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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Effect of hydroxychloroquine on glucose control in patients with and without diabetes: a systematic review and meta-analysis of randomized controlled clinical trials

Luis E. Simental-Mendía[1] · Mario Simental-Mendía[2] · Adriana Sánchez-García[3] · Enrique Linden-Torres[1]

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Abstract

Purpose The aim of this meta-analysis of randomized controlled trials was to evaluate the effect of hydroxychloroquine on glucose control.

Methods Randomized controlled trials examining the impact of hydroxychloroquine on glycemic markers were searched in PubMed, Web of Science, Scopus, and Google Scholar databases. Meta-analysis was performed using a random-effects model and sensitivity analysis through the leave-one-out method.

Results Meta-analysis revealed a significant reduction of fasting glucose (WMD: − 8.05 mg/dl; 95% CI: − 11.17, − 4.93; $I^2 = 75\%$; $p < 0.0001$), 2-h postprandial glucose (WMD: − 15.52 mg/dl; 95% CI: − 20.61, − 10.42; $I^2 = 53\%$; $p < 0.00001$), and glycated hemoglobin (HbA1c) values (WMD: − 0.19%, 95% CI: − 0.37, − 0.02; $I^2 = 94\%$; $p = 0.03$) after hydroxychloroquine treatment. Otherwise, meta-analysis showed no significant effect of hydroxychloroquine on insulin levels (WMD: 16.52 µUI/ml; 95% CI: − 16.35, 49.40; $I^2 = 90\%$; $p = 0.32$) and HOMA-β (WMD: − 14.62; 95% CI: − 45.84, 16.59; $I^2 = 0\%$; $p = 0.36$).

Conclusion The present meta-analysis revealed that treatment with hydroxychloroquine improves glucose control through the reduction of fasting glucose, 2-h postprandial glucose, and HbA1c values. Given that the effect of hydroxychloroquine on beta-cell function is based only on two clinical trials, it is not possible to draw definitive conclusions.

Keywords Hydroxychloroquine · Glucose · Glycated hemoglobin · Insulin · Meta-analysis

Introduction

Type 2 diabetes, a chronic noncommunicable disease, is one of the main causes of morbidity and mortality in the USA [1]. Additionally, the global prevalence was estimated at 9.3%, 10.2%, and 10.9% by 2019, 2030, and 2045, respectively [2].

Type 2 diabetes is characterized by insulin resistance in the muscle, adipose, and liver tissues, and β-cell dysfunction. Nonetheless, the pathophysiology of type 2 diabetes is very complex, including the interaction between genetic and environmental factors [3]. Therefore, the optimal treatment to achieve the therapeutic goal is currently a challenge. Accordingly, this complex pathophysiology requires an elaborate scheme of drugs to achieve and maintain the therapeutic goals of its treatment. Although there is a wide variety of therapeutic options for the management of type 2 diabetes, the glycemic control is still difficult to maintain in these patients [4]. Thus, alternative antidiabetic drugs capable of improving glucose metabolism are of great interest.

Hydroxychloroquine is a drug that was initially introduced as antimalarial; however, due to its immunoregulatory and anti-inflammatory properties, it is also indicated for the treatment of systemic lupus erythematosus and rheumatoid arthritis [5]. Besides, it has been reported that hydroxychloroquine may have hypoglycemic effects [6, 7]; even it was approved for the management of type 2 diabetes as third-line drug in uncontrolled

✉ Luis E. Simental-Mendía
luis_simental81@hotmail.com

[1] Unidad de Investigación Biomédica, Delegación Durango, Instituto Mexicano del Seguro Social, Durango, Dgo, México

[2] Department of Orthopedics and Traumatology, Hospital Universitario "Dr. José E. González", Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, NL, México

[3] Endocrinology Division, Hospital Universitario "Dr. José E. González", Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, NL, México

patients despite lifestyle management plus metformin and sulfonylurea combination therapy in India [8, 9]. However, the underlying mechanisms involved in the antidiabetogenic properties of hydroxychloroquine are still unclear and poorly investigated. Therefore, this meta-analysis of randomized controlled trials aimed to evaluate the effect of the hydroxychloroquine on glucose control.

Methods

Search strategy

According to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [10], the present study was carried out. PubMed-Medline, Web of Science, SCOPUS, and Google Scholar databases were searched using the following search terms within titles and abstracts (also in combination with MESH terms): (hydroxychloroquine) AND (glucose OR postprandial glucose OR insulin OR insulin resistance OR insulin sensitivity OR "HOMA" OR HbA1c OR hemoglobin A1c OR glycated hemoglobin OR glycosylated hemoglobin). The wild-card term ''*'' was used to increase the sensitivity of the search strategy. There was no language restriction in the search process. The literature was searched from inception to August 7, 2020.

Study selection

Eligible studies were selected when they met the following inclusion criteria: (1) being a randomized controlled trial; (2) examining the impact of hydroxychloroquine on either fasting glucose, 2-h postprandial glucose, insulin, or glycated hemoglobin (HbA1c) values; (3) treatment period of at least one month; (4) providing sufficient information on fasting glucose, 2-h postprandial glucose, insulin or HbA1c values at baseline and at the end of follow-up in each group or presenting the net change values. Exclusion criteria were (1) non-interventional trials; (2) lack of a placebo or control group for hydroxychloroquine treatment; (3) observational studies with case–control, cross-sectional or cohort design; and (4) insufficient data on the baseline or follow-up fasting glucose, 2-h postprandial glucose, insulin or HbA1c values. Study selection was performed by two independent authors, and disagreements were resolved with a third author.

Results

Flow and characteristics of included studies

A total of 88 studies were identified in the multiple databases after search strategy. Then, 71 were excluded following the screening of titles and abstracts. Next, 17 full-text articles were carefully reviewed for eligibility and 6 studies were excluded for treatment duration < 1 month ($n = 1$), not presenting numerical values ($n = 2$), and incomplete data on glycemic parameters ($n = 3$). Thus, 11 clinical trials were selected for meta-analysis (Fig. 1).

Table 1 summarizes the characteristics of the included studies and baseline parameters. A total of 2208 subjects

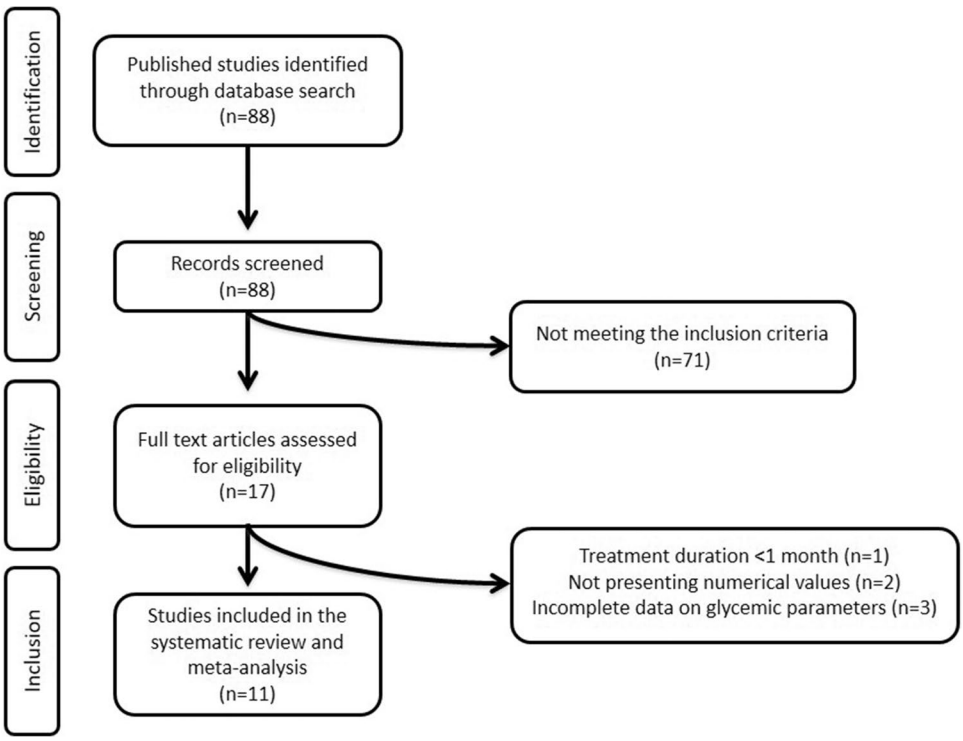

Fig. 1 Flow chart of the number of studies selected for meta-analysis

Table 1 Demographic characteristics of the included studies

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI (kg/m2)	Fasting glucose (mg/dl)	Postprandial glucose (mg/dl)	Fasting insulin (μUI/ml)	HOMA-β	HbA1c (%)
Baidya and Ahmed (2018) [11]	Randomized, open-label, active-controlled	Type 2 diabetes	24 weeks	50	Metformin 2000 mg/day + glimepiride 2 mg/day	49.2 ± 6.3	30 (60)	27.8 ± 4.1	149 ± 20.4	240.4 ± 34.4	ND	ND	7.9 ± 0.4
				50	Metformin 1000 mg/day + glimepiride 2 mg/day + HCQ 400 mg/day	49.5 ± 5.6	31 (62)	27.8 ± 4.1	150 ± 20.2	242.1 ± 36.4	ND	ND	8.0 ± 0.4
				50	Metformin 1000 mg/day + glimepiride 4 mg/day	50.1 ± 6.2	29 (58)	28.1 ± 3.9	152.4 ± 19.8	244.3 ± 37.5	ND	ND	7.9 ± 0.4
Baidya et al. (2018) [12]	Randomized, open-label, active-controlled	Type 2 diabetes	24 weeks	50	HCQ 400 mg/day + metformin 1000 mg/day + glimepiride 2 mg/day	58.3 ± 8.5	30 (60)	26.9 ± 5.2	149.6 ± 28.4	240.4 ± 44.4	ND	ND	7.8 ± 0.9
				50	Vildagliptin 100 mg/day + metformin 1000 mg/day + glimepiride 2 mg/day	56.2 ± 7.4	29 (58)	26.2 ± 4.9	150.4 ± 19.8	241.3 ± 38.5	ND	ND	7.9 ± 0.8
Chakravarti and Nag (2020) [13]	Randomized, double-blind, placebo-controlled	Type 2 diabetes	12 weeks	61	Placebo	53.3 ± 7.8	29 (47)	25.1 ± 2.5	157 ± 32	269 ± 58	ND	ND	7.7 ± 0.5
				61	HCQ 200 mg/day	53.3 ± 8.5	22 (36)	24.3 ± 2.1	164 ± 38	275 ± 53	ND	ND	7.8 ± 0.5
				61	HCQ 300 mg/day	51.7 ± 8.0	20 (32)	24.8 ± 2.3	168 ± 42	278 ± 56	ND	ND	7.8 ± 0.5
				121	HCQ 400 mg/day	52.9 ± 9.6	40 (33)	25.5 ± 2.6	170 ± 45	282 ± 51	ND	ND	7.9 ± 0.5
Hsia et al. (2019) [14]	Randomized, open-label, active-controlled	Type 2 diabetes	16 weeks	15	HCQ 400 mg/day	53 ± 10	11 (73)	35.3 ± 5.7	179 ± 53	ND	11.0 ± 8.7	53.2 ± 66.6	8.6 ± 1.0
				7	Pioglitazone 45 mg/day	57 ± 13	6 (85)	34.1 ± 5.2	170 ± 50	ND	9.6 ± 5.5	35.5 ± 14.3	9.1 ± 0.7
Kumar et al. (2018) [15]	Randomized, open-label, active-controlled	Type 2 diabetes	24 weeks	300	HCQ 400 mg/day	58.3 ± 9.1	136 (45)	26.6 ± 3.6	179.1 ± 59.6	292.1 ± 66.4	ND	ND	8.6 ± 0.5
				300	Sitagliptin 100 mg/day	57.2 ± 9.3	142 (47)	27.1 ± 3.4	175.8 ± 51.6	290.9 ± 68.0	ND	ND	8.7 ± 0.5
Pareek et al. (2014) [16]	Randomized, double-blind, active-controlled	Type 2 diabetes	12 weeks	135	HCQ 400 mg/day	52.6 ± 8.5	76 (56)	ND	180.0 ± 50.4	261.0 ± 64.8	ND	ND	9.2 ± 1.2
				132	Pioglitazone 15 mg/day	52.2 ± 8.3	68 (51)	ND	172.8 ± 55.8	259.2 ± 66.6	ND	ND	9.1 ± 1.1
Pareek et al. (2015) [17]	Randomized, double-blind, placebo-controlled	Primary dyslipidemia	24 weeks	167	Placebo	50.1 ± 9.6	96 (57)	26.1 ± 3.5	114.0 ± 32.9	ND	ND	ND	6.4 ± 0.9
				161	HCQ 200 mg/day	49.2 ± 9.5	88 (54)	25.6 ± 3.5	110.6 ± 30.8	ND	ND	ND	6.4 ± 0.9
Ranjan et al. (2018) [18]	Randomized, open-label, active-controlled	Type 2 diabetes	24 weeks	148	HCQ 400 mg/day	55 ± 8	69 (47)	25.7 ± 2.4	134.0 ± 16.4	239.8 ± 21.5	ND	ND	8.3 ± 0.5
				152	Teneligliptin 20 mg/day	56 ± 9	68 (45)	25.3 ± 2.0	135.0 ± 16.5	234.7 ± 23.1	ND	ND	8.2 ± 0.5
Sheikhbahaie et al. (2016) [7]	Randomized, double-blind, placebo-controlled	Prediabetes	12 weeks	20	HCQ 6.5 mg/kg/day	45.9 ± 7.3	15 (75)	ND	97.1 ± 8.4	131.4 ± 39.4	12.3 ± 10.6	ND	5.2 ± 0.5
				19	Placebo	46.7 ± 6.3	12 (63)	ND	107.9 ± 16.3	137.9 ± 32.5	9.8 ± 5.3	ND	5.3 ± 0.9

Table 1 (continued)

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI (kg/m2)	Fasting glucose (mg/dl)	Postprandial glucose (mg/dl)	Fasting insulin (µUI/ml)	HOMA-β	HbA1c (%)
Solomon et al. (2014) [19]	Randomized, double-blind, placebo-controlled, cross-over	Rheumatoid arthritis	8 weeks	33	Overall	56 ± 11.4	22 (95)	25.6 (22.9–29.8)*	115.4 ± 34.2	ND	37.1 ± 31.6	116.5 ± 100.4	ND
				33	HCQ 6.5 mg/kg/day								
				33	Placebo								
Wasko et al. (2015) [6]	Randomized, double-blind, placebo-controlled	Non-diabetic individuals	13 weeks	15	Placebo	44.9 ± 16.8	9 (60)	35.9 ± 6.2	98.5 ± 14.2	ND	9.6 ± 5.3	ND	5.6 ± 0.4
				17	HCQ 400 mg/day	50.1 ± 14.5	15 (88)	34.1 ± 7.2	92.9 ± 8.8	ND	8.7 ± 8.7	ND	5.7 ± 0.3

Values are expressed as mean ± SD

ND, no data; *BMI*, body mass index; *HCQ*, hydroxychloroquine

*Median (interquartile range)

were included from 11 randomized controlled trials, comprising 1172 and 1036 participants in the treatment and control arms, respectively. Selected studies were published between 2014 and 2020. The range of intervention periods was from 8 to 24 weeks [6, 7, 11–19]. Almost all included clinical trials had a parallel design; only one study was cross-over [19]. Selected studies enrolled patients with type 2 diabetes [11–16, 18], primary dyslipidemia [17], prediabetes [7], rheumatoid arthritis [19], and non-diabetic individuals [6].

Risk of bias assessment

Four studies [11, 12, 14, 18] were characterized by lack of information regarding sequence generation. Additionally, several trials exhibited insufficient information for allocation concealment. Also, five studies [11, 12, 14, 15, 18] had a high risk of bias with respect to the blinding of participants, personnel, and outcome assessors. However, all included studies showed a low risk of bias according to incomplete outcome data and selective outcome reporting. The quality of bias assessment for each study is provided in Table 2.

Effect of hydroxychloroquine on glycemic parameters

A total of ten, seven, ten, two, and two clinical trials reported data for fasting glucose, 2-h postprandial glucose, Hb1Ac, insulin, and HOMA-β, respectively. Meta-analysis revealed a significant reduction of fasting glucose (WMD: − 8.05 mg/dl; 95% CI: − 11.17, − 4.93; $I^2 = 75\%$; $p < 0.0001$; Fig. 2), 2-h postprandial glucose (WMD: − 15.52 mg/dl; 95% CI: − 20.61, − 10.42; $I^2 = 53\%$, $p < 0.00001$; Fig. 3), and HbA1c values (WMD: − 0.19%; 95% CI: − 0.37, − 0.02; $I^2 = 94\%$; $p = 0.03$; Fig. 4) after hydroxychloroquine treatment. The leave-one-out sensitivity analysis was robust for fasting glucose and 2-h postprandial glucose (Table S1 and S2), while the estimated effect size was sensitive to four studies for HbA1c [6, 7, 18, 20] (Table S3). Otherwise, meta-analysis showed no significant effect of hydroxychloroquine on insulin levels (WMD: 16.52 µUI/ml; 95% CI: − 16.35, 49.40; $I^2 = 90\%$; $p = 0.32$; Fig. 5) and HOMA-β (WMD: − 14.62; 95% CI: − 45.84, 16.59; $I^2 = 0\%$; $p = 0.36$; Fig. 6).

Publication bias

Funnel plots were generated only for fasting glucose (Fig. S1A) and Hb1Ac (Fig. S1B). After visual inspection, asymmetry was not observed for fasting glucose; however, one study [14] was in the non-significance area (right) for Hb1Ac.

Table 2 Quality of bias assessment of the included studies according to the Cochrane guidelines

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Baidya and Ahmed 2018 [11]	U	U	H	L	L	U
Baidya et al. 2018 [12]	U	U	H	L	L	U
Chakravarti and Nag 2020 [13]	L	U	U	L	L	U
Hsia et al. 2019 [14]	U	U	H	L	L	U
Kumar et al. 2018 [15]	L	U	H	L	L	U
Pareek et al. 2014 [16]	L	L	L	L	L	L
Pareek et al. 2015 [17]	L	U	U	L	L	U
Ranjan et al. 2018 [18]	U	U	H	L	L	U
Sheikhbahaie et al. 2016 [7]	L	U	U	L	L	U
Solomon et al. 2014 [19]	L	L	L	L	L	L
Wasko et al. 2015 [6]	L	L	L	L	L	L

L, low risk of bias; *H*, high risk of bias; *U*, unclear risk of bias

Discussion

This meta-analysis supports that hydroxychloroquine lowers fasting glucose, 2-h postprandial glucose, and HbA1c values, but it does not affect insulin levels and HOMA-β.

Previously, experimental studies in induced diabetic models suggested beneficial effects of hydroxychloroquine on glucose control [20]. Then, observational and cohort studies showed a significant decrease in fasting glucose, 2-h postprandial glucose, and HbA1c values in patients with type 2 diabetes [21, 22]. Additionally, in line with our results, a recent systematic review of preclinical and clinical studies described that treatment with hydroxychloroquine improves fasting plasma glucose, 2-h postprandial glucose, and HAb1c concentrations [23]. Although the authors of this review included 15 clinical studies, only 6 were randomized controlled trials and the meta-analysis was not performed.

We found a robust effect of hydroxychloroquine on both fasting glucose and 2-h postprandial glucose, although the effect size was sensitive for HbA1c. It is noteworthy that only the study by Hsia et al. [14] had conflicting results for HbA1c; this could be explained by the small sample size including 15 subjects in the hydroxychloroquine group versus 7 into the pioglitazone group. Nonetheless, the overall effect of this antimalarial significantly decreased HbA1c values.

Interestingly, hydroxychloroquine treatment did not affect insulin levels and HOMA-β. However, it is important to note that this finding is based on the analysis of only two arms for each parameter; therefore, it is not possible to draw definitive conclusions on the effect of hydroxychloroquine on beta-cell function. In this context, only one study reported the impact of hydroxychloroquine on insulin resistance through HOMA [19], and no significant changes were observed; hence, this parameter was not analyzed in our meta-analysis. Thus, further clinical trials investigating the impact of hydroxychloroquine on surrogate markers of insulin resistance and beta-cell function are needed to clarify the potential benefits of this drug as antidiabetic.

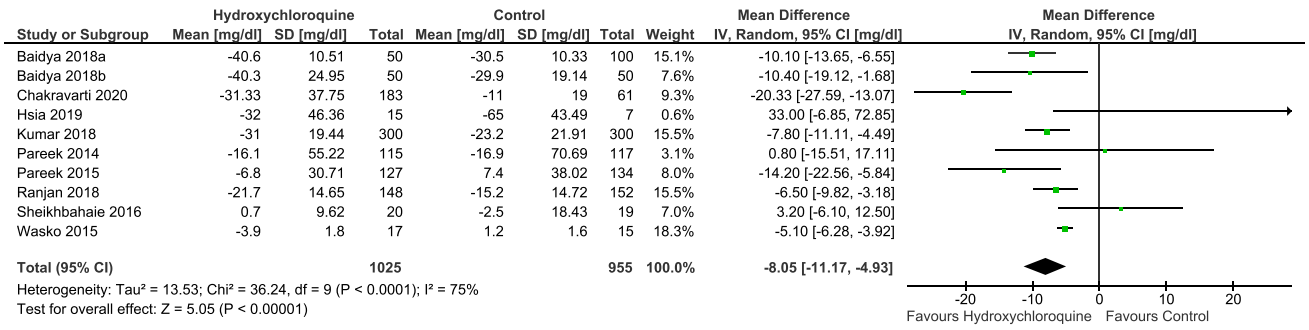

Fig. 2 Forest plot displaying the mean difference and 95% confidence intervals for the impact of hydroxychloroquine on fasting glucose

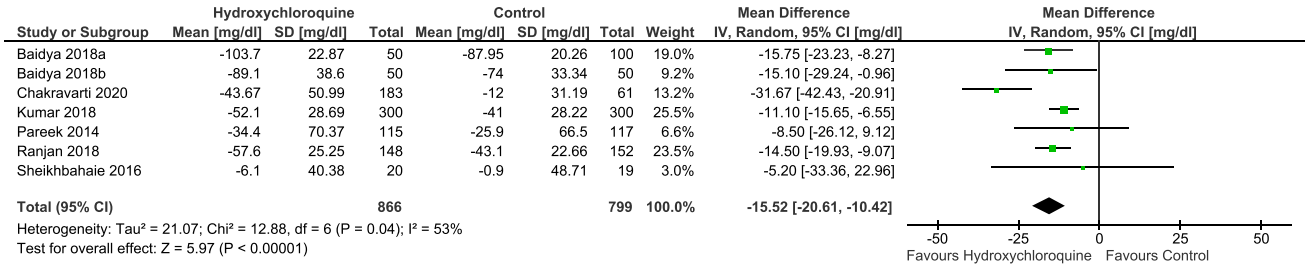

Fig. 3 Forest plot displaying the mean difference and 95% confidence intervals for the impact of hydroxychloroquine on 2-h postprandial glucose

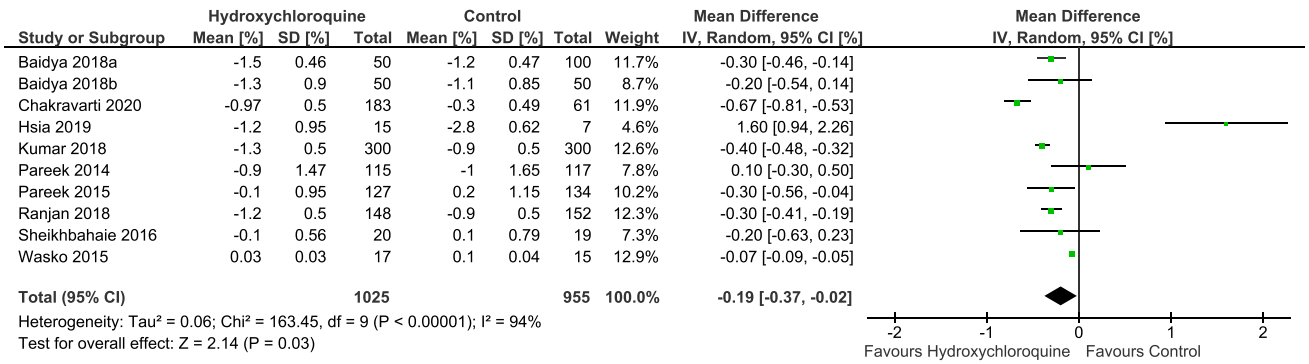

Fig. 4 Forest plot displaying the mean difference and 95% confidence intervals for the impact of hydroxychloroquine on HbA1c values

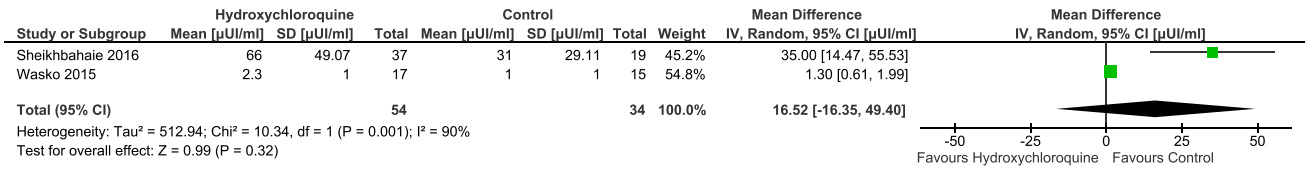

Fig. 5 Forest plot displaying the mean difference and 95% confidence intervals for the impact of hydroxychloroquine on insulin levels

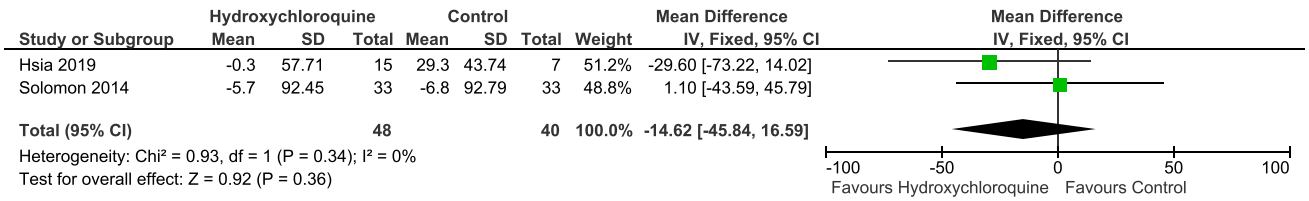

Fig. 6 Forest plot displaying the mean difference and 95% confidence intervals for the impact of hydroxychloroquine on HOMA-β

Hydroxychloroquine, a drug extensively used for the treatment of malaria and autoimmune diseases, has immunomodulatory and anti-inflammatory properties [24, 25]. However, the mechanisms involved in improving glycemic control are not well-established. In this regard, it has been suggested that hydroxychloroquine may decrease the dissociation of the insulin-receptor complex, increasing its half-life and enhancing insulin action [26]. Furthermore, an experimental study reported that hydroxychloroquine reduces the lysosomal degradation of insulin, leading to an increase in insulin concentration and decreased glucose levels [27]. Also, hydroxychloroquine inhibits the insulin degrading enzyme by increasing intracellular pH and consequently improves the biological action of insulin [28]. Moreover, it has been observed that chloroquine, a hydroxychloroquine analog, induces glucose uptake and glycogen synthase via Akt activation [29].

There were some limitations in our study. Some clinical trials included a small sample size. Besides, only two arms were analyzed for insulin levels and HOMA-β, which is insufficient to draw definitive conclusions on the effects of hydroxychloroquine on beta-cell function. In this regard, it is important to note that C-peptide is a more reliable marker of beta-cell function. Also, the included studies were heterogeneous in terms of target population including patients with type 2 diabetes, primary dyslipidemia, prediabetes, rheumatoid arthritis, and non-diabetic individuals. Additionally, the present meta-analysis was limited to this study design; however, this study design exhibits the highest level of evidence among clinical trials. Due to the heterogeneity of the included clinical trials, our findings should be treated with caution. Finally, the quality of some studies was unclear; therefore, this could have introduced a potential source of bias.

Conclusion

According to our findings, hydroxychloroquine treatment improves glucose control through reduction of fasting glucose, 2-h postprandial glucose, and HbA1c values. However, additional studies are still needed to determine the potential hypoglycemic properties of this drug, as well as clarify the molecular mechanisms involved.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-021-03144-7.

Author contribution All authors have participated in the design and approved the final version of the manuscript, taking responsibility for the contents of the article. LESM and MSM equally analyzed and interpreted data and wrote the manuscript. ASG collected analyzed data, and reviewed and edited the manuscript. ELT collected analyzed data, and reviewed and edited the manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

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