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Cross Sectional Study on Prevalence of Falsely Low Hba1c in Diabetic Patients on Dapsone Therapy

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Abstract:

Background: Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1]

Objective: The aim of our study was to establish the prevalence of falsely low HbA1c in diabetes patient on dapsone therapy and the possible mechanism behind it.

Study design: we conducted a retrospective Cross-sectional study on 30 subjects more than or equal to 18yrs attending the Endocrinology and Dermatology outpatient department (OPD) ,patients with diabetes mellitus on oral anti diabetic drugs and or insulin therapy on dapsone therapy and patients on documented dapsone therapy for Hansen's disease or any other skin condition were eligible for enrolment. HbA1c measured by HPLC(high performance liquid chromatography) was compared with expected A1c value suggested by other parameters like fructosamine assay and mean blood glucose. Also other parameters of haemolysis was measured to establish the possible mechanism behind the falsely low A1c.

Results: Out of 30 subjects 25 patients were found to have low HbA1c value compared to their fructosamine assay and expected HbA1c. Prevalence of inappropriately low A1c was 25(83.45%) ,16 of them in diabetic group (53.3%) and 9 in non-diabetic group (30.0%).. There were higher number of subjects in discordance group with >2% methaemoglobin with marginally positive correlation .Factors of haemolysis too was higher in more number of subjects [reticulocyte count (18.2%) mcv(90.9)LDH(86.6%)] in discordance Hba1c group compared to cordance HbA1c group but was not statically significant owning to small sample size.

Conclusion: The prevalence of falsely low A1c in patient on dapsone therapy was as high as 83.5% and possible reason for this being hemolysis suggesting there are a number of drugs, some of them quite commonly used, which can cause inappropriately high or low HbA1c levels for the degree of glycemia

Keywords: Glycated haemoglobin, diabetes mellitus ,dapsone

Introduction

Diabetes mellitus is a major cause of mortality and morbidity in India and all over the world .In the past three decades the prevalence of diabetes has risen dramatically in countries of all income levels. (About 422 million people worldwide have diabetes, particularly in low-and middle-income countries as per WHO.)

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the pancreatic β-cells with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.[2]

A1C is a widely used marker of chronic glycemia, reflecting average blood glucose levels over a 2- to 3-month period of time. The test plays a critical role in the management of the patient with diabetes, since it correlates well with both microvascular and, to a lesser extent, macrovascular complications and is widely used as the standard biomarker for the adequacy of glycemic management. Prior Expert Committees have not recommended use of the A1C for diagnosis of diabetes, in part due to lack of standardization of the assay. However, A1C assays are now highly standardized so that their results can be uniformly applied both temporally and across populations. In their recent report (3), an International Expert Committee, after an extensive review of both established and emerging epidemiological evidence, recommended the use of the A1C test to diagnose diabetes, with a threshold of ≥6.5%, and ADA affirms this decision. The diagnostic A1C cut point of 6.5% is associated with an inflection point for retinopathy prevalence, as are the diagnostic thresholds for FPG and 2-h PG (3). The diagnostic test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial reference assay. Point-of-care A1C assays are not sufficiently accurate at this time to use for diagnostic purposes.

There is an inherent logic to using a more chronic versus an acute marker of dysglycemia, particularly since the A1C is already widely familiar to clinicians as a marker of glycemic control. Moreover, the A1C has several advantages to the FPG, including greater convenience, since fasting is not required, evidence to suggest greater preanalytical stability, and less day-to-day perturbations during periods of stress and illness.[3] A number of methods are in use for measuring HbA1c. The most widely used assay utilizes high-performance liquid chromatography (HPLC). Other methods include boronate affinity assay and immunoassays.

Although HbA1c is, in general, a robust marker of glycemia, there are certain conditions in which the test can be unreliable. Use of the newer assays like HPLC can eliminate some, but not all of these errors. [4]Any drug which causes hemolysis can potentially lower the HbA1c by reducing erythrocyte lifespan.Dapsone can also promote the oxidation of hemoglobin to methemoglobin, which may interfere with the HPLC assay used to measure HbA1c. Dapsone has also been postulated to reduce erythrocyte survival independent of its hemolytic effect.The potential HbA1c lowering effect of dapsone assumes special significance in India in view of the widespread use of this agent in the treatment of Hansen's disease and many other condition. Dapsone is a bacteriostatic antibacterial sulfonamide drug used in the treatment of numerous systemic and dermatologic conditions. Dapsone has excellent bioavailability when absorbed from the gastrointestinal tract and equal efficacy when used in a topical formulation. Once absorbed, dapsone demonstrates a unique metabolic phenomenon known as fast and slow acetylation. This means certain individuals will metabolize it faster than others, however, there has been no difference noted in efficacy or side effect profiles. With three different mechanisms of action, dapsone has established a broad area of coverage in both systemic and skin diseases. As an antibiotic, dapsone is commonly used to treat mycobacterium leprae, the causative organism of leprosy. Also, it is used to prophylax against Pneumocystis pneumonia and toxoplasmosis in HIV patients as well as an adjuvant treatment for malaria.

As an anti-inflammatory agent, dapsone finds utility in treating numerous blistering dermatologic diseases such as:

Pemphigus vulgaris
IgA pemphigus
Bullous pemphigoid
Bullous form of systemic lupus erythematosus
Linear IgA dermatoses associated with medication exposure, especially vancomycin
Dermatitis herpetiformis associated with the gluten hypersensitivity known as celiac disease.

Furthermore, dapsone is also used in the management of dermatoses characterized by neutrophilic or eosinophilic cutaneous infiltrates like Sweet's syndrome and pyoderma gangrenosum[5]

Methods and methodology

It was a Cross-sectional study for a duration of 3 months on 30 patients (20 diabetic and 10 who had euglicemic status) meeting inclusion and exclusion criteria .Inclusion criteria being patients with diabetes mellitus on oral anti diabetic drugs and or insulin therapy on dapsone therapy and patients on documented dapsone therapy for Hansen's disease or any other skin condition. Patients with known history haematological disorder ,chronic kidney disease ,chronic liver disease, pregnancy, psychiatric illness ,HIV were excluded. Patient who received blood transfusion over past 3months and those who were on drugs known to cause low A1c was also excluded.pror written consent was obtained from all subjects.HbA1c measured by HPLC(high performance liquid chromatography) was compared with expected A1c value suggested by other parameters like fructosamine assay and mean blood glucose. Also parameters of haemolysis was measured to establish the possible mechanism behind the falsely low A1c.clinical parameters like height,weight,BMI,waist circumference and blood pressure and biochemical parameters like fasting and post prandial blood sugar,haemoglobin,serum creatinine,HbA1c,serum fructosamine assay ,LDH,reticulocyte count,methemoglobin level,MCV,vitaminB12 level,estimated average glucose values were measured.

Parameters Subjects N =30 (Mean ± SD)	
Age (years)	45.4 ± 11.9
Height (cms)	166.8 ± 7.4
Weight (kgs)	67.3 ± 11.5
BMI (kg/m2)	25.4 ± 7.7
Systolic blood pressure (mmHg)	121 ± 15.5
Diastolic blood pressure (mmHg)	74.8 ± 5.9
Duration of Dapsone therapy (weeks)	40.7 ± 37.1
Sex (male : female)	20 (66.7) : 10 (33.3) *
Type (Diabetes : Non diabetes)	20 (66.7) : 10 (33.3) *
G6PD	Nil

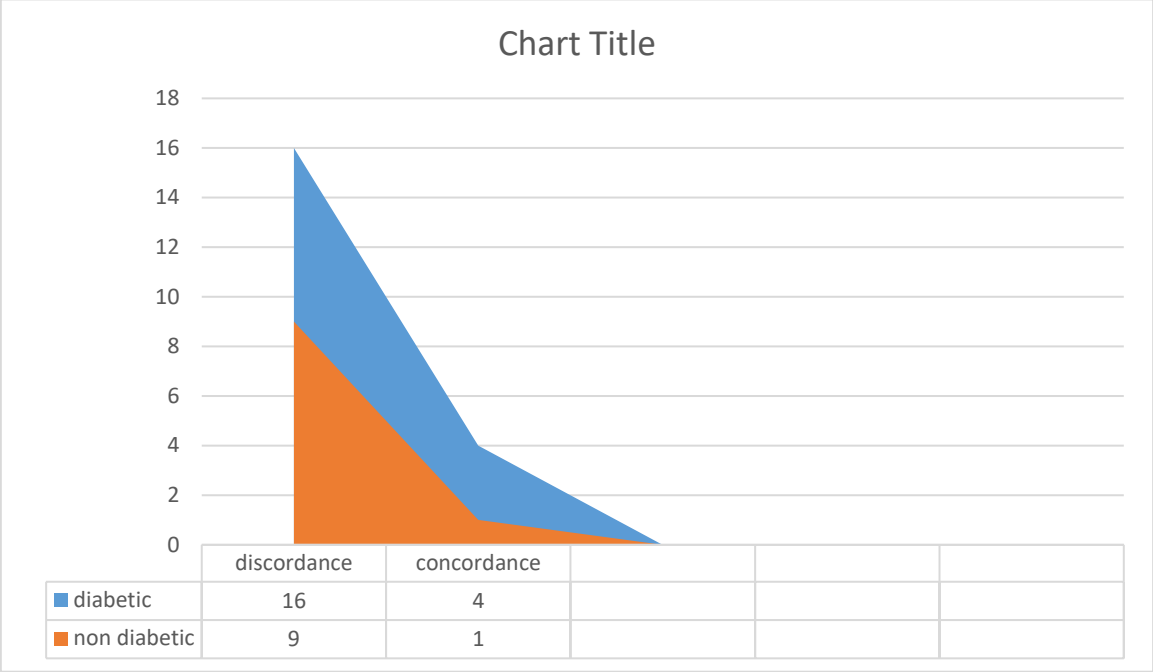
The mean age (in years) of patients with diabetes mellitus was 49±10.6 and non diabetes mellitus was 37±10.6. The mean HbA1c in patients with diabetes was 5.0±1.1(%) and in those without diabetes was 4.1±0.6(%) (P- 0.006).The mean estimated average glucose (eAG) in patients with and without diabetes were 98.2 ± 31.7(mg/dl) and 71.5±17.3 (mg/dl)(P-0.006). The mean fructosamine was 278.1±63.9(mmol/l) and 237.4±33.0(mmol/l) respectively. (P- 0.029).

Variables	Non diabetic (Mean ± SD)	Diabetic (Mean ± SD)	P value(Independent T-test)
Glucosefasting(70-100 mg/dL)	112.1 ± 40.6	88.1 ± 7.3	0.018*
PC Glucose(<140 mg/dL)	177.7 ± 75.0	114.1 ± 22.6	0.002**
HbA1c(<5.7%)	5.0 ± 1.1	4.1 ± 0.6	0.006**
Creatinine(0.5-1.0 mg/dL)	0.8 ± 0.2	0.7 ± 0.2	0.957
Hemoglobin(m-13-17 g/dL)(f-11-15 g/dL)	11.7 ± 1.9	11.0 ± 1.7	0.298
MCV80- 100 fL)	89.9 ± 6.5	89.3 ± 8.5	0.850
Methemoglobin	2.6 ± 2.5	2.4 ± 0.9	0.744
Fructosamine(upto 290 m.mol/L)	278.1 ± 63.9	237.4 ± 33.0	0.029*
Reticulocyte(0.5 - 2.5%)	2.9 ± 1.4	3.8 ± 2.4	0.271
LDH (225-460 U/L)	553.2 ± 224.9	660.4 ± 335.8	0.378
Triglycerides(<150 mg/dL)	128.8 ± 60.5	122.8 ± 71.0	0.822
eAG (mg/dl)	98.2 ± 31.7	71.5 ± 17.3	0.006**
Age (years)	49.4 ± 10.6	37.3 ± 10.6	0.009**

BMI (kg/m2)	**25.1 ± 4.4**	**26.2 ± 12.1**	**0.797**

Result :

Table 1: Discordant and Concordant HbA1c



In this study population out of 30 ,25 subjects had discordant HbA1c according to the fructosamine assay and estimated average blood glucose level.Out of 20 diabetes subjects, 16 (80%) had discordance HbA1c and 4(20%) had concordance HbA1c.In non-diabetes group 9(90%) had discordance HbA1c and 1(10%) had concordance HbA1c

The mean HbA1c of concordance HbA1c was 5.7±0.45 and discordance HbA1c group was 4.8±1.1 (P-0.04). The mean fructosamine level in concordance HbA1c [D1] study was 243.2±16.3 (mmol/l) and in discordance HbA1c study group was 287.5±68.2 (mmol/l) (P- 0.031). The mean estimated average glucose (eAG) in concordance HbA1c study was 116.8±13.0 (mg/dl) and in discordance HbA1c study group was 93.5±33.5(mg/dl) with significant p value of 0.04. This was suggestive of statistically significant low HbA1c in diabetes discordance HbA1c subjects.

The mean MCV and the mean Hemoglobin failed to achieve statistical significance but mean MCV was numerically high and mean Hemoglobin was numerically low in discordance HbA1c study group. This was suggestive of dapsone induced hemolyis.

While other variables such as age, sex, BMI, reticulocyte count and LDH fail to achieve statistical significance.

Factors affecting HbA1c in diabetic patients on dapsone therapy

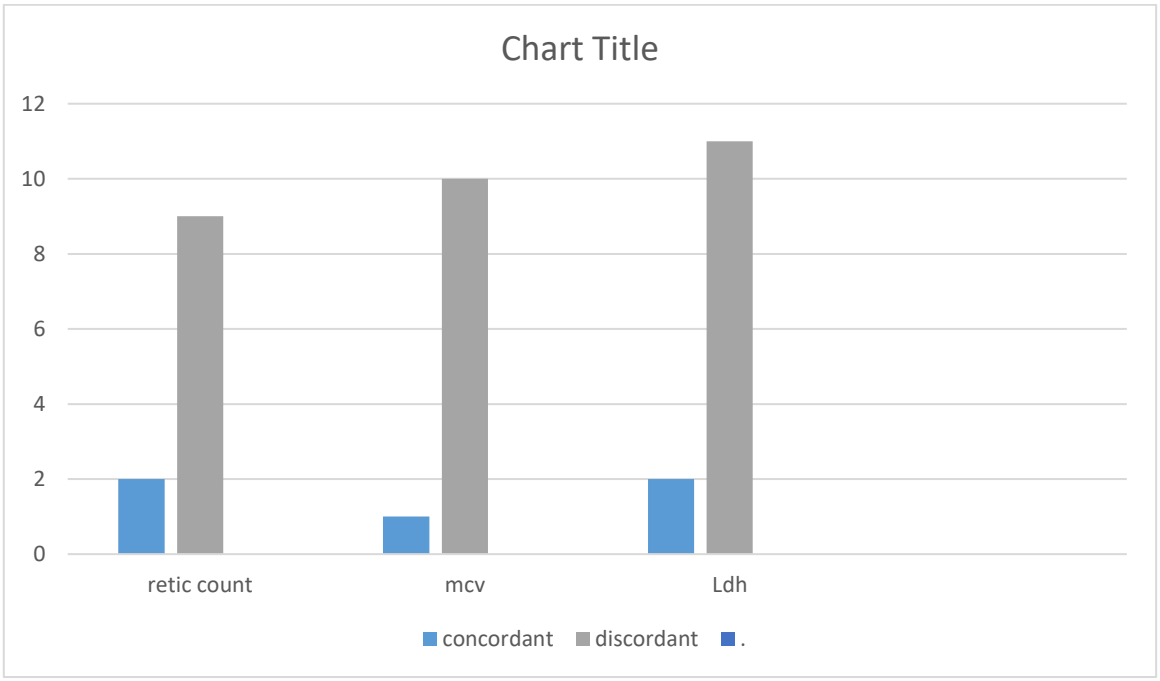
	METHEMAGLOBIN		**Total**
	At risk (>2)	**Not risk (<2)**	

Diabetes patient group with concordant HbA1c	**0**	**4**	**4**
Diabetic patient group with discordant HbA1c	**2**	**14**	**16**

Out of 16 subjects in discordant HbA1c group, 2 (12.5%) subjects had >2% methemoglobin and 14 (87.5%) subjects had <2% methemoglobin. In concordance HbA1c group all 4 subjects had <2% methemoglobin level.

There were higher number of subjects [2(12.5%)] in discordance group with >2 % methemoglobin compared to the concordance group though it was not significant. This suggests that methemoglobinemia may also be a possible mechanism for falsely low glycated hemoglobin.

Other factors of hemolysis



There were higher number of subjects in discordance HbA1c group with Reticulocyte count(18.2%), MCV(90.9%), and LDH (86.6%) levels compared to concordance HbA1c group.

Statistical analysis

The mean HbA1c ,mean fructosamine and mean estimated average glucose between discordance and cordance diabetic subjects were found to be statistically significant with p value 0.04,0.031,0.04 respectively. There were higher number of subjects in discordance group with >2% methaemoglobin with marginally positive correlation($p = 0.05$).The other factors of heamolysis too was higher in more number of subjects [reticulocyte count(18.2%)mcv(90.9)LDH(86.6%)] in discordance Hba1c group compared to cordance HbA1c group but was not statically significant owning to small sample size .

Discussion:

There were no studies on inappropriately low HbA1c and Dapsone as of now from India, only isolated case scenarios and reports are published.

Ranjit unnikrishnan et al in 2012 reported a patient with falsely decreased HbA1c in type 2 diabetes mellitus patient who was treated with dapsone. The patient was a 36 years old gentleman who presented in January 2012 for evaluation of diabetes mellitus. He was diagnosed to have type 2 diabetes mellitus since the past 10 years and was initially managed with oral anti diabetic drugs alone. Worsening control of diabetes necessitated the addition of insulin therapy. He was also diagnosed to have lepromatous leprosy an year ago and has been initiated on multidrug therapy, including dapsone. His fasting and post prandial blood glucose levels were 167 and 289 mg/dl respectively. However, his glycated hemoglobin level, measured by HPLC method was surprisingly low (4.4%), which remained unaltered on repeat testing on another machine the following day. In view of discrepancy between the plasma glucose and the HbA1c levels, a serum fructosamine assay was carried out, which revealed a poor glycemic control. In view of the history of chronic dapsone use, the possibility of drug induced alteration in the HbA1c level was considered and patient was further investigated along those lines. Hemograms showed a mild anemia with an elevated leucocyte count. Serum bilirubin was normal, however, the reticulocyte count and lactate dehydrogenase were found to be elevated, suggestive of hemolysis. The methomoglobin level was also found to be elevated, suggesting a possible additional mechanism for lowering of HbA1c.[7]

Eric S. Albright et al in 2002 document a case report on Artifactually low hemoglobin A1c that was suspected to be caused by the concomitant use of dapsone. They reported a 35-year old white woman with type 1 diabetes since the age 12 year who had historically poor glycemic control, with HbA1c values ranging from 10 to 13% range. This suboptimal control had led to all the mico and macrovascular complications. She also was documented to have euthyroid hashimoto'sthyroiditis, stress incontinence, lumbar and cervical disk disease, depression, and dermatitis herpetiformis. Although the patient's home-monitored blood glucose values remain high (250 to 350 mg/dl), her HbA1c had declined to the 6 to 7% range over 2 year. In addition, her serum fructosamine level checked was increased to 3.6 mmol/l (upper limit of normal- 2.6) compared to the prior readings. Despite continued high blood glucose values, her HbA1c further decreased to the level of 3 to 4% range. A review of her medications demonstrated a recent increase in her dose of dapsone; hence the cause for the low HbA1c level was discovered to be due to dapsone. Institution of dapsone therapy at 50 mg/day had caused an initial decrease in the HbA1c value, and an increase in dosage to 100 mg daily was associated with a further decline in her HbA1c levels. When the dapsone dosage was reduced to 50 mg daily, the HbA1C returned to the 6 to 7% range, in conjunction with continued increases in plasma glucose concentration, home-monitored blood glucose value, and high fructosamine levels.[8]