

Subash Chandra Satpathy<sup>1</sup>, Indranil Purkait<sup>2</sup>, Avinash Talware<sup>2</sup>

<sup>1</sup>Consultant Diabetologist, Kolkata, India

<sup>2</sup>Medical Affairs, IPCA Laboratories Limited, Mumbai, India

# Improvement of type 2 diabetes mellitus control with hydroxychloroquine added to triple oral antidiabetic drugs: a case report

## ABSTRACT

Hydroxychloroquine, an antimalarial drug has also been found to possess antidiabetic action. It inactivates insulin degradation enzymes and also delays the dissociation of insulin from the insulin receptor thus also lowering the insulin resistance and increasing insulin sensitivity. Here we report a case of a male patient with uncontrolled type 2 diabetes mellitus (T2DM) who obtained a better glycemic control when hydroxychloroquine was added to the existing pharmacotherapy. The patient has been taking metformin, glimepiride and acarbose for the last 2 years but his diabetes was poorly controlled with glycated haemoglobin (HbA<sub>1c</sub>) of 9.6%. Patient was proposed to intensify the treatment with insulin however he refused it. He was subsequently prescribed hydroxychloroquine 400 mg. Patient responded well to the therapy of hydroxychloroquine and subsequent follow-ups showed good glycaemic control. (Clin Diabetol 2017; 6, 6: 211–214)

**Key words:** type 2 diabetes mellitus, hydroxychloroquine, oral hypoglycemic agents

Address for correspondence:

Dr. Indranil Purkait

IPCA Laboratories Limited, Plot No. 125

Kandivali Industrial Estate

Kandivali (West) Mumbai 400067, India

Phone: +91 22 62105770/+91 9819593065

Fax: +91 22 28686613

e-mail: indranil.purkait@ipca.com

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## Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous disease characterized by chronic hyperglycemia caused by increased insulin resistance and impaired insulin secretion. The prevalence of T2DM is rising in both developed and developing countries. T2DM and its complications constitute a major worldwide public health concern and are associated with considerable morbidity and mortality [1].

In T2DM, controlling blood glucose level is of vital importance in order to prevent microvascular and macrovascular complications [2]. Blood glucose control is generally achieved by the administration of oral antidiabetic drugs (OADs) or insulin along with physical exercise and dietary restrictions. In the management of T2DM, metformin is generally prescribed as first-line therapy and when it loses effectiveness, other OADs are added, with sulfonylureas being preferred as second-line treatment. It is observed that many patients become unresponsive to the combination of metformin and sulfonylureas over a period of time, which necessitates the addition of a third-line agent.

We report the case of a patient with T2DM uncontrolled with the use of metformin, sulfonylurea and acarbose combination who's blood glucose control was improved when hydroxychloroquine was added to the therapy.

## Case presentation

### Patient characteristics and diagnosis

A 51-year-old man presented at our clinic with uncontrolled T2DM. A medical examination conducted way back in 2008 had revealed impaired glucose tolerance. Lifestyle modification was recommended at that time but the patient failed to follow it.

4 years later, in February 2012, he was diagnosed with T2DM and was prescribed OADs to control blood glucose levels. During the early stages, he had received monotherapy with metformin hydrochloride but it was no longer effective after 3 years of treatment, even after an increase in the dosage. Therefore, additional OADs were introduced. After addition, the patient was on the following OHA therapy-metformin hydrochloride, 1000 mg/day; glimepiride, 4 mg/day; acarbose, 300 mg/day. Insulin therapy was recommended at that time to achieve glycemic control and to prevent diabetic complications but the patient refused it.

The patient presented at our clinic on February 10, 2017, seeking to reduce blood glucose levels with OADs. On presentation, his fasting blood glucose was 345 mg/dL and had glycated haemoglobin (HbA<sub>1c</sub>) 9.6%. However, he did not complain of symptoms of diabetes decompensation and was following exercise and dietary recommendations.

Patient physical examination: weight: 80 kg (178 lb); height: 157 cm (5'2"); body mass index (BMI): 32.6 kg/m<sup>2</sup>. Blood pressure: lying, right arm 154/96 mm Hg; sitting, right arm 140/90 mm Hg. Pulse: 88 bpm; Respiratory rate: 20 per minute. Eyes: corrective lenses, pupils equally reactive to light. Ophthalmological examination revealed clear fundus, no arteriovenous nicking and no evidence of retinopathy. Thyroid glands and lungs were normal in physical examination.

The heart rate and rhythm were regular, no murmurs or gallops were found. Vascular assessment revealed no carotid bruits, femoral, popliteal, and dorsalis pedis pulses were bilaterally palpable normally. Neurological assessment showed diminished vibration sense in the forefoot, ankle reflexes were absent and monofilament (5.07 Semmes-Weinstein) was felt only above the ankle.

### Laboratory testing

Results of laboratory tests done on 10<sup>th</sup> Feb 2017 were as follows: fasting blood glucose (FBG): 345 mg/dL; HbA<sub>1c</sub>: 9.6%; creatinine: 1.0 mg/dL, blood urea nitrogen: 18 mg/dL, sodium: 141 mg/dL, potassium: 4.3 mg/dL, total cholesterol: 162 mg/dL, HDL cholesterol: 43 mg/dL, LDL cholesterol (calculated): 84 mg/dL, triglycerides: 442.48 mg/dL, cholesterol-to-HDL ratio: 3.8; urine microalbumin: 45 mg (normal: < 30 mg).

### Change in treatment regimen

The physical examination of the patient showed signs of peripheral neuropathy and the laboratory examination showed poor glycemic control. This patient needs urgent intervention to control blood glucose level, preferably insulin therapy. But as the patient

expressed anxiety over the use of injectable insulin, hydroxychloroquine 400 mg per day was added to the existing therapy.

### Treatment outcomes

The patient continued his modified drug therapy, exercise, and dietary control from 10<sup>th</sup> February 2017 for a period of approximately 24 weeks. Regular tests were performed in the interim period to monitor glycemic control. Baseline FBG and HbA<sub>1c</sub> were 345 mg/dL and 9.6% respectively. Patient's FBG and HbA<sub>1c</sub> reduced by 70.72% and 32.29% respectively from baseline within a period of 24 weeks. Ophthalmologic examination was performed which revealed no signs of retinopathy. Thus target HbA<sub>1c</sub> levels were achieved with the addition of hydroxychloroquine 400 mg per day and the therapy was well tolerated by the patient.

The results of the follow-up are provided in the Figure 1 and Figure 2.

### Discussion

Hydroxychloroquine is the hydroxyl derivative of chloroquine. It is used, either alone or in combination with other agents, in the management of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other autoimmune diseases [3].

Hydroxychloroquine has also been found to possess antidiabetic effect. It inactivates the insulin degradation enzymes and also delays the dissociation of insulin from the insulin receptor [4, 5]. It also lowers the insulin resistance, improves  $\beta$ -cell function and increases insulin sensitivity [6, 7]. In one observational study conducted by Wasko M et al., long term use of hydroxychloroquine was associated with 77% reduced the risk of incident diabetes [8]. Few case reports have been also published indicating hypoglycemic effect of hydroxychloroquine.

Antidiabetic effect of hydroxychloroquine has been explored by many investigators. Gerstein H et al. [9] observed an improvement in glycemic control in patients with T2DM who were unresponsive to sulfonylurea. In that particular study, addition of hydroxychloroquine to sulfonylurea decreased HbA<sub>1c</sub> by an absolute amount of 1.02% compared to placebo.

A double-blinded, randomized study of 267 patients with uncontrolled T2DM was conducted by Pareek et al. [10] in 2014 in India. This study conclusively showed that hydroxychloroquine had a similar anti-hyperglycaemic effect as pioglitazone among the patients refractory to metformin and sulfonylurea treatment. Based on this study, hydroxychloroquine 400 mg has been officially approved by drug regulatory authority of India to improve glycemic control of T2DM

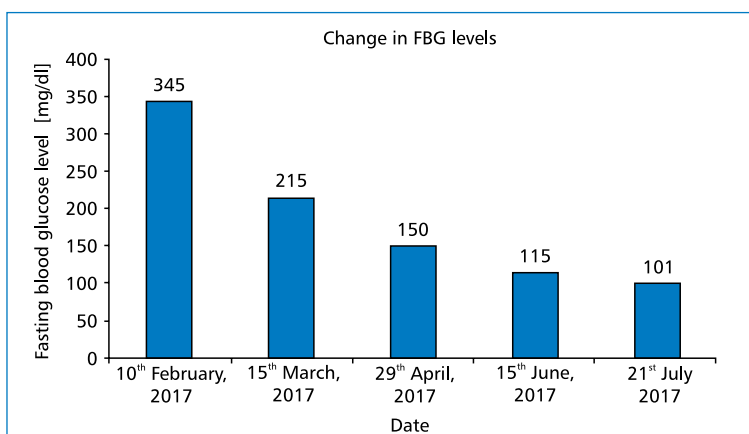


Figure 1. Change in fasting blood glucose (FBG) levels

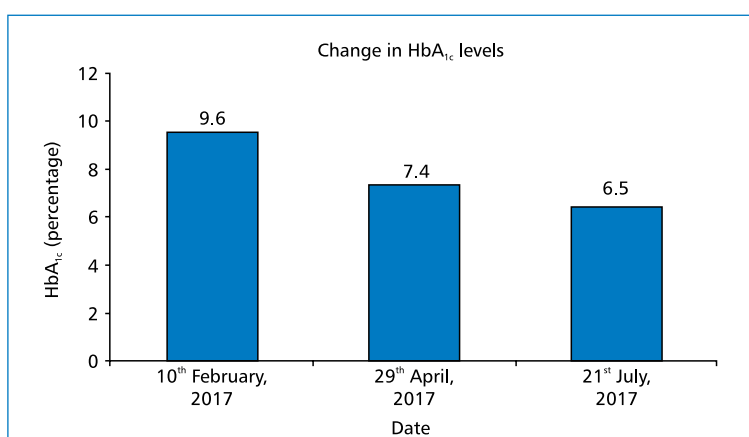


Figure 2. Change in glycated haemoglobin (HbA<sub>1c</sub>) levels

patients on metformin, sulfonylurea combination as an adjunct to diet and exercise therapy.

This patient has been suffering from T2DM for a period of 5 years. He has been on triple drug combination therapy of metformin, glimepiride and acarbose but still his blood glucose was not well controlled. He presented to the clinic on February 2017 with poor glycemic control and diminished vibration sensation in the lower extremities. This patient required an intensive add-on therapy. He refused insulin therapy because of fear of injection. In this scenario, having limited options we put the patient on hydroxychloroquine 400 mg once a day in addition to existing triple OAD combination therapy. At the end of 24 weeks of treatment the patient achieved good glycemic control. In patients who are refractory to the combination treatment of metformin and sulphonylurea and reluctant to injectable therapy, hydroxychloroquine should be considered to bring down blood glucose levels.

However, there are some adverse effects reported for hydroxychloroquine which include gastrointestinal upset, infrequent central nervous system effects like headache, pruritus, acute generalized dermatologic eruptions and hyperpigmentation [11]. Hypoglycemia has also been reported when hydroxychloroquine is administered with OADs and insulin for which, reduction in the dosage of OADs and insulin has been recommended [12].

Retinal toxicity is an important concern linked with the use of hydroxychloroquine. In a study done by Mavrikakis et al. [13] among 400 patients, the incidence of retinopathy was observed to be 0.5% when the drug was used for 8.7 years. The risk of retinopathy increases with higher dosage (> 5.0 mg/kg body weight), use for more than five years, pre-existing renal disease, maculopathy and simultaneous tamoxifen use. The 2016 American Academy of Ophthalmology (AAO) guidelines [14] recommended that, baseline ophthal-

mological screening should be done before initiation of hydroxychloroquine therapy and yearly screening should be performed after five years of use when other concomitant risk factors are absent. Regular annual ophthalmological screening is recommended for the patients with risk factors.

## Conclusion

The glycemic control gained by the patient discussed in this case study substantiates the effectiveness of hydroxychloroquine as add-on therapy in T2DM. Addition of hydroxychloroquine exerted good glycemic control in the patient who was refractory to combination of OADs. The outcome of this case study indicates that, hydroxychloroquine has a potential to become an important alternative in the management of T2DM in the future.

## Competing interest

Dr. Subash Chandra Satpathy has no competing interests. Dr. Indranil Purkait and Mr. Avinash Talware are the employees of IPCA Laboratories Ltd., who are involved in the research studies of hydroxychloroquine.

## Author contribution

Dr. Subash Chandra Satpathy was involved in the conception, design, and interpretation of the data. All the authors including Dr. Indranil Purkait and Mr. Avinash Talware were involved in the execution of written article.

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