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In a cohort of individuals with type 2 diabetes using the drug sulfasalazine, HbA1c lowering is associated with haematological changes

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Abstract
Objectives: Several small studies indicate the sulphonamide component of the drug sulfasalazine lowers HbA1c. We investigated reduction of HbA1c following incident prescription of sulfasalazine and related aminosalicylates, lacking the sulphonamide group, in an observational cohort.

Research Design and Methods: Individuals in the Scottish Care Information Diabetes Collaboration (SCI-Diabetes) with type 2 diabetes and incident prescription for an aminosalicylate drug (sulfasalazine, mesalazine, olsalazine or balsalazide) were identified. Baseline and 6-month HbA1c were required for eligibility, to calculate HbA1c response. To investigate association with haemolysis, change in components of full blood count was assessed. Paired t-tests compared difference in baseline and treatment HbA1c measures and other clinical variables.

Results: In all, 113 individuals treated with sulfasalazine and 103 with mesalazine (lacking the sulphonamide group) were eligible, with no eligible individuals treated with olsalazine or balsalazide. Baseline characteristics were similar. Mean (SD) HbA1c reduction at 6 months was −9 ± 16 mmol/mol (−0.9 ± 1.4%) (p < 0.0001) in those taking sulfasalazine with no reduction in those taking mesalazine (2 ± 16 mmol/mol (0.2 ± 1.4%). Sulfasalazine but not mesalazine was associated with a mean (SD) increase in mean cell volume of 3.7 ± 5.6 fl (p < 0.0001) and decrease in red cell count of −0.2 ± 0.4 × 10−12/L (p < 0.0001).

Conclusions: In this observational, population-based study, sulfasalazine initiation was associated with a 6-month reduction in HbA1c. This correlated with haematological changes suggesting haemolytic effects of sulfasalazine. Haemolysis is proposed to contribute to HbA1c lowering through the sulphonamide pharmacophore. This suggests that HbA1c is not a reliable measure of glycaemia in individuals prescribed sulfasalazine.

KEYWORDS
Sulfasalazine, HbA1c, type 2 diabetes, glucose, sulphonamide, haemolysis

Samira M. S. N’Dow and Louise A. Donnelly have contributed equally to this work.

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1 | INTRODUCTION

HbA1c testing has a significant role in management of diabetes because it gives an average indication of glycaemic control, avoiding day-to-day variations evident in glucose monitoring. In addition, HbA1c is a strong predictor of risk for development of diabetes-related complications, as well as being a cornerstone of glycaemic control targets and diagnosis of diabetes in national and international guidelines. Haematological abnormalities including haemolytic anaemias, haemoglobinopathies, splenomegaly, blood loss/transfusion and chronic liver disease are known to interfere with the accuracy of the HbA1c test. However, there are few large-scale studies examining changes in HbA1c following incident drug treatment. Previously, the sulphonamide drugs dapsone, sulamethoxazole and sulfasalazine have been reported to lower HbA1c in case reports and case series. One study attributed the effect of sulfasalazine on HbA1c to glucose lowering; however, most other studies attribute lowering of HbA1c to haematological changes in dapsone and sulfasalazine-treated individuals. Consistent with a ‘false’ lowering of HbA1c, measures of glucose and fructosamine, which is an additional measure of long-term glucose control, were unaffected by these drugs. Previous work suggests that even mild, subclinical haemolysis that does not produce anaemia could have significant impacts on HbA1c.

Dapsone and sulamethoxazole are prescribed only rarely in Scotland but in contrast sulfasalazine was prescribed 112,765 times in the most recent year for which data were available, accounting for around 0.1% of all prescriptions, placing it in the top 10% of drugs prescribed in a population of just over five million people. In the current study, we have compared the effects of sulfasalazine and related 5-aminosalicylate (5-ASA) drugs on HbA1c. Sulfasalazine was the first ASA drug effective in inflammatory bowel disease (IBD), a term mainly used to describe Crohn’s disease and ulcerative colitis. Sulfasalazine consists of 5-ASA joined with a sulphonamide group by a diazo bond (see Figure 1). The action of sulfasalazine in IBD relies on the diazo bond being cleaved in the colon, releasing the 5-ASA (reviewed in ). The 5-ASA component is poorly absorbed from the gastrointestinal tract, reaching its highest concentration in the colon and rectum. The sulphonamide moiety is well absorbed from the gut; systemic absorption of the sulphonamide moiety is likely to cause the classical adverse effects of sulfasalazine such as: blood dyscrasias, hypersensitivity reactions and infertility in men, as well as more common effects such as headaches and nausea. These adverse effects often result in difficulty titrating the drug to a high enough dose for therapeutic anti-inflammatory effect of the 5-ASA.

Further therapies were developed with the aim of making the therapy more targeted to avoid sulfasalazine’s side effects. The development of 5-ASA drugs lacking the sulphonamide group eliminated the side effects associated with sulfasalazine. Oral 5-ASA on its own is not an effective therapy as the drug is not concentrated in the distal gut. Newer drugs such as mesalazine, balsalazide and olsalazine release the active compound when the drug reaches the distal small bowel area, allowing the benefits of 5-ASA in IBD without the systemic adverse side effects of sulfasalazine.

The aim of this study was to analyse the association of aminosalicylate drugs sulfasalazine, mesalazine, olsalazine and balsalazide on HbA1c in individuals with type 2 diabetes.

What is already known about the subject?

- In case reports and case series, sulphonamide-based drugs (including sulfa-antibiotics and dapsone) have been associated with reduction of HbA1c.
- Haemolytic effects of the drugs have been suggested to underlie this effect.

What has this study found?

- Sulfasalazine is associated with HbA1c lowering.
- This effect is correlated with haematological changes consistent with haemolysis.

What are the clinical implications of the study?

- HbA1c may not be a reliable marker of glycaemia in individuals using drugs which cause haemolysis. These groups may need to employ different glycaemic monitoring tools to prevent diabetes-related complications. In these patients, HbA1c may not be a reliable diagnostic tool in type 2 diabetes.
Based on previous case report/series evidence, we hypothesised that sulfasalazine but not mesalazine, olsalazine or balsalazide, would lower HbA1c. In addition, we investigated the effect of these drugs on markers of haemolysis, including full blood count–red blood cells (RBC), mean cell haemoglobin (MCH) and haematocrit (HCT).

2 | MATERIALS AND METHODS

2.1 | Data source & linkage

An observational cohort study was performed using comprehensive electronic medical records. Individuals with type 2 diabetes in Tayside and Fife were identified from The Scottish Care Information-Diabetes Collaboration (SCI-Diabetes) and linked to clinical, laboratory and encashed prescription datasets. Data were collected and integrated by the Healthcare Informatics Centre (HIC) of University of Dundee, conforming to ISO27001. This is a HIC project using anonymised data in line with HIC standard operating procedures and has Caldicott approval. Data linkage was through the Community Health Index number which is used widely in the NHS with over 99% accuracy for individuals with diabetes in Scotland.

2.2 | Study population

Complete prescribing data for aminosalicylates (defined as British National Formulary chapter 1.5.1) were available from 1st January 2005 and 1st January 2009, in Tayside and Fife, respectively, until 30th April 2017. All users of sulfasalazine, mesalazine, balsalazide and/or olsalazine within the study period were identified. To be eligible for the study, all individuals must have received no prescriptions for aminosalicylates in the calendar year 2005 and 2009 for Tayside and Fife, respectively, and could thus be considered treatment naïve. Individuals whose first prescription was prior to diabetes diagnosis were also excluded. Therefore, the study population was defined as individuals with an incident prescription (a first prescription occurring in the specified time period) of sulfasalazine, mesalazine, balsalazide and/or olsalazine on or after 1st January 2006 in Tayside or 1st January 2010 in Fife and after diagnosis of type 2 diabetes.

2.3 | Definition of HbA1c response and other clinical variables

Baseline HbA1c was defined as closest measure between 6 months prior and 7 days after drug start date. The 6-month treatment HbA1c measure was defined as the measure closest to 6 months after drug start date but within a 3- to 9-month window. Although results are largely focused on 6-month response, a 1-year treatment HbA1c measure was also defined as the measure closest to 1 year after drug start date but within a 9- to 15-month window. HbA1c response was calculated as the difference between the baseline and treatment HbA1c. For inclusion in the study, individuals were required to have a baseline and treatment measure to allow response to be assessed.

Baseline BMI, biochemical and haematological variables were defined as the closest measure between 1 year prior and 7 days after drug start date. Treatment BMI, biochemical and haematological variables were defined as measures closest to 6 months in a 3- to 12-month window. These results were solely examined for a 6-month response. Individuals were required to have both a baseline and treatment measure for the stated variables, allowing for change in study period to be assessed.

2.4 | Study population derivation

A detailed flow chart of the study population is presented in Figure 2. There were 1046 individuals with an incident 5-ASA prescription during the study period; 523 individuals treated with sulfasalazine, 506 treated with mesalazine, 53 treated with balsalazide and 11 treated with olsalazine (some individuals had prescriptions for more than one of the drugs during the study period, hence the total is 1093).

A total of 305 and 255 individuals were eligible for analysis in the sulfasalazine and mesalazine groups, respectively. Due to very small numbers in the olsalazine and balsalazide groups, these drugs were excluded from the study. Of the 305 individuals in the sulfasalazine group, 113 (37%) had a baseline and 6-month HbA1c measure, and of the 255 individuals in the mesalazine group, 103 (40%) had a baseline and 6-month HbA1c measure.

2.5 | Covariates

Individual characteristics of interest at baseline were gender, health board (Fife or Tayside), age at first prescription, age at type 2 diabetes diagnosis, HbA1c, BMI, bilirubin, RBC, MCH, HCT, haemoglobin (Hb) and mean cell corpuscular volume (MCV).

2.6 | Co-prescribing

Co-prescribed drugs which could alter HbA1c were identified from an initial list of all co-prescribed drugs. These drugs included hydroxychloroquine, opiates, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, folic acid, iron supplements and diabetes treatment.
2.7 | Anaemia definition

Mild anaemia was defined as haemoglobin below 12 \text{ g/dl} for women and below 13 \text{ g/dl} for men, and moderate anaemia was defined as below 11 \text{ g/dl} for both men and women, based on World Health Organisation (WHO) definitions.

2.8 | Statistical analyses

Comparisons of baseline characteristics and co-prescribing frequency by drug group were by t-test for continuous variables and Chi-square test for categorical variables.
Paired t-tests were used to compare the difference in baseline and treatment measures of HbA1c and other clinical variables. All analyses were performed using SAS 9.4 and a p value of <0.05 considered statistically significant. No adjustment was made for multiplicity of statistical tests. Scatter graphs and Pearson correlation coefficients were used to identify linear relationships between significant haematological changes (MCV, MCH, RBC) and HbA1c change at 6 months.

2.9 | Sensitivity analyses

Individuals in the sulfasalazine group taking relevant co-prescribed drugs and anaemic individuals were removed from the study population and the HbA1c results re-analysed. In addition, statistically significant changes in haematological variables were analysed for any correlation with HbA1c response.

3 | RESULTS

3.1 | Baseline characteristics of the sulfasalazine and control group

There were a total of 113 eligible individuals in the sulfasalazine group and 103 in the mesalazine group (control group).

A comparison of the two drug groups at baseline is presented in Table 1. Importantly, there was no statistically significant difference between the groups in baseline HbA1c or any of the variables tested.

The frequency of drugs co-prescribed during the study period that may affect HbA1c are presented in Table 2. Drugs exhibiting statistically significant differences in prescribing between drug groups were as follows: methotrexate, hydroxychloroquine, opiates, non-steroidal anti-inflammatory drugs and folic acid, which were each prescribed more commonly in the sulfasalazine cohort. The sulfasalazine group were prescribed less anti-diabetic drugs with 50% on diet or monotherapy treatment compared with 30% of the mesalazine group.

3.2 | HbA1c response and haematological responses in the sulfasalazine group

Initiation of sulfasalazine was associated with a mean (SD) HbA1c reduction of $-9 \pm 16$ mmol/mol ($-0.9 \pm 1.4\%$) ($p < 0.0001$) in a 6-month period (Table 3). HbA1c remained lowered by $-6 \pm 16$ mmol/mol ($-0.5 \pm 1.6\%$) ($p = 0.004$) after 1 year. In contrast, initiation of mesalazine was associated with a non-significant increase in HbA1c by $2 \pm 16$ mmol/mol ($0.2 \pm 1.6\%$) ($p = 0.23$). HbA1c response 1 year from incident mesalazine prescription was $0 \pm 18$ mmol/mol ($0.1 \pm 1.8\%$) ($p = 0.99$). Other statistically significant changes in the sulfasalazine group were decreased RBC and increased

| Table 1 | Comparison of baseline characteristics. Data are mean (SD) or N(%); Comparisons are by t-test for continuous variables and Chi-square test for categorical variables |
|---|---|---|---|---|
| Variable | Sulfasalazine | N | Mesalazine | N |
| Gender | | | | |
| Men | 59 (52%) | 113 | Men | 64 (62%) | 103 |
| Women | 54 (48%) | | Women | 39 (38%) | |
| Location | | | | |
| Fife | 49 (43%) | 113 | Fife | 39 (38%) | 103 |
| Tayside | 64 (57%) | | Tayside | 64 (62%) | |
| Age (years) | 66.4 ± 11.5 | 113 | 65.6 ± 12.5 | 103 |
| Age at type 2 diabetes diagnosis (years) | 58.0 ± 12.2 | 113 | 58.2 ± 12.7 | 103 |
| HbA1c (mmol/mol%) | 57 ± 17 (7.4 ± 1.6) | 113 | 61 ± 18 (7.7 ± 1.6) | 103 |
| BMI (kg/m²) | 32.3 ± 6.5 | 105 | 31.6 ± 6.4 | 97 |
| Bilirubin (µmol/L) | 7.8 ± 5.4 | 111 | 8.9 ± 4.7 | 103 |
| RBC (x10¹²/L) | 4.4 ± 0.5 | 112 | 4.4 ± 0.6 | 97 |
| MCH (pg) | 29.2 ± 2.4 | 112 | 29.7 ± 2.3 | 97 |
| HCT (L/L) | 0.4 ± 0.04 | 112 | 0.4 ± 0.05 | 97 |
| Hb (g/dl) | 12.8 ± 1.6 | 112 | 13.2 ± 2.0 | 97 |
| MCV(µl) | 90.4 ± 6.2 | 112 | 90.9 ± 5.3 | 96 |
| Mild anaemia | 50 (45%) | 112 | 35 (36%) | 97 |
| Moderate anaemia | 15 (13%) | 112 | 13 (13%) | 97 |

Percentages are presented in italics.
MCH and MCV levels. There were no significant changes in the mesalazine group. Figure 3 demonstrates the correlation observed between these haematological factors and the HbA1c response. The HbA1c response was correlated with significantly increased MCV ($p = 0.01$) and significantly decreased RBC ($p = 0.01$). A non-statistically significant correlation with decreasing MCH ($p = 0.13$) was also observed.

### 3.3 Impact of co-prescribing and anaemia

We performed sensitivity analyses on the sulfasalazine group, with individuals on specific co-prescribed drugs excluded (Table 4). The lowering effect of sulfasalazine on HbA1c was still evident despite the removal of these individuals. Further sensitivity analysis excluded anaemic individuals from the cohort (Table 5). This also had little impact on the HbA1c response.

### 4 DISCUSSION

#### 4.1 Principal findings

In this study, we analysed data from 216 individuals with type 2 diabetes, to study effects of the sulphonamide group of the drug sulfasalazine on HbA1c. Mesalazine acted as a control, as it lacks a sulphonamide group. There was no significant difference in baseline measurements including HbA1c between the two groups. The principal finding is that sulfasalazine introduction was associated with a statistically significant and clinically important decrease in HbA1c, while mesalazine introduction was not. This finding suggests that the effect in the sulfasalazine-treated group depends on the systemically available sulphonamide moiety, which is absent in mesalazine, rather than being an effect of the gut-confined 5-ASA. The HbA1c reduction was still evident in sensitivity analyses which excluded possible effects of co-prescribed drugs, including diabetes medications.

Our study suggests that haemolysis mediates the effect of sulfasalazine on HbA1c. Haemolysis is a known adverse effect of sulphonamide drugs. Sulphonamide-induced haemolysis was first described in the early 1900s. Significantly increased MCV, MCH and a significantly decreased RBC with incident sulfasalazine treatment are suggestive of macrocytosis and possibly mild haemolysis. These changes were correlated with HbA1c lowering (as shown in Figure 3), suggesting that they may be mechanistically linked. Haemolysis...
may lower HbA1c by shortening lifespan of red blood cells. With an increase in red blood cell turnover, the period of time which the haemoglobin is exposed to blood glucose will be shorter, reducing the degree of glycation. This presents a possible limitation of HbA1c as a glycaemic control marker in this cohort of people, as well as suggesting that HbA1c is not a reliable diagnostic tool in individuals taking sulfasalazine. Consistent with sulfasalazine inducing only a mild, subclinical level of haemolysis, we did not detect an increase in the bilirubin levels in the blood, nor was there any significant change in haemoglobin levels. There is a well-established link between sulfasalazine use and megaloblastic anaemia, which is associated with a decrease in cell turnover, allowing the red cell to have an increased exposure time to circulating glucose and ultimately increasing glycation of haemoglobin.

We investigated the possibility that megaloblastic anaemia could have masked an even more profound HbA1c effect in the sulfasalazine group but in sensitivity analysis, anaemia did not have a significant impact on the effect of sulfasalazine on HbA1c.

### TABLE 4
Changes in 6 month HbA1c in sulfasalazine group with individuals coprescribed specific drugs excluded. Data are mean (SD) from paired t-tests comparing treatment – baseline measurement

| Drug group excluded | N  | HbA1c response (mmol/mol/%) | p value |
|---------------------|----|----------------------------|--------|
| Hydroxychloroquine  | 73 | −8 ± 13 (−0.7 ± 1.2)        | <0.0001|
| Methotrexate        | 52 | −9 ± 13 (−0.8 ± 1.2)        | <0.0001|
| Folic acid          | 51 | −9 ± 13 (−0.8 ± 1.2)        | <0.0001|
| NSAIDs              | 63 | −10 ± 18 (−0.9 ± 1.7)       | <0.0001|
| Opiates             | 13 | −17 ± 20 (−1.6 ± 1.8)       | 0.01   |
| Steroids            | 62 | −6 ± 12 (−0.6 ± 1.1)        | 0.0002 |
| Iron supplements    | 84 | −9 ± 15 (−0.8 ± 1.4)        | <0.0001|
| Anti-diabetics      | 25 | −7 ± 6 (−0.6 ± 0.5)         | <0.0001|

Percentages are presented in italics.

### TABLE 5
Changes in 6-month HbA1c in sulfasalazine group with individuals with anaemia excluded. Data are mean (SD) from paired t-tests comparing treatment – baseline measurement

| Level of anaemia excluded | N  | HbA1c response (mmol/mol/%) | p value |
|---------------------------|----|----------------------------|--------|
| Mild                      | 62 | −9 ± 15 (−0.8 ± 1.4)        | <0.0001|
| Moderate                  | 97 | −10 ± 16 (−0.9 ± 1.5)       | <0.0001|

Percentages are presented in italics.

aMild anaemia was defined as haemoglobin below 12g/dL for women and below 13g/dL for men.

bModerate anaemia was defined as below 11g/dL for both men and women.
Further work will be required to determine whether other sulphonamide drugs, particularly those which are very commonly prescribed, such as furosemide, elicit similar effects on HbA1c. In addition, other drugs with different structure are known to affect haematological components and some of these, such as thiazides, are commonly prescribed as well; however, there has been little investigation of effects of these drugs on the HbA1c test either. Alongside the suggestion that subtle abnormalities of red cells (with or without anaemia, through various mechanisms) are enough to have a significant impact on HbA1c, further work should examine in depth the link between red cell component abnormality and HbA1c.

4.2 Limitations of this study

Our study was observational and consequently we cannot exclude that differences between the drug groups may owe to individual characteristics, particularly their disease profile. Mesalazine is prescribed only in IBD, whereas the systemic anti-inflammatory effects of sulfasalazine have led to its use in rheumatoid arthritis as well. In addition, there were some factors that this study could not account for, such as effects of short-term inflammatory or comorbid conditions, subsequent hospital admissions, medication compliance and their effects on HbA1c. The study was also limited to the data available; therefore, some factors could not be analysed. These factors could have helped us to study the mechanism behind the sulfasalazine effect on HbA1c further, they include vitamin B12 and folate levels, insulin, C-peptide and other markers of haemolysis such as reticulocyte count, lactate dehydrogenase and haptoglobin. In addition, oral glucose tolerance testing, fasting plasma glucose levels and fructosamine measurements were not available as alternative measures of short-term and long-term glucose control.

Despite these limitations, baseline characteristics were broadly similar between the cohorts suggestive of minimal ascertainment bias, and the use of sensitivity analyses also found little evidence of other confounding factors that could have had an influence on the final HbA1c response.

We do not exclude possible mechanisms other than haemolysis underlying the effect of sulfasalazine on HbA1c. Sulphonamides are structurally reminiscent, for example, of sulfonylureas and some evidence suggests they may induce insulin secretion.

5 SUMMARY

In conclusion, we have used analysis of a cohort of individuals with type 2 diabetes in Tayside and Fife to replicate at a population level, evidence from several much smaller studies suggesting that sulfasalazine mediates a clinically relevant suppression of HbA1c. The effect of sulfasalazine on HbA1c is likely to be mediated by the sulphonamide moiety of the drug, through a mechanism involving haemolysis. These findings suggest that HbA1c is not a reliable measure of glycaemia and therefore should not be used for diagnosis and monitoring of type 2 diabetes in individuals prescribed sulfasalazine.

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REFERENCES

1. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycaemia in diabetes. Diabetes Care. 2004;27:1761–1773.
2. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405–412.
3. SIGN. Updated version 2017. Management of diabetes: a national clinical guideline (SIGN guideline 116).
4. IDF. Global guideline for type 2 diabetes. 2012.
5. Ranjit U, Mohan AR, Viswanathan M. Drugs affecting HbA1c levels. Indian J Endocrinol Metab. 2012;16:528–531.
6. Radin MS. Pitfalls in Hemoglobin A1c Measurement: When Results may be Misleading. J Gen Intern Med. 2014;29:388–394.
7. Mitchell K, Mukhopadhyay B. Drug-induced falsely low A1C: report of a case series from a diabetes clinic. Clinical Diabetes. 2018;36:80.
8. Lai Y-C, Wang C-S, Wang Y-C, Hsu Y-L, Chuang L-M. Falsely decreased HbA1c in a type 2 diabetic patient treated with dapsone. J Formos Med Assoc. 2012;111:109–112.
9. Albright ES, Ovalle F, Bell DSH. Artificially low HbA1c caused by use of dapsone. Endocrine Practice. 2002;8:370–372.
10. Unnikrishnan R, Anjana RM, Jayashri R, Mohan V. Unexpectedly low HbA1c levels in two diabetes patients following dapson use. Indian J Endocrinol Metab. 2012;16:658–659.
11. Kesson CM, Whitelaw JW, Ireland JT. Drug-induced haemolysis and fast haemoglobin A1 in diabetes mellitus. Br Med J. 1979;2:1037–1038.
12. Tack CJ, Wetzeljs JF. Decreased HbA1c levels due to sulphonamide induced haemolysis in two IDDM patients. Diabetes Care. 1996;19:775–776.
13. Haas RM, Li P, Chu JW. Glucose-lowering effects of sulfasalazine in type 2 diabetes. Diabetes Care. 2005;28:2238.
14. 2015/6. NHS national services Scotland prescription costs analysis.
15. Desreumaux P, Ghosh S. Review article: mode of action and delivery of 5-aminosalicylic acid – new evidence. Aliment Pharmacol Ther. 2006;24:2–9.
16. British National Formulary. London: BMJ Group and Pharmaceutical Press.
17. Qureshi AI, Cohen RD. Mesalamine delivery systems: do they really make much difference? *Adv Drug Deliv Rev.* 2005;57:281–302.
18. Kracke RR. The effects of sulfonamide drugs on the blood. *Am J Clin Pathol.* 1944;14:191–199.
19. Punchard NA, Greenfield SM, Thompson RPH. Mechanism of action of 5-aminosalicylic acid. *Mediators Inflamm.* 1992;1:151–165.
20. Davenport J. Macrocytic anaemia. *Am Fam Physician.* 1996;53:155–162.
21. Barcellini W, Fattizzo B. Clinical applications of hemolytic markers in the differential diagnosis and management of hemolytic anemia. *Disease Markers:* Article ID 635670. 2015.
22. Rao KV. Drug induced hematologic disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, eds. *Pharmacotherapy: A Pathophysiologic Approach.* LM Posey: McGraw-Hill Medical; 2017.
23. English E, Idris I, Smith G, Dhatariva K, Kilpatrick E, John W. The effect of anaemia and abnormalities of erythrocyte indices on HbA1c analysis: a systematic review. *Diabetologia.* 2015;58(7):1409–1421.
24. Loubatieres-Mariani MM. The discovery of hypoglycemic sulfonamides. *J Soc Biol.* 2007;201:121-125.

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