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Effectiveness and Safety of Hydroxychloroquine compared to Teneligliptin in uncontrolled T2DM patients as add-on Therapy*

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Abstract

Objectives. Hydroxychloroquine (HCQ) 400 mg is approved by the Drug Controller General of India (DCGI) and recommended by the Research Society for the Study of Diabetes in India (RSSDI) clinical practice recommendations 2017 as add-on therapy after metformin and sulfonylurea in Type 2 Diabetes (T2DM) patients. The aim of this observational study is to compare the efficacy and safety of hydroxychloroquine 400 mg and teneligliptin 20 mg when used as add-on therapy in Indian Type 2 DM patients who were inadequately controlled (HbA1c ≥7.5%) with metformin 1000 mg and glimepiride 2 mg combination.

Methodology. This study is a prospective observational study to be conducted in 2 diabetic centres of Patna city between October 2017 and May 2018 involving 180 patients followed up for 6 months. One group (N=90) of patients received hydroxychloroquine 400 mg + metformin 1000 mg + glimepiride 2 mg, the other group (N=90) received teneligliptin 20 mg + metformin 1000 mg + glimepiride 2 mg. Efficacy was assessed by fasting blood glucose (FBG), post prandial blood glucose (PPBG) and glycated haemoglobin (HbA1c) reduction. Safety was evaluated by the number of hypoglycaemic events and changes in serum creatinine levels. Home based glucose monitoring was used to detect the hypoglycaemic events. Patients who had any type of retinopathy/maculopathy were excluded.

Results. Mean age of entire population was 66±8 years with mean 6±2 years of DM with 102 males. Mean body weight was 71±12 kg. Baseline HbA1c was 8.1±0.3 in the hydroxychloroquine group and 8.2±0.2 in the teneligliptin group.

At 24 weeks there were statistically significant reductions in mean HbA1c in the hydroxychloroquine group (1.1±0.3) as compared to the teneligliptin group (0.82±0.3) (P≤0.001). The mean FBG and PPBG was 169±18 mg/dl and 232±18 mg/dl respectively in hydroxychloroquine group which was reduced to 121±15 mg/dl and 161±19 mg/dl at the end of 24 weeks. In the teneligliptin group, FBG and PPBG was 171±16 mg/dl and 239±21 mg/dl at baseline, which was reduced to 121±15 mg/dl and 161±19 mg/dl respectively in same period of time (P≤ 0.005). There were 4 incidences of hypoglycaemic events in the hydroxychloroquine group (4.4%) and 6 in the teneligliptin group (6.67%). No patients required medical assistance for hypoglycaemic events. There was no statistically significant change in body weight in both the groups. No marked changes in creatinine levels were found in patients in both the groups.

Conclusion. In conclusion, treatment with hydroxychloroquine 400 mg for 24 weeks reduces glycaemic parameters more aggressively than teneligliptin 20 mg in Indian type 2 diabetes patients.

Key words: hydroxychloroquine, teneligliptin, FBG, PPBG, HbA1c

INTRODUCTION

The incidence of diabetes has increased by multiple folds over the past 40 years in India. Over this time, rapid socioeconomic development and demographic changes, along with increased susceptibility for Indian individuals, have led to the explosive increase in the prevalence of diabetes mellitus in India.[1] The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.

The management of type 2 diabetes mellitus (T2DM) involves lifestyle measures (diet and exercise), oral antidiabetic drugs, and eventually, the use of insulin. Metformin and sulfonylureas (SU) are the most commonly used oral antidiabetic agents. However, SU have a greater tendency to cause hypoglycaemia and weight gain and hence, many patients will eventually need to be shifted to another class of oral antidiabetic agents or insulin therapy.[2] In type 2 diabetic patients, the main pathophysiologic mechanisms of hyperglycaemia involve insulin resistance, impaired insulin secretion and increased hepatic glucose output. Type 2 diabetes is a progressive disease characterized by insulin resistance and diminished insulin secretion.[3] Neither sulfonylureas nor metformin are able to preserve ß-cell function, and many patients

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with type 2 diabetes fail to reach target [glycosylated hemoglobin (HbA1c) <7.0%], despite combined metformin/sulfonylurea therapy.[4-7] Hence, many patients with type 2 diabetes will eventually require insulin therapy.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, which act in a blood glucose-dependent manner, carries a low risk of hypoglycaemia.[8] In Japan, DPP-4 inhibitors, including teneligliptin (TNL), are the most commonly prescribed antidiabetic drugs,[9] and are suitable for both elderly and dialysis patients.[10] In addition, DPP-4 inhibitors are weight neutral.[11-13]

Hydroxychloroquine (HCQ), a long-standing safe and inexpensive treatment for autoimmune disorders, may theoretically improve glucose tolerance and prevent diabetes. Hydroxychloroquine has a novel mechanism of action, i.e., post receptor inhibition of insulin degradation for reducing blood glucose levels. Reduction in FBG, PPG and HbA1C (0.87-3.3%) is established in various settings.[14-18] Hydroxychloroquine 400 mg is approved by DCGI (Drug Controller General of India) and recommended by RSSDI (Research Society for the Study of Diabetes in India) clinical practice recommendations 2017 as add-on therapy after metformin and sulfonylurea in T2DM patients.

This 24-week open-label, randomized, parallel-group study is to compare the efficacy and safety of hydroxychloroquine 400 mg and teneligliptin 20 mg when used as add-on therapy in Indian Type 2 DM patients who were inadequately controlled (HbA1c ≥7.5%) with metformin 1000 mg and Glimepiride 2 mg combination.

METHODOLOGY

This study is a prospective observational study to be conducted in 2 diabetic centres of Patna city in between October 2017 to May 2018 among 180 patients with a 6 month follow up period.

A sample size of 180 subjects, 90 in each arm, is sufficient to detect a clinically important difference of 0.5 between groups in reducing glycaemic level assuming a standard deviation of 1.195 using a two-tailed t-test of difference between means, with 80% power and a 5% level of significance.

Inclusion criteria were (1) weight ≥60 kg,[2] haemoglobin A1c ≥7.5%,[3] treatment with metformin 1000 mg and glimepiride 2 mg for at least 2 weeks prior to the study. Exclusion criteria were[1] type 1 diabetes,[2] severe complications of diabetes, micro or macrovascular, any type of retinopathy/maculopathy,[3] severe renal and liver dysfunction,[4] severe infections,[5] pregnant or nursing women and those who might be pregnant,[6] alcoholism, and[7] any patients whom the investigators judged to be inappropriate for this study.

Initially, 240 patients were assessed for eligibility, among which 180 patients were selected and continued. There was a 2 weeks run-in period of strict diet control and treatment with metformin 1000 mg and glimepiride 2 mg. All patients were then randomly allotted into two groups. One group (N=90) of patients received hydroxychloroquine 400 mg + metformin 1000 mg + glimepiride 2 mg, other group (N=90) received teneligliptin 20 mg + metformin 1000 mg + glimepiride 2 mg. Efficacy was assessed by FBG, PPBG and HbA1c reduction and safety was evaluated by number of hypoglycaemic events and changes in serum creatinine levels. A blood sugar level below 70 mg/dl is considered as hypoglycaemia and a blood sugar level below 54 mg/dl is considered as sever hypoglycaemia. Home based blood glucose monitoring was used to detect the hypoglycaemic events. Patients who had any type of retinopathy/maculopathy were excluded.

We performed the current study in accordance with the declaration of Helsinki and the study was carried out after an approval from the ethical committee of the hospital. All subjects were given an explanation of the details of this clinical study and provided written informed consent.

Statistical analysis

The sample size was determined by assuming that add-on treatment drug would improve HbA1c by at least 0.5%, based on a previous study which assessed efficacy of hydroxychloroquine 400 mg and teneligliptin 20 mg in patients with T2DM .[16] It was statistically determined that 90 patients in each group (in account of the potential loss of subjects) were needed to detect a significant difference with at least a power of 80% and statistical significance of 5%. Data was arranged in MS Excel. Student's t test was used to compare difference in mean values between the two groups. Chi-square test was used for categorical variables. Paired t-test has been used for within group analysis. For every outcome variable, results are presented as mean±SD (Standard Deviation), p value <0.05 was considered statistically significant. STATA 12.0 (STATA Corp, Houston, TX, USA) statistical software has been used for data analysis.

RESULTS

The mean age of the patients was 66±9 and 66±7 years respectively, with mean duration of diabetes of 6±2 years in the HCQ group and mean of 6±3 years in the teneligliptin group. Mean body weight was 70±8 kg and 70±8 kg respectively in HCQ and teneligliptin group. Baseline HbA1c was 8.1±0.3 in the hydroxychloroquine group and 8.2±0.2 in the teneligliptin group. The patient's baseline characteristics was almost similar in both the groups (Table 1).

At 24 weeks there were statistically significant reduction in mean HbA1c in the hydroxychloroquine group (1.1±0.3) as compared to the teneligliptin group (0.82±0.3) (P≤0.001) (Table 1 and Figure 1). The mean FBG and PPBG was 169±18 mg/dl and 232±18 mg/dl respectively in the hydroxychloroquine group which was reduced to 121±15 mg/dl and 161±19 mg/dl at the end of 24 weeks. In the teneligliptin group, FBG and PPBG was 171±16 mg/dl and 239±21 mg/dl which reduced to 121±15 mg/dl and 161±19 mg/dl respectively in same period of time (p≤0.005) (Table 2). Comparisons of change in baseline to 24 weeks between hydroxychloroquine and teneligliptin groups was also statistically significant (≤0.001), which indicates the superiority of hydroxychloroquine in reducing glycaemic parameters.

Table 1. Patient characteristics at the beginning of the study

Characteristic	HCQ group (N=90)	Teneligliptin group (N=90)	p value
Age (years)	66±9	66±7	0.827
Weight (kg)	70±8	72±13	0.253
Gender (male/female)	54/36	47/43	0.531
Duration of diabetes (Years)	6±2	6±3	0.741
Family history of diabetes	69 (77%)	72 (80%)	0.983
HbA1c (%)	8.1±0.3	8.2±0.2	0.137
Fasting blood glucose (mg/dl)	169±18	171±16	0.213
Post Prandial Blood Glucose	232±18	239±21	0.134
Creatinine (mg/dl)	0.85±0.2	0.88±0.1	0.549
Presence of comorbidities			
Hypertension	74 (82%)	76 (84%)	0.437
Dyslipidemia	64 (71%)	61 (68%)	

Table 2. Changes in variables in the two groups after 6 months

Parameters	HCQ Group (N=90)				Teneligliptin group (N= 90)				p value
	Baseline	24 Week	Δ Change	p value	Baseline	24 Week	Δ Change	p value	
FBG (mg/dl)	169±18	121±15	-48±17	<0.001	171±16	121±15	-50±15	<0.005	<0.001
PPBG (mg/dl)	232±18	161±19	-71±18	<0.001	239±21	161±19	-78±20	<0.005	<0.001
HbA1c (%)	8.1±0.3	7±0.3	-1.1±0.3	<0.001	8.2±0.2	7.38±0.3	-0.82±0.3	<0.001	<0.001

Table 3. Changes in variables to access safety and tolerability in the two groups after 3 months

Parameters	HCQ Group (N=90)				Teneli Group (N= 90)				p value
	Baseline	24 weeks	Δ Change	p value	Baseline	24 weeks	Δ Change	p value	
Weight (kg)	70±8	69±6	1±3	0.983	72±13	72±10	0±6	0.961	0.681
Sr. Cr (mg/dl)	0.85±0.2	0.84±0.2	0.01±0.02	0.934	0.88±0.1	0.89±0.1	+0.01±0.01	0.729	0.927

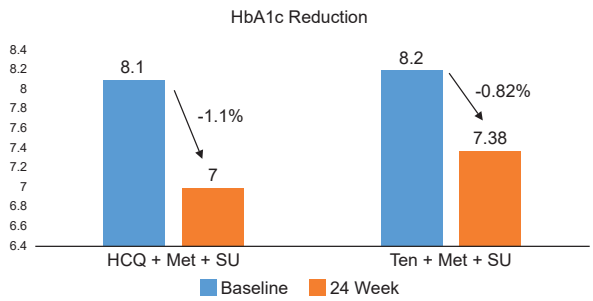

Figure 1. Change in HbA1c in two groups.

There was no statistically significant change in body weight of both the groups (Table 2). No marked changes in creatinine levels were found in patients in both the groups (Table 3).

There were no meaningful differences between groups in incidences of overall clinical adverse experiences or of those assessed as serious, drug-related, or leading to discontinuation. There were 4 incidences of hypoglycaemic events in the hydroxychloroquine group (4.4%) and 6 in the teneligliptin group (6.67%). No patients required medical assistance for hypoglycaemic events. There was no statistically significant change in body weight of both the group. No marked changes in creatinine levels were found in patients in both the groups.

In has been noted that in HCQ treated group there was a significant number of patients who achieved target glycaemic control (≤6.5%). Forty eight percent of patients have achieved HbA1c ≤6.5% in the HCQ treated group, compared to 29% with the teneligliptin treated group.

DISCUSSION

Type 2 diabetes is a major risk factor for developing both microvascular and macrovascular complications.[19] Systemic inflammation is reported to be a strong predictor of atherosclerosis.[20] The primary goal of treatment is to target glycaemic control by maintaining the HbA1c level near 6–7% in order to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycaemia.[21] If diabetes remains uncontrolled with first-line therapy, medications including insulin, SU, thiazolidinediones (TZDs), gliptins, GLP-1 analogs or gliflozins may be employed.[22] The use of these traditional agents may be limited, however, because of several factors. Biguanides and TZDs improve insulin resistance, but do not address the progressive decline in beta-cell function. SUs can lose their effectiveness over time, while TZDs increase the risk of fracture and cardiac failure. Hence, new treatment options are sought. Hydroxychloroquine has been shown to reduce inflammatory markers in diabetes mellitus.[23, 24]

This study was performed to provide an assessment of the efficacy and tolerability of hydroxychloroquine at doses of 400 mg once daily as add on therapy in patients with type 2 diabetes with inadequate glycaemic control on metformin and sulfonylurea. Treatment with hydroxychloroquine provided clinically meaningful reductions in A1C, FBG, and PPBG compared with teneligliptin.

Overall assessment of safety demonstrated that both hydroxychloroquine and teneligliptin were well tolerated in this observational real-world efficacy and safety assessment study. No meaningful differences were found in the adverse experience profiles between

hydroxychloroquine and teneligliptin treatments. There was a very low incidence of hypoglycaemia with hydroxychloroquine that was similar to teneligliptin. Slightly higher, but not statistically significant, incidences of gastritis, constipation, and diarrhea were reported with hydroxychloroquine, but these events were generally mild or moderate, self-limited, and not temporally related to initiation of study medication. There were two cases of mild pigmentation with hydroxychloroquine therapy, but both patients have continued HCQ.

Pioglitazone and metformin are anti-diabetic drugs, and both are specifically reported to effectively improve insulin resistance.[25] Insulin resistance is also associated with the progression of atherosclerotic disease in a study of a Japanese population.[26] Pioglitazone has anti-atherogenic effects[27] by increasing adiponectin, which is derived from adipose tissue.[28] In a similar way, hydroxychloroquine has also demonstrated its effect on increasing adiponectin levels, and this possibly mediates the favourable effects on glucose metabolism.[29] The role of adiposity on the regulation of the inflammatory response is well known. Adipose tissue itself is a source of CRP and is also a major producer of interleukin-6, which is a key stimulator of CRP secretion. In obesity and type 2 diabetes, adipose tissue contains an increased number of resident macrophages and T cells, which interact closely with adipocytes to modulate the inflammatory response.[30] In this study, the mechanism underlying these anti-inflammatory effects has been attributed to the improvement of insulin resistance and favourable effect on glycaemic parameters were observed with hydroxychloroquine 400 mg.

Teneligliptin and hydroxychloroquine are two anti-diabetic drugs which were recently approved by DCGI (Drug Controller General of India) to treat type 2 diabetes. Both teneligliptin and hydroxychloroquine are available in India at economical prices which can be afforded by a patient who are financially unstable or belong to the middle-class.

The main rationale to conduct this study is to evaluate the efficacy and safety of two newly approved drugs among Indian type 2 diabetes patients. The result clearly demonstrates that hydroxychloroquine can offer tighter glycaemic control than teneligliptin in a real world set up.

Limitations

The present study has certain limitations, including the short duration of treatment and also small sample size. Prospective multicentre clinical trials with longer follow-up of subjects are warranted to confirm the results of the present study and to investigate long-term therapeutic effects of hydroxychloroquine in preventing disease progression in Indian subjects with T2DM.

CONCLUSIONS

Both hydroxychloroquine and teneligliptin-based treatments resulted in significant and improvements in metabolic parameters for different baseline HbA1c levels. Hydroxychloroquine treatment exhibited greater effectiveness in decreasing FBG, PPBG and HbA1c than teneligliptin in a real world setting. In conclusion, treatment with HCQ 400 mg OD for 24 weeks led to statistically significantly greater lowering of the HbA1c than teneligliptin 20 mg in this cohort of Indian Type 2 diabetes patients, although the difference is modest.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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References

1. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol. 2016;12(6):357–70. PMID: 27080137. https://doi.org/10.1038/nrendo.2016.53.
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53. PMID: 9742976.
3. Kahn SE. The relative contributions of insulin resistance and β-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia. 2003;46(1):3-19. PMID: 12637977. https://doi.org/10.1007/s00125-002-1009-0.
4. UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: A progressive disease. UK Prospective Diabetes Study Group. Diabetes. 1995;44(11):1249-58. PMID: 7589820.
5. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia. 2005;48(6):1093–104. PMID: 15889234. https://doi.org/10.1007/s00125-005-1751-1.
6. Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH; QUARTET Study Group. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. Diabetes Care. 2004;27(1):141-7. PMID: 14693980.
7. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427-43. PMID: 17145742. https://doi.org/10.1056/NEJMoa066224.
8. Rehman MB, Tudrej BV, Soustre J, et al. Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: Meta-analysis of placebo controlled randomized clinical trials. Diabetes Metab. 2017;43(1):48–58. PMID: 27745828. https://doi.org/10.1016/j.diabet.2016.09.005.
9. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: Focus on East Asian perspectives. J Diabetes Investig. 2016;7 Suppl 1:102-9. PMID: 27186364. PMCID: PMC4854513. http://doi.org/10.1111/jdi.12490.
10. Hinnen D. Dipeptidyl peptidase-4 inhibitors in diverse patient populations with type 2 diabetes. Diabetes Educ. 2015;41(1 Suppl):19S–31S. PMID: 26453595. https://doi.org/ 10.1177/0145721715609420.
11. de Wit HM, Te Groen M, Rovers MM, Tack CJ. The placebo response of injectable GLP-1 receptor agonists vs. oral DPP-4 inhibitors and SGLT-2 inhibitors: A systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(1):301-14. PMID: 26935973 PMCID: PMC4917794. https://doi.org/10.1111/bcp.12925.
12. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: Systematic review and meta-analysis. BMJ. 2012;344:e1369. PMID: 22411919. https://doi.org/10.1136/bmj.e1369.
13. Aroda VR, Henry RR, Han J, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: Meta-analysis and systematic review. Clin Ther. 2012;34(6):1247–58.e22. PMID: 22608780. https://doi.org/10.1016/j.clinthera.2012.04.013.
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 pioglitazone. Curr Med Res Opin. 2014;30(7):1257-66. PMID: 24669876. https://doi.org/10.1185/03007995.2014.909393.
15. 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):209-19. PMID: 11850097.
16. Singh UP, Baidya B, Singla M,et al. Efficacy and safety of substituting teneligliptin with hydroxychloroquine in inadequately controlled type 2 diabetes subjects with combination therapy of teneligliptin, metformin and glimepiride with or without other antidiabetic therapy:

The TENE-HYQ SHIFT Study. Clinical Diabetology. 2018;7(5): 209–14. https://doi.org/10.5603/DK.2018.0025.
17. Rekedal LR, Massarotti E, Garg R, et al. Changes in glycated hemoglobin after initiation of hydroxychloroquine or methotrexate in diabetic patients with rheumatic diseases. Arthritis Rheum 2010;62(12):3569-73. PMID: 20722019. PMCID: PMC2992611. https://doi.org/10.1002/art.27703.
18. Quatraro A, Consoli G, Magno M, et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? Ann Intern Med. 1990;112(9):678-81. PMID: 2110430.
19. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854-65. PMID: 9742977.
20. Ross R. Atherosclerosis: An inflammatory disease. N Engl J Med. 1999;340(2):115–26. PMID: 9887164. https://doi.org/10.1056/NEJM199901143400207.
21. Choy M, Lam S. Sitagliptin: a novel drug for the treatment of type 2 diabetes. Cardiol Rev. 2007;15(5):264-71. PMID: 17700385. https://doi.org/10.1097/CRD.0b013e318123f771.
22. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38(1):140-9. PMID: 25538310. https://doi.org/10.2337/dc14-2441.
23. Detert J, Klaus P, Listing J, et al. Hydroxychloroquine in patients with inflammatory and erosive osteoarthritis of the hands (OA TREAT): Study protocol for a randomized controlled trial. Trials. 2014;15:412. PMID: 25348033. PMCID: PMC4219005. https://doi.org/10.1186/1745-6215-15-412.
24. Hage MP, Al-Badri MR, Azar ST. A favorable effect of hydroxychloroquine on glucose and lipid metabolism beyond its anti-inflammatory role. Ther Adv Endocrinol Metab. 2014;5(4):77-85. PMID: 25343023. PMCID: PMC4206615. https://doi.org/10.1177/2042018814547204.
25. Durbin RJ. Thiazolidinedione therapy in the prevention/delay of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance. Diabetes Obes Metab. 2004;6(4):280-5. PMID: 15171752. https://doi.org/10.1111/j.1462-8902.2004.0348.x.
26. Fujiwara T, Saitoh S, Takagi S, et al. Development and progression of atherosclerotic disease in relation to insulin resistance and hyperinsulinemia. Hypertens Res. 2005;28(8):665-70. PMID: 16392771. https://doi.org/10.1291/hypres.28.665.
27. Satoh N, Ogawa Y, Usui T, et al. Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. Diabetes Care. 2003;26(9):2493-9. PMID: 12941708.
28. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol. 2004;24(1):29-33. PMID: 14551151.https://doi.org/ 10.1161/01.ATV.0000099786.99623.EF.
29. 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):2336-43. PMID: 26197707. PMCID: PMC4575248. https://doi.org/10.1007/s00125-015-3689-2.
30. Belalcazar LM, Reboussin DM, Haffner SM, et al. A 1-year lifestyle intervention for weight loss in individuals with type 2 diabetes reduces high creactive protein levels and identifies metabolic predictors of change. Diabetes Care. 2010;33(11):2297-303. PMID: 20682679. PMCID: PMC2963483. https://doi.org/10.2337/dc10-0728.