What can the clinician expect from the laboratory in terms of diagnosis and management of diabetes?

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Diabetes has become a major global public health problem. The reasons for the fast expansion of this pandemic is partly to be found in urbanisation and a general acceptance of so called "Western Life Style". The patients suffering from this disease are exposed to the risk of very serious complications. These are, however, avoidable if the patients are given appropriate care. The disease shortens life expectancy by about 10 years and even more if the disease has had an early debut. The concept of diabetes contains two very different pathological entities, diabetes type 1 and diabetes type 2, both having in common the chronic elevation of the blood glucose concentration and the risk of complications related to the hyperglycaemia.

TYPE 1 DIABETES

Type 1 diabetes is the less frequent than Type 2: about 10% of the total number in the western world. The global prevalence is from 0.25% in Great Britain. This type preferentially affects young adults but sometimes also occurs in children. There are great regional differences in incidence. The annual incidence in Europe, before the age of 16, varies between 40•2 and 3•2 per 100 000 inhabitants, with a pronounced north-south gradient.

Physiopathology

Type 1 diabetes is an autoimmune disease. The islets of Langerhans in the pancreas, containing the ß-cells that specialise in the production of insulin, is the site of an inflammation which eventually will lead to their irreversible destruction.

There is a genetic predisposition for this disease and it is significantly more frequent in subjects carrying the haplotypes HLA DR3 and DR 4. Subjects carrying HLA Dq b-57 ala/val are at risk whereas the HLA Dq b-asp has a protecting role. The possible benefit of the research on these markers has so far not been put to practicable use. But, on the other hand, it has been of great interest for epidemiological studies. The role of the genetics in the occurrence of the disease is secondary: as shown by the weak concordance for this disease in homozygous twins, <30%, in contrast to the situation for diabetes, type 2.

Triggering environmental factors, are ill understood, but seem to play a decisive role; e.g. it has been shown that the occurrence of type 1 diabetes can be linked to coxacki B4 viral infection or to the ingestion of cow's milk before the age of two months. The proposed explanation is that there exists an antigenic kinship between certain antigenic constituents of the ß-cell and these infectious or alimentary agents: between the epitopes of glutamic acid decarboxylase (GAD), a constituent of the ß cell, and the coxacki B4 virus or the islet cell antigen, ICA 69, and the albumin of cow's milk. The normal immunological rejection of such uninvited guests, infectious or alimentary, may in certain genetically predisposed persons result in a chronic pathological auto-immune reaction which may, several years later, when 90% of the ß-islet tissue is destroyed result in the clinically overt phase of the disease.

Clinical manifestations

The patients suffers, apparently unexpectedly, from an intensive increase of the blood glucose concentration which provokes polyuria, thirst, loss of weight followed by acidosis and coma. At this stage the diagnosis is evident and a fasting blood glucose concentration well above 11 mmol/L (2 g/L) only confirms the diagnosis.

The signs of this auto-immune aggression can be noticed in the blood at an early stage well before the clinical phase in the shape of antibodies; anti-islet tissue (ICA), anti-insulin (IIA), anti-tyrosinephosphatase (IA2) and above all anti-GAD, the earliest detectable antibody (Fig 1). Further research in this field may be of interest in two situations: in discovering people at risk for developing type 1 diabetes. This would only be of interest if there was a specific immunomodulating treatment available, which is effective and not iatrogenic and capable of interrupting the auto-immune disease at such an early stage that the main part of the ß-islet tissue would be preserved. This means it has to instituted well before the clinical stage after which it is definitely too late. This type of treatment is at present not available. But several clinical trials are under way (ant-CD 3, DIAPEP 277).

The research on these markers has an interest for the individualisation of LADA or slow type 1 diabetes. This type of diabetes presents itself in the beginning as a type

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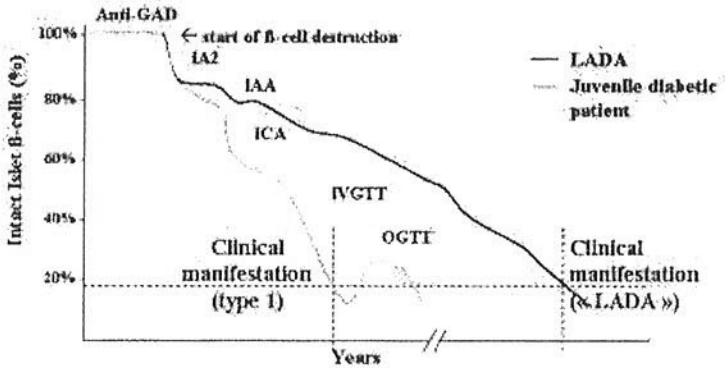

Figure 1
Type 1 Diabetes: sequence of immunologic and metabolic index

2 diabetes but transforms rapidly, during a few years, into a stage of underproduction of insulin and requires an early treatment with this hormone. Among 1360 subjects participating in the UKPDS and tested at the time of diagnosis, 11•8% showed the presence of anti-GAD and 7•8% anti-islet cell with variable concentrations (1).

The treatment of type 1 diabetes

In the clinical phase of the disease the therapeutic strategy is aimed at preventing acute metabolic accidents like acidosis and also preventing late-occurring chronic complications: complications connected to the retinal or renal microangiopathy or neuropathy. But also non-specific complications, frequently occurring in diabetics, like peripheral macroangiopathy or coronary angiopathy. It generally takes about ten years of badly controlled blood glucose concentration to create these complications. There is, however, a pronounced individual variation, which in the case of at least the nephropathy is probably connected to genetic factors that are still poorly known.

The lesson learned from the DCCT

The multicentre prospective study by the Diabetes Control and Complication Trial (DCCT) (2) published in 1993 showed that intensive insulin treatment could reduce the appearance of specific diabetes complications or at least slow their evolution. This study was performed on 1441 type 1 diabetic patients, half of them not suffering from retinopathy and the other half showing a mild retinopathy. The patients were treated for 1 - 15 years before they were randomly divided into two groups.

The first group was treated in a conventional way (at that time) with one to two injections per day, and self-monitoring of the blood or urine glucose concentration and with the goal of the absence of functional signs of the disease.

The second group was treated in a more aggressive way with three to four injections per day or an external pump (40% of the subjects at the time of the study); at least four blood glucose concentration controls per day; daily adjustment of the insulin dose; monthly consultation with specialists; and interactive telephone contacts. This treatment brought the mean HbA1c down to less than 7•5% with the goal set at reaching the normal range (<6•05%). The mean HbA1c of the conventionally treated patients remained at about 9%. There was a reduction of the adjusted mean risk of developing retinopathy by 76% in the intensively treated patients in the primary prevention group and its progression was reduced by 54% in the patients treated in the same way in the secondary prevention group. Comparable results were obtained for nephropathy and neuropathy.

The DCCT has in this way clearly shown that the appearance of diabetes-specific complications is directly correlated with the HbA1c percentage. This will consequently be the key test to follow and adjust the therapy in these patients (Fig 2). This study has also shown that there is a price to pay for obtaining a normal glucose concentration; the appearance of severe hypo-glycemia is inversely correlated to the HbA1c percentage (Fig 3). The use of ultra-rapid insulin analogues (and soon the slow analogues) and the more frequent use of insulin pumps, should, at least in theory, permit the use of intensive therapeutic schedules of the type basal bolus with insulin therapy functionally adapted to food intake. This therapeutic schedule ought to make it easier to obtain good glycaemic control, i.e. the HbA1c at less than 7% and also a lower risk for hypoglycaemia.

In practice, due to the lack of consensus regarding therapeutic principles, and probably also the lack of human resources for education and intensive follow-up of these patients, the situation will stay heterogeneous and not always satisfactory even in those countries that are blessed with a strong public health infrastructure. Thus, a recent French survey showed that in France less than 1/3 of the patients suffering from type 1 diabetes had HbA1c at less than 7•5% even though 36 different insulin schedules were utilised and without showing any correlation between number of injections and HbA1c.

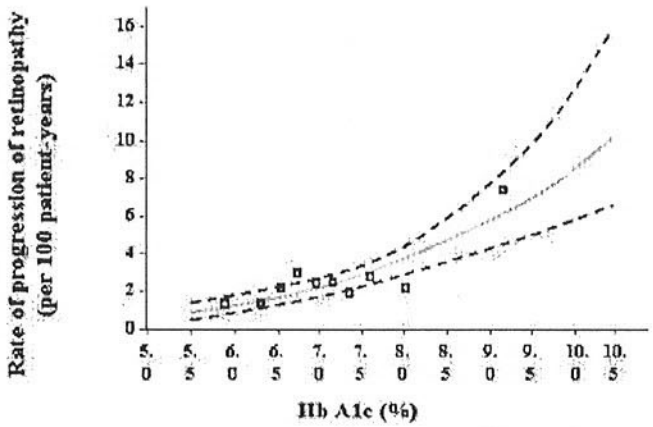

Figure 2
The DCCT: relation between mean HbA1c and rate of progression of retinopathy (per 100 patient-years)

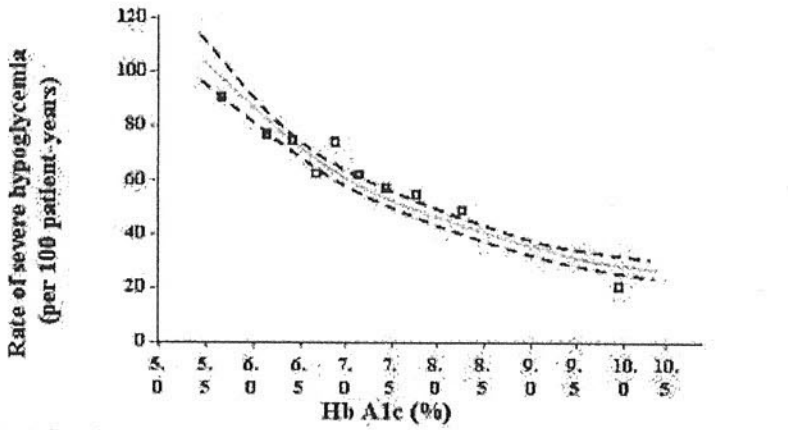

Figure 3
The DCCT: the prince to pay for "Good" glycemic control

TYPE 2 DIABETES

Type 2 diabetes poses radically different problems

Pathophysiology

Three mechanisms compete in this disease to increase the hyperglycemia: peripheral insulin resistance leading to a diminished muscular glucose up-take, an increased hepatic glucose production which is the principal reason for the fasting hyperglycaemia at the end of the night and, lastly, diminished insulin production. All these anomalies deteriorate progressively with time, resulting in an incapacity to withstand the insulin resistance and the progressive aggravation of the metabolic disorder. The precise origin of these metabolic anomalies is not known. They are clearly "genetically programmed": the concordance for type 2 diabetes is more than 90% in homozygous twins. The history of this type of diabetes is clearly familial and this is even more evident if the disease affected the parents at a young age. The gene, or rather the genes, responsible are not known, (except perhaps Capsain-10). But it is assumed that type 2 diabetes is genetically heterogeneous involving a few genes, which suggests heterogeneity in the clinical phenotype. This disease is thought to be provoked by a combination of several genetic variants, where none of these alone is sufficient to produce the disease. It is very possible that these individual genes are not pathogenic on their own. The genes involved could be genes of "energy storage" and type 2 diabetes could be induced by "thrifty genotypes": genes favourable in an ancestral situation of severe famine and turned unfavourable in a situation of food in surplus and physical idleness leading to obesity and later diabetes.

Environment factors

There are, however, some factors that play a major role in the genesis of the disease: the prevalence of type 2 diabetes in the Japanese living in Japan is not higher than 1% but increases to 10% if the same ethnic group moves to Hawaii or to the west coast of the USA adopting the so called "American way of life" with food containing a large intake of glucose and lipids and little physical activity. The same phenomenon is observed with the Chinese living in China (1•6%) or living on island of Mauritius (13•1%) and the same phenomenon has been described in several analogue situations. The role of these genetic and environment factors is well illustrated by the great difference in the prevalence of the disease in ethnic groups living in the United States, genetically different but living under the same circumstances with over-eating and reduced physical activity (Fig 4).

An other important environment factor is the increased life expectancy as the prevalence of this type of diabetes increases with age.

Thus, the fact that the population is getting older in the "developed countries" as well as in many "developing countries", the universal urbanisation with a sedentary way of life with little physical activity and eating foods rich in lipids and refined sugar can well explain the alarming global increase of the diabetes pandemic. The number of diabetics was estimated to 145 millions in the year 2000 and is expected to surpass 300 millions in the year 2025. This expansion is found principally in the 45-60 year age group in the "developing countries" and in the age group > 65 in the "developed countries" (Fig 5).

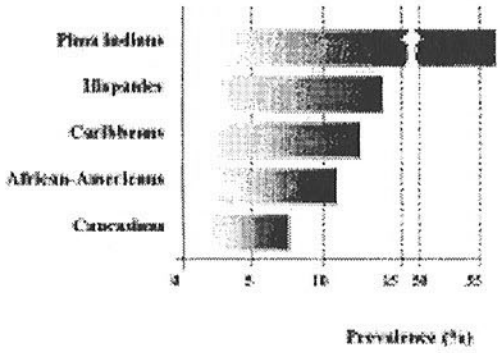

Figure 4
Prevalence of type 2 diabetes in USA

Clinical manifestations of type 2 diabetes

The diagnostic criteria are given in Fig 6. The early clinical picture of this disease is rather treacherous as, in contrast to type1diabetes, the increase in hyperglycemia is very slow and the patients can stay unsymptomatic for several years. If there is no screening program for diabetes it may well happen that the diagnosis is not made before the appearance of the cardinal symptoms like (thirst, polyuria, and loss of weight) and when the fasting blood glucose concentration is above14 mmol/L (2•5 g/L). It may well be that the clinical diagnosis is not made before 10 years after the biological first appearance. In that situation diagnosis is often made at the occurrence of micro-or macro vascular complications. In the United Kingdom Prospective Diabetes Study (UKPDS) 50% of the patients had at least one complication at the time of diagnosis! In order to make the diagnosis as early as possible before the complications are overt the checking, on at two occasions, if the fasting plasma glucose concentration is above 7•0 mmol/L is of great importance. Unfortunately there is no international consensus about the rules for a systematic screening procedure. However, it is certain that that subjects having a family history of diabetes run a big risk as well as obese people or those having waist/hip ratio >0•8 for women and >1 for men. The same holds true for women having a history of gestational diabetes. In certain ethnic groups this risk is considerable where people just over 60 years of age have the same prevalence as the

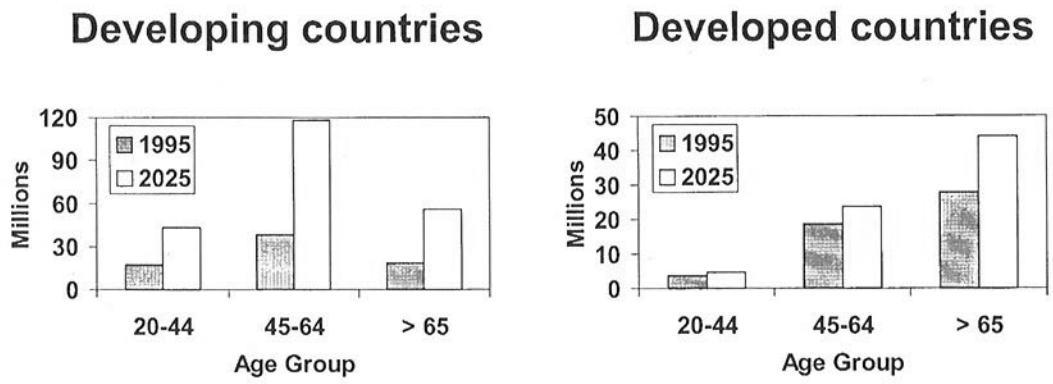

Figure 5
Diabetes worldwile: an epidemic. Number of people with diabetes per age group. Total numbers are 1985: 30 000 000; 2000: 145 000 000; 2025: 300 000 000

- *Diabetes if*
- Fasting plasma glucose (FPG) > 7.4 mmol/l (126 mg/dl)
- Or 2 h after 75 g glucose per os (OGGT) > 11.1 mmol/l (200 mg/dl)
- *Impaired glucose tolerance (IGT) if*
- OGGT–2h 7.8 to 11.1 mmol/l (140 to 200 mg/dl)
- *Impaired fasting glycaemia (IFG) if*
- FPG 6.1 to 7.0 mmol/l (110 to 126 mg/dl)
- *Normal if*
- FPG < 6.0 mmol/l (110 mg/dl)
- And OGGT-2h < 7.8 mmol/l (140 mg/dl)

Figure 6
Diabetes: new diagnosis criteria (ADA, 1997; WHO, 1998)

aged. The age when to begin a screening procedure or the frequency of sampling is so far not defined.

Subjects having a blood glucose concentration below the threshold defining diabetes (Fig 6) but having a value above the mean or slightly higher are those who run the highest risk of developing diabetes. The DPP3 study showed that 30% of the patients having a fasting plasma glucose concentration of between 5•3 and 7•0 mmol/L (0•95 and 1•25 g/L) and between 7•8 and 11•0 mmol/L (1•40 and 1•99 g/L) after glucose load developed diabetes within the next three years. The same study showed that if you could detect these subjects through a simple blood sample and modifying their "life style" one could reduce the incidence by 58% during the three year period.

The treatment of type 2 diabetes, the lesson learned from UKPDS

The UKPDS1 consists of 5000 patients suffering from a recently diagnosed type 2 diabetes. These patients were randomly grouped into two groups. One group treated with rather slack therapeutic objectives and the other treated with strict therapeutic goals.

This study demonstrated two fundamental facts that are essential to know about the effective treatment of type 2 diabetes.

- A reduction of 0•9% of the group mean value for HbA1c in the strictly treated group resulted in a 21% reduction of retinopathy during a 10 year period, a 33% reduction of nephropathy and there was evidence of 16% reduction of coronary infarcts. There exists a correlation between the appearance of micro- or macro-vascular complications and the period mean HbA1c value.
- Each of the drugs used initially (insulin, sulfonylurea, or metformin - for the obese) in single drug therapy failed, after a transitory effective phase, without one being better than the other in controlling the glycaemia. This phenomenon was parallel to the diminishing insulin secretion.

The therapeutic strategy for type 2 diabetes should evidently be a strategy in which new therapeutic modes/agents are added whenever the glycemic goals are not achieved: the first step based on diet and physical activity, after that Metformin or Sulfonylurea is added, then both together and then perhaps a tri-therapy with ascarbose or thiazolidinedione (no consensus). As a final step a change to insulin and to begin with a mixed treatment with insulin NPH at bed time and then after a few years when this mixed treatment fails one can use treatment with several injections per day and stop of oral anti-diabetics using therapeutic schedules very similar to those used in the treatment of type 1 diabetes (no consensus).

Glycaemia goals

There exist several rather similar national and international recommendations. The French National Agency for Evaluation, ANAES, recommends an optimal threshold value for HbA1c of 6.5% (with a normal range of < 6%). This is very ambitious with the aim of eliminating the diabetic complications. The treatment must be modified if the HbA1c is above 8%. In the interval between these two levels, the treatment should be strengthened in accordance with the expected advantages and disadvantages.

The value of HbA1c is the decisive parameter for deciding the therapeutic course to be taken by the physician. This makes it necessary that the result is correct, reproducible and comparable to other laboratories. Nevertheless the standardisation of this test is not always realised; in France in 1999 the inquiry DIABEST made it clear that there were at least 28 different standards, 56% of upper reference ranges given were higher than 6%.

The treatment of type2 diabetes is not based only on the blood glucose concentration but includes also the active consideration of other vascular risk factors.

- High blood pressure is present in more than 50% of the patients. The UKPD study showed that the active treatment of this complication gave a better result on morbidity/ mortality in cardiovascular complications than correction of the hyperglycaemia. The therapeutic goals must be stricter for these patients as compared to a non-diabetic population (running a lower risk of cardio-vascular disease). A number of very similar recommendations have been published. We keep to the ANAES which recommends the resting blood pressure should be below 140/80 mmHg.
- Type 2 diabetes is very often associated with dyslipidaemia. The serum LDL cholesterol concentration ought to be kept below 1•30 g/L (primary prevention) or below 1•0 g/L (secondary prevention) by dietary restrictions or if necessary by drug therapy. Also the serum triglycerides, atherogenic in diabetics, should be kept at below 2 g/L (primary prevention) or below 1•5 g/L (secondary prevention) by dietary restriction or eventually with the addition of fibrates.
- all this should be coupled to fighting smoking and sedentary life style.

Paying this price it may be possible to avoid the chronic diabetic complications. It would be advantageous to per-

form a very early thorough check up on these patients. It is frequently recommended to make this check up annually in the future.

This check up should include the search for signs of retinopathy by retinal examination, the nephropathy by determining the 24 h microalbumin excretion the serum creatinine concentration and the neuropathy by clinical examination (diapason or monofilament) looking for carotid arteritis or thermo by palpating the pulse and auscultation over the arteries and in the case anomalies supplemented by a Doppler examination. Discovering coronary insufficiency is more problematic, it is often silent in diabetics and clinical examination and ECG taken at rest add little. However, coronary accidents are responsible for more than 50% of the increased mortality in type 2 diabetes. Physical exertion tests and pharmacological tests could be used in a situation of particular risk. Unfortunately, there is no evident consensus concerning these situations. The risk equations ought to be a useful aid for the definition of patients to be further examined.

CONCLUSION

In type 1 and type 2 diabetes the therapeutic decisions and the clinical prognosis rely to a very large extent on laboratory test results. It is of great importance for the clinician to have a correct and reliable determination of the blood glucose concentration, and the HbA1c which ought to be standardised, the urine microalbumin excretion rate, the serum creatinine, the serum LDL cholesterol and the triglyceride concentrations.

Concerning type 2 diabetes systematic screening of the general population or at least of risk groups for fasting blood glucose concentration would be suitable for making an early diagnosis and permit a real prevention of diabetic complications.

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