Clinical usefulness of the measurement of serum fructosamine in childhood diabetes mellitus

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Purpose: Glycosylated hemoglobin (HbA1c) is often used as an indicator of glucose control. It usually reflects the average glucose levels over two to three months, and is correlated with the development of long-term diabetic complications. However, it can vary in cases of hemoglobinopathy or an altered red blood cell lifespan. The serum fructosamine levels reflect the mean glucose levels over two to three weeks. This study was designed to determine the clinical usefulness of the combined measurement of serum fructosamine and HbA1c in the management of childhood diabetes mellitus and the correlation between them.

Methods: Clinical data on 74 Korean children and adolescents with diabetes mellitus who were under management at the Department of Pediatrics of Dankook University Hospital were evaluated. Their fructosamine and HbA1c levels were reviewed based on clinical information, and analyzed using IBM SPSS Statistics ver. 21.

Results: Their HbA1c levels showed a strong correlation with their fructosamine levels ($r=0.868$, $P<0.001$). The fructosamine level was useful for the prompt evaluation of the recent therapeutic efficacy after the change in therapeutic modality. It was also profitable in determining the initial therapeutics and for the estimation of the onset of the disease, such as fulminant diabetes.

Conclusion: The measurement of both fructosamine and HbA1c was useful in managing childhood diabetes mellitus, especially when there was discrepancy between the clinical information and the HbA1c level.

Keywords: Fructosamine, Glycosylated hemoglobin A, Diabetes mellitus, Child

Introduction

Uncontrolled diabetes mellitus in childhood and adolescence can result in impairment of physical and emotional development as well as long-term complications including nephropathy, neuropathy and retinopathy. Therefore, intensive glycemic control is important in managing childhood diabetes mellitus.

HbA1c is often used as an indicator of glucose control over the recent two to three months and is correlated with the development of long-term diabetic complications. It is a widely used method for assessing long term diabetic control. However, it can vary in cases of hemoglobinopathy or an altered red blood cell (RBC) lifespan. It also does not reflect recent changes in blood glucose in relation to disease management. In contrast, measurement of the concentration of serum glycosylated proteins can be used as a more rapidly responding parameter. Serum fructosamine, another nonenzymatic glycosylated substance in the blood, reflects the mean glucose levels over the recent two to three weeks. It can be obtained very quickly and is inexpensive to perform. Baker et al. reported that estimation of fructosamine concentrations may provide a simple means of screening for diabetes mellitus. Various other studies support the clinical significance of measuring fructosamine in diabetes mellitus as a
marker of glycemic variability or glucose control in patients with hemoglobinopathy or renal failure. This study was designed to determine the clinical usefulness of measuring serum fructosamine in the management of childhood diabetes mellitus and the correlation between HbA1c and fructosamine levels.

Materials and Methods

1. Subjects

A total of 74 Korean diabetic children and adolescents who had undergone laboratory tests (HbA1c, fructosamine, and random glucose) were enrolled in this study. They were under management at the Department of Pediatrics of Dankook University Hospital from December 2009 to December 2012. The subjects were classified into type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) according to their clinical and biochemical characteristics. The subjects with low serum/urine C-peptide, absolute insulin requirement (>0.5 U/kg/day) for survival, or initial presence of anti-insulin/anti-islet autoantibodies were classified into T1DM, and the others were classified into T2DM. Subjects who had significant anemia or hypoalbuminemia were excluded.

2. Methods

Clinical data were collected retrospectively from a review of the medical records of the study subjects. The clinical and biochemical parameters on their age and gender, the duration of their disease, and their hemoglobin, albumin, HbA1c, and fructosamine levels were reviewed. Their serum albumin, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine levels as well as fructosamine levels were measured using an modular EVO automated chemistry analyzer (Roche, Basle, Switzerland).

The subjects’ HbA1c levels were measured with Bio-Rad Variant II TURBO (Bio-Rad Laboratories, Tokyo, Japan) via high-performance liquid chromatography (HPLC). Their hemoglobin levels were determined through the cyanide-free sodium lauryl sulphate (SLS) method using the Sysmex XE-5000 automated hematology system (Sysmex Corp., Kobe, Japan). Their total T3, free T4, and TSH concentrations were analyzed in a Cobas 6000 (Roche, Tokyo, Japan) autoanalyzer according to the results of an electrochemiluminescence immunological test (ECLIA).

The levels of serum fructosamine and plasma HbA1c, as well as of blood glucose, were reviewed based on clinical information. The correlation among plasma HbA1c, serum fructosamine, and estimated fructosamine levels was investigated, and they were compared with the average glucose level estimated via HbA1c and that estimated via fructosamine.

3. Statistics

All the data were expressed as mean±standard deviation values. All the statistical analyses were performed using IBM SPSS Statistics ver. 21 (IBM Co., Armonk, NY, USA). Independent samples t-test was used to compare the clinical and biochemical parameters between the T1DM and T2DM groups. To evaluate the relationship between HbA1c and fructosamine,
a linear regression analysis was used. A P value of <0.05 was considered statistically significant.

4. Ethics statement

The study was approved by the Institutional Review Board of Dankook University Hospital (IRB No. 2014-07-015). Informed consent was waived by the IRB.

Results

Among 74 patients, 37 were male and 37 were female. A total of 245 samples were assayed for HbA1c and fructosamine. Their mean±standard deviation values were 9.05%±2.56% and 393.53±143.49 μmol/L, respectively. The mean age at the time of diagnosis and assay, and the duration of the disease at assay, were 9.87, 12.94, and 3.31 years, respectively (Table 1). The HbA1c levels showed strong correlations with the fructosamine levels (r=0.868, P<0.001), and were also applied to both T1DM and T2DM groups as well as to both the male and female patients (Fig. 1, Table 2). An equation was formulated to estimate the average plasma glucose levels using the fructosamine levels to evaluate glycemic control (Table 2, Fig. 1). To derive the relationship between HbA1c and the estimated average glucose, the following formula was used: eAG (mg/dL)=(28.7×HbA1c)–46.7, \( r^2=0.84 \).

The correlated formula about estimated fructosamine values was obtained from our results: estimated fructosamine=48.55×HbA1c–45.84 (Fig. 1). This equation, eAG (mg/dL)=0.59×fructosamine (μmol/L)–19.6, is considered useful in evaluating recent clinical findings and the efficacy of the treatment (Table 3). Because the fructosamine levels indicated the average glucose concentration over the previous two to three weeks, the measurement of serum fructosamine was useful in evaluating recent clinical findings and the efficacy of the treatment.

| Table 2. Average fructosamine levels according to HbA1c |
|----------------------------------------------------------|
| HbA1c (%), mean (range) | Fructosamine levels by assay (μmol/L) | Fructosamine levels by calculation (eFructosamine)\(^a\) (μmol/L) | Mean blood glucose levels estimated by HbA1c (mg/dL) |
|------------------------|----------------------------------------|---------------------------------|----------------------------------|
| 5.5 (5.1–5.8), n=17    | 225.25                                 | 221                             | 111.2                            |
| 6 (5.5–6.4), n=30      | 246.83                                 | 245                             | 125.5                            |
| 7 (6.5–7.5), n=48      | 297.06                                 | 294                             | 154.2                            |
| 8 (7.5–8.6), n=48      | 339.15                                 | 343                             | 182.9                            |
| 9 (8.6–9.4), n=36      | 393.61                                 | 391                             | 211.6                            |
| 10 (9.5–10.5), n=24    | 444.22                                 | 440                             | 240.3                            |
| 11 (10.6–11.5), n=19   | 491.26                                 | 488                             | 269.0                            |
| 12 (11.5–12.6), n=25   | 534.83                                 | 537                             | 297.7                            |

\( r^2=0.753 \) (Fig. 1).

The eFructosamine was similar to the average of fructosamine levels by assay. eAG\(=\)0.59xfructosamine–19.6.

HbA1c, glycosylated hemoglobin; eAG, estimated average glucose by HbA1c; eAG\(’, \) estimated average glucose by fructosamine.

\( a\) Calculated by regression equation (eFructosamine=48.55xHbA1c–45.84), \( r^2=0.753 \) (Fig. 1).

| Table 3. Summary of four specific cases |
|----------------------------------------|
| Case | Time of the assay | HbA1c Fructosamine | Clinical interpretations |
|------|-------------------|---------------------|-------------------------|
| 1    | At diagnosis      | 5.6                 | 244                     | Fulminant diabetes       |
|      | At 8 months after the diagnosis | 7.4 | 341               |                          |
|      | At 1 year after the diagnosis | 7.6 | 301               |                          |
| 2    | At time of DKA (5 years after the diagnosis) | 7.5 | 409               | Causes of DKA: omitting insulin injection or recent precipitating insult |
| 3    | At diagnosis (exercise and diet recently) | 11.9 | 408 | History of recent exercise and balanced diet: add metformin instead of insulin injection |
| 4    | At diagnosis (fever and diarrhea recently) | 11.5 | 586 | Recent history of fever and diarrhea: start insulin, initially |

HbA1c, glycosylated hemoglobin; DKA, Diabetic ketoacidosis.
selecting the initial therapeutics and promptly evaluating the therapeutic efficacy after a change in therapeutic modality (Table 3). It was also useful in estimating the onset of the disease, e.g., fulminant diabetes (Table 3).

These are four typical cases that show the clinical usefulness of fructosamine in the management of diabetes mellitus. In case 1, there was no hyperglycemic symptom such as polyuria, polydipsia, nocturia, thirst, or weight loss before the onset of nonketotic hyperosmolar coma. On the first visit to Emergency Department, the plasma glucose level was 723 mg/dL. The level of HbA1c was 3.6%, and the fructosamine level was 244 μmol/L (normal range, 205–285 μmol/L). The hemoglobin was 4.4 g/dL and the fasting serum C-peptide was 0.8 mg/mL. The patient was managed with insulin based on a diagnosis of fulminant diabetes and was discharged with improved condition. In case 2, the patient visited Emergency Department with symptoms such as vomiting, headache, and general weakness. Her laboratory test revealed 499 mg/dL of serum glucose, positive serum ketone, and 7.26 of blood pH. Her HbA1c and serum fructosamine were 7.5% and 409 μmol/L. A day before the onset of her symptoms, she was out camping and omitted insulin injection in the evening. From the biochemical and clinical features, we could assume that her average glucose levels during the recent three to four months, and the recent two to three weeks were 168 mg/dL and 221.7 mg/dL, respectively, although her serum glucose levels were 11.9%, 408 μmol/L, and 247 mg/dL, respectively. His plasma HbA1c, serum fructosamine, and fasting serum glucose levels were 11.9%, 408 μmol/L, and 247 mg/dL, respectively. His estimated average glucose levels over the recent three to four months and for the recent two to three weeks were 297.7 mg/dL and 221.1 mg/dL, respectively. We concluded that he did not assume that his diabetes mellitus was aggravated by his recent infection. Therefore, we added insulin therapy for management.

In the fourth case, the patient had been experiencing weight loss, polyuria, and polydipsia for 8 months. Four days prior to admission, he had fever, diarrhea, and lower extremity weakness. His initial blood glucose was 303 mg/dL and urinalysis revealed positive urine glucose. His HbA1c, fructosamine, serum insulin, and C-peptide were 11.5%, 586 μmol/L, 10.5 μIU/mL, and 2.1 ng/mL, respectively. It can be assumed that his diabetes mellitus was aggravated by his recent infection. Therefore, we added insulin therapy for management.

Discussion

It is well known that intensive control of blood glucose in diabetes mellitus is very important in the prevention of acute complications such as diabetic ketoacidosis as well as chronic complications such as nephropathy, retinopathy, and neuropathy. For better control of diabetes mellitus, it is important to maintain balanced energy intake, active exercise, regular insulin injection or medication of oral hypoglycemic agents as well as frequent blood glucose monitoring. A minimum of four daily blood glucose measurements should be performed, although more frequent blood glucose monitoring may be needed in some children and adolescents. Because of the difficulties in balancing insulin injections with the activities and diet, as many as 31% of all children with T1DM were reported to experience one or more episodes of severe hypoglycemia. This happens more commonly in children with good controlled diabetes mellitus.

Glycemic biomarkers are used as important tools in determining whether metabolic control has been kept within the target range. They are also surrogate markers for estimating the risk of chronic complications such as nephropathy, retinopathy, and neuropathy. HbA1c is considered the gold standard for the measurement of glycemic control. HbA1c levels reflect the mean glucose levels over the recent two to three months. HbA1c is highly positively correlated with the occurrence of chronic diabetic complications, and interventions that reduce HbA1c correspondingly reduce the risk of complications. Both observational studies and controlled clinical trials have demonstrated the strong correlation between HbA1c and HbA1c results. RBCs that have a short lifespan secondary to destruction (i.e., hemolytic anemia, destruction via passage through abnormal heart valves, or splenomegaly) will reduce the level of HbA1c which is independent of the mean serum glucose levels. Hemoglobinopathies such as sickle cell traits, and other abnormal hemoglobin variants such as hemoglobin C and E, can lead to falsely high or low HbA1c values, depending on the laboratory methodology used.

In the negative iron balance status, iron and hemoglobin deficiencies can be followed by deficient RBC production which translates to a slow turnover of RBCs. In this situation, more time for glycosylation of RBCs falsely increases the HbA1c values. Patients with chronic kidney disease present anemia of multifactorial etiology including erythropoietin deficiency, decreased RBC survival, decreased response of marrow precursor cells to erythropoiesis signals, and iron deficiency. The uremic state also affects the accuracy of the HbA1c assay. In uremia, there are direct interactions with glycosylated hemoglobin analyses and uremic conditions induce hemoglobin modification to carbamylated hemoglobin which interferes with the laboratory analysis. Moreover, HbA1c has a limited ability to reflect short-term glycemic changes, and cannot separately reflect postprandial hyperglycemia and fasting hyperglycemia. More evidences suggest that postprandial hyperglycemia and glycemic variability may be independent risk factors of macrovascular complications in patients with diabetes mellitus.
For better control of diabetes mellitus to prevent acute or chronic complications, frequent surveillance is beneficial, especially in children. Therefore, another biomarker indicating short-term glucose control will be required. Fructosamine, glycosylated albumin, and 1.5-anhydroglucitol (1.5-AG) have been drawing attention for use in populations whose HbA1c levels may be difficult to interpret[30-33], such as those with anemia, hemolysis, or renal disease[30,34-36]. Fructosamines are circulating biomarkers that reflect short-term glucose control in DM[37]. Fructosamine is a measure of glycosylated serum proteins, the most common of which is albumin. Fructosamine levels are correlated with the average glucose levels in the previous 10–14 days, and can be used clinically as complementary markers of short-term changes in glucose management[37]. Baker et al.[38] reported that concentrations of fructosamine appeared more useful in monitoring short-term changes after alterations in the management of diabetes. In addition, measurement of fructosamine offers many advantages of technical simplicity, low cost, and ease of automation using standard laboratory equipment[39].

Several studies have evaluated the association between fructosamine and postprandial hyperglycemia or glycemic fluctuations[6,9,38]. When the treatment modality is changed, fructosamine is useful because it reflects short-term glucose control[6,9,38,39]. The four cases presented in the paper (Table 3) illustrate the usefulness of measuring fructosamine levels in the management of childhood diabetes mellitus. The fructosamine level is useful in the prompt evaluation of the recent therapeutic changes after alterations in the management of diabetes. In addition, measurement of fructosamine offers many advantages of technical simplicity, low cost, and ease of automation using standard laboratory equipment[6].

In conclusion, the combined measurement of both serum fructosamine and plasma HbA1c is useful in the management of childhood diabetes mellitus, especially when there is discrepancy between the clinical information and the HbA1c level.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Alemzadeh R, Ali O. Diabetes mellitus in children. In: Kliegman RM, Stanton BF, St. Geme JW 3rd, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier Saunders, 2011:1968-97.
2. Haemoglobin A1 and diabetes; a reappraisal. Br Med J 1980;281:1304-5.
3. Graf JB, Halter JB, Porte D Jr. Glycosylated hemoglobin in normal subjects and subjects with maturity-onset diabetes. Evidence for a satural system in man. Diabetes 1978;27:834-9.
4. Boden G, Master RW, Gordon SS, Shuman CR, Owen OE. Monitoring metabolic control in diabetic outpatients with glycosylated hemoglobin. Ann Intern Med 1980;92:357-60.
5. Kennedy AL, Merimee TJ. Glycosylated serum protein and hemoglobin A1 levels to measure control of glycemia. Ann Intern Med 1981;95:56-8.
6. Baker JR, O’Connor JP, Metcalf PA, Lawson MR, Johnson RN. Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus. Br Med J (Clin Res Ed) 1983;287:863-7.
7. Chen HS, Wu TE, Lin HD, Jap TS, Hsiao LC, Lee SH, et al. Hemoglobin A(1c) and fructosamine for assessing glycemic control in diabetic patients with CKD stages 3 and 4. Am J Kidney Dis 2010;55:867-74.
8. Shafi T, Sozio SM, Plantinga LC, Jaar BG, Kim ET, Parekh RS, et al. Serum fructosamine and glycosylated albumin and risk of mortality and clinical outcomes in hemodialysis patients. Diabetes Care 2013;36:1522-33.
9. Chon S, Lee YJ, Fraterrigo G, Pozzilli P, Choi MC, Kwon MK, et al. Evaluation of glycemic variability in well-controlled type 2 diabetes mellitus. Diabetes Technol Ther 2013;15:455-60.
10. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473-8.
11. Desrocher M, Rovet J. Neurocognitive correlates of type 1 diabetes mellitus in childhood. Child Neuropsychol 2004;10:36-52.
12. Daneman D, Frank M, Perlman K, Tamm J, Ehrlich R. Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. J Pediatr 1989;115(5 Pt 1):681-5.
13. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Impact of improved glycaemic control on rates of hypoglycaemia in insulin dependent diabetes mellitus. Arch Dis Child 1998;78:111-5.
14. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care 2003;26:163-7.
15. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes
Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86.

16. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-17.

17. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:877-86.

18. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34:518-23.

19. Sabanayagam C, Liew G, Tai ES, Shankar A, Lim SC, Subramaniam T, et al. Relationship between glycated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? Diabetologia 2009;52:1279-89.

20. Wright LA, Hirsch IB. The challenge of the use of glycemic biomarkers in diabetes: reflecting on hemoglobin A1C, 1,5-Anhydroglucitol, and the glycated proteins fructosamine and glycated albumin. Diabetes Spectrum 2012;25:141-8.

21. Panzer S, Kronik G, Lechner K, Bettelheim P, Neumann E, Dudczak R. Glycosylated hemoglobins (GHb): an index of red cell survival. Blood 1982;59:1348-50.

22. Shapira Y, Vaturi M, Sagie A. Hemolysis associated with prosthetic heart valves: a review. Cardiol Rev 2009;17:121-4.

23. Jain N, Kesimer M, Hoyer JD, Calikoglu AS. Hemoglobin Raleigh results in factiously low hemoglobin A1c when evaluated via immunoassay analyzer. J Diabetes Complications 2011;25:14-8.

24. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. Clin Chem 2001;47:153-63.

25. Eschbach JW. The anemia of chronic renal failure: pathophysiology and the effects of recombinant erythropoietin. Kidney Int 1985;35:134-48.

26. Ly J, Marticorena R, Donnelly S. Red blood cell survival in chronic renal failure. Am J Kidney Dis 2004;44:715-9.

27. Derr R, Garrett E, Stacy GA, Saudek CD. Is HbA1c affected by glycemic instability? Diabetes Care 2003;26:2728-33.

28. Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? Diabetes 2005;54:1-7.

29. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681-7.

30. Jurachek SP, Steffes MW, Miller ER 3rd, Selvin E. Alternative markers of hyperglycemia and risk of diabetes. Diabetes Care 2012;35:2265-70.

31. Rondeau P, Bourdon E. The glycation of albumin: structural and functional impacts. Biochimie 2011;93:645-58.

32. Buse JB, Freeman JL, Edelman SV, Jovanovic I, McGill JB. Serum 1,5-anhydroglucitol (GlycoMark ™): a short-term glycemic marker. Diabetes Technol Ther 2003;5:355-63.

33. Rubino KB, Hirsch JB. Reexamining metrics for glucose control. JAMA 2011;305:1132-3.

34. Freedman BI, Shenoy RN, Planer JA, Clay KD, Shihabi ZK, Burkart JM, et al. Comparison of glycated albumin and hemoglobin A1c concentrations in diabetic subjects on peritoneal and hemodialysis. Perit Dial Int 2010;30:72-9.

35. Peacock TP, Shihabi ZK, Bleyer AJ, Dolbare EL, Byers JR, Knovich MA, et al. Comparison of glycated albumin and hemoglobin A(1c) levels in diabetic subjects on hemodialysis. Kidney Int 2008;73:1062-8.

36. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T, et al. Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. J Am Soc Nephrol 2007;18:896-903.

37. True MW. Circulating biomarkers of glyceremia in diabetes management and implications for personalized medicine. J Diabetes Sci Technol 2009;3:743-7.

38. Baker JR, Johnson RN, Scott DJ. Serum fructosamine concentrations in patients with type II (non-insulin-dependent) diabetes mellitus during changes in management. Br Med J (Clin Res Ed) 1984;288:1484-6.

39. Tattersall R, Walford S, Peacock I, Gale E, Allison S. A critical evaluation of methods of monitoring diabetic control. Diabetes Care 1980;3:150-4.

40. Hanafusa T, Imagawa A. Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. Nat Clin Pract Endocrinol Metab 2007;3:36-45.