Attachment 1. 8-D

Date _____

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr B. Seaton

Application No. 82-023(P)

Title of Study Effects of Chronic Malnutrition on the Levels of Haemoglobin A1c

Trainee Investigator (if any) —

Supporting Agency (if Non-ICDDR,B) —

Project status:
(✓) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects — (Yes) ~~No~~
   (b) Non-ill subjects — (Yes) ~~No~~
   (c) Minors or persons under guardianship — (Yes) ~~No~~
2. Does the study involve:
   (a) Physical risks to the subjects — ~~Yes~~ (No)
   (b) Social Risks — ~~Yes~~ (No)
   (c) Psychological risks to subjects — ~~Yes~~ (No)
   (d) Discomfort to subjects — (Yes) ~~No~~
   (e) Invasion of privacy — ~~Yes~~ (No)
   (f) Disclosure of information damaging to subject or others — ~~Yes~~ (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) — ~~Yes~~ (No)
   (b) Use of fetal tissue or abortus — ~~Yes~~ (No)
   (c) Use of organs or body fluids — (Yes) ~~No~~
4. Are subjects clearly informed about:
   (a) Nature and purposes of study — (Yes) ~~No~~
   (b) Procedures to be followed including alternatives used — (Yes) ~~No~~
   (c) Physical risks — (Yes) ~~No~~
   (d) Sensitive questions — ~~Yes~~ ~~No~~ N/A
   (e) Benefits to be derived — (Yes) ~~No~~
   (f) Right to refuse to participate or to withdraw from study — (Yes) ~~No~~
   (g) Confidential handling of data — (Yes) ~~No~~
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — ~~Yes~~ ~~No~~ N/A
5. Will signed consent form be required:
   (a) From subjects — ~~Yes~~ (No)
   (b) From parent or guardian (if subjects are minors) — ~~Yes~~ (No)
6. Will precautions be taken to protect anonymity of subjects — (Yes) ~~No~~
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   N/A Informed consent form for subjects
   N/A Informed consent form for parent or guardian
   ✓ Procedure for maintaining confidentiality
   N/A Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Principal Investigator

Trainee

82-023(P)
25/5/82

LIMITED STUDY

SECTION I - RESEARCH PROTOCOL

1. Title : The Effects of Chronic Caloric Malnutrition on the Levels of Haemoglobin Aic.

2. Principal Investigator : Dr. Brian Seaton

3. Co-Investigator :

4. Starting Date : June 1982

5. Completion Date : August 1982

6. Total Direct Cost : $ 950

7. Scientific Program Head :

This protocol has been approved by the Nutrition Working Group.

Scientific Program Head — Date: 14/5/1982

8. Abstract Summary

Haemoglobin Aic is a glycosylated haemoglobin formed by a non-enzymatic irreversible reaction between Haemoglobin Aic and glucose. Thus, the levels of Haemoglobin Aic reflect the average glucose concentration to which red-cells are exposed during their life-span. Haemoglobin Aic is extensively used to monitor hyperglycemia in diabetic patients. The purpose of this study is to investigate whether Haemoglobin Aic may also be of value in monitoring hypoglycemia associated with chronic malnutrition.

9. Reviews

a) Research Involving Human Subjects _____

b) Research Review Committee _____

c) Director _____

d) BMRC _____

e) Controller/Administrator _____

SECTION II - RESEARCH PLAN

A. INTRODUCTION

1) The objective of this study is to determine whether the levels of haemoglobin A_1 (HbAic) are correlated with chronic calorie malnutrition.

2) Background and Rationale

HbAic is a glycosylated haemoglobin formed by an irreversible, non-enzymatic reaction between glucose and haemoglobin A. Because of the mechanism of its formation HbAic levels are determined by the average glucose concentration to which normal HbAic is exposed during its life-time (in the red blood cell). Thus, HbAic has found considerable clinical application in the monitoring of glucose status in patients with diabetes mellitus. The chemistry and clinical significance of HbAic has been well summarised in a review by Jovanovic and Peterson, a copy of which is attached.

Despite the well-established correlation between elevated glucose levels and HbAic levels in diabetic patients, there have been no investigations to determine whether HbAic levels are reduced in chronic calorie malnutrition where the patient might be moderately to severely hypoglycemic. If such a correlation were established it would provide a useful, objective biochemical monitor of calorie nutritional status where, at present, none exists (Alleyny et al).

B. SPECIFIC AIMS

1) To determine whether chronic calorie malnutrition is associated with abnormally low levels of HbAic.

2) To assess the usefulness of HbAic determinations as an objective indicator of calorie malnutrition.

C. METHODS OF PROCEDURE

Two subject populations will be studied:-

a) Apparently healthy women of different nutritional status participating in the protocol "Effects of Nutritional Status on the Pharmacokinetics of DMPA in Rural Bangladeshi Women" (Protocol N. 82-004).

b) Children attending the Children's Nutrition Unit of the Save the Children Fund (CNU) or the ICDDR,B Treatment Centre or Hospital.

15-24 subjects in each group will be studied. In the case of the adult female population (a) the subjects will be stratified into three groups, high medium and low nutritional status on the basis of average (left and right arms) mid-arm skin-fold thickness (15 mm, 15-10 mm, 10 mm respectively). In the case of the children (b) the subjects will be stratified

into three groups, milk, moderate and severe caloric malnutrition on the basis of clinical assessment by an experienced clinician (Dr. Sultana at CNU, Dr. M. Molla at ICDDR,B). In both cases anthropometric measurements (height, weight, age, mid-arm circumstance (L&R) and mid-arm skin-fold thickness (L&R) will be made.

Subjects will be selected to give roughly equal numbers in each of the three groups.

Assays

50 ul blood will be taken from each subject by fingerstick on 2 consecutive days for determination of HbAic. Since the HbAic level will not change significantly within 24 hrs the duplicate determinations will establish the reproducibility of the method.

The level of HbAic is subject to confounding variables of which the most important is turn-over rate of the red blood cells since a more rapid turnover of cells means that the average duration of exposure of the haemoglobin to glucose is reduced resulting in lower HbAic levels. To minimise interference from this effect two additional tests will be done where feasible:-

1) a blood smear will be taken and stained by Wright's or Leischman's method. The red-cell morphology will be examined for evidence of unusually rapid red-cell turn-over.

2) where a venepuncture blood sample has been taken from the subject for other clinical or research purposes (venepuncture blood will not be drawn specifically for this study) blood folate and vitamin B_{12} will be assayed. Both folate and vitamin B_{12} deficiencies cause anemia and such deficiencies are common in conditions of malabsorbtion (eg in association with sprue) or chronic malnutrition.

In addition to the above two tests, the total haemoglobin level, determined as part of the HbAic assay will also be a valuable indicator of anemia and, hence, rapid red-cell turn-over.

Haemoglobin Aic will be determined by ion-exchange chromotographic separation (Bio-Rad Laboratories) from other hamoglobins followed by quantification of the haemoglobin Aic and total haemoglobin by colouremetry.

Blood folate and vitamin B_{12} will be determined by a double radioimmunoassay procedure (Quantaphase, Bio-Rad Laboratories).

Data Analysis

The data will be analysed by the usual statistical procedures to determine whether any correlations exist between the biochemical, anthropometric and clinical parameters. Any correlations will be carefully reviewed with experienced clinicians to assess their rel vance to the diagnosis and management of the chronically malnourished.

D. SIGNIFICANCE

If a clinically significant correlation were found to exist between HbAic and chronic malnutrition it could be or considerable potential value both for the diagnosis and management of the chronically malnourished and as an objective parameter in other research projects.

E. FACILITIES REQUIRED

1) The office space currently occupied by the PI is adequate.

2) Laboratory space will be required for performance of the various assays.

3) Hospital resources are not required for this study.

4) Animal resources are not required.

5) Logistic support. CRL transport will be required for travel in and around Dacca.

6) All major items of equipment required are available.

7) There are no special requirements.

F. COLLABORATIVE ARRANGEMENTS

This study will be undertaken in collaboration with the children's Nutrition Unit of the Save the Children Fund.

G. REFERENCE

G.A.O. Alleyne, R.W. Hay, D.I. Picou, J.P. Stanfield and R.G. Whitehead. The assessment of Nutritional Status. In: Protein-energy malnutrition 1977. (Publ. Edward Arnold).

SECTION III - BUDGET

1) Personnel Services

SL. No.	Name	Position	Monthly Rate	Person Month	Est.Cost $, 1982
1)	Dr. Brian Seaton	Scientist	Paid by ODM	2 x 0.1	-
2)	Travel and Transportation of Person				nil
3)	Transportation of Materials				nil
4)	Rent, Communication and Utilities				
	c) Postage, telephone, cable etc.				10
5)	Printing and Reproduction				
	d) Xeroxing				20
6)	Other Contructual Services				nil
7)	Supplies and Materials				
	h) Office supplies and stationery				20
8)	Equipment				nil
9)	Transport				
	ICDDR,B transport in Dacca				60
10)	Patient Hospitalisation				nil
11)	Out-Patient Care				nil
12)	Laboratory Tests				
	150 HbAic @ $4.33 per test				650
	50 Folate/B_{12} @		$ 3.8 per test		190
13)	Construction, Renovation & Alteration				nil
14)	Income				nil
	TOTAL COST				$ 950

ABSTRACT SUMMARY FOR ERC

1) The nature of this study is such that it necessarily requires a human population. A study population of children is necessary since this group is particularly at risk of chronic malnutrition.

2) There are no risks to the subject since the study requires only fingerstick blood and venepuncture blood and no sensitive data will be generated. It should be noted that the venepuncture blood will not be taken solely for the purpose of this study. Investigations will be done on venepuncture blood only when such samples have been taken for other authorised purposes. If a correlation is established between data obtained from venepuncture and fingerstick blood it will eliminate the necessity for using venepuncture blood in any subsequent studies.

3) Samples will be taken only by experienced personnel using established procedures.

4) Data will be kept locked in the Principal Investigator's Office and the identity of subjects will be confirmed to those directly involved in the study.

5) Since there are no risks to the subject, and venepuncture blood will be used only if taken for another authorised purpose, a signed consent form will not be required. A verbal statement will be read to the subject who will either agree or not to allow a fingerstick blood sample to be taken.

6) No interview is required.

7) The study will not be of direct benefit to the subject but will benefit society by establishing a useful procedure for the diagnosis and management of malnutrition.

8) The study will require access to simple, relevant medical history data and the use of small blood samples only.

Effects of Nutritional Status on Haemoglobin Aic Levels

Verbal Consent

Statement to be read to Subject

The ICDDR,B is undertaking a study to determine whether what, and how much, you or your child eat affects the levels of certain substances of blood. For this we need to take a small sample of blood by pricking your, or your child's finger. We should also like a second sample tomorrow. In addition, if the doctor has to take a sample of blood from your arm as part of your or your child's treatment we should like your permission to test that also. However, if the blood sample from your, or your child's arm is not required as part of your treatment we will not take it just for this study.

Helping us in this way will not create any risk for you or your child and we will not tell anyone else anything about you. These tests will not benefit you or your child directly and if you do not wish to help us it will not create any problem for you and you will still get the normal medical treatment.

Thank you for your assistance.

bs:fs:00023

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Frontiers in laboratory medicine

Hemoglobin A_{Ic} — the key to diabetic control

The measurement of hemoglobin A_{Ic} promises to help the clinician in the diagnosis and treatment of diabetes mellitus.

By Lois Jovanovic, M.D., and Charles M. Peterson, M.D.

Are your diabetic patients well-controlled? Until recently there was no reliable way to determine how well your diabetic patients managed their disease, short of multiple daily measurements of blood glucose, or the documentation of the extremes of hyperglycemia, hypoglycemia, or ketoacidosis. Fasting or postprandial blood glucose levels are often not representative of the daily mean glucose concentration. How much better it would be if one number could reflect the adequacy of control between visits to your office. The measurement of hemoglobin A_{Ic} may give you that number.

What is it?

Hemoglobin A_{Ic} (Hb A_{Ic}) is a minor component of hemoglobin comprising four to six percent of the total hemoglobin in normals as shown in Figure I.[1] In the diabetic, Hb A_{Ic} is synthesized at a constant rate throughout the life span of the red cell.[2]

Because circulating red cells are unable to initiate protein synthesis, the production of Hb A_{Ic} is a post-synthesis modification of hemoglobin, and the rate at which hemoglobin is modified depends upon the mean blood glucose level to which the red cell is exposed.

Hemoglobin A_{Ic} is produced by the addition of a glucose molecule to the N-terminus of the beta chains of normal adult hemoglobin (hemoglobin A). See Figure II. This is a nonenzymatic reaction and requires the formation of a Schiff base between the aldehyde of the carbohydrate and the amino-terminal valine of the beta

The authors are, respectively, instructor in medicine at Cornell University Medical Center, and attending physician at New York Hospital; and associate professor of medicine at The Rockefeller University in New York City.

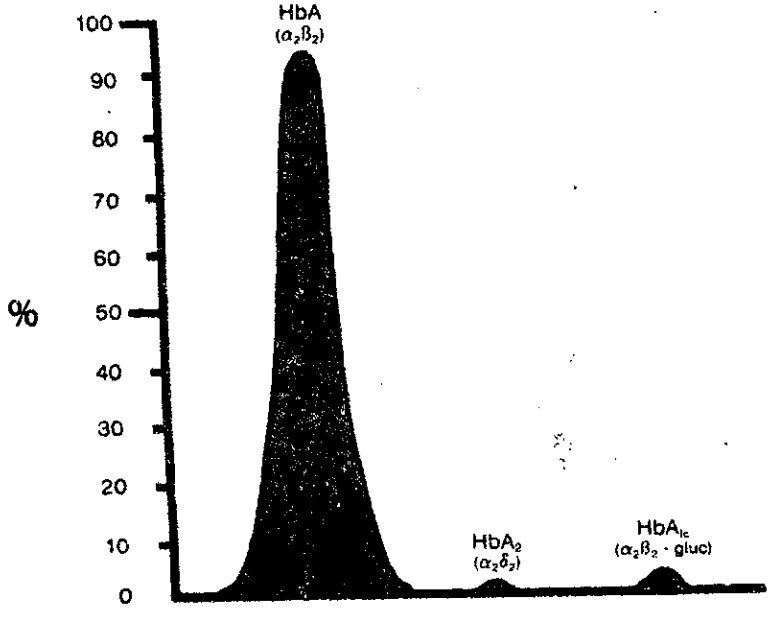
chain; followed by an Amadori rearrangement from the relatively unstable aldimine to the relatively stable ketamine, as shown in Figure III.

Hemoglobin A_{Ic} was first noted to be elevated in diabetics in 1968, but its potential *clinical* relevance to diabetes was not recognized at that time.[1] Today it appears that measurements of Hb A_{Ic} may be clinically relevant to three problem areas: (1) the diagnosis of diabetes mellitus; (2) the monitoring of diabetic control; and (3) the pathogenesis of the sequelae of diabetes mellitus through the use of Hb A_{Ic} as a biochemical marker.

It isn't easy to diagnose mild diabetes. Diabetologists, for example, argue about what constitutes an abnormal glucose tolerance test. The ability of the glucose tolerance test to accurately diagnose diabetes depends on adhering to a strict protocol which requires the consumption of an unpleasant sickly-sweet glucose drink, three days of preparation with a high carbohydrate intake, fasting on the day of the test, and five venipunctures at accurately timed intervals. Even the measurement of glucose varies with the method used. This will alter the criteria for an abnormal test.

Hemoglobin A_{Ic} levels correlate with glucose tolerance tests in patients with either juvenile or adult onset diabetes mellitus, as is shown in Figure IV.[4] Therefore, this single blood test may provide a convenient alternative to the glucose tolerance test. Hemoglobin A_{Ic} reflects the mean blood glucose concentration over the last three weeks to two months, and thus might be used to separate diabetics from nondiabetics. Whether Hb A_{Ic} levels will *actually* be useful as a means of screening populations for diabetes — or can distinguish chemical from overt diabetes — remains to be determined in more extensive clinical trials. Initiation of large-scale trials will require the development of inexpensive, rapid, and reliable assays. Fortunately, such methods are in development.

Figure I



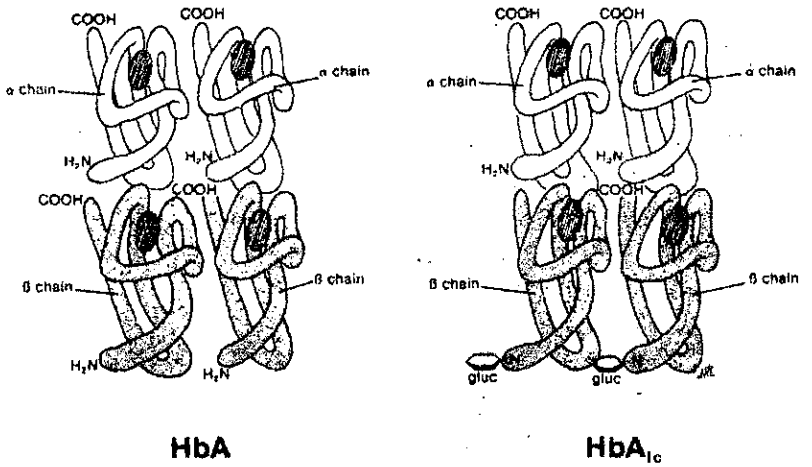
Composition of adult Hb

Adequacy of control

A large number of studies have shown that Hb A_{Ic} is a measure of the carbohydrate status of individual patients with diabetes mellitus. Strict carbohydrate control in a hospital setting, for example, lowers Hb A_{Ic} three to four weeks after the start of optimum control as has been shown in Figure V.[5] Outpatient studies in patients with juvenile onset diabetes have shown a good correlation between Hb A_{Ic} and 24-hour urinary glucose determinations measured one, two, and three months *before* the Hb A_{Ic} determinations.[6]

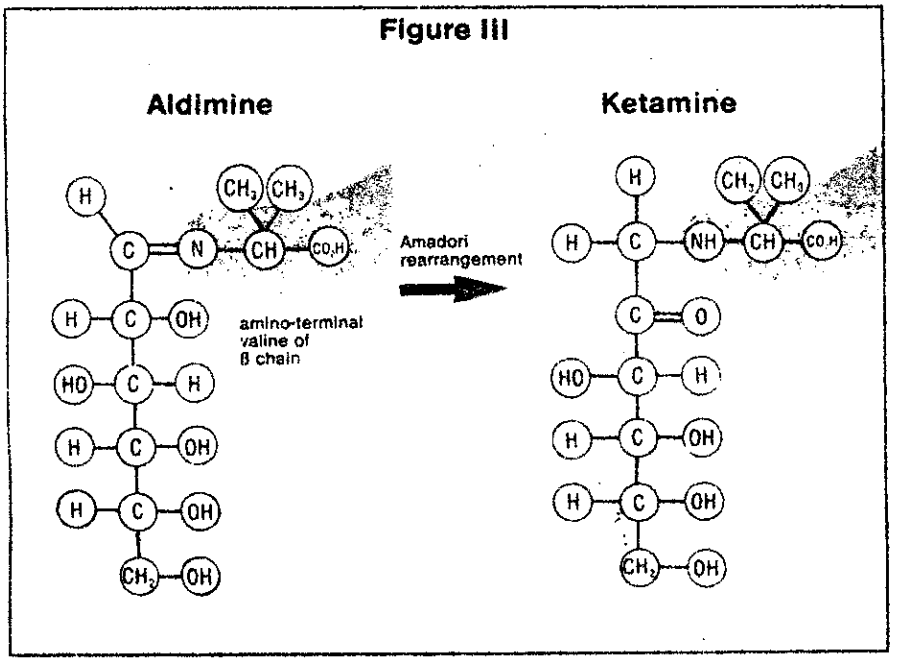
Hemoglobin A_{Ic} assays have proven to be valuable in the management of the diabetic during pregnancy. At no other time in the life of a diabetic woman is control as important as it is during pregnancy.[7,8,9] A measurement that would reflect control would provide clinicians with a better means to evaluate the course of the pregnancy. Hemoglobin A_{Ic}

Figure II



Schematic comparison of HbA and HbA_{Ic}. HbA_{Ic} is produced by the addition of a glucose molecule to the terminus of the β chains of normal adult hemoglobin.

Figure III



The nonenzymatic production of HbA_{Ic} requires the formation of a Schiff base between the aldehyde of the glucose and the amino-terminal valine of the beta chain, followed by an Amadori rearrangement to the relatively more stable Ketamine.

has proven to be that measurement. Two cases demonstrate the usefulness of Hb A_{Ic} in the management of the pregnant diabetic.

Case 1: A 21-year-old woman, who required insulin for the past 12 years, came to us in her twelfth week of pregnancy for control of diabetes. On 40 units of NPH insulin a day, her mean glucose per 24 hours (24 separate blood glucose determinations) was 160 mg/dl; her 24-hour urinary glucose was 50 grams; and her Hb A_{Ic} was 11.5 percent (normal less than 5.5 percent). Her insulin dosage was adjusted in order to lower the mean blood glucose.

After 10 days, the mean blood glucose per 24 hours was 100 mg/dl, and the 24-hour urinary glucose excretion was less than 5 grams. She was discharged on her new dosage schedule and Hb A_{Ic} was measured at three-week intervals. Two months later her Hb A_{Ic} was down to 4.5 percent and remained between 3.5 and 4.5 percent for the duration of her pregnancy. Because good glucose control was well documented, the pregnancy was allowed to go to term without any intervening hospitalization. She gave birth to a 6-pound, 4-ounce infant at term, and mother and child had an uneventful postpartum stay.

This case illustrates the use of Hb A_{Ic} as a monitor of control. The next case shows the use of Hb A_{Ic} for the detection of diabetes.

Case 2: A 27-year-old woman, with a past history of gestational diabetes mellitus, came to us in her sixth week of pregnancy. A glucose tolerance test, 24-hour urinary

glucose, and 24-hour blood glucose monitor, were all within normal limits. Hemoglobin A_{Ic} was 4.5 percent. Serial Hb A_{Ic} determinations were obtained every three weeks. At 18 weeks gestation her Hb A_{Ic} had risen to 6.5 percent; but her 24-hour urinary glucose was less than 5 grams, and her fasting blood sugar was normal. She was admitted in order to measure blood glucose every hour for 24 hours. She was found to have a mean glucose per 24 hours of 140 mg/dl.

After an unsuccessful trial of diet therapy she was treated with an appropriate dose of insulin. Over the course of several weeks her Hb A_{Ic} level fell back to 4.5 percent, and remained within normal limits throughout the remainder of her pregnancy. At delivery her child was of normal size and there was no evidence of neonatal hypoglycemia.

These cases illustrate the utility of Hb A_{Ic} as a measure of control. Hemoglobin A_{Ic} can be assayed at three- to four-week intervals while insulin and diet are adjusted. Although the relevance of hyperglycemia to prognosis in diabetes is still debated, the evidence is weighted towards tight control.[19]

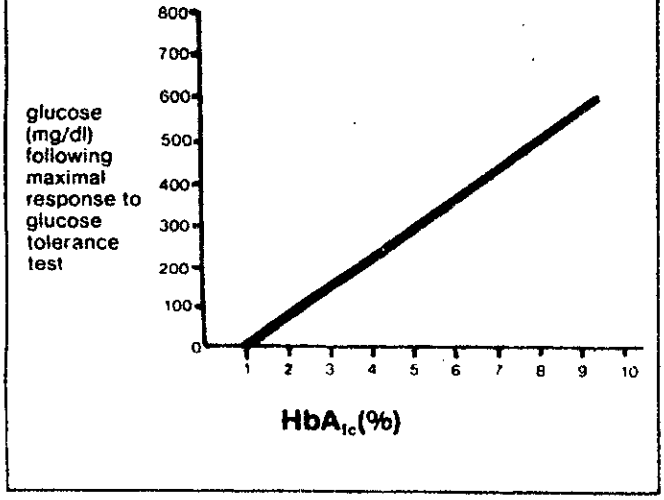
The unique aspect of Hb A_{Ic} is that it appears to be an index or integrator molecule that reflects the patient's mean blood glucose concentration for the preceding weeks to months. Short-term fluctuations in blood sugar minimally influence the measurement, whereas changes lasting more than one week are reflected in the Hb A_{Ic} levels. Periodic evaluation of Hb A_{Ic} levels should provide a more objective assessment of carbohydrate control than has been previously possible.

Because patients with shortened red blood cell survival (such as hemolysis or bleeding) have lower than expected Hb A_{Ic} levels, a complete blood count and reticulocyte count should also be performed. Hemoglobin A_{Ic} levels cannot be used reliably in patients with hemoglobinopathies, because Hb A_{Ic} is a direct modification of normal adult hemoglobin only. Splenectomy will elevate Hb A_{Ic} because of lengthened red blood cell survival.

Hb A_{Ic} and diabetic sequelae

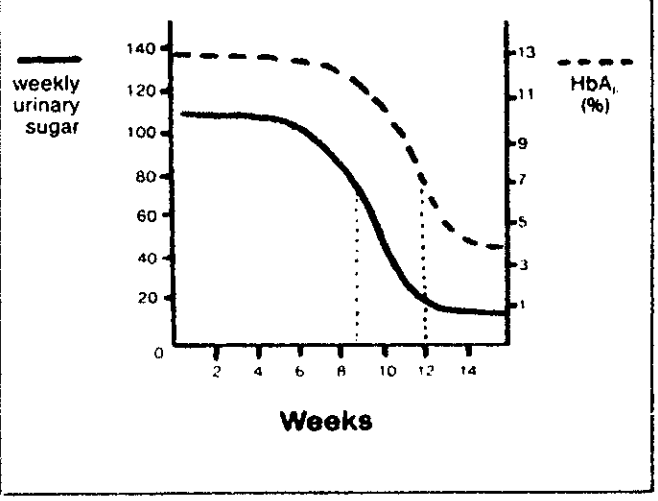
The measurement also provides the clinical investigator with the opportunity to re-examine the relationship of hyperglycemia to certain sequelae resulting from hyperglycemia. These studies will need to be undertaken prospectively because the time course of Hb A_{Ic} formation — and the development of reti-

Figure IV



This graph indicates that increasing levels of glucose following maximal response in glucose tolerance tests correlate with increasing HbA_{Ic} levels in diabetic patients.

Figure V



The curves of weekly urinary sugar and HbA_{Ic} levels following hospitalization indicate a drop in HbA_{Ic} levels three to four weeks after strict carbohydrate control is reached.

Hemoglobin At a Glance

Hemoglobin A_{Ic} (it's pronounced "A-one-see") is one of several minor hemoglobin components found in the human red cell. Early on it was appreciated that there were at least two kinds of human hemoglobin: hemoglobin A (for Adult), and hemoglobin F (for Fetal). As separation techniques became more sophisticated, it became apparent that there were a number of variant hemoglobins such as hemoglobin S, which causes sickle cell disease.

When hemoglobin from a normal adult is passed through a chromatographic column it separates into several fast moving minor components: Hemoglobin A_{Ia} through A_{Ie}, and a major slower moving component, hemoglobin A_{II}. Hemoglobin A_{II} is an alternate term for unmodified hemoglobin A. The Roman numeral and alphabetical subscripts simply indicate which components come off first. Hemoglobin A_{Ia}, for example, moves faster than hemoglobin A_{Ic}; and hemoglobin A_{Ic} moves faster than hemoglobin A_{II}.

Roman rather than Arabic numbers are used in order to differentiate hemoglobins A_I and A_{II} from still another minor hemoglobin component: hemoglobin A_2. Hemoglobin A_2 is made up of alpha and delta chains, rather than the usual alpha and beta chains, and is elevated in patients with beta thalassemia minor.

The minor hemoglobin A_{Ia-c} are elevated in diabetes mellitus. Hemoglobin A_{Ic} is present in greatest amount, is chemically characterized, and is easiest to measure. Therefore, this is the component most frequently reported. Some methods report hemoglobins A_{Ia-c} (all three) as "fast hemoglobin," "glycohemoglobin," or "glucose hemoglobin."

This latter approach will naturally result in higher normal values, so it is important to know which method is used, and what is reported.

nopathy, neuropathy, and micro- and macrovascular complications — are obviously disparate.

Certain short-term sequelae have already proved amenable to correlation with Hb A_{Ic} levels. Cholesterol and triglyceride levels in diabetic patients have been shown to be directly correlated with Hb A_{Ic}.[6, 11] Abnormalities of erythrocyte, leukocyte, and platelet function, have also been shown to be corrected toward normal in diabetic patients when carbohydrate control is optimized as measured by standard methods and by Hb A_{Ic} determinations.[12] Fibrinogen survival has also been shown to be shortened in hyperglycemic diabetics, but returns to normal when euglycemia is re-established.[13]

The correlation of Hb A_{Ic} levels with lipid levels and coagulation function are especially intriguing because of the recognized role of these factors in micro- and macrovascular disease. The mechanisms whereby hyperglycemia might contribute to lipid levels; fibrinogen survival; or abnormal platelet, leukocyte and erythrocyte function, still need to be determined. It will take even longer to obtain convincing evidence of the correlation of Hb A_{Ic} levels with basement membrane thickness, neuropathy, nephropathy, retinopathy, and other vascular sequelae of diabetes.

Hemoglobin A_{Ic} is a new test that should be of great value to the clinician. It will document how well a diabetic is controlled. And it may also finally provide an unequivocal answer to the question of the relationship of hyperglycemia to the numerous late sequelae of diabetes mellitus. □

REFERENCES

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