CLINICAL RESEARCH

Changes in glycosylated haemoglobin after oral glucose load

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Abstract

To study the relation between hyperglycaemia and a change in the concentration of glycosylated haemoglobin (HbA_1) blood glucose and HbA_1 concentrations were measured during an oral glucose tolerance test and for 120 days afterwards in 20 normal subjects. These measurements showed that a minor degree of hyperglycaemia led to a significant increase in glycosylated haemoglobin concentrations. The increase appeared 10 days after the test, and values remained raised until 30 days and returned to normal 60 days after the test.

If such a minor fluctuation of blood glucose can lead to a significant increase in HbA_1 concentrations the test may be too sensitive as an index of long-term blood glucose control in diabetics.

Introduction

The concentration of glycosylated haemoglobin (HbA_1) is used widely as an index of long-term blood glucose control in diabetics as it is thought to reflect the mean blood glucose concentration over the preceding eight to 10 weeks.[1] To determine the increase in HbA_1 concentrations after minor hyperglycaemia and to examine the time relation between hyperglycaemia and a change in HbA_1 we decided to monitor HbA_1 concentrations after a standard oral glucose tolerance test in normal subjects.

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Methods

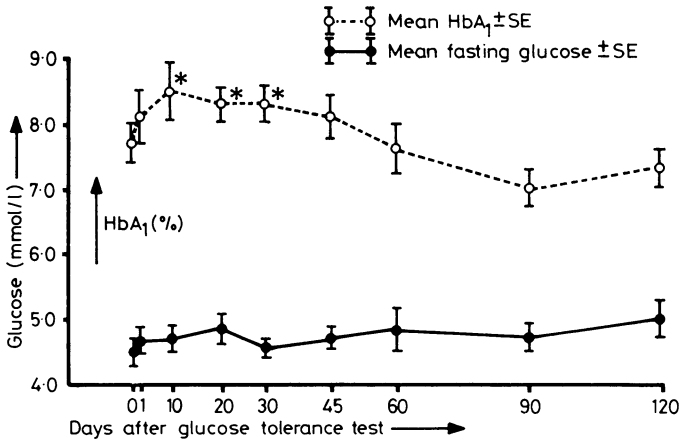
A standard oral glucose tolerance test using 50 g dextrose was performed in 20 healthy volunteers (aged 22-70 years) after an overnight fast. Blood glucose and total HbA_1 concentrations were measured at 0, 30, 60, 90, and 120 minutes after ingestion of the glucose and thereafter at 1, 10, 20, 30, 45, 60, 90, and 120 days after the test in the non-fasting state. All samples were withdrawn at the same time of day and preserved for a similar length of time before analysis of HbA_1 in the days after the glucose tolerance test. Blood glucose was measured with a Beckman glucose analyser and total HbA_1 by a microcolumn technique (Bio-Rad Haemoglobin A_1 Column Test) in a temperature-controlled environment. The data were analysed by the Kruskal-Wallis Test for analysis of variance of ranks using a computer program written in BASIC and by the Wilcoxon signed rank test.

Results

Mean blood glucose concentrations during the oral glucose tolerance test rose from 4·5 mmol/l $\pm$(SEM) 0·2 mmol/l at time 0 to 7·0 mmol/l $\pm$0·3 mmol/l at 30 minutes and 6·6 mmol/l $\pm$0·35 mmol/l at 60 minutes, the changes in mean blood glucose concentration at 30 and 60 minutes being highly significant ($p < 0·001$). Throughout the 120 days after the test, however, there was no significant trend in the mean blood glucose concentration (see figure). During the oral glucose tolerance test no significant difference was found in HbA_1 values, which fell within the range 7·55-7·75% of total haemoglobin, but at days 10, 20, and 30 after the test the mean HbA_1 values were significantly higher than the baseline values ($p < 0·05$) using the Wilcoxon signed rank test (see figure). The overall probability that this distribution was not significant was $< 0·001$ (Kruskal-Wallis analysis of variance of ranks). The mean values of HbA_1 at days 10, 20, and 30 were 8·5%, 8·28%, and 8·28% of total haemoglobin respectively.

Discussion

The formation of HbA_1 is usually considered to be a slow irreversible non-enzymatic process occurring within the erythrocyte at a rate dependent on the blood glucose concentration.[1] These results provide information on the size of the change in blood glucose concentration that can modify the HbA_1 value and, more important, on the time relation between an episode of hyperglycaemia and a subsequent increase in HbA_1 concentration. We found that a rise in blood glucose



Glucose and HBA_1 values in the 120 days after an oral glucose tolerance test. *Result differs significantly from baseline value ($p<0.05$).

concentration of some 2·5 mmol/l could produce a significant increase in HbA_1 concentration of almost 1% of total haemoglobin and that this increase appeared 10 days after the hyperglycaemia and values remained high until 30 days later, then fell to normal by 60 days after the test. These data differ slightly from those of a similar study[2] in which 75 g glucose was used in that we observed a significant rise in HbA_1 concentration earlier.

These findings raise doubts about the validity of using HbA_1 concentrations as an index of time-integrated blood glucose concentration since the blood sugar concentrations of insulin-dependent diabetics may vary widely and frequently throughout the day. This criticism would not apply, of course, in uncontrolled or poorly controlled diabetics, in whom persistent significant increases in blood glucose concentrations produce a marked increase in HbA_1 values. In these circumstances there is no doubt about the value of HbA_1 measurement. Perhaps, however, HbA_1 measurements are too sensitive in well-controlled insulin-dependent diabetics and those with mild maturity onset diabetes since our findings show that a minor transient period of hyperglycaemia will result in a significant increase in HbA_1 concentrations.

It is now established that there is an unstable component of HbA_1 (Schiff base fraction) which accounts for the rapid increase in HbA_1 values in response to a short-term increase in blood glucose concentration.[3] The microcolumn technique does not differentiate between unstable and stable (ketoamine) fractions of HbA_1, but an increase in the unstable fraction would be expected to produce some increase in total HbA_1. We did not observe this during the glucose tolerance test or the next morning, but possibly the degree of hyperglycaemia might not have been sufficient to produce this effect. Alternatively we may have missed the effect occurring later in the day of the test. The labile fraction is thought to decrease again within six hours, once normoglycaemia is achieved,[4] so it may have disappeared by the following morning.

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Carbon monoxide and exercise tolerance in chronic bronchitis and emphysema

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Abstract

The effects of carbon monoxide on exercise tolerance as assessed by the distance walked in 12 minutes were studied in 15 patients with severe chronic bronchitis and emphysema (mean forced expiratory volume in one second 0·56 l, mean forced vital capacity 1·54 l). Each subject walked breathing air and oxygen before and after exposure to sufficient carbon monoxide to raise their venous carboxyhaemoglobin concentration by 9%. There was a significant reduction in the walking distance when the patients breathed air after exposure to carbon monoxide ($p<0.01$), and the significant increase in walking distance seen after exercise when breathing oxygen at 2 l/minute via nasal cannulae was abolished if carbon monoxide had previously been administered.

Thus concentrations of carboxyhaemoglobin frequently found in bronchitic patients who smoke may reduce their tolerance of everyday exercise, possibly by interfering with the transport of oxygen to exercising muscles.

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Introduction

British cigarettes produce appreciable quantities of carbon monoxide, which is formed by the incomplete combustion of tobacco in those cigarettes without ventilated filters. When inhaled this carbon monoxide readily combines with haemoglobin to form carboxyhaemoglobin. Carboxyhaemoglobin concentration has been related to cigarette consumption,[1] and concentrations of 5-15% are common in patients who continue to smoke (table I). In normal healthy volunteers the maximum oxygen uptake during bicycle exercise was reduced when the carboxyhaemoglobin concentration was raised to 20% by