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Originals

Glycosylated Haemoglobin in Renal Failure

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Summary. The level of the glycosylated haemoglobin HbA_{1c} was measured in (1) subjects with normal renal function, (2) patients with renal failure and (3) patients on intermittent haemodialysis. In 60 subjects with normal renal function but with a varying degree of glucose tolerance, there was a significant correlation between HbA_{1c} and fasting blood-glucose. In 20 patients with renal failure the mean value of HbA_{1c} was 6.6 ± 1.3% (mean ± SD) whereas in 17 subjects with normal renal function, but with the same degree of glucose tolerance, this value was 4.7 ± 0.9%. In 30 patients on intermittent dialysis the mean level of HbA_{1c} was 6.3 ± 1.5%. This level did not fall after 3 months of dialysis with a glucose-free fluid. In both groups of patients with renal failure there was no correlation between HbA_{1c} and fasting blood-glucose. – It is concluded that renal failure itself causes an increase in HbA_{1c}.

Key words: HbA_{1c}, glycosylated haemoglobin, uraemia, haemodialysis, glucose metabolism.

The level of the glycosylated haemoglobin HbA_{1c} reflects the mean blood-glucose level during the erythrocyte life span and has proved to be a useful parameter of diabetic control [1–4]. We have drawn attention to the elevated levels of HbA_{1c} in non-diabetic patients on intermittent haemodialysis [5], but we did not find a correlation between the HbA_{1c} levels and the blood-glucose levels after dialysis in these patients. Stanton et al. [6] also reported raised values of glycosylated haemoglobins in patients on intermittent dialysis, suggesting that the frequently occurring hyperglycaemia in these patients could explain the increase of HbA_{1c}. Data from patients with renal failure not undergoing dialysis were not given.

Knowledge of HbA_{1c} in patients with renal failure could be important. Thus a high level of HbA_{1c} in patients with renal failure could have implications for assessment of diabetic control in patients with diabetic nephropathy. We have therefore investigated HbA_{1c} levels in patients with normal renal function, in patients with impaired renal function and in patients on intermittent haemodialysis, and related these levels to glycaemic status.

Patients and Methods

Three groups of subjects were studied.

Group 1 consisted of 60 subjects (39 women and 21 men, mean age 35 years, range 13–75 years) with normal renal function (serum creatinine concentration < 100 μmol/l), but with a varying degree of glucose tolerance, including patients with newly discovered, overt diabetes. In these subjects there was no evidence of other diseases. HbA_{1c} and fasting blood-glucose levels were measured in all subjects. In 17 subjects of this group (12 women and 5 men, mean age 44 years, range 13–67 years), without overt diabetes, an oral glucose tolerance test (OGTT) was performed.

Group 2 consisted of 20 patients with renal failure (10 women and 10 men, mean age 54 years, range 38–73 years), who had not yet been treated with any form of dialysis. Creatinine clearance was less than 10 ml/min in 10, between 10 and 20 ml/min in 6 and between 20 and 30 ml/min in 4 patients. In none of these patients had creatinine clearance changed more than 10% during the 3 months preceding this study. There were no cases of overt diabetes. Measurement of fasting blood-glucose and HbA_{1c} levels and an OGTT were performed in all subjects of this group.

Group 3 consisted of 30 patients with renal failure who were on intermittent haemodialysis (11 women and 19 men, mean age 42 years, range 21–70 years). Dialysis took place twice a week for six to nine h against a fluid containing 5 g glucose/100 ml. In all patients fasting blood-glucose and HbA_{1c} levels were measured. In six patients of this group these measurements were repeated after dialysis against a glucose-free fluid for more than three months.

None of the subjects was on a calorie-restricted diet, insulin or oral hypoglycaemic drugs. All subjects were informed that they would participate in an investigation of glucose metabolism.

HbA_{1c} was determined by column chromatography on Bio-Rex 70, of haemolysates, according to Trivelli et al. [8], with minor

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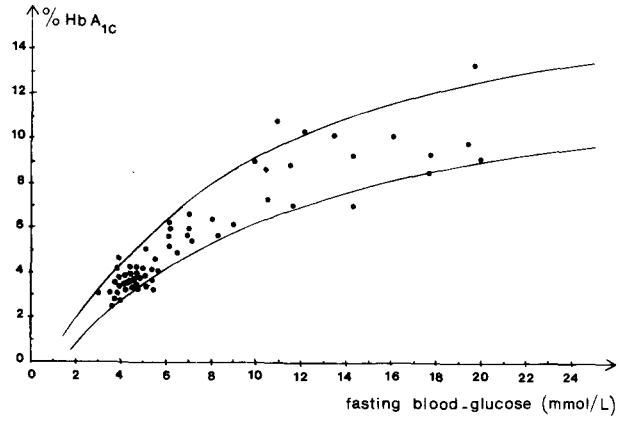

Fig. 1. Relation between fasting blood-glucose and HbA_{1c} in subjects with normal renal function (group 1). The parabolic function that fits best (r = 0.92) to these points is characterised by the equation: y (HbA_{1c}) = 4.08 $\sqrt{x(\text{glucose}) - 2.16}$ − 2.5 95% confidence limits are shown

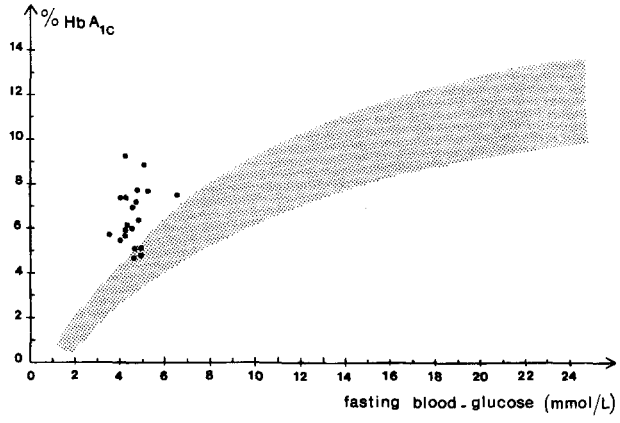

Fig. 2. Relation between fasting blood-glucose and HbA_{1c} in non-diabetic patients with renal failure (group 2). Shaded area encompasses range in subjects with normal renal function (95% confidence limits, see Fig. 1)

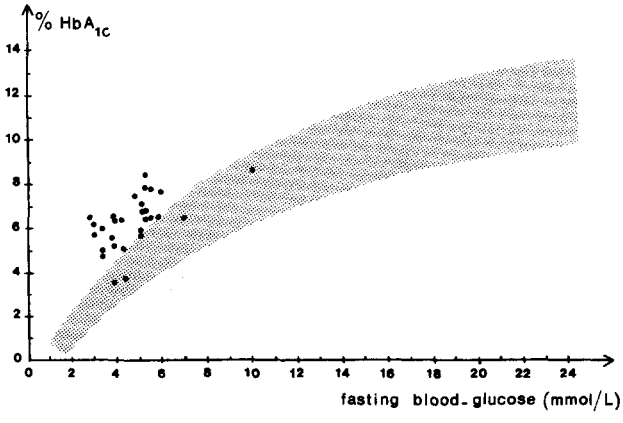

Fig. 3. Relation between fasting blood-glucose and HbA_{1c} in non-diabetic patients on intermittent haemodialysis (group 3). Shaded area encompasses range in subjects with normal renal function (95% confidence limits, see Fig. 1)

modifications [5]. The within-run coefficient of variation (C. V.) was 5.2% (n = 24) and the day-to-day C. V. was 6.7% (n = 28).

OGTT was performed by administering 50 g glucose after an overnight fast. Capillary blood samples were taken before and 30, 60, 90 and 120 min after ingestion of the glucose. The sum of the glucose values at 0, 30, 60 and 120 min was used as an estimate of glucose tolerance [7].

Blood glucose was measured enzymatically (Boehringer Cat no 124001, GOD-PAP without deproteinisation). Creatinine and urea in serum were determined by automated continuous flow methods [9, 10]. Creatinine clearance was calculated from a nomogram [11].

Statistical comparisons of groups were made with Student's t-test and Wilcoxon's rank sum test. Results are given as mean ± SD.

Results

Relation between Fasting Blood-Glucose and HbA_{1c}

In subjects with normal renal function (group 1) the relation between the fasting blood glucose level and the percentage of HbA_{1c} was curvilinear (Fig. 1). A parabolic function best fits these points (r = 0.92).

In the 20 patients with renal failure of group 2, the mean HbA_{1c} was 6.6 ± 1.3%. The points relating fasting blood-glucose and HbA_{1c} in these patients are situated above the normal range (Fig. 2) and differ significantly from normal ($p < 0.01$).

The mean HbA_{1c} in 30 patients on haemodialysis (group 3) was 6.3 ± 1.5%. As shown in Figure 3, this group also differs from group 1 ($p < 0.025$).

There was no significant difference between group 2 and group 3. In both groups there was no significant correlation between HbA_{1c} and fasting glucose ($r = 0.51$, $p > 0.05$).

Relation between Result of OGTT and HbA_{1c}

Mean HbA_{1c} and mean blood-glucose levels during the OGTT in patients from groups 1 and 2 are shown in Table 1. There were no significant differences in the mean blood-glucose between the two groups. However, the difference in mean HbA_{1c} was highly significant ($p < 0.01$).

There was no significant correlation between HbA_{1c} and any point of the OGTT, except for the fasting value in the patients of group 1.

Relation between HbA_{1c} and Glucose Content of Dialysis Fluid

In 6 patients on intermittent dialysis, fasting blood-glucose and HbA_{1c} were measured during dialysis against a glucose-containing fluid and after dialysis against a glucose-free fluid for at least three months. There was no significant difference between the

Table 1. HbA_{1c} (%) and blood glucose-values during an oral glucose tolerance test in subjects with normal renal function (from group 1) and in patients with renal failure (group 2)

		Blood-glucose (mmol/l)					
Patients	HbA_{1c}	0 (fasting)	30 min	60 min	90 min	120 min	"sum"[a]
Normal renal function n = 17	4.7±0.9[b]	4.9±0.7	8.3±2.1	8.3±3.0	7.2±3.0	6.0±2.6	27.6±7.8
Impaired renal function n = 20	6.6±1.3[b]	4.6±0.6	7.7±1.2	8.4±2.0	7.5±2.1	6.7±2.3	27.4±5.5

All values are mean ± 1 SD
[a] for calculation of sum see methods section
[b] $p < 0.01$

mean fasting glucose and mean HbA_{1c} before and after this period: glucose before 5.0 ± 1.3 and after 5.2 ± 0.9 mmol/l; HbA_{1c} before 6.1 ± 1.5 and after 6.3 ± 1.1%.

Relation between HbA_{1c} and Degree of Renal Failure

In group 2 there were 10 patients with a creatinine clearance of less than 10 ml/min (mean fasting blood-glucose 4.5 ± 0.4 mmol/l, mean HbA_{1c} 6.8 ± 1.3%) and 10 patients with a value between 10 and 30 ml/min (mean fasting blood-glucose 4.7 ± 0.8 mmol/l, mean HbA_{1c} 6.2 ± 1.3%). These subgroups were not significantly different in glucose tolerance or HbA_{1c} level. Furthermore, no significant correlations were found between HbA_{1c} and creatinine clearance ($r = 0.32$; $p > 0.05$), serum creatinine ($r = 0.09$; $p > 0.05$) and serum urea ($r = 0.17$; $p > 0.05$).

Discussion

In subjects with normal renal function a significant correlation was found between fasting blood-glucose and HbA_{1c} levels. This is in agreement with Graf and Porte [12] regarding normal subjects and untreated diabetic patients and the finding of Ditzel and Kjaergaard [13] in newly discovered diabetics. The parabolic relationship between fasting blood-glucose and HbA_{1c} supports the findings of several others [14, 15, 16] who suggest a saturable system of glycosylation of haemoglobin.

It is striking that no correlation was found between HbA_{1c} and oral glucose tolerance. This is in contrast to the findings of Santiago et al. [17] in subjects preselected because of postprandial hyperglycaemia. These workers found a significant correlation between the 1- and 2-hour plasma glucose values after oral glucose and HbA_{1c}. This apparent contradictory result is probably due to selection of a different patient population.

The situation in patients with renal failure is quite different. No correlation between fasting blood-glucose and HbA_{1c} could be demonstrated. Although the mean fasting blood-glucose and the results of the OGTT in our patients with renal failure are the same as in a group of 17 of our patients with normal renal function, the mean HbA_{1c} in patients with renal failure is significantly higher. We have not estimated blood-glucose throughout the day, but we assume that the two groups do not differ in this respect. Taking into account the shortened life span of erythrocytes in chronic renal failure [18] and the lower level of HbA_{1c} in young red cells [19], the HbA_{1c} levels in our patients with renal failure should have been lower than in our control group of patients with normal renal function if the blood-glucose level were the only determinant.

The level of HbA_{1c} in uraemic patients who are undergoing intermittent haemodialysis is similar to that in nondiabetics with renal failure. The high level of HbA_{1c} in patients dialysed against a glucose-free fluid suggests that this increased value is not the result of the glucose content of the fluid, but is the result of the impaired renal function in these patients.

Under normal conditions two factors determine the level of HbA_{1c} in the erythrocyte i. e. the glucose level in the blood in the previous weeks and the life span of the erythrocyte. Impaired glucose metabolism, may occur in about 50% of the patients with renal failure [20], but this did not play a major role in the formation of the glycosylated haemoglobin HbA_{1c}. A further possibility is that in uraemic blood some unknown compound attaches to HbA and is measured instead of authentic HbA_{1c}. In patients with renal failure, therefore, an increase in HbA_{1c} does not necessarily mean impaired glucose metabolism.

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