetes—a Double-blind, Placebo-controlled Crossover Study (MAKROTAD)* PI: Jansson, P.A Sahlgrenska University Hospital at University of Göteborg, Sweden Started November 2015 Competed January 2019	23 patients with T2D; 40 to 70 years, either gender	Oral intake of Tadalafil 20 mg o.d. for 6 weeks; *Primary Endpoints:* Insulin sensitivity; Time Frame: 6 week treatment with drug or placebo	Results not available	Completed, but results are not published yet

Table 1 (continued)

Trial ID and other information	Number of T2D patients and their health conditions	HCQ dosage, protocol, endpoints	Key clinical and basic research findings	Current status
8 Randomized, double-blind, placebo-controlled trial NCT01803828 *REmodelling in Diabetic CardiOmapathy: Gender Response to PDE5i InhibiTORs (RECOGITO)* PI: Isidori, A.M., University of Roma La Sapienza, Italy Started May 2014 Competed July 2019	120 patients with T2D; 45 to 80 years, either gender, HbA1c < 10%; normal blood pressure or controlled hypertension; BMI < 40	Oral intake of Tadalafil 20 mg per day for 5 weeks; *Primary Endpoints:* Change from baseline in Left Ventricular torsion at 5 months; Time Frame: time 0, 5 months *Secondary Endpoints:* Change from baseline in cardiac shortening (Strain %) at 5 months	A total of 122 men and women (45 to 80 years) with long-duration (> 3 years) and well-controlled T2D (HbA1c < 86 mmol/mol) were selected. At 20 weeks, there was an improved cardiac torsion (− 3.40°, − 5.96; − 0.84, P = 0.011) in men but not women In both sexes, tadalafil improved has-miR-199-5p expression, a biomarker of cardiovascular remodeling, albuminuria, renal artery resistive index, and circulating Klotho concentrations. Immune cell profiling revealed tadalafil-induced improvement in low-grade chronic inflammation	Completed and results published in Pofi R et al. 2022 [46]

Hydroxychloroquine in treatment of diabetes

Hydroxychloroquine (HCQ), an analogue of the parent compound chloroquine, is a first-in-line anti-malarial drug widely used in the patients. HCQ has multiple therapeutic properties including anti-inflammatory, immunomodulating, anti-infective, and antithrombotic actions [47]. This drug has been routinely used to treat systemic lupus erythematosus and rheumatoid arthritis [48, 49]. Recent studies have suggested that chloroquine interferes with different metabolic pathways including cholesterol, glucose, amino acids, and mitochondria metabolism [50]. Chloroquine is reported to improve insulin sensitivity through the activation of Akt which increases glucose uptake and glycogen synthesis in L6 muscle cell lines [51]. A few clinical case reports indicated that both chloroquine and HCQ improved glycemic control in patients with type 1 diabetes, partially through the inhibition of insulin degradation [52, 53]. A 3-day oral treatment with chloroquine in 20 patients led to improved serum lipid profile along with increased fasting insulin levels in T2D patients [54]. In alloxan-induced diabetic rats, a high dose combination of HCQ (10 mg/kg) and lipid-lowering drug, atorvastatin (200 mg/kg) demonstrated 21% reduction in blood glucose levels than low dose combinations and individual treatments [55]. HCQ inhibits the degradation of insulin, which enhances the metabolic effects and improves insulin sensitivity [56]. HCQ users among rheumatoid arthritis patients had lower risk of developing diabetes [57] suggesting a potential protective effect of HCQ against insulin resistance.

It is noteworthy that the use of HCQ in diabetic patients appears to be safe, based on a prospective, randomized, placebo, double-blind 6-month trial conducted in 1990 on HCQ therapy (200 mg × 3 times per day) in 38 decompensated, treatment-refractory T2D patients [58]. After 6 months, 11 patients who received insulin and HCQ had a significant decrease in blood glucose (− 11.7 mmol/L) and glycated hemoglobin A1c (HbA1c, − 3.3%). No major side effects were detected. In addition, Gerstein et al. conducted a randomized trial in 2002 in 135 patients with obesity and T2D who were refractory to sulfonylureas [59]. The results showed that HCQ decreased HbA1c and improved glucose tolerance without significant adverse effects during the first 6 months of treatment [59]. Another randomized, double-blind, parallel-arm (placebo vs HCQ 400 mg/day) trial in non-diabetic individuals [60] reported that HCQ treatment significantly improved insulin sensitivity, β-cell function as well as fasting plasma glucose and HbA1c. Again, there were no serious or unexpected adverse effects in HCQ-treated participants. These authors also found that

HCQ elevated adiponectin, which may mediate the HCQ-induced improvement in glucose metabolism. Table 2 provides a summary of the completed and ongoing clinical trials using HCQ in management of T2D patients.

Therapeutic effects of tadalafil and hydroxychloroquine against myocardial ischemia/reperfusion injury in type 2 diabetes

Based on the abovementioned cardioprotective of PDE5 inhibitors and anti-ischemic effects HCQ [61, 62], we contemplated that combination treatment with TAD and HCQ may synergistically protect type 2 diabetic db/db mice from I/R injury. Accordingly we conducted a study in adult male *db/db* mice with T2D (fasting glucose levels ranging 200–400 mg/dL). Oral dose of HCQ 50 mg/kg/day [63] was administered, which is compatible with the human dose of 250 mg/day for rheumatoid arthritis and systemic lupus erythematosus. The co-treatment with TAD and HCQ for 7 days significantly reduced myocardial infarct size following I/R injury and increased cardiac ATP production [64]. The cardioprotective effects of TAD and HCQ combination also improved lipid and glucose profiles and upregulated the levels of insulin and insulin-like growth factor-1 (IGF-1), which possibly lead to activation of PI3K/Akt/mTOR pathway in β-cells [64]. The mass of pancreas and insulin + β-cell area was increased in TAD- and HCQ-treated groups, suggesting their protective effect on β-cells [64]. Interestingly, previous clinical studies also reported improvement in β-cell function with HCQ or TAD in human subjects [60, 65].

IGF-1 system is interrelated with the insulin signaling [66] to control blood glucose levels [67]. Both insulin and IGF-1 bind to insulin receptors and IGF-1 receptors with different affinity, regulating cell survival through activation of the PI3K-Akt pathway [68, 69]. The co-treatment of TAD + HCQ showed higher plasma levels of IGF-1 as compared to the single drug treatment [64]. Treatment with TAD, HCQ or their combination significantly increased Akt phosphorylation at Thr308, suggesting enhanced cell survival signaling. It has been shown that insulin can protect against I/R injury via facilitating glucose transport [70], inhibition of apoptosis and inflammation [71], and suppression of reactive oxidative species [72]. Insulin and IGF-1 could also improve mitochondrial function through PI3K/Akt pathway [73]. In addition, IGF-1 exerts its indirect cardioprotective effect by increasing insulin sensitivity in various organs/tissues [74].

Potential anti-inflammatory properties of tadalafil and hydroxychloroquine

The anti-inflammatory properties of HCQ have been recognized and utilized for treatment of rheumatoid arthritis in patients around 1950s–1960s [75]. The immunomodulatory effects of HCQ have also been increasingly recognized and utilized as monotherapy or in conjunction with other drugs for the treatment of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and antiphospholipid antibody syndrome [76]. HCQ is considered as a critical medication in SLE with a broad spectrum of disease-alleviating benefits including reduction of cutaneous disease and inflammatory arthralgias, thrombosis, and increased longevity, and better glycemic control [77]. In an in vivo mouse model of acute kidney I/R injury and in vitro cultured HK-2 human renal proximal tubule cells exposed to hypoxia/reoxygenation, HCQ pretreatment provided significant renal protection against I/R injury, along with reduction in macrophage and neutrophil infiltration, pro-inflammatory cytokine production, and Nod-like receptor (NLR), the family of innate immune cell sensors, such as the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome activation [78].

Many inflammatory mediators including tumor-necrosis factor (TNF), interleukins, and the cytokine-like proteins known as 'adipokines' have been linked to the development of various forms of metabolic disorders and T2D [79, 80]. IL-1β is a prominent proinflammatory cytokine because it generates other inflammatory mediators through signaling via IL-1 receptor, thus initiating a self-amplifying cytokine network [81]. It has been suggested that NLRP3 (also known as cryopyrin), inflammasome promotes autocatalytic activation of the cysteine protease caspase-1 and mediates the cleavage of inactive pro-IL-1β and IL-18, among other proteins, into their active forms. Cryopyrin functions as a danger sensor ultimately causing the autocatalytic cleavage and activation of caspase-1 [82]. Activation of the inflammasome is complex and involves the components ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), cryopyrin, and pro-caspase-1 [83]. Unlike other caspases of apoptotic pathway, caspase-1 is a key modulator of the inflammatory response to tissue injury [82, 84–87]. In the heart, genetic deletion of caspase-1 reduced early mortality and ventricular dilatation while its overexpression leads to heart failure [88, 89]. Inflammasome plays a role in the development of insulin resistance [90–94]. Genetic ablation of the cytoplasmic receptor NLRP3 (*Nlrp3*$^{-/-}$ mice) or NLRP3 inflammasome-associated ASC (PYCARD;

Table 2 Representative completed or ongoing clinical trials and/or published clinical studies concerning the therapeutic effects of hydroxychloroquine (HCQ) on type 2 diabetes (T2D)

Trial ID and other information	Number of T2D Patients and their health conditions	HCQ dosage, protocol, endpoints	Key clinical and basic research findings	Current status
1 Prospective, randomized, placebo-controlled, double-blind trial (6 months) PI: Giugliano, D., University of Naples, Italy Completed: 1990	38 T2D patients resistant to commonly used therapies (oral drugs, insulin, and their combination (17 in HCQ group, 15 in placebo group); 18 to 85 years, either gender group; Fasting glucose 100–125 mg/dL; BMI > 25; Fasting serum insulin > 7 uU/mL	HCQ 400 mg p.o. once daily for 3 months vs. placebo; *Primary Endpoints:* Insulin sensitivity (by glucose tolerance test) at the baseline and 3 months post-drug; *Secondary Endpoints:* Pancreatic beta cell function	At 6 months, significant improvement occurred in the 11 patients who received the insulin and HCQ (glucose profile decrease, − 11.7 mmol/L; 95% CI, − 13.9 to − 9.5, $p < 0.01$; glycated hemoglobin A1c decrease, − 3.3%; 95% CI, − 3.9 to − 2.7, $p < 0.01$). No significant changes were seen in patients on placebo. The daily insulin dose in patients treated with the combined insulin and HCQ therapy had to be reduced an average of 30%. No important side effects were detected	Completed and results published in Quatraro A et al. 1990 [58]
2 Randomized double-blind placebo-controlled trial of 3 days of oral drug treatment PI: Powrie, J.K., United Medical and Dental Schools of Guy's and St. Thomas's Hospital, London, U.K Completed: August 1990	20 T2D patients controlled by diet; 10 in Chloroquine group and 10 in placebo group (8 males, 2 females in each group); 43 to 65 years	Chloroquine phosphate, 250 mg four times daily; *Primary Endpoints:* Rates of glucose appearance (Ra) and disappearance (Rd) were evaluated by infusion of stable isotopically labeled D-glucose ([6,6-2H2]glucose) during hyperinsulinemic euglycemic clamps before and after treatment with chloroquine or placebo	Chloroquine treatment significantly improved fasting plasma glucose from 199.8 ± 8.6 to 165.6 ± 7.6 mg/dl ($p < 0.01$). Total exogenous glucose infusion required to maintain euglycemia significantly increased due to an increase in Rd without change in Ra. Metabolic clearance rate of insulin decreased by 39%. Chloroquine increased fasting C-peptide secretion by 17% and reduced feedback inhibition of C-peptide	Completed and results published in Powrie JK et al. 1991 [140]
3 Randomized, double-blind, parallel-arm trial NCT01326533 *Reducing Risk of Type 2 Diabetes: Hydroxychloroquine Use in Pre-Diabetes* PI: Toledo, F., University of Pittsburgh, USA Started: March 2011 Completed: March 2013	32 pre-diabetes participants (17 in HCQ group, 15 in placebo group); 18 to 85 years, either gender, any ethnic group; Fasting glucose 100–125 mg/dL; BMI > 25; Fasting serum insulin > 7 uU/mL	HCQ 400 mg p.o. once daily for 3 months vs. placebo; *Primary Endpoints:* Insulin sensitivity (by glucose tolerance test) at the baseline and 3 months post-drug; *Secondary Endpoints:* Pancreatic beta cell function	Insulin sensitivity ↑ HCQ + 20.0 ± 7.1% vs. Placebo − 18.4 ± 7.9%, $p < 0.01$; Beta cell function ↑ HCQ + 45.4 ± 12.3% vs. Placebo 19.7 ± 13.6%, $p < 0.01$; Fasting plasma glucose and HbA1c ↓ HCQ vs. Placebo, $p < 0.05$; Circulating markers of inflammation (IL-6, IL-1, TNF-α, soluble intercellular adhesion molecule) → Adiponectin levels ↑ HCQ + 18.7% vs. Placebo + 0.7%, p$p < 0.001$ No serious/unexpected adverse effects	Completed and results published in Wasko MC et al. 2015 [60]

Table 2 (continued)

Trial ID and other information	Number of T2D Patients and their health conditions	HCQ dosage, protocol, endpoints	Key clinical and basic research findings	Current status
4 Randomized, placebo-control trial NCT02026232 *Metabolic Effects of Hydroxychloroquine (MetaHcQ)* PI: Semenkovich, C Washington University School of Medicine, USA Started March 2012	30 T2D participants; 18 to 75 years, either gender, any ethnic group; A1c of 6.5–9.0%; BMI > 27 but < 45; Treated with at least 1000 mg of metformin daily with or without a dipeptidyl peptidase-4(DPP4) inhibitor, sulfonylurea, bromocriptine or colesevelam	HCQ 200 mg p.o. twice daily or placebo for 4 weeks; *Primary Endpoints:* Insulin sensitivity determined by hyperinsulinemic euglycemic clamp; *Secondary Endpoints:* Fasting blood glucose, low-density lipoprotein (LDL), Serum biomarkers of inflammation	Not yet published	Suspended due to COVID-19
5 Randomized, prospective, open-label comparison trial NCT02303405 *Hydroxychloroquine Versus Pioglitazone in Combination Treatment for Type 2 Diabetes Mellitus* PI: Hsia, S.H., Charles Drew University of Medicine and Science, USA Started Nov. 2014	17 T2D participants; 18 to 75 years, either gender, any ethnic group; HbA1c of 7.5–11%; BMI < 45; Treated at least 3 months with maximum tolerated doses of metformin and a sulfonylurea	HCQ 400 mg p.o. once daily or Pioglitazone 45 mg p.o. once daily for 4 months; *Primary Endpoints:* Hemoglobin A1c; *Secondary Endpoints:* Fasting blood glucose, lipids, Body weight and BMI, Serum biomarkers of inflammation, HOMA-IR, Adverse events	Results submitted, but not yet posted	Terminated (Investigator decision)
6 Randomized, triple-blind, placebo-controlled trial NCT02648464 *Hydroxychloroquine for the Prevention of Cardiovascular Events in Myocardial Infarction Patients—a Safety Pilot Trial (OXI)* PI: Sinisalo, J., Helsinki University Central Hospital, Finland Started Feb. 2016	125 myocardial infarction patients; 18 to 80 years, either gender, any ethnic group	HCQ 300 mg p.o. once daily for 6 months or placebo p.o. once daily for 6 months; *Primary Endpoints:* 12-month rate of major cardiovascular adverse events (Myocardial infarction, mortality, hospitalization for unstable angina, and heart failure) *Secondary Endpoints:* 12-month Rate of the primary endpoint plus stroke and urgent coronary revascularization; 6 month Incidence of T2D and the level of HbA1c, LDL, HDL, total cholesterol, triglyceride, hs-CRP TNFalpha, IL-6, IL-1beta, IL-18	Results submitted, but not yet posted	Completed on December 2019; Protocol published in Hartman O et al. 2017 [141]

Table 2 (continued)

Trial ID and other information	Number of T2D Patients and their health conditions	HCQ dosage, protocol, endpoints	Key clinical and basic research findings	Current status
7 Randomized, double-blind, placebo-controlled, parallel-arm study PI: Nag, A., Medical College and Hospital, Kolkata, West Bengal, India Published June 2020	304 inadequately controlled T2D patients; 18 to 80 years, either gender, any ethnic group	HCQ 200, 300, 400 mg p.o. once daily or placebo (based on body weight of the subject) In follow-up of 400 mg once daily was once again divided to 200 mg twice daily (BD) to study the effect on tolerability profile for further 12 weeks HCQ 300 mg p.o. once daily for 6 months or placebo p.o. once daily for 6 months; *Primary Endpoints:* 12-week change of HbA1c *Endpoints:* 12-week Fasting blood glucose, lipids; Body weight	HbA1c ↓ in 12 weeks HCQ vs. Placebo, $p < 0.005$, i.e., − 0.78%, − 0.91% and 1.2% for 200, 300, and 400 mg HCQ, respectively, versus 0.13% with placebo; Fasting blood glucose ↓ − 25 to − 38 mg/dl and 34–53 mg/dl; Body weight ↓	Results published in Chakravarti HN & Nag A. 2021 [142]

Pycard$^{-/-}$ mice) and caspase-1 (*Casp1*$^{-/-}$ mice) leads to improved glucose tolerance and insulin sensitivity in high fat diet fed mice thereby linking NLRP3 inflammasome to insulin resistance. Moreover, ROS are important activators of cryopyrin, which trigger inflammasome formation [85, 87]. We reported that mitochondrial ROS (H_2O_2) in the hearts from db/db mice, which was significantly attenuated by treatment with TAD [41] suggesting the possibility that combination treatment with TAD and HCQ may exert even more powerful effect in the inhibition of inflammasome, which could contribute to significant reduction of infarct size as compared to monotherapy (Fig. 1).

PDE5 inhibitors and hydroxychloroquine treatment in diabetic patients—a prevention strategy for COVID-19?

Both obesity and T2D are recognized risk factors in developing severe form of COVID-19, with a higher death rate. In fact, the co-morbid conditions like diabetes, hypertension, and obesity have significant correlation with severity of COVID-19 with T2D alone contributing to 10–40% cases of severity and mortality [95, 96]. Fasting glucose level at the time of hospital admission predicted 28-day mortality even in those without a previous diagnosis of diabetes [97]. Glycemic control and body mass index along with older age, male sex, socio-economic deprivation, non-white ethnicity, and pre-existing renal and CV disease all independently increased mortality [98]. There is also significant endothelial damage in COVID-19, which appears to play key pathophysiological role in the onset and the progression of the disease [99]. The impaired vascular homeostasis secondary to the endothelial dysfunction contributes to the systemic proinflammatory state and multiorgan hypoxia and failure in COVID-19 patients [100].

COVID-19 is suggested to be associated with the imbalance in the generation of NO from the iNOS and eNOS enzymes. The NO generation from eNOS is generally protective of the tissue, whereas excessive formation of NO from iNOS is pro-inflammatory due to oxidative stress [101]. PDE5 inhibitors initiated NO-cGMP-PKG pathway could be potentially beneficial for COVID-19 patients. This is because eNOS activation is in part mediated by AMPK; a serine-threonine protein kinase [101], which may suppress inflammation through inhibition of iNOS. We previously showed that PDE5 inhibitor, TAD triggered AMPK/eNOS/NO signaling and protected against I/R injury in db/db diabetic mice through improvement of mitochondrial dysfunction [41] and suppressing inflammatory cytokines [39]. It has been reported that sildenafil treatment in patients with cerebellar demyelination caused downregulation of both the inactive AMPK and iNOS [102]. Thus, enhancing the

AMPK/eNOS/NO/cGMP pathway can potentially counteract inflammation and thromboembolism in patients with T2D [101]. Moreover, because of the higher PDE5 expression in the lungs, treatment with the PDE5 inhibitors may improve the prognosis of pulmonary inflammation caused by SARS-CoV-2 infection.

It has also been suggested that PDE5 inhibitors may potentially block the replication of SARS-CoV-2 [103]. The polyproteins produced by coronaviruses are further processed by certain viral proteases, especially the $3CL^{pro}$, into the functional form which then mediates the replication of the virus. The protease inhibitors have been reported to lower mortality of patients with SARS [104]. Based on the crystal structure of the SARS-CoV-2 $3CL^{pro}$ [105], a computational study revealed that among other drugs, clinically approved PDE5 inhibitors such as TAD, sildenafil were potent inhibitors of $3CL^{pro}$ suggesting that these drugs may block the replication of SARS-CoV-2 at clinically relevant doses [106]. However, a definite clinical evidence is currently unavailable.

The inhibitory effects of HCQ or chloroquine on SARS-CoV2 appear to be multi-factorial and remain incompletely understood [107]. The antiviral effects of HCQ against Zika, Chikungunya, HIV, as well as SARS-CoV2 are likely due to its annulation of endosomal/lysosomal acidification [76]. A recent study with in-silico approaches showed that in the presence of HCQ, the S (Spike) protein of SARS-CoV2 was no longer able to bind gangliosides and, in turn, HCQ would deactivate this new type of ganglioside-binding domain at the N-terminal domain of SARS-CoV-2 S protein and consequently disrupt the viral attachment to lipid rafts as well as its contact with human ACE2 receptors for host cell entry [108]. In addition, it was recently suggested that suppression of coronavirus replication could be attained by interrupting the autophagy pathway [109], since HCQ is a well-known inhibitor of autophagolysosome and it has been shown to potently inhibit SARS-CoV-2 viral replication in vitro [109–111]. Collectively, the newly identified direct anti-SARS-CoV2 action of HCQ provided a potential utility in management of COVID-19 patients at the early stage of viral invasion to vital organs. However, a randomized controlled trial (NCT04321616) from Norway indicated that neither remdesivir nor HCQ affected viral clearance in the hospitalized patients with COVID-19 and also both drugs did not affect the degree of respiratory failure or circulating inflammatory markers of the patients [112]. These negative results suggest that the timing of early treatment/preventive intervention prior to the disease advancement to hospitalization stage may be critical, since early prescription of HCQ, prednisone or both to 717 consecutive SARS-CoV-2-positive Brazilian patients (> 40 years old) significantly reduced hospitalization risk by 50–60% [113]. Thus, based on the compelling evidence of anti-diabetic effects of the class of PDE5 inhibitors and HCQ (Fig. 1), we speculate that combination treatment with these clinically approved drugs may support added benefits including the alleviation of diabetes and reducing the severity of SARS-CoV-2 symptoms [108, 114].

Potential adverse effects of PDE5 inhibitors and hydroxychloroquine in diabetes

Potential dose- and duration-dependent cardio- and neurotoxicities of HCQ have been recognized in the past decades [115]. It was summarized that HCQ is a generally well-tolerated medication with long-term (years) toxicities may include retinopathy, neuromyotoxicity, cardiac conduction abnormalities, and cardiomyopathy [115, 116]. Deaths from HCQ overdoses most often result from CV collapse [115]. The recent experimental emergency use of HCQ in COVID-19 patients has heightened the concerns on its cardiac toxicity. For example, a retrospective comparative observational study, using the French Pharmacovigilance network database between 1985 and May 2020, found that the estimated incidence of cardiac adverse drug reactions was significantly higher among COVID-19 patients exposed to off-label use of HCQ (2.90%) than those treated with its approved indications such as lupus and rheumatoid arthritis prior to COVID-19 pandemic (0.01%, $P < 0.001$) [117]. HCQ treatment may cause cardiac QT prolongation and increased dispersion may occur in patients with MI leading to higher susceptibility to ventricular tachyarrhythmias [118]. There is also concern that therapeutic doses of HCQ could trigger cardiac arrhythmic events, which caused sudden cardiac arrest in COVID-19 patients [119–122]. Furthermore, a population-based study reported a considerably high prevalence of increased QT prolongation and dispersion in T2D diabetic patients [123], indicating a possible excessive mortality risk in these patients.

Conversely, several observational analyses revealed efficacy of HCQ in treating COVID-19 in humans [124–126], including significant reduction of in-hospital mortality in the 2541 COVID-19 patients admitted to The Henry Ford Health System in United States [124]. A similar report by the CORIST Collaboration study in Italy revealed that the use of HCQ among 3451 hospitalized patients with COVID-19 was associated with 30% lower 35-day mortality [127]. Such analyses like the CORIST Collaboration can be useful to generate new hypotheses for treating COVID-19 at its earlier stage with a lower dose of HCQ than those of previously used in RECOVERY and SOLIDARITY trials and also need to be further confirmed by large-scale randomized trials [128]. Nevertheless, extra caution should be taken during

the course of treatment with HCQ in COVID-19 patients, who need careful monitoring for CV adverse events [129].

Co-administration of PDE5 inhibitor(s) may potentially overcome the occurrence of HCQ-triggered QT prolongation and ventricular arrhythmias, considering that sildenafil treatment reduced ischemia-induced ventricular arrhythmias in dogs [130]. In fact, a more recent study in sheep model of dofetilide-induced QT prolongation demonstrated that treatment with sildenafil suppressed the occurrence of afterdepolarizations and ventricular arrhythmias within 90s of administration [131]. The protective effects of sildenafil were mediated by a PKG-dependent reduction of sarcoplasmic reticulum Ca^{2+} content. Thus, careful preclinical investigations need to be performed to demonstrate the antiarrhythmic effects of the combination PDE5 inhibitors in combination with HCQ. Nevertheless, as recently suggested by Dutta et al. [132], HCQ should not be used in patients with diabetic maculopathy and retinopathy. Blood glucose levels need to be closely monitored to reduce the risk of hypoglycemia in the HCQ-treated patients T2D [129].

Conclusion and perspectives

Repositioning, reprofiling and repurposing for old drugs has become a highly beneficial strategy to bring new drugs into clinical reality. This is because the existing drugs have undergone extensive testing, allowing them to move quickly into clinical trials and accelerating their potential. We have provided promising evidence for the efficacy of PDE5 inhibitors and HCQ in protection of diabetic heart. Therefore, combination treatment with TAD and HCQ could potentially lead to a novel line of pharmacotherapy in diabetes to manage CV risk factors and improve clinical outcomes of diabetic patients with acute MI even more effectively. HCQ was considered as one of the repurposed early treatments of COVID-19 infection although with mixed clinical results. Because obesity and T2D are recognized risk factors in developing severe form of COVID-19 with higher mortality rate, we speculate that combination pretreatment therapy with PDE5 inhibitors as well as HCQ may provide additional benefits including the alleviation of diabetic and SARS-CoV2 symptoms (Fig. 1). Nevertheless, future well-designed clinical trials are needed to establish or refute the value of TAD and HCQ combination as potential prophylactics and/or treatments. This notion, in fact, was partially endorsed by the new results from a multicenter, randomized, double-blind, placebo-controlled OXI pilot trial among 125 patients with MI in Finland, which indicated that early administration of HCQ within 48 h after MI (300 mg once daily for 6 months) significantly reduced serum levels of interleukin-6 (IL-6), a key pro-inflammatory marker and did not cause any significant adverse events [133].

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Data availability Data sharing not applicable to this review article as no datasets were generated during the current review work. All data analyzed in this review article are based on the published journal articles assessable via PUBMED (https://pubmed.ncbi.nlm.nih.gov/) and the clinical trials summarized in Tables 1 and 2 were extracted from the information registered by the original trial investigators through https://clinicaltrials.gov/.

Declarations

Conflict of interest All authors declare no known competing financial interests or personal relationships that could have influenced the publication of this review article.

Ethical approval Not applicable. The present review article does not involve intervention on humans and/or animals directly and it only analyzes and summarizes the information gathered from the published articles.

Consent to participate Not applicable. The present review article does not involve intervention on humans and/or animals directly and it only analyzes and summarizes the information gathered from the published articles.

Consent for publication Not applicable. The present review article does not involve intervention on humans and/or animals directly and it only analyzes and summarizes the information gathered from the published articles.

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