Diabetologia (1983) 24: 391–393

Diabetologia

The Relationship Between Glycosylated Haemoglobin Levels and Various Degrees of Glucose Intolerance

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Summary. To assess the use of glycosylated haemoglobin to discriminate between various degrees of glucose intolerance, glycosylated haemoglobin levels were determined in 107 subjects (48 males and 59 females, age range 18–80 years). Following a 75 g oral glucose tolerance test and according to World Health Organization criteria, subjects were classified as normal ($n=32$), diabetic ($n=46$) or as having impaired glucose tolerance ($n=29$). Mean glycosylated haemoglobin levels were $5.8 \pm 1.3\%$ (range 4%–9%) in normal subjects, $7.1 \pm 1.7\%$ in subjects with impaired glucose tolerance (range 4.1%–10.1%) and $10.1 \pm 2.6\%$ (range 4.7%–18.8%) in diabetic patients. The difference between the groups was highly significant ($p<0.01$). Twelve per cent of normal subjects exceeded and 52% of subjects with impaired glucose tolerance fell below 7.4% (mean ± 2SD, considered as the upper limit of normal values). A significant correlation was observed between glycosylated haemoglobin values and fasting blood glucose ($r=0.68$, $p<0.01$). These results provide evidence that glycosylated haemoglobin levels are influenced by slightly reduced carbohydrate tolerance. Glycosylated haemoglobin may be a useful test to improve the specificity of the oral glucose load to select and to follow-up subjects with impaired glucose tolerance.

Key words: Blood glucose, oral glucose tolerance test, subjects with impaired glucose tolerance, glycosylated haemoglobin.

There is convincing evidence that glycosylated haemoglobin (HbA_1) may be an indicator of the integrated plasma glucose level over several weeks [1–3]. In fact, a number of clinical studies have shown a high degree of correlation between HbA_1 and several indices of diabetic control [4–6]. In addition, HbA_1 measurements might also provide an alternative method of screening for diabetes, since some authors have challenged the concept of the oral glucose tolerance test in the early diagnosis of diabetes and because its prognostic value is rather low [7, 8]. There are few studies on HbA_1 levels in subjects with minor carbohydrate tolerance as shown by an impaired glucose tolerance test response [9–12], and it has not been established whether HbA_1 can be used as a marker of reduced glucose tolerance.

We have therefore investigated HbA_1 levels in various degrees of glucose intolerance with respect to the possible application of HbA_1 determination for the early diagnosis of diabetes.

Material and Methods

One hundred and seven subjects (48 males and 59 females, age range 18–80 years) were recruited from Laurino, a rural community in Southern Italy where a high prevalence of diabetes was found, following an epidemiological investigation [13]. On the basis of a 75 g oral glucose load and according to World Health Organization criteria [14] they were classified as diabetic ($n=46$), normal ($n=32$) or as subjects with impaired glucose tolerance ($n=29$).

After an overnight fast, blood samples were drawn into a heparinized tube and tested within 4 h. The proportion of HbA_1 in whole blood was determined by the cation exchange column chromatographic method, carried out at 23 ± 0.3 °C (Bio Rad, Milan, Italy). Blood glucose was determined by a glucose oxidase method (Boehringer Mannheim, FRG).

For statistical evaluation variance analysis and regression analysis were used.

Results

The mean HbA_1 levels were $5.8 \pm 1.3\%$ (range 4%–9%) in the normal subjects and $7.1 \pm 1.7\%$ (range 4.1%–10.1%) in the subjects with impaired glucose tolerance. In the diabetic group mean HbA_1 was $10.1 \pm 2.6\%$ with a range of 4.7%–18.8%. The differences between groups were highly significant ($p<0.01$).

Figure 1 shows the distribution of HbA_1 values among subjects with normal glucose tolerance, subjects with impaired glucose tolerance and diabetic patients. If we take 7.4% as the upper limit of normal (mean ±

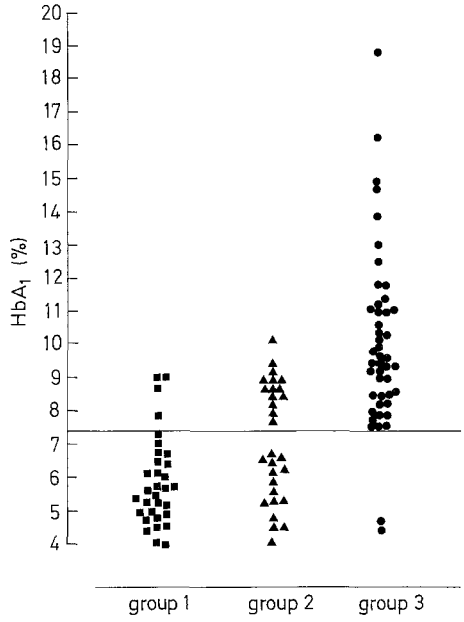

Fig. 1. Glycosylated haemoglobin levels in subjects with normal response to the oral glucose load (group 1), subjects with impaired glucose tolerance (group 2) and diabetic patients (group 3) respectively. The horizontal line drawn at 7.4% indicates the upper limit of the normal (mean + 2 SD)

2 SD), 15 subjects with impaired glucose tolerance (51.8%) and two diabetic patients (4.3%) had HbA_1 concentrations below this level, that is, they were within the normal range. No significant correlation was found between fasting blood glucose and HbA_1 concentrations in normal subjects or in subjects with impaired glucose tolerance; this correlation became significant in the diabetic patients ($r=0.69$, $p<0.001$). The overall coefficient of correlation of the 107 subjects examined was highly significant ($r=0.68$, $p<0.01$).

A weak positive correlation was found between HbA_1 values and blood glucose levels 2 h after an oral glucose load in normal subjects ($r=0.40$, $p<0.05$) and in those with impaired glucose tolerance ($r=0.59$, $p<0.01$), but not in the diabetic patients ($r=-0.044$). However, the correlation was significant when all the subjects were considered ($r=0.48$, $p<0.05$).

No clear relationship was observed between age and HbA_1 levels ($r=0.20$, not significant); similarly, sex appeared of little importance in determining the HbA_1 level ($r=0.21$).

Discussion

The results of this study confirm that HbA_1 levels are higher in diabetic subjects than in people with normal glucose tolerance [15, 16]. In addition, HbA_1 values were significantly higher in subjects with impaired glucose tolerance than in normal subjects. This increase in HbA_1 concentrations might be due to the hyperglycaemic peaks after carbohydrate consumption in subjects with impaired glucose tolerance. Because these peaks may occur for only a few hours a day, the HbA_1 increase was slight but significant compared with the normal subjects. However, half of those with impaired glucose tolerance had HbA_1 values in the normal range. These normal HbA_1 determinations cannot be explained by differences in plasma glucose response to the oral glucose load compared with the other 14 subjects with elevated HbA_1 values. These findings seem to suggest that subjects with impaired glucose tolerance are an heterogeneous group with respect to HbA_1 levels. The degree of discordance between the results of the two tests is not surprising, for conceptually, they measure quite different aspects of glucose metabolism. Thus, whereas one, the oral glucose tolerance test, is potentially capable of detecting impairment of physiological reserve before overt decompensation, the other, HbA_1, should reflect only changes in ambient diurnal blood glucose concentrations [17]. Similarly, if early decompensation of blood glucose control were characterized by exaggerated glycaemic swings without a change in the mean value, one would not expect to see a change in HbA_1, but this would most probably be detectable on oral glucose tolerance testing. The positive correlation in diabetic patients between HbA_1 values and fasting plasma glucose but not the glucose level 2 h following an oral glucose load is in keeping with this concept. Finally, whereas the oral glucose tolerance test provides a measure of glucose homeostasis at the time of the test, HbA_1 values are thought to provide an integral of the antecedent blood glucose concentration [18]. All of these reasons suggest that there are adequate grounds to expect discrepancies between the results of the two tests. However, there are several findings showing that the oral glucose load has a reduced validity as a reference test. Thus, the test is poorly reproducible [19], the validity of the diagnosis of mild forms of diabetes by these means is highly controversial [20], and the concordance in diagnosis of diabetes with the other major test of glucose tolerance, the intravenous glucose tolerance test, is poor. In addition, its ability to predict either the later onset of overt diabetes or the increased prevalence of diabetic complications is scanty to the extent that some have advocated that the diagnosis of diabetes is not warranted unless the fasting blood glucose is also substantially elevated [20]. Importantly for the present study, therefore, the potential value of HbA_1 measurements in the diagnosis of diabetes cannot be decided by comparison with oral glucose load results alone [21]. Prospective trials of its use for this purpose will be necessary.

With these limitations in mind, this study provides evidence that: (a) HbA_1 values are influenced by slightly reduced carbohydrate tolerance; (b) subjects with impaired glucose tolerance are heterogeneous in terms of HbA_1; (c) HbA_1 measurement is more specific in detecting subjects with carbohydrate intolerance than the oral

glucose load, while the oral glucose tolerance test might be more sensitive; and (d) HbA_1 detection may provide a useful test for improving the specificity of the oral glucose load to select and to follow-up subjects with impaired glucose tolerance.

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Received: 7 June 1982
and in revised form: 1 December 1982

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