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Elevation of the Glycated Albumin to Hemoglobin A1c Ratio Is an Index of Ineffective Erythropoiesis in Myelodysplastic Syndromes

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Abstract

Background: The index for estimating ineffective erythropoiesis in bone marrow failure syndromes has not been standardized. Thus, this study aimed to investigate the glycated albumin to hemoglobin A1c ratio (GA/HbA1c) as a useful index for evaluating ineffective erythropoiesis status in bone marrow failure syndromes. **Methods:** This study included patients who were diagnosed with either myelodysplastic syndromes, aplastic anemia, myeloproliferative diseases, anemia of chronic diseases, or autoimmune hemolytic anemia. The index of GA/HbA1c was determined, and haptoglobin was measured in each patient. Laboratory data, including bone marrow aspiration, were collected from electronic medical records. **Results:** A total of 53 cases were studied. GA/HbA1c was significantly elevated in myelodysplastic syndromes, aplastic anemia, and autoimmune hemolytic anemia compared to that in controls. Haptoglobin depletion was observed in 9 of 18 cases of myelodysplastic syndromes and in none of 9 cases of aplastic anemia. GA/HbA1c was significantly elevated in myelodysplastic syndromes with haptoglobin depletion, suggesting enhanced ineffective erythropoiesis in this group. **Conclusions:** Determining GA/HbA1c, as well as the haptoglobin level, is a useful surrogate index for detecting ineffective erythropoiesis in bone marrow failure syndromes.

Keywords

Anemia, Red Blood Cells Life Span, Glycated Albumin, Hemoglobin A1c, GA/HbA1c, Ineffective Erythropoiesis

1. Introduction

Anemia is generally classified into two types: insufficient red blood cells (RBCs) production and loss of RBCs from the body. Aplastic anemia (AA), which is caused by insufficient hematopoiesis that occurs due to hematopoietic stem cell abnormality, is mainly classified as the former type of anemia. Anemia due to bleeding or hemolysis is classified as the latter type, in which hematopoiesis is accelerated to compensate for the lost RBCs in the body.

The pathological condition of ineffective erythropoiesis (IE) is complicated, although anemia predominantly emerges from the loss of RBCs. IE is a condition in which erythroblasts in the bone marrow are destroyed by disturbances in hemoglobin (Hb) or DNA synthesis, resulting in decreased RBCs in the peripheral blood. In this condition, the destruction of erythroblasts and immature erythroid cells is predominant, although the production and differentiation of erythroid cells remain. IE is recognized in myelodysplastic syndromes (MDSs), pernicious anemia, myeloproliferative disorders, or thalassemia. IE evaluation is important in diagnosing bone marrow failure syndromes, including MDS and AA.

The normal life span of RBCs is approximately 115 days [1] [2]. The life span of RBCs decreases in anemic diseases with IE, in which free Hb released from RBCs is scavenged by haptoglobin (Hp), and free Hb is formed into the Hb-Hp complex. This complex is degraded by lysosomes, and Hp is decreased by its consumption [3]. Therefore, the depletion of the Hp value, which is well known in hemolytic anemia, is recognized in IE [4] [5].

A study for estimating the life span of RBCs has been developed. Several methods using radioactive isotopes, such as ^{51}Cr, ^{14}C-glycine, ^{15}N, and ^{59}Fe, were established [2]. However, these methods have not been widely prevalent in clinical use until now because of the toxic aspects of exposing isotopes to the body and limited radiation facilities. The carbon monoxide (CO) method [6] is a procedure using a non-isotopic substance, but with less accuracy. The biotin labeling method [7] is a representative non-isotopic method that is safe and more accurate, but this method contains complicated procedures, including biotin-labeled RBCs infusion and RBCs measurement with multicolor flow cytometry [1]. The biotin labeling method has not been routinely widespread. Other than the above methods, mean corpuscular volume (MCV) [8] or bone marrow reticulocyte/peripheral blood reticulocyte ratio [9] [10] are used as an index to estimate the life span of RBCs. Even now, the index for clinical practice to conveniently predict the shortening of the life span of RBCs concerning IE remains inadequate.

Hemoglobin A1c (HbA1c) is a glycated formation of Hb, the value of which is influenced by the life span of RBCs. HbA1c is a candidate for a surrogate marker for RBCs survival [11]. HbA1c is affected by blood sugar concentration and is frequently used in daily practice as a control index for diabetes mellitus (DM). On the contrary, glycated albumin (GA) is another control index of blood sugar concentration in DM, which is not affected by the life span of RBCs. The index of GA/HbA1c calculated by dividing the GA value (%) by the HbA1c value (%) is

reported to be approximately 2.5 - 2.7 in healthy controls [12]-[14]. Additionally, GA/HbA1c is affected by several diseases. Conversely, GA/HbA1c is elevated in patients undergoing hemodialysis, with DM control deterioration and liver dysfunction, including liver cirrhosis [14]. GA/HbA1c is elevated in patients with anemic diseases caused by shortening of the life span of RBCs, including hemolytic anemia [15] or macrocytic anemia [14]. No study has been reported regarding GA/HbA1c in anemia related to IE.

IE evaluation in bone marrow failure syndrome, including MDS and AA, needs to be more precise in daily clinical practice. This study aims to investigate the utility of GA/HbA1c as well as the Hp value for IE evaluation.

2. Materials and Methods

2.1. Patients and Samples

This prospective observational study recruited patients who were admitted to our institute from January 2016 to March 2020 and fulfilled the following criteria: 1) patients who were diagnosed as either MDS, AA, myeloproliferative diseases (MPDs), including myeloproliferative neoplasms and secondary polycythemia, anemia of chronic diseases (ACDs), or autoimmune hemolytic anemia (AIHA); 2) patients who have not received any RBCs, fresh frozen plasma, or platelet concentrate transfusion within 3 months before entry; 3) patients who underwent clinical laboratory tests, including complete blood cell count with reticulocyte count and percentage, and blood chemistry tests, including hepatic function, renal function, direct and indirect bilirubin tests, and serum lactate dehydrogenase (LD) test within 30 days before entry; 4) patients who underwent bone marrow aspiration (BMA) test within 30 days before entry.

The exclusion criteria were as follows: 1) patients with diabetes mellitus or impaired metabolism of glucose, who had a value of more than 6.0 % of HbA1c or more than 200 mg/dL of random venous plasma glucose concentration, 2) patients who had renal dysfunction, expressed with a serum creatinine value of 2.0 mg/dL or higher; 3) patients who had chronic hepatitis or liver cirrhosis with any Child-Pugh score; 4) patients who were complicated with trauma or burn because these diseases result in low albumin concentration; 5) patients who were defined by a doctor as inappropriate for entry due to poor general condition; and 6) patients who were diagnosed with paroxysmal nocturnal hemoglobinuria, megaloblastic anemia due to lack of vitamin B12 or folic acid, or iron deficiency anemia. Additionally, patients diagnosed with acute or chronic leukemia, multiple myeloma, and monoclonal gammopathy of undetermined significance were excluded. We selected patients with B cell lymphoma who had no lymphoma infiltration of bone marrow according to the BMA test as the control group for bone marrow status.

2.2. Evaluation of IEs

The values of HbA1c, GA, and Hp in each patient were determined with the samples obtained within the next 30 days from the day of study entry. The samples of

patients who received any hematologic disease treatments were excluded. HbA1c (NGSP, %) was measured by high-performance liquid chromatography (Arkray, Kyoto, Japan). GA (%) was measured by enzymatic method. GA and Hp were measured by the outsourcing company SRL (Tokyo, Japan). The lower cut-off value of Hp was set at 25 mg/dL, according to the hemolytic diseases reported by Marchand *et al.* [16].

Data on nuclear cell count (NCC), erythroid cell count (RCC), and erythroid cell percentage (ECP) were referred to regarding the BMA test. The information on reticulocyte count (REC) and reticulocyte percentage (REP) in peripheral blood, and serum LD value was collected from electronic medical records.

2.3. Statistical Analysis

All statistical analyses were performed using KaleidaGraph™ 4 (Hulinks©). Comparisons of values regarding each item were calculated using Student's t-test. Values were expressed as "mean ± standard deviation (SD)". *P*-values of <0.05 were considered statistically significant in all analyses, and all statistical tests were two-sided.

3. Results

3.1. Relationship with MCV and Hb Values

This study included 44 patients (18 with MDS, 9 with AA, 5 with MPD, 6 with ACD, and 6 with AIHA) and 9 patients defined as normal controls of bone marrow. All patients were listed in Table 1. We investigated the relationship between MCV and Hb values in 53 cases and revealed a trend of inverse correlation between MCV and Hb values ($r = 0.51$) (Figure 1(A)).

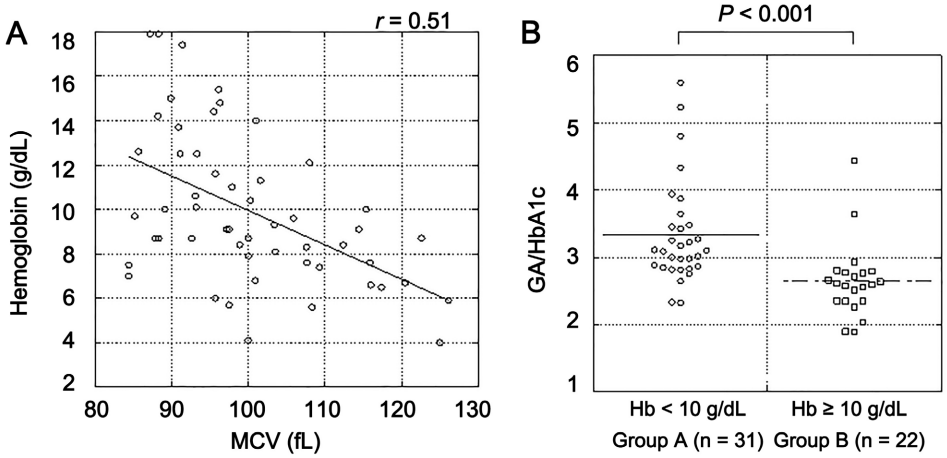

Figure 1. (A) Relationship between the mean corpuscular volume (MCV) of RBCs and hemoglobin (Hb) values. The correlation formula is [$Y = 25.4 - 0.16X$] ($r = 0.51$). A trend of inverse correlation was found between the MCV value and the Hb value. (B) GA/HbA1c classified by Hb level. All 53 cases were divided by the cut-off value of 10 g/dL of Hb. GA/HbA1c of Group A, whose Hb was <10 g/dL, was (mean ± SD) 3.32 ± 0.76, while that of Group B (Hb of ≥10 g/dL) was 2.64 ± 0.55. GA/HbA1c of Group A was significantly higher than that of Group B.

Table 1. Patient characteristics.

Classification	All (n = 53)
Normal bone marrow	9
Myelodysplastic syndromes (MDSs)*	18
MDS with single lineage dysplasia*	(8)
MDS with multilineage dysplasia*	(6)
MDS with ring sideroblasts*	(2)
MDS with excess blasts-1*	(1)
MDS with excess blasts-2*	(1)
Aplastic anemia (AA)	9
Myeloproliferative disorders (MPDs)*	5
Polycythemia vera*	(1)
Essential thrombocytopenia*	(1)
Secondary erythrocytosis	(2)
Chronic myelomonocytic leukemia*	(1)
Anemia of chronic diseases (ACDs)	6
Autoimmune hemolytic anemia (AIHA)	6

*Each disease in hematological malignancy was expressed by the World Health Organization 2016 classification.

Then, we divided 53 cases into two groups by Hb level, of which 31 and 22 cases have Hb values of <10 g/dL (Group A) and ≥10 g/dL (Group B), respectively. GA/HbA1c in these two groups was compared, revealing a mean ± SD of 3.32 ± 0.76 and 2.64 ± 0.55 in Groups A and B, respectively. GA/HbA1c of Group A was significantly higher than that of Group B ($P < 0.001$), suggesting that some causes in anemic conditions may increase GA/HbA1c in this cohort (**Figure 1(B)**).

3.2. Distribution of GA/HbA1c Classified by MCV Value and by Anemic Diseases

We stratified 53 cases into three groups to confirm the difference in GA/HbA1c among MCV values; in which 28, 17, and 8 cases have MCV values of <100 fL (Group C), 100 - 115 fL (Group D), and >115 fL (Group E), respectively. GA/HbA1c (mean ± SD) in Groups C, D, and E are 2.73 ± 0.53, 3.21 ± 0.68, and 3.79 ± 1.03, respectively. We compared GA/HbA1c between the three groups and revealed that GA/HbA1c in Groups D or E was significantly elevated compared to Group C ($P = 0.020$ and $P = 0.021$, respectively) (**Figure 2(A)**). No statistical difference was found between Groups D and E ($P = 0.164$). This result suggests that GA/HbA1c is increased in cases with an MCV value of ≥100 fL.

We investigated the distribution of GA/HbA1c among 6 categories, *i.e.*, control group, MDS, AA, MPD, ACD, and AIHA. Each of GA/HbA1c (mean ± SD) is as follows: control group, 2.59 ± 0.19; MDS, 3.25 ± 0.54; AA, 2.85 ± 0.30; MPD, 2.32 ±

0.36; ACD, 2.72 ± 0.54; and AIHA, 4.31 ± 1.10. GA/HbA1c in MDS, AA, and AIHA was significantly elevated compared to the control group ($P < 0.001$, $P = 0.039$, and $P = 0.012$, respectively) (Figure 2(B)). GA/HbA1c in MDS is significantly more elevated than that of AA ($P = 0.022$), indicating that the mean life span of RBCs in MDS is shorter than that in AA.

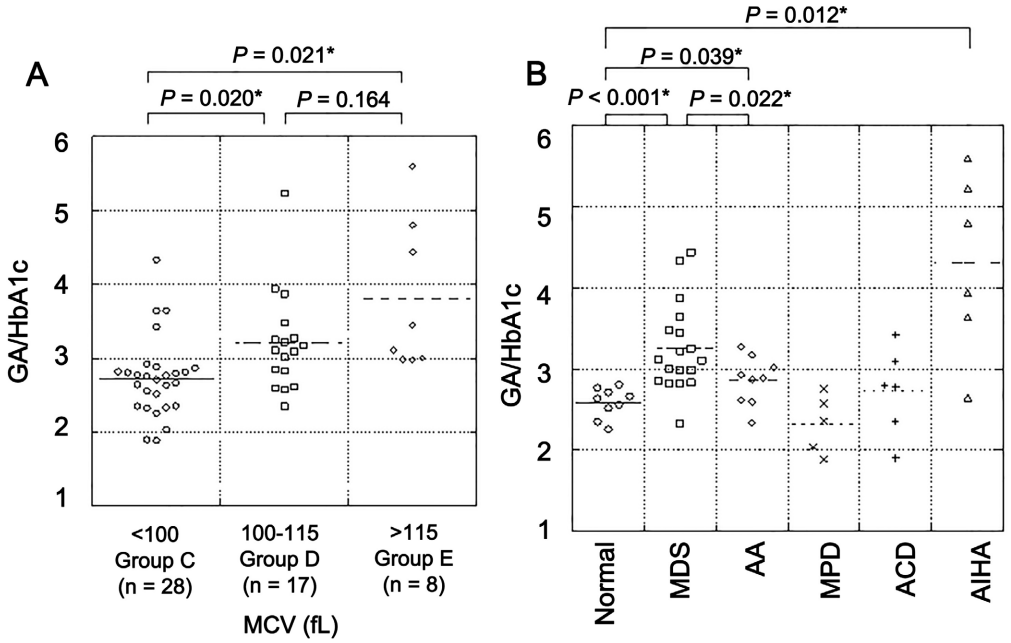

Figure 2. (A) Distribution of GA/HbA1c classified by the MCV value. All 53 cases were classified into three cases according to the MCV value. GA/HbA1c (mean ± SD) in Groups C (MCV value of <100 fL), D (MCV value of 100 - 115 fL), and E (MCV value of >115 fL) were 2.73 ± 0.53, 3.21 ± 0.68, and 3.79 ± 1.03, respectively. GA/HbA1c in Groups D or E is significantly elevated compared with Group C. (B) Distribution of GA/HbA1c among the six categories. GA/HbA1c (mean ± SD) in the control group, MDS, AA, MPD, ACD, and AIHA is 2.59 ± 0.19, 3.25 ± 0.54, 2.85 ± 0.30, 2.32 ± 0.36, 2.72 ± 0.54, and 4.31 ± 1.10, respectively. GA/HbA1c in MDS, AA, and AIHA was significantly elevated compared to that in the control group.

3.3. Relationship between Hp Levels and Erythropoiesis

Serum Hp depletion will be observed in IE other than hemolysis. We determined the Hp value in patients with MDS and AA to examine the relationship between the Hp value and erythropoiesis. We divided all 53 cases into 2 groups based on the definition of Hp depletion as ≤25 mg/dL or lower, in which 17 cases have Hp depletion (Group F) and 36 cases have a normal Hp value (Group G). We compared GA/HbA1c between the two groups and found that GA/HbA1c (mean ± SD) in Group F (3.70 ± 0.92) was significantly higher than that in Group G (2.73 ± 0.40) ($P < 0.001$) (Figure 3(A)). We confirmed that GA/HbA1c in Group F was elevated, while the level of GA/HbA1c in Group G was close to the level of the control group in Figure 2(B).

The above-mentioned results indicated a relationship between Hp depletion and elevation of GA/HbA1c. We set these cases into 3 groups because Hp depletion

was observed in 9 cases out of all 18 MDS cases and none out of 9 AA cases in this cohort, *i.e.*, 9 cases of MDS with Hp depletion (Group H), 9 cases of MDS without Hp depletion (Group I), and 9 cases of AA without Hp depletion (Group J). GA/HbA1c (mean ± SD) in Groups H, I, and J are 3.52 ± 0.20, 2.98 ± 0.33, and 2.85 ± 0.30, respectively. We compared GA/HbA1c among the three groups and revealed that GA/HbA1c in Group H was significantly elevated compared to that in Group I ($P = 0.034$) and Group J ($P = 0.011$). No statistical difference was found in GA/HbA1c between Groups I and J ($P = 0.405$) (Figure 3(B)). This result suggested that IE mainly exists in MDS with Hp depletion status.

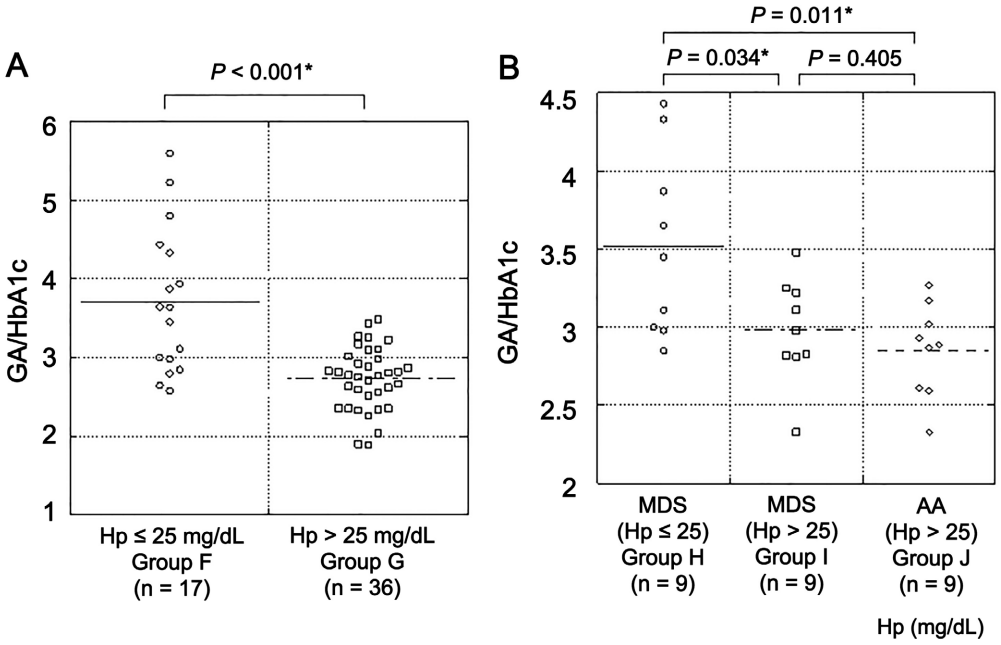

Figure 3. (A) Relationship between Hp depletion and erythropoiesis. The 53 cases were divided into 2 groups: Hp depletion cases (Group F) or normal Hp value cases (Group G). GA/HbA1c (mean ± SD) in Group F (3.70 ± 0.92) was significantly higher than that in Group G (2.73 ± 0.40). (B) Relationship between Hp depletion and GA/HbA1c. Comparison of GA/HbA1c among MDS with Hp depletion (Group H), MDS without Hp depletion (Group I), and AA without Hp depletion (Group J). GA/HbA1c (mean ± SD) in Groups H, I, and J is 3.52 ± 0.20, 2.98 ± 0.33, and 2.85 ± 0.30, respectively. GA/HbA1c in Group H was significantly elevated compared to Groups I and J.

3.4. Hematopoiesis in MDS and AA

We compare the above-mentioned three groups (Groups H, I, and J) regarding bone marrow NCC, bone marrow erythroid cell count (ECC), and erythroid cell percentage (ECP) to determine the features of hematopoiesis in bone marrow in relation to MDS and AA (Table 2). NCC ($\times 10^4/\mu L$) (mean ± SD) in Groups H, I, and J was 10.99 ± 7.32, 4.06 ± 3.20, and 2.48 ± 3.12, respectively. NCC in Group H is significantly elevated compared to Groups I ($P = 0.025$) or J ($P = 0.009$). ECC ($\times 10^4/\mu L$) (mean ± SD) in Groups H, I, and J was 4.53 ± 4.32, 0.94 ± 0.72, and 0.611 ± 1.37, respectively. ECC in Group H is significantly elevated compared to Groups I ($P = 0.038$) or J ($P = 0.028$). A similar difference was observed in ECP. Addition-

ally, we attempted to compare peripheral blood reticulocyte cell count (RCC) and reticulocyte cell percentage (RCP), and serum LD level in these three groups (Table 2). We did not find a statistical difference between Groups H and I or Group J regarding RCC, RCP, and serum LD levels (Table 2). These results indicate that hematopoiesis is increased more in MDS with Hp depletion than in MDS without Hp depletion or AA. Bone marrow hematopoiesis may be accelerated by compensation for cell destruction in MDS with IE.

Table 2. Hematopoietic status in myelodysplastic syndromes classified by haptoglobin level and aplastic anemia.

Source	Index	Group H (n = 9)	Group I (n = 9)	Group J (n = 9)	Groups H vs. I	Groups H vs. J	Groups I vs. J
		MDS (Hp ≤ 25) mean (±SD)	MDS (Hp > 25) mean (±SD)	AA (Hp > 25) mean (±SD)	(*P*-value)	(*P*-value)	(*P*-value)
Bone marrow	Nuclear cell count ($\times 10^4/\mu L$)	10.99 (±7.32)	4.06 (±3.20)	2.48 (±3.12)	0.025*	0.009*	0.305
Bone marrow	Erythroid cell percentage (%)	37.49 (±14.32)	23.16 (±8.18)	14.00 (±12.69)	0.022*	0.002*	0.091
Bone marrow	Erythroid cell count ($\times 10^4/\mu L$)	4.53 (±4.32)	0.94 (±0.72)	0.61 (±1.37)	0.038*	0.028*	0.548
Peripheral blood	Reticulocyte percentage (%)	1.68 (±0.99)	2.21 (±1.18)	1.96 (±1.36)	0.315	0.628	0.676
Peripheral blood	Reticulocyte count ($\times 10^4/\mu L$)	3.42 (±1.63)	5.26 (±2.77)	4.38 (±1.96)	0.111	0.279	0.450
Serum	Lactate dehydrogenase (IU/L)	270.7 (±139.1)	221.6 (±100.3)	182.8 (±74.8)	0.404	0.120	0.368

*Statistical significance by Student's t-test ($P < 0.05$). Abbreviation: AA: Aplastic anemia; MDS: Myelodysplastic syndromes; Hp: Haptoglobin; SD: Standard deviation.

4. Discussion

Currently, there is no simple clinical test to determine the lifespan of RBCs. HbA1c is a candidate index for estimating the lifespan of RBCs [2] [11] [15], but it has not been widely applied as a marker of the lifespan of RBCs in clinical practice. The HbA1c value changes due to the effect of blood glucose concentration, and avoiding the effect of blood glucose concentration is necessary for HbA1c to be used as an index of the life span of RBCs. Conversely, GA is commonly used as another index of blood glucose concentration. GA is an early Amadori-type glycation protein and reflects the average blood glucose concentration within 3 weeks. GA does not affect the life span of RBCs but affects albumin half-life. Hence, GA/HbA1c is thought to reflect the life span of RBCs. GA/HbA1c was approximately 2.5 - 2.7 in the normal population [12]-[14], and this index increases under the shortening of the life span of RBCs. We previously reported the usefulness of GA/HbA1c as an index of the life span of RBCs in a preoperative autologous blood transfusion model for surgical operation, in which blood loss by autologous blood collection and compensatory erythrocyte hyperproduction decreases GA/HbA1c [17]. We speculate that GA/HbA1c is applicable to estimate the life span of RBCs; however, several factors need to be considered. GA/HbA1c will increase through dialysis, liver dysfunction, including liver cirrhosis, and deterioration in diabetes control. Conversely, GA/HbA1c will decrease in nephrotic syndromes [14] [18]. Thus, patients with these comorbidities should be excluded from the application.

GA/HbA1c (mean ± SD) of the controls that we provided in this study was 2.59 ± 0.19. GA/HbA1c of healthy persons in previous reports was approximately 2.5 - 2.7 [12]-[14], the value of which was similar to our control value. Thus, our control value was considered to need no correction. We revealed the inverse relationship between MCV and Hb values (**Figure 1(A)**), the result of which is consistent with a previous report [8]. Additionally, anemic cases had an increasing trend of GA/HbA1c (**Figure 1(B)**). Therefore, macrocytic anemia increases in younger erythrocyte populations by an increase in erythropoiesis, resulting in GA/HbA1c elevation. We will make a supplementary statement that megaloblastic anemia due to vitamin B12 deficiency or folic acid deficiency was excluded from this study cohort.

Moreover, we confirmed that GA/HbA1c elevation is predominant in patients with Hp depletion. With respect to each disease, GA/HbA1c was elevated not only in patients with AIHA but also in those with MDS carrying Hp depletion. Regarding hematopoiesis in IE, immature RBC production was accelerated due to mature RBC destruction by apoptosis, resulting in the mean life span reduction of RBCs [19]. GA/HbA1c elevation in MDS with Hp depletion may arise from IE status. In this scenario, Hp consumption is accelerated by eliminating RBCs. Shichishima *et al.* revealed that patients with MDS with Hp depletion are significantly more likely to have anemia and hyperferritinemia compared with patients with MDS without Hp depletion, and emphasized that MDS with Hp depletion is mainly caused by IE [20]. We revealed that MDS that carried Hp depletion had the trend of GA/HbA1c elevation. We speculate that an increase in GA/HbA1c will become a surrogate index of IE because evaluating the existence of IE remains difficult [21]. Determination of Hp level as well as GA/HbA1c is important for understanding the pathology of MDS. Recent study revealed that mutant alleles encoding splicing factors and erythrocyte membrane components contribute to anemia with Hp depletion in MDS. Spliceosome (SF3B1, U2AF1) and epigenetic regulator (EZH2) may affect the condition of IE with Hp depletion in MDS patients [22]. Further studies will explore the relationship between mutated genes and IE in bone marrow failure syndromes.

In restriction to MDS and AA, we confirmed that bone marrow NCC, ECC, and ECP were increased in MDS with Hp depletion, in which erythropoiesis is more accelerated compared with MDS without Hp depletion or AA cases. MDS with Hp depletion can compensate for anemic status by accelerating erythropoiesis. Conversely, we did not find any difference regarding RCC, RCP, and serum LD levels among the classified three groups in MDS and AA. Choi JW reported that reticulocytes in peripheral blood are not supplied from intramedullary reticulocytes in IE status, resulting in the expansion of the bone marrow reticulocyte/peripheral blood reticulocyte ratio [21]. RCC is not different with respect to Hp depletion level in patients with MDS and AA in a previous report [20], the result of which is consistent with ours.

This study has some limitations, including the small sample size, which conse-

quently suggests a small impact on the result. Additionally, the relationship between GA/HbA1c and the existing index for estimating the lifespan of RBCs, such as radioisotope or CO, was not investigated. Moreover, the bone marrow reticulocyte/peripheral blood reticulocyte ratio was not determined in this study; thus, the role of the bone marrow reticulocyte/peripheral blood reticulocyte ratio was not considered. We think that this study is meaningful for speculating the existence of IE, although an adequate index for IE remains lacking.

5. Conclusion

An increased GA/HbA1c will indicate the shortening of the lifespan of RBCs by IE in patients with MDS. GA/HbA1c determination, as well as the Hp level, is useful as a surrogate index for detecting IE in MDS.

Compliance with Ethical Standards

This study has been reviewed and approved by the Institutional Review Board of Kita-Harima Medical Center in Ono, Japan (approval number: H27-19; approval date: January 8, 2016).

Data Availability Statement

The data set used in this study is available in our institutional database.

Authors' Contributions

T.S. designed the study, analyzed the data, performed the statistical analysis, and wrote the first draft of the manuscript. K.M. and H.T. supported the analysis. H.G. reviewed the data and the manuscript. All authors approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Franco, R.S. (2012) Measurement of Red Cell Lifespan and Aging. *Transfusion Medicine and Hemotherapy*, **39**, 302-307. https://doi.org/10.1159/000342232

[2] Franco, R.S. (2009) The Measurement and Importance of Red Cell Survival. *American Journal of Hematology*, **84**, 109-114. https://doi.org/10.1002/ajh.21298

[3] Kristiansen, M., Graversen, J.H., Jacobsen, C., Sonne, O., Hoffman, H., Law, S.K.A., *et al.* (2001) Identification of the Haemoglobin Scavenger Receptor. *Nature*, **409**, 198-201. https://doi.org/10.1038/35051594

[4] Shinton, N.K., Richardson, R.W. and Williams, J.D.F. (1965) Diagnostic Value of Se-

rum Haptoglobin. *Journal of Clinical Pathology*, **18**, 114-118. https://doi.org/10.1136/jcp.18.1.114

[5] Owen, J.A., Smith, R., Padanyi, R. and Martin, J. (1964) Serum Haptoglobin in Diseases. *Clinical Science*, **26**, 1-6.

[6] Strocchi, A., Schwartz, S., Ellefson, M., Engel, R.R., Medina, A. and Levitt, M.D. (1992) A Simple Car-Bon Monoxide Breath Test to Estimate Erythrocyte Turnover. *Journal of Laboratory and Clinical Medicine*, **120**, 392-399.

[7] Mock, D.M., Widness, J.A., Veng-Pedersen, P., Strauss, R.G., Cancelas, J.A., Cohen, R.M., *et al.* (2014) Measurement of Posttransfusion Red Cell Survival with the Biotin Label. *Transfusion Medicine Reviews*, **28**, 114-125. https://doi.org/10.1016/j.tmrv.2014.03.003

[8] Van Der Vegt, S.G.L., Ruben, A.M.T., Werre, J.M., Palsma, D.M.H., Verhoef, C.W., de Gier, J., *et al.* (1985) Counterflow Centrifugation of Red Cell Populations: A Cell Age Related Separation Technique. *British Journal of Haematology*, **61**, 393-403. https://doi.org/10.1111/j.1365-2141.1985.tb02843.x

[9] Choi, J.W. and Pai, S.H. (2001) Reticulocyte Subpopulations and Reticulocyte Maturity Index (RMI) Rise as Body Iron Status Falls. *American Journal of Hematology*, **67**, 130-135. https://doi.org/10.1002/ajh.1091

[10] Hirose, A., Yamane, T., Shibata, H., Kamitani, T. and Hino, M. (2005) Automated Analyzer Evaluation of Reticulocytes in Bone Marrow and Peripheral Blood of Hematologic Disorders. *Acta Haematologica*, **114**, 141-145. https://doi.org/10.1159/000087887

[11] Cohen, R.M., Franco, R.S., Khera, P.K., Smith, E.P., Lindsell, C.J., Ciraolo, P.J., *et al.* (2008) Red Cell Life Span Heterogeneity in Hematologically Normal People Is Sufficient to Alter Hba1c. *Blood*, **112**, 4284-4291. https://doi.org/10.1182/blood-2008-04-154112

[12] Lee, M., Hsu, W., Lai, C., Chen, S. and Liang, C. (2019) The Association between Glycated Albumin, Glycohemoglobin, and Glycated Albumin to Glycohemoglobin Ratio in Diabetic Retinopathy of Prediabetes. *The Kaohsiung Journal of Medical Sciences*, **35**, 695-701. https://doi.org/10.1002/kjm2.12125

[13] Akatsuka, J., Mochizuki, M., Musha, I., Ohtake, A., Kobayashi, K., Kikuchi, T., *et al.* (2015) The Ratio of Glycated Albumin to Hemoglobin A1c Measured in IFCC Units Accurately Represents the Glycation Gap. *Endocrine Journal*, **62**, 161-172. https://doi.org/10.1507/endocrj.ej14-0066

[14] Miyamoto, H., Tao, X., Kohzuma, T. and Ohnishi, A. (2018) Influences of Anemia, Kidney Disease, Thyroid Dysfunction, and Liver Disease on the Ratio of Glycated Albumin to Hemoglobin A1C. *Journal of Diabetes Science and Technology*, **12**, 1082-1083. https://doi.org/10.1177/1932296818767452

[15] Ho, C.-H., You, J.-Y., Chau, W.-K., Hsu, H.-C., Gau, J.-P., Chen, C.-C., *et al.* (2003) Diagnostic Value of Serum Transferrin Receptor and Glycosylated Hemoglobin on Hemolytic Anemia. *Annals of Hematology*, **82**, 228-230. https://doi.org/10.1007/s00277-003-0623-3

[16] Marchand, A., Galen, R.S. and Van Lente, F. (1980) The Predictive Value of Serum Haptoglobin in Hemolytic Disease. *JAMA*: *The Journal of the American Medical Association*, **243**, 1909-1911. https://doi.org/10.1001/jama.1980.03300450023014

[17] Sugimoto, T., Hashimoto, M., Hayakawa, I., Tokuno, O., Ogino, T., Okuno, M., *et al.* (2014) Alterations in HBA1C Resulting from the Donation of Autologous Blood for Elective Surgery in Patients with Diabetes Mellitus. *Blood Transfusion*, **12**, S209-S213.

[18] Enomoto, H., Aizawa, N., Nakamura, H., Sakai, Y., Iwata, Y., Tanaka, H., *et al.* (2014)

An Increased Ratio of Glycated Albumin to Hba1c Is Associated with the Degree of Liver Fibrosis in Hepatitis B Virus-Positive Patients. *Gastroenterology Research and Practice*, **2014**, Article ID: 351396. https://doi.org/10.1155/2014/351396

[19] Huang, H., Xu, C., Gao, J., Li, B., Qin, T., Xu, Z., *et al.* (2020) Severe Ineffective Erythropoiesis Discriminates Prognosis in Myelodysplastic Syndromes: Analysis Based on 776 Patients from a Single Centre. *Blood Cancer Journal*, **10**, Article No. 83. https://doi.org/10.1038/s41408-020-00349-4

[20] Shichishima, T., Ikeda, K., Takahashi, N., Kameoka, J., Tajima, K., Murai, K., *et al.* (2010) Low Concentration of Serum Haptoglobin Has Impact on Understanding Complex Pathophysiology in Patients with Acquired Bone Marrow Failure Syndromes. *International Journal of Hematology*, **91**, 602-610. https://doi.org/10.1007/s12185-010-0559-z

[21] Choi, J.W. (2006) Ratio of Bone Marrow Reticulocytes to Peripheral Corrected Reticulocytes for Evaluating Ineffective Erythropoiesis. *Annals of Clinical & Laboratory Science*, **36**, 439-441.

[22] Komrokji, R., Aguirre, L.E., Al Ali, N., Hussaini, M., Sallman, D., Rollison, D., *et al.* (2023) U2AF1 and EZH2 Mutations Are Associated with Nonimmune Hemolytic Anemia in Myelodysplastic Syndromes. *Blood Advances*, **7**, 1-8. https://doi.org/10.1182/bloodadvances.2022007504