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Comparison of HbA_1 and Fructosamine in Diagnosis of Glucose-Tolerance Abnormalities

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Total glycosylated hemoglobin (HbA_1) and fructosamine were evaluated as screening tools for detection of glucose-tolerance abnormalities in 144 asymptomatic subjects undergoing a 75-g oral glucose tolerance test. Subjects were classified according to World Health Organization criteria as having normal (n = 78), impaired (n = 40), or diabetic (n = 26) glucose tolerance. We found good specificity for HbA_1 and fructosamine (100 and 97%, respectively) but low sensitivity (15 and 19%, respectively). At the intersection of the curves of sensitivity and specificity drawn from various thresholds of normality, both sensitivity and specificity were 75% for HbA_1 and 55% for fructosamine. Thus, neither HbA_1 nor fructosamine seems to be suitable for the diagnosis of mild abnormalities in glucose tolerance. *Diabetes Care* 13:898–900, 1990

The oral glucose tolerance test (OGTT) is widely used for diagnosis of diabetes and impaired glucose tolerance (1). Determination of glycosylated hemoglobin (HbA_1 or HbA_{1c}) and more recently of glycosylated total serum proteins (fructosamine) has been proposed as an alternative method of screening. The usefulness of these alternatives will only be found in longitudinal surveys, which will determine the relationship between these parameters and the risk of long-term complications. The aim of our cross-sectional study was to compare the values of fructosamine and HbA_1 for the purpose of diabetes screening with the OGTT as the reference method.

RESEARCH DESIGN AND METHODS

In this study, we included 144 consecutive subjects referred for screening of metabolic abnormalities. All were free of any signs or symptoms of overt diabetes mellitus. All subjects underwent a standard 2-h OGTT according to the World Health Organization (WHO) recommendations (1). Blood samples for HbA_1 and fructosamine determination were drawn at the same time as a fasting plasma glucose sample. Subjects were classified as having normal glucose tolerance (n = 78) when fasting and 2-h postload plasma glucose values were <7.8 mM. Impaired glucose tolerance (IGT; n = 40) was defined as fasting plasma glucose <7.8 mM and 2-h plasma glucose ≥7.8 and <11.1 mM. Fasting plasma glucose ≥7.8 mM and/or 2-h plasma glucose ≥11.1 mM was diagnostic for diabetes mellitus (asymptomatic diabetes; AD; n = 26). In the AD group, fasting plasma glucose ranged between 4.9 and 9.9 mM, with values ≥7.8 mM in 5 subjects. HbA_1 and fructosamine were also determined in a series of 10 consecutive patients with overt diabetes mellitus seen in our department at the beginning of the study.

Venous plasma glucose was determined by the glucose dehydrogenase method. Total HbA_1 was measured by the microcolumn method (Bio-Rad, Paris) with temperature control (2). Intra-assay and interassay coefficients of variation (based on 30 replicates) were 4.3 and 5.3%, respectively. Fructosamine was assessed as previously described (3) after adaptation for a centrifugal

analyzer (Rotochem IIa). Intra-assay and interassay coefficients of variation were 1.6 and 5.8%. Normal ranges (means ± 2SD) for HbA_1 (6.1 ± 2.4%) and for fructosamine (1.30 ± 0.48 mM) were established by measuring both variables in 53 nondiabetic control subjects with a normal 75-g OGTT according to WHO criteria (1).

Comparison of means between groups was performed by analysis of variance (4). If significant, the Tukey method was used for a posteriori tests. This method maintains global α-risk at a maximum of 5% and is one of the most conservative methods available. Diagnostic values of fructosamine and HbA_1 were assessed by calculating sensitivity and specificity. Plots of sensitivity and specificity were established for various thresholds of normality to choose the cut-off point leading to the best performance.

RESULTS

Plasma glucose, HbA_1, and fructosamine concentrations according to glucose-tolerance category are given in Table 1. Figure 1 shows the important overlap between the values of HbA_1 and fructosamine in the first three groups. In the AD group, HbA_1 and fructosamine values were both higher than the upper limit of the normal range in two subjects. HbA_1 alone was elevated in two subjects, and fructosamine alone was elevated in three subjects. In the group with overt diabetes, HbA_1 and fructosamine values were all higher than the upper limit of the normal range. Sensitivity and specificity of HbA_1 and fructosamine were calculated for the diagnosis of diabetes with the usual threshold of mean + 2SD. When the aim was to separate AD from IGT and normal glucose tolerance, HbA_1 sensitivity (15%) and fructosamine sensitivity (19%) were low, whereas specificity was high (100 and 97%, respectively). When the aim was to separate IGT and AD from normal glucose tolerance, HbA_1 and fructosamine sensitivities were even lower (6 and 12%, respectively), whereas specificity was 100%. When the 10 overtly diabetic patients were included for these calculations, HbA_1 and fructosamine sensitivity increased to 39 and 40%, respectively. Furthermore, when the AD group was eliminated from the sample so that all diabetic subjects had overt diabetes, HbA_1 and fructosamine sensitivity reached 100%. Among the 144 asymptomatic subjects, curves of sensitivity and specificity were established for various thresholds for normality. The cut-off point leading to the best performance for both specificity and sensitivity is at the intersection of the curves. For HbA_1, the intersection was at 6.7%, which is 0.5SD above the mean, and the specificity and sensitivity were 75%. For fructosamine, the intersection was 1.34 mM, very close to the mean, and the specificity and sensitivity were 55%.

DISCUSSION

We investigated the performance of HbA_1 and fructosamine for the diagnosis of diabetes and IGT with a view to their use in screening in developed countries, which concerns mainly asymptomatic subjects as in our study. We observed good specificity of HbA_1 and fructosamine, but clearly there is an unacceptably low sensitivity when mean + 2SD is chosen for upper limit of the the normal range. When 10 overtly diabetic patients were included in our series, sensitivity improved. This example demonstrates the favorable effect on the results when including patients with frank hyperglycemia. We also determined the threshold value giving the best sensitivity and specificity. With this method, we calculated a sensitivity and specificity of 75% for HbA_1 and of 55% for fructosamine. If we were to apply such a value to a screening program in a large town (1 million inhabitants) in a country with a 5% diabetes prevalence, there would be 12,500 false-negative and 237,500 false-positive results according to HbA_1 determination. The results obtained with fructosamine would be even worse. Previous studies based on patients with normal or near-normal fasting plasma glucose indicate that HbA_1 or HbA_{1c} determination performs poorly for diabetes screening (5–7). For Baker et al. (8), the fructosamine assay appeared to be a useful index, but patients with frank fasting hyperglycemia were included in their experiments. The results of two other studies without such

TABLE 1
Concentrations according to glucose-tolerance category

	Glucose tolerance		Diabetes	
	Normal	Impaired	Asymptomatic	Overt
n	78	40	26	10
Plasma glucose (mM)				
Fasting	5.3 ± 0.7	5.7 ± 0.9*	6.9 ± 1.2	14.7 ± 2.9
2 h	5.7 ± 1.2	9.1 ± 0.8	12.7 ± 2.0	20.0 ± 6.2
HbA_1 (%)	6.2 ± 0.8	6.5 ± 0.7*	7.6 ± 1.7	15.0 ± 2.5
Fructosamine (mM)	1.20 ± 0.29	1.42 ± 0.34*	1.44 ± 0.37*	3.72 ± 1.30

Values are means ± SD, with *P* determined by analysis of variance.
*NS, $P < 0.001$ for all other comparisons.

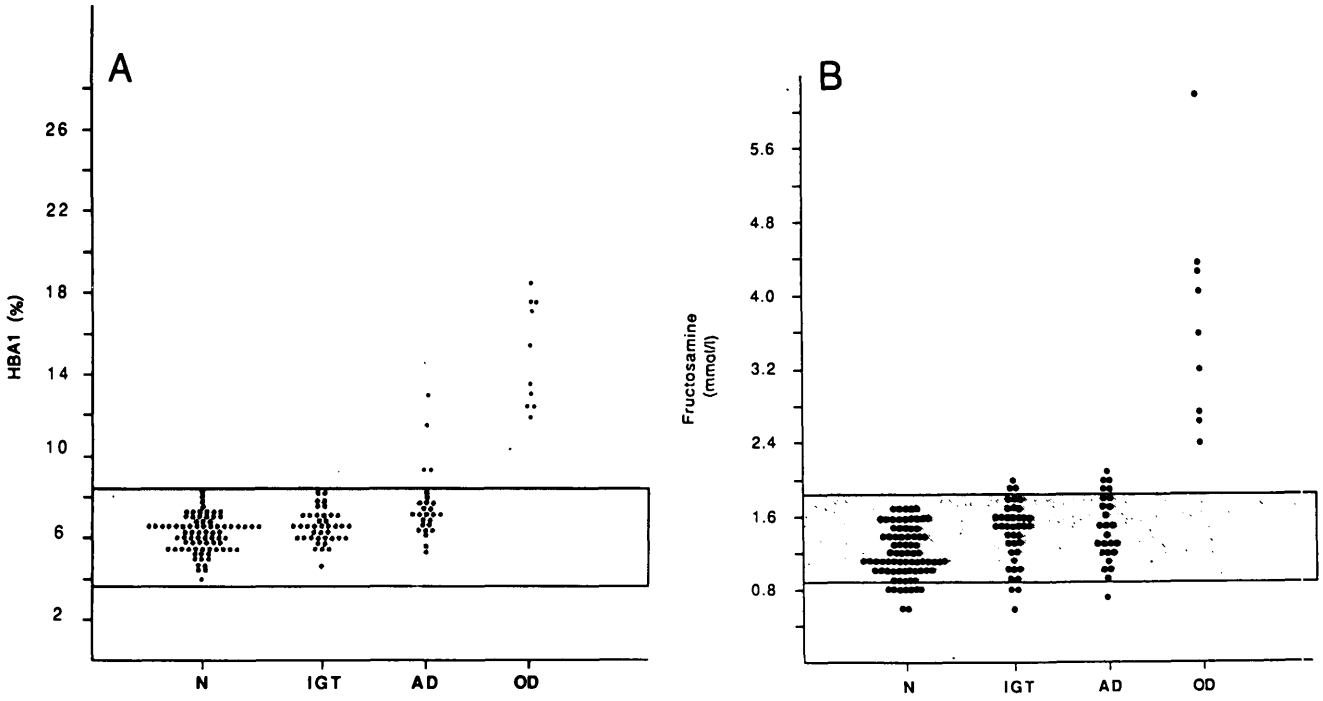

FIG. 1. HbA_1 (*A*) and fructosamine (*B*) levels in 78 subjects with normal glucose tolerance (N), 40 subjects with impaired glucose tolerance (IGT), 26 patients with asymptomatic diabetes (AD), and 10 patients with overt diabetes (OD). *Shaded areas*, normal range (mean ± 2SD).

recruitment bias are in agreement with ours (9,10). These results indicate that neither HbA_1 nor fructosamine is useful for diabetic screening when an OGTT is used as the reference method.

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