PAPERS AND ORIGINALS

Haemoglobin A_{Ic} concentrations after initial insulin treatment for newly discovered diabetes

JØRN DITZEL, JENS-JØRGEN KJÆRGAARD

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Summary and conclusions

Glycosylated haemoglobins A_{Ia+Ib} and A_{Ic} were measured serially in 10 consecutive cases of newly discovered non-acidotic diabetes before and after diet and insulin treatment. The average concentration of Hb A_{Ic} was 11·4% in untreated diabetics as compared with 4·3% in healthy controls. With prolonged optimal regulation of blood glucose Hb A_{Ic} slowly decreased to a mean concentration of 5·5%. The concentration of Hb A_{Ic} was significantly correlated with the fasting blood sugar value.

The findings suggest that determining Hb A_{Ic} may give valuable information on the regulation of carbohydrate metabolism in the preceding one to two months and thus become an important aid to management.

Introduction

In cases of diabetes mellitus the concentration of the glycosylated haemoglobin A_{Ic}, and to a less extent Hb A_{Ia+Ib}, may serve as an indicator of the mean blood sugar concentration during the previous few months.[1-4] Such studies suggest that measuring Hb A_I may give an improved estimate of diabetic blood glucose control and thus be useful in the management of diabetes. Most data on glycosylated haemoglobins have derived from single determinations in ambulatory patients. We therefore decided to examine the fractions of glycosylated haemoglobins serially in cases of newly discovered insulin-dependent diabetes before and after insulin treatment. This type of diabetes is generally easily controlled by diet and insulin, and after weeks of intensive treatment some cases may remit spontaneously.

Department of Medicine, Section of Endocrinology and Metabolism, Aalborg Hospital, Aalborg, Denmark

JØRN DITZEL, MD, PHD, chief of department of medicine
JENS-JØRGEN KJÆRGAARD, MB, senior medical registrar

Patients and methods

Ten consecutive patients admitted to hospital with newly discovered diabetes were studied before their first insulin injection and then serially for three to four months. Their mean age was 30 years (see table). All were poorly controlled on admission and one (case 10) was slightly ketoacidotic. Blood sugar concentrations were reduced to more optimal values in one to two weeks after admission and remained so for two to four months. With careful regulation of diet and the use of insulin complete remission was obtained in four cases.

Several methods were used to assess the regulation of carbohydrate metabolism in each patient. By means of an autoanalyzer the fasting, morning, and afternoon blood sugar concentrations were determined while in hospital, and thereafter fasting blood sugar values were determined biweekly. All other laboratory studies were done on the same day. Urinary sugar was measured quantitatively during the hospital stay and thereafter semi-quantitatively by the patients two to four times daily with the Clinitest. Twenty-one healthy subjects of similar age served as controls. Heparinised blood samples were used for haemoglobin isolation and quantification. Hb A_{Ia+Ib} and Hb A_{Ic} were isolated in duplicate by means of a modified[5] column chromatographic technique.[6] Serum cholesterol and triglyceride concentrations were measured by standard methods.

Wilcoxon's test for paired samples was used to test the significance of differences between mean values.

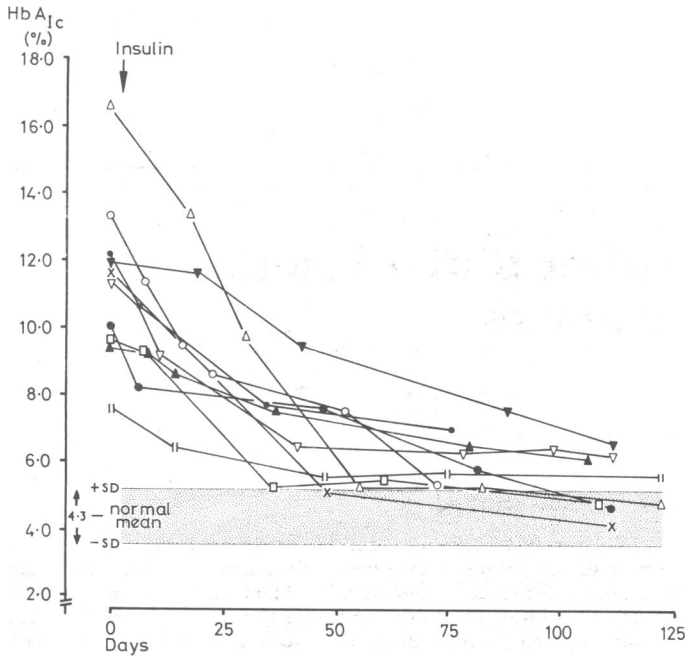
Results

The table lists the results of tests before insulin treatment and after optimal control for 72-123 days on diet and insulin. Metabolic control improved during the first two weeks and remained good during the study: fasting blood glucose concentrations fell to near-normal values, four patients (cases 2, 4, 5, and 7) went into remission, hyperlipaemia disappeared in all cases (1, 2, 6, and 10) in which it had been noted, and urinary glucose excretion (measured by the patients) seldom exceeded 0·5% and was usually zero.

The mean concentration of Hb A_{Ia+Ib} on admission (4·3%) was significantly higher than the value (3·0±SD 0·57%) in the controls ($P<0·001$). During optimal control the concentration fell to 2·5% ($P<0·001$). The mean concentration of Hb A_{Ic} was 11·4% (range 16·6-7·6%) in the newly discovered diabetics as compared with 4·3±0·7% in the controls ($P<0·001$). There was no overlapping of values between the diabetic and control groups. The mean Hb A_{Ic} concentration decreased from 11·4% to 5·5% (range 4·6-6·9%) after prolonged optimal control ($P<0·001$).

There was a significant correlation between the Hb A_{Ic} and Hb

A_{Ia+Ib} concentrations ($r=0.49$; $P<0.05$) and a highly significant correlation between the Hb A_{Ic} and fasting blood sugar concentrations ($r=0.79$; $P<0.001$). The concentration of Hb A_{Ic} was also correlated with the serum cholesterol and plasma triglyceride concentrations ($r=0.61$ and $P<0.01$ in both cases) when the highest and lowest Hb A_{Ic} values were applied. The figure shows the decrease in Hb A_{Ic} with time. Hb A_{Ic} decreased in all the patients, with complete return to normal values in four. The rate of decrease varied with the initial concentration and degree of control of carbohydrate metabolism.



Decrease in Hb A_{Ic} concentrations during prolonged optimal regulation of blood glucose in 10 newly discovered diabetics.

Discussion

These results confirm that concentrations of the minor haemoglobin fractions—namely, Hb A_I, and particularly Hb A_{Ic}—are increased in poorly controlled, newly diagnosed diabetes.[1 2 6] They further clearly show that improved metabolic control leads to significant decreases towards normal concentrations of these fractions. Return to normal or near-normal values took 25-80 days, depending on the initial Hb A_{Ic} concentration and degree of blood glucose control. Our findings thus support and extend the contention that the concentration of Hb A_{Ic} is an expression of the average blood glucose value in the preceding one to two months. We believe that the determination of Hb A_{Ic} will become an important aid to the management of diabetes.

There is another aspect of the glycosylated haemoglobins that may have a major clinical implication. Like carboxyhaemoglobin, Hb A_{Ic} has an increased affinity for oxygen and thus decreases the availability of oxygen to the tissues.[7] The diabetic organism reacts to excessive amounts of Hb A_{Ic} by increasing oxygen-carrying capacity and red-cell 2,3-diphosphoglycerate (2,3-DPG).[8 9] This compensatory mechanism, however, cannot be maintained indefinitely. The unavoidable administration of insulin (particularly to patients with high glucose concentrations) and the lowering of the blood pH, as in ketoacidosis, prevent the formation of optimal 2,3-DPG levels.[10–12] Hence the immediate compensatory response to decreased oxygen availability occurs in the microcirculation as a dilatation of venules and the venous part of the capillaries.[13 14] This aggravates the effect of simultaneously increased blood viscosity and red-cell aggregation—all of which changes may participate in the insidious development of microvascular disease in diabetes.[15]

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Details of patients on admission before insulin treatment (initial) and after optimal control for 72-123 days (controlled)

Case No	Sex and age	Fasting blood sugar (mmol/l)		Urinary glucose (mmol/24 h)		Serum cholesterol (mmol/l)		Plasma triglycerides (mmol/l)		Hb A_{Ia+Ib} (%)		Hb A_{Ic} (%)		Hb $A_{Ia+Ib+Ic}$ (%)	
		Initial	Controlled	Initial	Controlled	Initial	Controlled	Initial	Controlled	Initial	Controlled	Initial	Controlled	Initial	Controlled
1	M 44	23·7	5·2	575	0	36·3	5·8	82·00	0·94	5·1	3·1	16·6	4·7	21·7	7·8
2	M 42	13·7	7·5	250	0	28·2	6·8	57·20	8·40	4·2	3·3	11·5	6·0	15·7	9·3
3	F 17	12·9	8·8	298	0	5·5	3·7	1·13	0·78	4·6	2·4	11·9	6·9	16·5	9·3
4	F 27	6·9	5·2	17	0	4·2	4·7	0·45	0·36	5·0	2·2	7·6	5·3	12·6	7·5
5	M 15	9·4	7·1	515	0	4·0	4·1	0·48	0·40	3·5	2·1	13·3	5·2	16·8	7·3
6	F 57	12·1	4·1	97	0	4·0	4·3	2·49	0·83	4·0	2·4	11·8	4·7	15·8	7·1
7	F 37	4·6	4·7	126	0	5·1	5·8	0·56	0·40	3·5	2·3	10·0	4·6	13·5	6·9
8	M 28	14·6	5·0	361	0	5·3	4·8	1·84	0·64	4·1	3·1	9·6	4·8	13·7	7·9
9	F 15	13·6	7·6	243	0	4·4	5·0	0·49	0·81	3·9	2·2	9·5	6·0	13·4	8·2
10	F 18	22·1	13·0	808	27	15·9	3·8	18·45	0·82	5·0	2·1	12·2	6·8	17·2	8·9
Mean		13·36	6·82	329·0	2·7	11·3	4·88	16·5	1·43	4·3	2·5	11·4	5·5	15·7	8·0
SD		5·97	2·66	243·3	8·53	11·75	0·99	29·10	2·45	0·60	0·46	2·47	0·87	2·66	0·88
P value		<0·01		<0·001		NS		<0·02		<0·001		<0·001		<0·001	

NS = Not significant.
Conversion: SI to traditional units—Blood sugar: 1 mmol/l ≈ 18 mg/100 ml. Urinary glucose: 1 mmol/24 h ≈ 0·2 g/24 h. Serum cholesterol: 1 mmol/l ≈ 38·7 mg/100 ml. Plasma triglycerides: 1 mmol/l ≈ 88·6 mg/100 ml.