THE DECODE STUDY

Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe

B. BALKAU

SUMMARY - The current criteria for the diagnosis of diabetes used in France are now based on those published by the American Diabetes Association in 1997: fasting plasma glucose \( \geq 7.0 \text{ mmol/l (126 mg/dl)} \) (previously \( \geq 7.8 \text{ mmol/l (140 mg/dl)} \)), 2-hour glucose \( \geq 11.1 \text{ mmol/l (200 mg/dl)} \) following a 75g oral glucose tolerance test. However, while the American Diabetes Association recommended that the post charge test not be used, both the World Health Organisation and the French Language Association for the study of Diabetes and Metabolic diseases (ALFEDIAM) retained this test. The DECODE (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) study analysed the effect of these changes on the prevalence of diabetes, and whether the changes were justified by the mortality in the various glycaemic groups, using epidemiological data on close to 30,000 subjects from twenty European epidemiological studies. The prevalence of diabetes, using fasting rather than the 2-hour glucose concentrations (as had previously been recommended for epidemiological studies) resulted in changes in the prevalence of diabetes, an increase or a decrease, depending on the population studied. The fasting criteria tended to diagnose younger and more obese subjects than the 2-hour criteria. The subjects who would now be diabetic with the new fasting diagnostic criteria suffered a high mortality, similar to that of other diabetic subjects, thus the new criteria can be justified. However, the diabetic subjects who only have a post-charge diabetic hyperglycaemia (\( \geq 11.1 \text{ mmol/l (200 mg/dl)} \)), are now even less likely to be screened as diabetic, despite the fact that they have a risk of premature death of the same order as other diabetic subjects.

Key-words: diabetes mellitus, diagnostic criteria, mortality, oral glucose tolerance test.

RÉSUMÉ - L’Etude DECODE. Les critères diagnostiques de diabète utilisés en France sont ceux publiés par l’Association Américaine de Diabète en 1997: glycémie plasmatique veineuse à jeun \( \geq 7.0 \text{ mmol/l (126 mg/dl)} \) (auparavant \( \geq 7.8 \text{ mmol/l (140 mg/dl)} \)), glycémie à 2-heures \( \geq 11.1 \text{ mmol/l (200 mg/dl)} \) après une charge en glucose de 75g per os. Si l’Association Américaine de Diabète a recommandé que l’hyperglycémie provoquée par voie orale ne soit plus utilisée, par contre l’Organisation Mondiale de la Santé et l’Association du Langue Française pour l’Etude du Diabète et des Maladies métaboliques (ALFEDIAM) n’ont pas écarté cette épreuve. L’Etude DECODE (Diabete Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) a analysé l’effet de ces changements sur la prévalence de diabète et a étudié si le changement de seuil pour la glycémie à jeun était justifié en termes de mortalité quelle que soit la cause; les données épidémiologiques de 30,000 sujets de vingt études européennes ont été analysées. La prévalence du diabète, en utilisant la glycémie à jeun au lieu de la glycémie 2-heures post-charge (qui était auparavant recommandée pour les études épidémiologiques) a abouti à un changement des taux, qui diffère selon l’étude. La glycémie à jeun dépiste des sujets plus jeunes et plus obèses que ceux qui sont dépistés par la glycémie à 2-heures. La mortalité des sujets diabétiques suivant le nouveau seuil de la glycémie à jeun, est similaire à celle des sujets reconnus diabétiques suivant les anciens critères, ce qui peut aussi justifier ce changement de seuil. Cependant, les sujets ayant une hyperglycémie post-charge isolée \( \geq 11,1 \text{ mmol/l (200 mg/dl)} \) risquent de ne plus être dépistés comme diabétiques, et pourtant leur risque de décès est similaire à celui des autres sujets diabétiques.

Mots-clés : diabète mellitus, critères diagnostiques, mortalité, hyperglycémie provoquée par voie orale.
In 1997, the American Diabetes Association (ADA), after several years of discussion, published new criteria for the diagnosis of diabetes [1] to replace the World Health Organization 1985 criteria [2]. To diagnose diabetes in the absence of symptoms, the ADA lowered the cut-point for fasting plasma venous glucose from 7.8 mmol/l (140 mg/dl) to 7.0 mmol/l (126 mg/dl). Further, they recommended that the simplified oral glucose tolerance test (OGTT), with a measure of glucose two hours after an oral charge of 75g glucose, should not be used, even though they did retain the cut-point of 11.1 mmol/l (200 mg/dl) as a diagnostic criterion for diabetes [3]. The recommendation of the French Language Association for the study of Diabetes and Metabolic Diseases (ALFEDIAM) was that the two hour glucose remained useful, even if in clinical practice, the diagnosis of diabetes did not always require its measure. The ALFEDIAM also followed the change in the cut-point for the diagnosis of diabetes using a fasting glucose.

The choice of glucose cut-points for the diagnosis of diabetes were based primarily on results from epidemiological studies which showed that the prevalence and the incidence of diabetic retinopathy was increased for higher glucose concentrations [1]. In 1985 the cut-point for fasting glucose was fixed at a value higher that the value where the frequency of retinopathy increased, so that subjects who were not fasting were not wrongly diagnosed as diabetic [2]. The ADA in 1997 decided that the cost associated with the oral glucose tolerance test, in both time and money, was more important than a wrong diagnosis, especially as the OGTT was little used in practice. With this lower cut-point for fasting plasma glucose, the diagnosis of diabetes should thus be earlier, limiting the damage caused by hyperglycaemia.

The DECODE Study (Diabetes Epidemiology: Collaborative analysis of diagnostic criteria in Europe) was conceived by the European Diabetes Epidemiology Group (EDEG). The aims of this study were to evaluate:

- the effect of the new criteria on the prevalence of diabetes in European populations, as the ADA had only described the effect in an American population [1].
- the mortality, from all causes and from cardiovascular disease according to the glucose categories defined either by fasting or by 2-hour glucose.

Analyses are based on 20 European epidemiological studies, about 30,000 men and women. Several articles have already been published from this study, and others are in preparation [5-11].

### THE DECODE STUDY

The first analysis from the DECODE study included 17,881 men and 8,309 women; 13 of the studies were population based, three occupation-based [5, 6]. France was well represented: 40% of the men came from the Paris Prospective Study [12] and 11% from the TELECOM Study [13], while 23% of the women were from the TELECOM Study.

Overall, 3.7% of the subjects were already known to have diabetes. If only a glucose level ≥ 11.1 mmol/l (200 mg/dl) 2-hours post charge were used to diagnose diabetes, as was the case in many of the epidemiological studies which used the 1985 WHO recommendations [2], the prevalence of newly diagnosed diabetes for all of the studies combined, was 7.2%. If diagnosis was based only on a fasting glucose level ≥ 7.0 mmol/l (126 mg/dl) the prevalence was 7.7%, an increase of 0.5%. However, even if this overall difference was small, there was a great diversity between studies, with a difference in prevalence which varied between 13% and -4%.

Amongst the 1517 subjects newly diagnosed as diabetic (either on the fasting or the 2-hour glucose criteria [3]), only 27% had both a fasting and a 2-hour diabetic hyperglycaemia, 40% had an isolated diabetic fasting glucose and 31% had an isolated 2-hour hyperglycaemia (Table I). The subjects diagnosed diabetic by an isolated fasting hyperglycaemia were younger and more obese than those diagnosed diabetic because of an isolated 2-hour hyperglycaemia. The title of the first article reflects this observation — “The diagnostic criteria — do they change the diabetic phenotype?”[5].

The second article discussed a strategy for screening for subjects with an isolated 2-hour glucose ≥ 11.1 mmol/l (200 mg/dl). If all the subjects with an impaired fasting hyperglycaemia (6.1-6.9 mmol/l (110-125 mg/dl)) were given an OGTT, this would involve 11% of the population (Table II) but only 40% of the diabetic subjects with an isolated post challenge diabetic glucose level would be detected, with all those not diagnosed having a normal fasting glucose < 6.1 mmol/l (110 mg/dl).

In parallel with diabetes, diagnosed either by the fasting or the 2-hour glucose, the intermediate groups of impaired glucose intolerance (2-hour glucose between 7.8 and 11.0 mmol/l (140-199 mg/dl)) and impaired fasting glucose (fasting glucose between 6.1 and 6.9 mmol/l (110-125 mg/dl)) did not involve the same subjects [7] (Tables II and III).

### EARLY MORTALITY ACCORDING TO FASTING AND 2-HOUR GLUCOSE LEVELS

The mortality study included approximately 18,000 men (7,000 from the Paris Prospective Study) and
When the subjects were classed according to the 2-hour glucose, the relative risk, in comparison with subjects with a normal 2-hour glucose level ($\geq 7.8$ mmol/l (140 mg/dl)) was 2.1 for the diabetic subjects, 1.5 for the impaired glucose tolerant (Table IV). When the subjects were classed according to fasting glucose, the relative risk for the diabetic subject was 1.9 with the former criteria ($\geq 7.8$ mmol/l (140 mg/dl)) and 1.7 for the subjects who would become diabetic with the new criteria (7.0 to 7.7 mmol/l (126 to 139 mg/dl)) (Table V). These relative risks did not differ significantly, justifying the lowering of the cut-point for the definition of diabetes. The cumulative mortality curves also show that the subjects with an impaired glucose tolerance had a mortality between that of the diabetic subjects (as defined by their 2-hour glucose) and the subjects with a normal glucose level (Fig. 1). For the subjects with an impaired fasting glucose, their mortality curve was closer to that for the subjects with a normal glucose level, than to that of the subjects diabetic on fasting glucose concentrations.

For the subjects diabetic according to the 2-hour glucose, the relative risk depended little on the fasting glucose (Table VI); the group with an isolated post-charge hyperglycaemia had a high risk of premature death, twice that of subjects normo-glycaemic on the same criteria. In fact, mortality was determined by the 2-hour glucose category: after adjustment for the 2-hour glucose concentration, the fasting glucose category was no longer predictive of mortality.

The diabetic subjects with an isolated post-charge hyperglycaemia, have been more closely studied in...
the subjects aged between 60 and 79 years [9-11]. For diabetic subjects, the relative risk of death, in comparison with the non-diabetic subjects (fasting glucose < 7.0 mmol/l (126 mg/dl) and 2-hour glucose < 11.1 mmol/l (200 mg/dl) was 1.8 with little difference between the three groups of diabetic subjects: those already known as diabetic, those diagnosed diabetic on the fasting glucose or those diagnosed by an isolated post-charge glucose.

**Table V.** Relative risks of death in comparison to subjects with a normal fasting glucose concentration (< 6.1 mmol/l (110mg/dl)) after an average follow-up for death of 7.3 years. Relative risks are adjusted for sex, age and the study [8]. Analysis of 24809 subjects not known as diabetic from the DECODE Study.

<table>
<thead>
<tr>
<th>Fasting glucose mmol/l (mg/dl)</th>
<th>Relative risk of death</th>
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<tbody>
<tr>
<td>Diabetic ≥ 7.8 (≥ 140)</td>
<td>1.9 (1.5-2.5)</td>
</tr>
<tr>
<td>Diabetic 7.0-7.7 (126-139)</td>
<td>1.7 (1.3-2.1)</td>
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<td>Impaired fasting glucose</td>
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<tr>
<td>6.1-6.9 (110-125)</td>
<td>1.2 (1.04-1.4)</td>
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<td>Normal &lt; 6.1 (&lt; 110)</td>
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**Table VI.** Relative risks of death in the 850 subjects diagnosed as diabetic by the 2-hour glucose concentration (= 11.1 mmol/l (200 mg/dl)) in comparison with the subjects normal according to both fasting (< 6.1 mmol/l (110 mg/dl)) and 2-hour glucose concentrations (< 7.8 mmol/l (140 mg/dl)) after an average follow up of 7.3 years. Relative risks adjusted for sex, age and the study [8]. Analysis of 24809 subjects not known as diabetic from the DECODE Study.

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<td>Normal &lt; 6.1 (&lt; 110)</td>
<td>2.0 (1.5-2.8)</td>
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**OTHER RESULTS IN PREPARATION**

Other analyses on this large cohort of subjects are underway, on the causes of death (in particular cardiovascular causes), on mortality as a function of glucose concentrations and on the group of subjects with isolated post-charge hyperglycaemia.

**CONCLUSIONS**

As screening for diabetes is largely based on fasting glucose concentrations, with the lowering of the fasting glucose cut-point, the number of diabetic subjects requiring care must increase. This change in cut-point is justified as the death rate for subjects with a fasting glucose between 7.0 and 7.7 mmol/l (126 to 139 mg/dl) is similar to that of subjects diagnosed diabetic by the previous cut-point (≥ 7.8 mmol/l (140 mg/dl)).

With the new recommendations, the oral glucose tolerance test, currently little used in practice, will be
even less used in the future, and is likely to be completely abandoned. This will mean that those subjects diabetic on both the fasting and the 2-hour criteria will not be able to be targeted with a more intensive care, even though they are at a higher risk of premature death that diabetic subjects diagnosed only on the fasting glucose concentration. However, it is more troubling that those subjects diabetic because of an isolated post-charge glucose, will no longer be treated, despite their higher risk of early death in comparison to subjects diabetic on the fasting glucose criterion.

REFERENCES

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