

Erroneous reduction of HbA1c levels in patients with type 2 diabetes mellitus on dapsone treatment for Hansen's disease - a single-center retrospective cohort study

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Abstract

Background: Dapsone treatment may reduce HbA1c levels in patients with diabetes.

Aims: To assess the prevalence and characteristics of dapsone associated reduction of HbA1c in patients with Hansen's disease.

Methods: A retrospective data review of outpatient and inpatient charts of consecutive patients with Hansen's disease and type 2 diabetes mellitus was conducted over two years from January 2014 to January 2016 at the Department of Dermatology, CMC Vellore, India.

Results: Of the 245 patients with a confirmed diagnosis of Hansen's disease who were on oral dapsone 100 mg/day as part of their treatment regimen, 49 patients had diabetes and were eligible for the study as per predetermined inclusion criteria. Of these, 35 subjects (71%) had an HbA1c discordantly lower than the corresponding mean plasma glucose levels. Patients with discordant HbA1c levels were more likely to be male and to have a higher RBC mean corpuscular volume (MCV). A greater reduction in HbA1c levels was seen during the initial 3 months of therapy of dapsone treatment.

Limitations: The small sample size and retrospective design were limitations of this study. Also, we did not analyze the role of methemoglobinemia or the utility of alternative measures of glycemic control in these patients.

Conclusion: We describe a high prevalence of dapsone associated inappropriate HbA1c lowering in type 2 diabetes mellitus patients. This may have serious implications for the management of diabetes in patients on therapy with dapsone.

Key words: Dapsone, HbA1c, Hansen's Disease

Introduction

Hansen's disease is a communicable disorder of considerable public health importance. In 2016, 127,326 new cases of Hansen's disease were detected in India¹ accounting for 60% of the global new cases². In the same year, there were

69.2 million persons with diabetes in India, comprising 7.3% of the living adult population³.

The role of HbA1c in the diagnosis of diabetes mellitus, monitoring of glycemic control, and prediction of

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complications of diabetes mellitus is well established⁴. HbA1c is a robust marker, but it may be unreliable in the presence of certain disorders⁵ or drugs⁶.

Although animal studies⁷ and sporadic case reports⁸⁻¹¹ have indicated an interaction of dapsone with HbA1c levels, this has not been systematically studied. We, therefore, conducted a retrospective study of patients with Hansen’s disease who were on dapsone as part of their multidrug therapy and had type 2 diabetes mellitus in order to evaluate the prevalence and characteristics of patients with inappropriate lowering of HbA1c levels.

Methods

A retrospective review of outpatient and inpatient charts of consecutive patients with Hansen’s disease on dapsone 100mg/day and type 2 diabetes mellitus over a period of two years from January 2014 to January 2016 at the department of dermatology, the Christian Medical College, Vellore, India, was conducted. Hansen’s disease was diagnosed as per existing diagnostic criteria¹² and diabetes mellitus was established in accordance with the American Diabetes Association criteria¹³. Patient data collected included the age, sex, the duration of diabetes and the duration of dapsone therapy. The levels of serum creatinine, LDL cholesterol, triglyceride, HbA1c, fasting and postprandial plasma glucose (FPG, PPG), hemoglobin concentration, and the mean corpuscular volume (MCV) were also noted. Estimated average glucose (eAG) was calculated from the HbA1c level using the formula: $eAG (mg/dL) = (28.7 * HbA1c) - 46.7$ ¹⁴. The mean plasma glucose was calculated from daily self-monitoring of blood glucose (SMBG) recordings noted in the patient’s logbook.

Discordance was defined as a difference of more than 28.7 mg/dL (1% change of HbA1c) between the estimated average glucose and the mean plasma glucose levels (derived from the self-monitoring of blood glucose recordings).

Results

Of the 59 patients who had both type 2 diabetes mellitus and Hansen’s disease, 49 had a documented HbA1c during dapsone therapy and plasma fasting glucose levels estimated within a week of each other. The concomitant plasma fasting and postprandial glucose levels of these patients were obtained from their charts, and the eAG levels calculated. Discordance was noted in 35 patients (Group A) while the remaining 14 (Group B) were concordant [Figure 1].

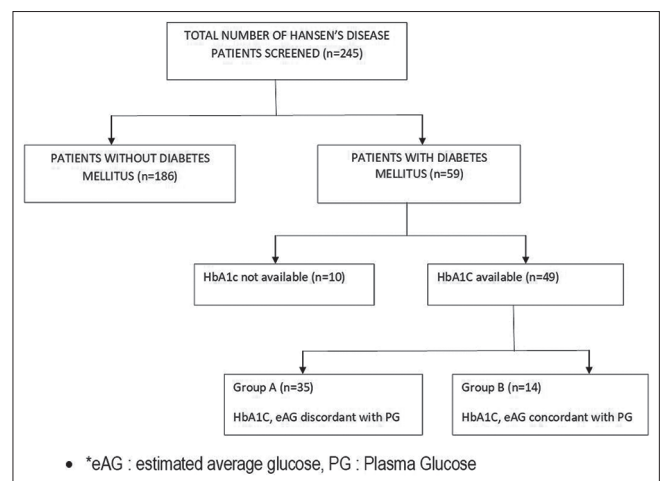


Figure 1: Flow-chart depicting the study design

Table 1: Baseline Characteristics of the patients

Characteristics	Group A (HbA1c discordant, n=35)	Group B (HbA1c concordant, n=14)	P
Age (yrs)	54.5±7.8	57.2±8.3	0.25
Male (in %)	63 (n=22)	57 (n=8)	0.04
Duration of diabetes (yrs)	5.8±1.8	6.2±2.5	0.41
Duration of dapsone therapy (months)	4.7±2.2	5.3±2.4	0.16
Mean Creatinine (mg/dL)	0.9±0.1	1.1±0.3	0.20
Mean LDL (mg/dL)	106±29	112±33	0.34
Mean Triglyceride (mg/dL)	158±56	166±64	0.18
Mean HbA1c (%)	4.4±1.8	7.9±2.1	0.01
Mean fasting plasma glucose (mg/dl)	136±33	145±43	0.66
Mean Postprandial glucose (mg/dl)	198±47	206±39	0.25
Mean Hb (gm%)	11.2±2.3	12.5±3.1	0.17
Mean Corpuscular Volume (MCV) (fL)	98.8±21.8	88.6±25.2	0.04
Mean Corpuscular Volume (MCV) >112 fL (%)	23(n=8)	3(n=1)	0.02

Table 2: HbA1c - eAG correlation with measured plasma glucose values

Mean values	HbA1c (%)	eAG (estimated average glucose)	Fasting glucose level (mg/dL)	Postprandial glucose level (mg/dL)	Mean glucose levels (mg/dL)
GROUP A Discordant (n=35)	4.4	80	136	198	167
GROUP B Concordant (n=14)	7.9	180	145	206	176

The baseline characteristics of the two groups are summarized in Table 1. Although a male preponderance was noted in both groups, the number of males in Group A was significantly higher ($P = 0.04$). The two groups were also similar with respect to their age, duration of diabetes mellitus, duration of dapsone therapy and all baseline laboratory parameters including the mean levels of serum creatinine, serum triglyceride, hemoglobin, B12 levels, and FPG and PPG [Table 1]. The mean eAG in Group A patients was 80 mg/dL (mean HbA1c 4.4%), which was significantly lower than the observed mean glucose levels of 167 mg/dL ($P = 0.01$), whereas in Group B the eAG of 180 mg/dL (mean HbA1c 7.9%) and observed mean glucose levels of 176 mg/dL were similar ($P = 0.65$) [Table 2].

The MCV was significantly higher in Group A ($P 0.04$), and 8 of these 35 patients (23%) had an MCV > 112 fL as compared to just 1 of 14 patients in Group B (3%). Despite the fact that all patients were diabetic, only 2 of the 35 Group A subjects had an HbA1c >6%, with 19 of these patients having an

HbA1c <4 [Table 3]. A greater reduction in HbA1c levels was seen in patients who had been on dapsone for less than 3 months in Group A. Further, 11 of the 19 (58%) patients with an HbA1c <4% had been on dapsone for less than 3 months [Table 4].

Stepwise regression analysis carried out to assess the influence of various factors associated with decreased HbA1c in dapsone treated patients showed that a higher baseline MCV and shorter duration of dapsone therapy were associated with greater reductions in HbA1c (standardized coefficient beta -0.585 and 0.215 respectively; $P < 0.01$). None of the other clinical or biochemical parameters had a significant influence on the change in HbA1c (all $P > 0.05$).

Discussion

Our results demonstrate a significant prevalence of dapsone induced reduction of HbA1c ($n = 35/49, 71%$) in patients with Hansen’s disease and type 2 diabetes mellitus. Both the groups (Groups A and B) were similar in terms of their age, sex distribution, duration of diabetes mellitus, duration of dapsone therapy and biochemical parameters. Although the mean FPG and PPG levels were similar in the two groups, the mean HbA1c and eAG were significantly lower in Group A. The mean MCV in group A was also significantly higher, and a greater number of patients in Group A had an MCV >112 fL (8/35, 23% vs 1/14, 3%).

Since the first case of falsely low HbA1c levels in a patient on dapsone for necrobiosis lipoidica and diabetes mellitus reported by Bertholon *et al*⁸ in 1994, only five cases have been reported including two from India^{6,9-11} [Table 5]. Although the

Table 3: Characteristics among the discordant group (Group A) according to HbA1c levels

HbA1c distribution (n=35)	<4%	4-6%	>6%	P
Numbers (%)	19	14	2	0.001

Table 4: Characteristics among the discordant group (Group A) according to duration of dapsone therapy

Duration of dapsone therapy	<3 months	3-6 months	>6 months	P
Mean HbA1c (%)	3.4	4.6	5.3	0.01
HbA1c <4 (%) (n=19)	58%(n=11)	32%(n=6)	10%(n=2)	0.001

Table 5: Summary of findings from previously reported cases of dapsone-associated inappropriate reductions in HbA1c levels

Previously reported cases in literature (Ref)	Details
Case 2-1994 ⁹	An 18-year old girl with type 1 diabetes, diagnosed to have necrobiosis lipoidica diabetorum, was treated with dapsone (100mg/day) and developed falsely low HbA1c levels (5.2%-5.6% despite discrepantly high plasma glucose levels (>200 mg/dl), possibly attributed to dapsone exposure.
Case 1-2002 ⁸	A 35-year-old patient with type I diabetes had high home-monitored blood glucose values, high clinic plasma glucose determinations, increased fructosamine levels, and low HbA1c values. The lowering of the HbA1c level was associated with use of dapsone, and the decrease in HbA1c value was proportional to the dose of dapsone.
Case 3-2012 ¹⁰	36-year-old male with type 2 diabetes since 10 years , initially managed with oral antidiabetic drugs alone with worsening control of diabetes necessitating the addition of insulin therapy since 4 years. He was also diagnosed to have lepromatous leprosy since one year and was on multidrug therapy, including dapsone, for the same ever since. He had discrepantly low HbA1c (4.4%) due to dapsone exposure.
Case 4-2012 ¹⁰	65-year-old male with type 2 diabetes of six years’ duration, on combination therapy with sulfonylurea and metformin. His HbA1c level were found to be discrepantly low (3.8%). Further enquiry revealed that the patient had consulted a dermatologist in August 2010 with complaints of scaly patches over the forearms and legs, and had been put on dapsone (100 mg/day) since then
Case 5-2012 ¹¹	A 52-year-old man, who was diagnosed with type 2 diabetes mellitus 5 years with diabetes being controlled by sulfonylurea and metformin. Patient developed leucocytoclastic vasculitis for which he was started on dapsone therapy (100mg/day). During the 3-years follow-up period, HbA1c dropped significantly during the addition of dapsone treatment, although plasma glucose levels remained stable. HbA1c levels were raised after discontinuation of dapsone. With rechallenge of dapsone usage, HbA1c decreased again.

coexistence of Hansen's disease and type 2 diabetes mellitus is not uncommon there are no previous studies of this phenomenon in literature. This is the first study of a single-center cohort demonstrating the frequent occurrence of reduced HbA1c in diabetic patients on dapsone. Further, the most pronounced effects on HbA1c reduction were seen in those receiving dapsone for less than 3 months.

Limitations of our study include the retrospective nature of the study and the relatively small sample size. Because of the retrospective design, it was not possible to identify the exact role of hemolysis, methemoglobinemia, or the utility of alternative markers of glycemic control in the reduction of HbA1c on dapsone therapy. Future prospective, larger studies could add valuable insight into this unique association of dapsone with low HbA1c which could have major implications for the managements of diabetes mellitus in patients with Hansen's disease.

Conclusion

Dapsone therapy interferes with HbA1c assessment, producing an inappropriately low HbA1c level in majority of diabetes patients with Hansen's disease. While the actual mechanism remains elusive, the role of hemotoxicity and methemoglobinemia needs further prospective studies. Our findings suggest the unreliability of HbA1c as a marker of glycemic control in presence of concomitant dapsone therapy, thus necessitating the need for alternatives such as serum fructosamine assays¹⁵. Given the huge burden of Hansen's disease and diabetes mellitus in developing countries, our findings have significant therapeutic ramifications.

Disclosure

All authors have contributed equally to the manuscript as per the ICMJE requirements.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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