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Fifty Years of Practical Clinical Research in the Pediatric Diabetology Center in Brussels that has Consistently had the Lowest HbA1c Values in the 4 Studies (1994-2009) by the Hvidoere International Study Group on Childhood Diabetes

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Abstract

My center in Brussels has consistently had the lowestHbA1c values in the 4 studies (1994-2009) by the Hvidoere International Study Group on Childhood Diabetes. The so-called Dorchy's recipes, in practice, have been published elsewhere. They are based on decades of experience from clinical studies summarized in this review. They concern the young type 1 diabetic patients followed by my multidisciplinary team in Brussels.

They have allowed to improve:

HbA1c Levels

It is inadequate to systematically assign the multiple injection regimen, or the pump therapy to "intensive" treatment, and some forms of the twice-daily injection regimen, abusively called "conventional", to a non-intensified therapeutic category of insulin therapy. Indeed, a multiple injection regimen, or the use of pumps, not associated with a good intensified and complete education, as well with the application of the consecutive knowledge, may have deleterious effects on HbA1c. The conclusion is: be dogmatic about outcome, but flexible in approach.

Biological variation of glycation and mean blood glucose have greater influence on HbA1c levels than glucose instability.

Quality of Care

The diet of young people with a type 1 diabetes must be normal and flexible. In many industrialized countries, the proportion of carbohydrates must be increased at the expense of that of fats.

The uptake of glucose persists after physical exercise, with a risk of hypoglycemia. To achieve sports performances similar to those of non-diabetics, an optimal HbA1c must be obtained.

Screening for Subclinical and Reversible Complications before Irreversible Lesions

To prevent or delay the onset of complications we have sought subclinical anomalies using sensitive methods before the onset of irreversible lesions (retinal fluorescein angiography, nerve conduction velocities, micro-albuminuria and β2-microglobulinuria, etc). The discovery of reversible anomalies further motivates patients to improve HbA1c levels.

The most interesting predictive marker of subclinical complications is the dosage of hs-CRP, before the CT/HDL-c ratio.

Low serum erythrocyte magnesium content and low T3 syndrome are related to glycemic control.

Quality of Life and Alexithymia

The better the glycemic control, the better the well-being. Family cohesiveness and maternal alexithymia have an impact on glycemic control. We showed, for the first time, that children who have difficulties in expressing their feelings

to others are more at risk of poor glycemic control.

Genetics and Immunology

Thanks to a particular case of neonatal diabetes, we have speculated on the existence of a gene on chromosome 6 involved in the differentiation of beta cells. We have concluded from a practical standpoint, that the detection of unipa-rental isodisomy of chromosome 6 in patients with neonatal diabetes may help identify a subgroup of patients in whom the disorder has a different pathogenicity and prognosis.

HLA-DQ genotypes are different in ethnic groups residing in Belgium, but not immune markers.

Earlier diagnosis through genetic and immunological screening of high-risk children could decrease DKA incidence at diabetes onset.

Type 1 diabetic patients should be screened annually for thyroid autoimmunity and celiac disease: 14.8% of the patients have positive thyroid Ab. The risk of developing thyroid Ab was clearly increased in girls.

The presence of beta cell autoantibodies (especially ICA) and other markers are related to lower residual insulin secre-tion.

Introduction and Background

In 2015, I received, in Australia, the "2015 ISPAD Lestradet Award for Education and Advocacy" (ISPAD= International So-ciety for Pediatric and Adolescent Diabetes) with the explanation "for his outstanding contributions in education and advocacy for children with diabetes". At that time, my diabetology team was following 1032 diabetic patients of which 527 were under <18 years old. Our center was following the most diabetic children compared to all the others in Belgium. Moreover, my pediatric center was allowed to continue the follow-up type 1 diabetic chil-dren into adulthood. We believe that this allows our professional multidisciplinary team to be better aware of the actual complica-tions that may only occur after longer duration of diabetes.

Since 1996, with my pediatric diabetologist comrade, Professor Stuart Brink (past President, International Society for Pediatric and Adolescent Diabetes "ISPAD"; clinical instructor of pediat-rics, Harvard Medical School, Boston, USA), we have traveled annually to Romania to help organize, administer and teach at an annual ISPAD-Timisoara Pediatric and Adolescent Diabetes Post-Graduate Course with Professor Viorel Serban. In 1999, we have been awarded a Doctor Honoris Causa (h.c.) in Romania, the country of Nicolae Paulescu, forgotten co-discoverer of in-sulin in 1921 [1, 2]. The following have also been named h.c. at the same university of Timisoara: Zvi Laron, Israel (2000; he described the type of dwarfism called Laron syndrome and was the first to introduce the multidisciplinary treatment for juve-nile diabetes); Gian Franco Bottazzo, United Kingdom (2005; he showed that type 1 diabetes is associated with antibodies against beta cells); Jørn Nerup, Denmark (2005; his research has focused on the role of auto-immunity in type 1 diabetes).

As a member of the Hvidoere International Study Group on Childhood Diabetes, my patients have the great honor of being the most successful study cohort: those with the lowest (i.e. best) levels of hemoglobin A1c. And they do so without excessive hy-poglycemia [1].

I was retiring in 2018 after a nearly fifty-year career since my medical degree from the Université Libre de Bruxelles [Free University of Brussels] in1969 and my PhD in 1981 from the same university. As of April 2024, my curriculum vitae contains 595 publications of which 162 are original, the others being medico-social or teaching, letters to editors, "abstracts/summa-ries" in international journals, chapters in multi-author books.

During those 50 years, clinical research has complemented the work as clinician. This research followed six key axes:

1. Insulin treatment, glycemic control and glycated hemoglo-bin (HbA1c)
2. Normal and flexible diet
3. Physical activity, insulin impregnation and HbA1c
4. Screening for complications at a subclinical stage and HbA1c
5. Quality of life, alexithymia and HbA1c
6. Genetics and immunology of DT1

The aim of this review is to summarize these clinical studies. They concern the young type 1 diabetic patients followed by my multidisciplinary team in Brussels. They have allowed to improve patient monitoring, quality of care, HbA1c levels, and have allowed to prevent or delay the onset of complications that we have sought using sensitive methods before the onset of irre-versible lesions. Key points summarize as much as possible the new and important facts.

Insulin Treatment and Glycemic Control and HbA1c

Dorchy's Recipes Explaining the" Intriguing Efficacity of Bel-gian Conventional Therapy", before the International Compar-isons of the Hvidoere International Study Group on Childhood Diabetes

Before the systematic use of glycated hemoglobin to objectively measure glycemic control, it was necessary to resort to less pre-cise clinical criteria [3, 4].

In the January 1993 issue of Diabetes Care, Bougnères et al [5] published the results of a French multicenter study compar-ing a three-injection insulin regimen (called intensified insulin therapy) with a conventional two-injection therapy in patients aged 7-18 years with >1-year duration of insulin-dependent di-abetes mellitus. They were evaluated after 1 year of treatment. The mean HbA1c levels decreased from 9.8% (i.e., 156% of upper normal values) in the two-injection group to 9.3% in the three-injection group (i.e.,139% of normal values).

In the September 1993 issue of Diabetes Care, I published a let-ter that presented my personal results in terms of HbA1c levels that can be achieved in an unselected population of young dia-betic patients, but without residual endogenous insulin secretion [6]. Patients were followed during 1 year, and I compared them with data from recent literature. In my study, mean ± SD HbA1c

levels were 6.9 ± 1.5%, e.i., 115% of normal values. No statistically significant difference was observed in metabolic control between the patients on only twice daily insulin injections and those on four injections using the basal-bolus regimen (113 and 118% of normal values respectively).

In a reply to my letter, Pierre Bougnères seemed especially impressed when considering the HbA1c levels obtained with only twice daily injections, and ironically asserted that my results were "out of reach for most (all?) groups in the world", and concluded "unless it remains a secret, every diabetologist/pediatrician will eagerly wait for H. Dorchy's recipes" [7]. This is the first time that the term "Dorchy's recipes" has appeared thanks to Bougnères...

I answered that It is inadequate to systematically assimilate the multiple-insulin injection to an "intensified insulin therapy" and the "conventional" two-injection regimen to a non-intensified insulin therapy. Indeed, a multiple-insulin injection regimen not associated with an intensified and correct education as well as with the application of the consecutive knowledge, may have deleterious effects on HbA1c levels [8]. Even at that time, in my experience the basal-bolus regimen, with increased flexibility in daily life and dietary freedom, cannot be applied successfully before adolescence. The twice-daily insulin regimen is appropriate for children and adolescents until the end of secondary school. The first injection (and insulin doses alteration) is done before school and the second injection (and insulin doses alteration) after school with the help of parents, if necessary. Our study has been published in full [9].

International Comparisons of HbA1c Levels by the Hvidoere International Study Group and Dorchy's Recipes

After the Franco-Belgian dispute in the American journal Diabetes Care, the Hvidoere International Study Group on Childhood Diabetes evolved during a workshop to discuss strategies that might be important in improving the quality of pediatric diabetes care.

In the 4 international comparisons of the "Hvidoere International Study Group on Childhood Diabetes" (years 1995, 1998, 2005, 2009) which included thousands of unselected children and adolescents in around twenty industrialized countries (Europe, USA, Canada, Australia, Japan) mean HbA1c levels and spreads in center mean (centralized assay in Denmark, DCCT aligned) were 8.3% (7.3-9.9); 8.4% (7.4-9.8); 8.2% (7.4-9.2); 8.0% (7.3-8.9) [10, 11]. In 2009, 33% of patients had an insulin pump and blood sugar levels were measured iteratively several times a day using a glucometer.

Cameron, et al. reviewed these 4 studies and they noticed that "one center has constantly had the lowest HbA1c values from 1995 to 2009" [10]. This is my center in Brussels as shown in their reference 26 with a mean HbA1c of 7.4 and 7.3% in the 4 studies [10, 11]. They draw the following lessons: "The Hvidoere member in question is highly charismatic and has a very prescriptive, 'recipe'-based approach to managing diabetes in his clinic. He prescribes mostly twice daily free mixing injections of insulin and eschews, a flexible approach to dietary intake. This does not appear to be at the expense of either hypoglycemia or QOL in his patient group. This experience is emblematic that consistently excellent outcomes can be achieved by simple, 'non-intensive' insulin regimens that are underpinned by a strong philosophy of care".

The recommendation by Cameron et al is: "be dogmatic about outcome and flexible in approach". Skinner, et al. tried to determine the reasons for center differences in metabolic control: "The diabetes care teams' cohesiveness and perspectives on treatment targets, expectations, and recommendations have an influence on parental targets, contributing to the differences in pediatric diabetes center outcomes" [12]. Indeed, we think that it is inappropriate to automatically designate the terms "intensive treatment" only to imply multidose insulin regimens or insulin pumps using algorithms when, in fact, it is the goals of glycemic control and A1c achievement, associated with good quality of life, that should define intensified treatment not the manner.

Figure 1, created from the results of the 2005 comparison in adolescents, shows glycemic control in the participating centers ranked according to mean hemoglobin A1c levels [13]. The insulin regimens were: twice-daily premix, twice-daily free mix, thrice daily, basal bolus, pumps.

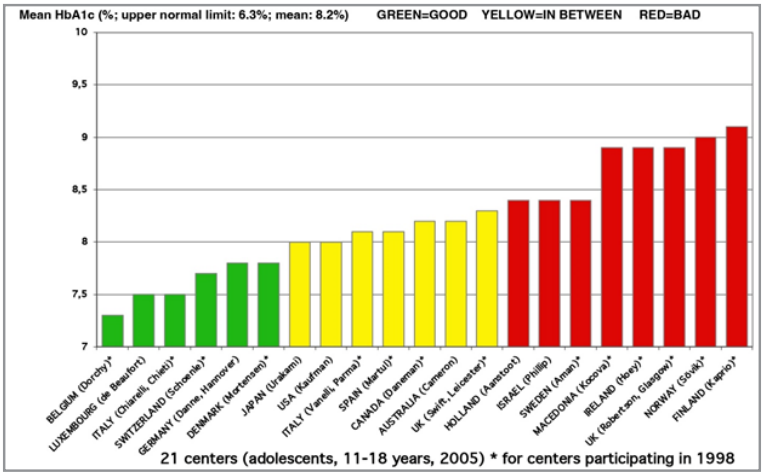


Figure 1: Comparison of glycated hemoglobin (HbA1c) rates in the third study of the Hvidoere Study Group (2005) which involved 2,062 adolescents aged 11 to 18 years, from 21 pediatric diabetology centers in 19 industrialized countries. The upper limit of normal values for HbA1c is 6.3%. The shortest bars correspond to the best results which are those of the Brussels team. The centers in green have results below average and the centers in red have results above average. The asterisks (*) indicate the 14 centers that participated in both comparisons in 1998 and in 2005.

Adolescents on twice-daily free-mix regimens (majority of my patients) have significantly lower A1c than those on basal-bolus or pumps. Adolescents on twice-daily premixed insulin regimens had significantly higher A1c than all other regimens. The conclusion of the paper by de Beaufort et al is "despite major and continuing changes in the use of newer insulin regimens (including CSII), modes of administration, glycemic control has not improved over the decade in the 21 centers" [13].

Our recipes have been published in details [11]. The 2 daily injection system imposes regularity in the timing of injections and meals, as well as a distribution of carbohydrates in 6 times, 3 classic meals and 3 "snacks". Once more, the advantages are: 1) there are only 2 injections made before breakfast and dinner, therefore in the presence of parents; 2) children can eat 6 times a day with only 2 shots; so, at school they can have lunch and snacks at 10 am and 3 pm without injection and by measuring their blood sugar only once before lunch. On the other hand, the basal-bolus system, although more difficult to apply correctly, offers more freedom for older teenagers.

A very common mistake made in adjusting insulin doses is to use only algorithms based on the blood sugar level that precedes the injection. It is necessary to consider especially the glycemic results that follow the injections of the previous days. If you want to know the winner of an 800m race, for example, you will know it at the finish and not at the start… All this is facilitated by the continuous sensors of interstitial glucose, not to mention that they reduce the risk of hypoglycemia.

Close-loop Control System of Insulin Delivery

Closed-loop control systems of insulin delivery may improve glycemic outcomes in young children with type 1 diabetes as shown in the multicenter PEDAP trial including 68 selected (not unselected as in the Hvidoere comparisons) young children in the "closed-loop group", during 13 weeks [14]. Eligible patients were randomly assigned into two groups. The children in the "standard-care group" were treated with an insulin pump or multiple injections and had a glucose sensor giving continuous glycemic measurements (Dexcom G6) to adapt the insulin doses, while the children in the "closed-loop group" also had the same continuous glucose sensor (Dexcom G6) providing information directly to an insulin pump using an algorithm (Control- IQ Technology). At the start of the study, the mean HbA1c levels were, respectively, 7.7 and 7.5% (criticism: dosage was not centralized). After 13 weeks, they were 7.5 (-0.2) and 7.0% (-0.5), which is a significant slight decrease. This is achieved with very expensive hardware and intense tracking, and not very different from my previous results in terms of HbA1c.

In conclusion, it is possible to obtain good HbA1c with much less expensive methods than those used in the PEDAP study, which is not to be neglected in countries where Social Security does not exist or if there are not enough resources in many countries. This good news should reassure many pediatric diabetology teams around the world [15].

Biological Variation of Glycation and Mean Blood Glucose have Greater Influence on HbA1c Levels than Glucose Instability

The aim of the study was to assess the relative influence of mean blood glucose (MBG), glucose instability (GI) and biological variation of glycohemoglobin (BVG) on HbA1c [16]. The study included 378 unselected young type 1 diabetic patients with a diabetes duration > 1 year. There were 1,409 visits with simultaneous HbA1c determinations and self-monitoring of BG meter downloads.

GI was quantified by measuring the standard deviation (SD) of the recorded BG values. A statistical model was developed to predict HbA1c from MBG. Hemoglobin glycation index (HGI) was calculated (HGI = observed HbA1c – predicted HbA1c) for each visit to assess BVG based on the directional deviation of observed HbA1c from that predicted by MBG in the model. Afterwards, the population was divided by thirds into high-, moderate-, and low-HGI groups, i.e. high-, moderate-, and low-glycators, reflecting BVG.

A total of 246,000 preprandial BG measurements were analysed, with a mean of 177 per visit. Grand MBG ± SD was 171 ± 40 mg/dl. Predicted HbA1c was calculated from the equation: 3.8399 + 0.0242 x MBG ($r = 0.66$; $p < 0.0001$). A MBG change of 40 mg/dl corresponded to 1% change in HbA1c, within the range 6-12%. Multiple regression analysis showed no significant relationship between SD and HbA1c, after adjustment for MBG. MBG was 10 times more important than SD to predict HbA1c.

MBG was not statistically different between the high- and low glycators, but HbA1c was significantly different. Multiple linear regression was used to predict HbA1c from MBG, SD and BVG (measured by HGI), adjusted for age, duration, gender and ethnic origin. BVG and MBG had large influences on HbA1c, the impact of BVG being 84% of the impact of MBG. On the other hand, GI had only 17% of the impact of MBG. In conclusion the effect of BVG on HbA1c is independent and much greater that the influence attributable to GI. Hemoglobin glycation phenotype, responsible for BVG, may be important for the clinical assessment of diabetic patients in order to avoid complications.

Key Points

Because recent multicenter studies, even those performed in developed countries without financial restriction, show that treatment of childhood, adolescent and young adult with type 1 diabetes, is inadequate in general and that levels of HbA1c are very different, diabetes treatment teams should individually explore the reasons for failure, without any prejudice or bias, in their own centers especially when center average A1c results are over 8%. The number of daily insulin injections, 2 or ≥ 4 or the use of pumps (with or without close-loop control system), by itself does not necessarily give better results.

Biological variation of glycation and mean blood glucose have greater influence on HbA1c levels than glucose instability.

Normal and Flexible Diet

The Age of Dogmatic Diets without Scientific Evidence

Diet has traditionally played an important role in diabetic therapy. Before the discovery of insulin, a restrictive diet, yielding more or less positive results in 80% of diabetic subjects, was the only therapy available. Later, it became evident that diet, as such, is the ideal treatment for obese diabetics of middle age (now called type 2 diabetes) that is beginning, however, to be encountered in children and adolescents with the rising rate of obesity since the problem is not based on a lack of insulin.

Over the years, various diets have been proposed often without scientific evidence. Restriction in calories, carbohydrates, or lipids was advocated, but also a high intake of the same nutriments or of proteins. "Free diet" as well as "anarchic" eating habits as opposed to "restricted" and "weighed" diets (thanks to a scale or "exchange lists") have been proposed [17-21].

A total caloric restriction inhibits growth and, associated with a lack of insulin, leads to the Mauriac syndrome [22]. One of the main errors was (is!), under the sweet name of "functional" insulin therapy, to speculate that there exists a direct linear correlation between the injection of x units of insulin and the utilization of y grams of glucose. If it was true, one should give more insulin to practice physical activity! In reality, it is the reverse! The reason is that the affinity of the muscular insulin receptors, as well as the activity of GLUT-4, is increased during (and even after) muscular work, but it is not the case for the hepatic insulin receptors [23]. Moreover, the regulation of glucose is dependent on a number of factors such as counter-regulatory hormones, gluconeogenesis, the relative use of glucose and non-esterified fatty acids as energy for muscular exercise, psychological factors (stress), and other mechanisms which are beyond our control.

Evolution to a Normal and Flexible Diet

In the 1950-60s, diabetic children were often followed by internists-endocrinologists and diets for diabetic children were most often rigid, weighed, restricted in carbohydrates, therefore a high fat diet. Henri Lestradet, in France, and Harry Dorchy, with his mentor, Helmut Loeb, in Belgium [17-21, 24] showed that the best metabolic control was obtained by a flexible and adapted diet. The adjustment of the diet and insulin doses by the patient and his family was first made according to urine tests, then by multiple daily measurements of blood glucose, then by continuous measurement of interstitial glucose by sensor.

Diabetic children have no fixed energy requirements because they grow and have variable physical activities. Energy intake may fluctuate from day to day without mandatory changes in the need for insulin or glycemic levels. To impose a weighed and measured diet is undesirable both for diabetic control and for psychological reasons.

Moreover, the notion of "measuring" leads to rejection of the entire therapeutic regimen and to emotional problems. A restricted diet that controls only carbohydrate intake and thus favors fat intake is potentially dangerous for the vascular system. On the other hand, even in the seventies we had observed a too high fat consumption in Belgian diabetic children (42.2% of the total caloric intake) and we had to concentrate our efforts on emphasizing fat rather than carbohydrate restriction, which is the case in many industrialized countries [24, 17].

We had also noted a positive correlation between the blood levels of HbA1c and those of total cholesterol and of triglycerides, which we confirmed later adding the LDL-cholesterol and apolipoprotein B. There was no relationship between HbA1c and HDL-cholesterol or its subfractions [25-27]. This means that lipid abnormalities are not necessarily related to a diet high in saturated fat, but are certainly related to HbA1c levels.

Quality of life is greatly improved by removing stupid dietary constraints and prohibitions.

Key Points

The diet of young people with type 1 diabetes must be normal and flexible. In many industrialized countries, the proportion of carbohydrates must be increased at the expense of that of fats. By increasing the proportion of carbohydrates in the diet to 50% of calories, the risk of atherosclerosis is reduced, and by making it flexible, all sports activities are allowed, not to mention the psychological well-being by removing harmful constraints.

Physical Activity, Insulin Impregnation and HbA1c

Insulin Impregnation and Glucose Uptake by Muscles

In the 1970's, we measured the rate of disappearance of blood glucose during exercise tests, with varying concentrations of insulin, in type 1 diabetic adolescents.

In a series of four clinical studies, we calculated the effect of an exercise work equal to 50% VO2max on the coefficient of assimilation (K) of intravenous injected glucose as a function of insulin dose [23].

1. In diabetics receiving insulin intravenously in amounts greater than was necessary to saturate the insulin receptors at rest, exercise increased K by 36%.
2. In diabetics injected intramuscularly with their usual insulin dose, K value increased by 160% during exercise.
3. In diabetics injected intramuscularly with their usual insulin dose, K value 30 min after exercise was 73% of the exercise K value and 146% of the resting K value of experiment.
4. In insulin-deprived diabetics, K did not change during exercise. Presence of insulin is thus necessary for the beneficial effect of exercise on glucose assimilation.

These experiments showed that insulin played at least a "permissive" role and that muscle avidity for glucose persisted after the end of physical activity, which explains the known risk of hypoglycemia after stopping sport.

Physical Effort, Oxygen Consumption and HbA1c

As early as 1986, we established the correlation between the ca-

pacity for effort, oxygen consumption and the level of HbA1c. The capacity for physical effort is all the higher as the HbA1c approaches normal values. It is obvious that if hemoglobin is burdened with too much glucose, it carries less oxygen [28].

The "International Olympic Committee" asked us to write recommendations for diabetic athletes [23]. They were published elsewhere in relationship with insulin regimens and diet [29, 30].

Reference 31 explains how, in practice, to organize the three pillars of treatment: insulin, diet, and physical exercise.

Key Points

The effects of physical exercise can be beneficial or harmful depending on the amount of exogenous insulin injected. The uptake of glucose persists after physical exercise, with a risk of hypoglycemia. To achieve sports performances similar to those of non-diabetics, an optimal HbA1c must be obtained.

Screening for Complications at a Subclinical Stage and HbA1c

1. ***Retinopahy***

Characterization of Early Stages of Diabetic Retinopathy: Fluorescein Leaks

Clinical studies, conducted since the 1970s by our pediatric diabetology team, have shown that screening for retinopathy, neuropathy, and subclinical nephropathy should be done from puberty, after 3 years of diabetes [32, 33]. This is to identify functional abnormalities, still reversible by improved metabolic control, preventing the occurrence of potentially irreversible incapacitating lesions.

As early as 1974, the late Daniel Toussaint (Ophthalmology Department of Brugmann University Hospital), and myself have shown, by fluorescein angiography, that microaneurysms of diabetic retinopathy, irreversible lesions, could be preceded by reversible fluorescein leaks, due to hyperpermeability of the blood-retinal barrier [34]. Figure 2 show, in a 14-year-old boy, several foci of fluorescein leaks without any other lesion. Fundus photography was normal.

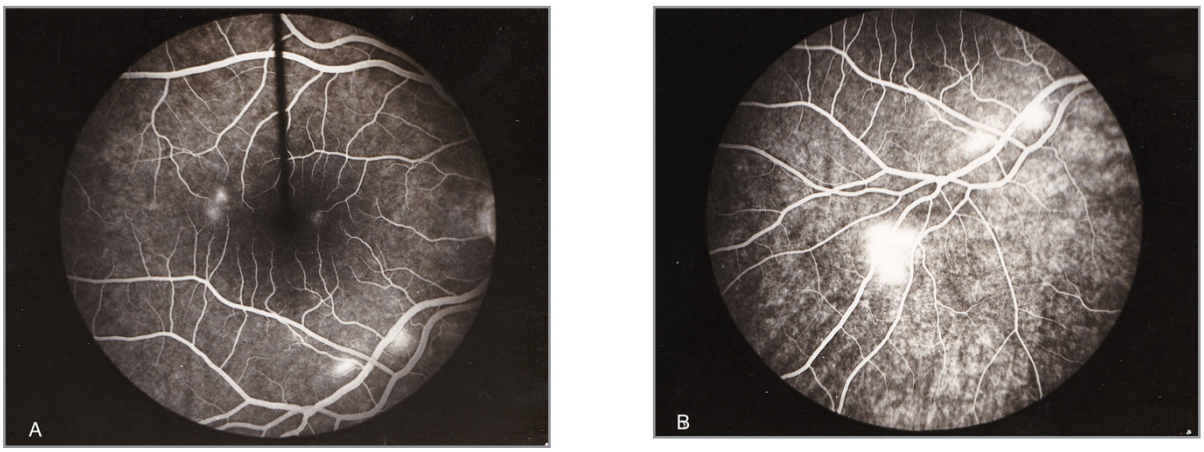


Figure 2: A & B. Patient I.R., at 14 years old, right eye. Retinal fluorescein angiography (venous time). Several foci of fluorescein leaks without any other lesion. The red-free photograph, not represented here, is normal.

These early leakages are different from those seen later in the (pre)proliferative stage [34-36]. Even though our first studies were published in French (not in English), in 1978, Arnall Patz, from the Wilmer Ophthalmological Institute of the John Hopkins Hospital, in fairness, wrote in the New England Journal of Medicine that: «Drs Dorchy and Toussaint have pioneered in the use of fluorescein angiography in the study of diabetic retinopathy and have defined early changes observed in patients with juvenile-onset diabetes... Their observations of capillary leakage as a result of vascular incompetence before specific morphologic lesions occur represent an important contribution» [37, 38].

However, nearly five decades after our first publication, it is difficult to persuade some diabetologists or ophthalmologists of the importance of fluorescein leaks as an incipient functional abnormality [39]. This is probably due to the fact that to see the early fluorescein leaks, it is mandatory to take photos 15 and 30 minutes after the fluorescein injection, which takes time… and is not practiced.

In 1991, we published a longitudinal study in order to detect the initial retinal abnormalities at fluorescein angiography in 161 type 1 diabetic children and adolescents [40]. Sixty-nine developed an incipient retinopathy at a mean age of 16.4 years, with a mean diabetes duration of 8.2 years. The types of incipient abnormalities and their frequency were: microaneurysms (50%), leakage of fluorescein (40%), retinal hemorrhages (19%), areas of capillary non-perfusion (8%), capillary remodeling (5%). Retinopathy was not found in children <12 years of age and was detected only after at least 3 years of diabetes. The type of initial lesion was unrelated to sex, age at onset of diabetes, or metabolic control.

Factors Related to Proliferative Retinopathy: Poor Metabolic Control and BMI

In the year 2000, 32 subjects among the 69 patients who developed early retinopathy were always treated by our team [41]. Their mean age was 33 years, and mean diabetes duration was 26 years. Some potential risk factors (HbA1c, total cholesterol, blood pressure, BMI, insulin dose, frequency of home

blood glucose monitoring and of clinic attendance, tobacco, and presence of other complications), measured during the whole follow-up, were analyzed in relation with the evolution of retinopathy to the proliferative stage using fluorescein angiography. In the statistical analysis, stepwise logistic regression was used to identify the most important parameters for the development of proliferative retinopathy. Proliferative retinopathy was diagnosed in six patients (19%), three men and three women. Its occurrence was significantly related to poor glycemic control during the preceding years (cumulated HbA1c was 143 vs. 120%; 100% being the upper normal limit, p = 0.049), cumulated cholesterol levels (>200 mg/dl, p = 0.014), higher BMI (27 vs. 22 kg/m2, p = 0.035), and the presence of other subclinical complications (p = 0.029).

However, higher levels of LDL cholesterol are related to poor metabolic control. In conclusion, our data suggest that the risk factors for developing proliferative retinopathy are poor long-term metabolic control, which is well known, and an elevated BMI, which is novel.

Subclinical Retinopathy and Role of Glycemic Control: Twins Experience

In 1999, we illustrated the major role of metabolic control in diabetic retinopathy with the case report of two homozygous twins becoming diabetic at age 8 yr [42]. They share the HLA-DQ genotype which is associated with the highest risk of type 1 diabetes in Belgium: A1*0301-B1*0302/A1*0501-B1*0201. Their personal medical history, blood pressure, lipoprotein levels and way of life were very similar, except that one brother had always been very compliant, which resulted in good metabolic control of its diabetes (hemoglobin A1c always <115% of normal values, the upper limit being 100%).

His brother, in contrast, had, since shortly after the onset of diabetes, shown a poor metabolic control (hemoglobin A1c from 130% to 150% of normal values). The twin with poor metabolic control had the first signs of retinopathy, as determined by fluorescein angiography, at age 17, three years before his brother and had a higher level of severity of retinopathy than his brother all through the follow-up. He had a major proliferative retinopathy with bilateral rubeosis at age 31, after 23 years of diabetes. At the same time, his brother only showed moderate background retinopathy.

At age 32, the twin with poor metabolic control had a slightly reduced peroneal motor nerve conduction velocity, but no abnormal microalbuminuria. He underwent vitrectomy and laser treatment. Since then, he continues to achieve good HbA1c and, nowadays, has not had any other diabetes-related complications.

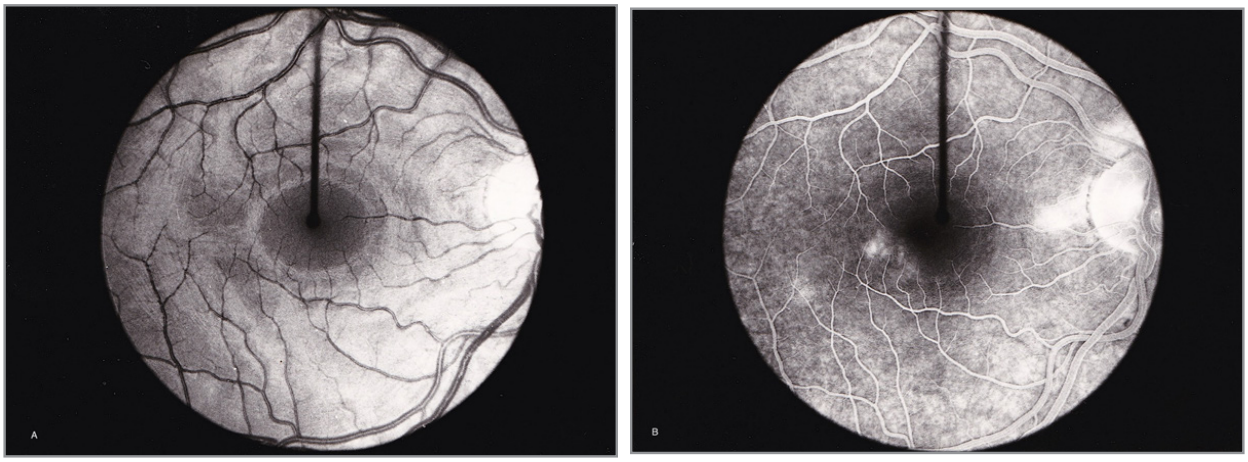
Screening for Diabetic Retinopathy: Retrospective Study of the Past 30 years

In a 2022 retrospective study of the past 30 years, including 4325 fluorescein angiographies representing 851 patients, we have described the prevalence and progression of diabetic retinopathy [43]. At diagnosis of incipient retinopathy, mean age was 22.8 years (range: 13.7-49.9) and mean diabetes duration was 13 years (range: 4.3-29.6).

Lesions requiring treatment were observed in 5.9% of the patients at a mean age of 32.4 years (range: 30.4-34.3) and a mean duration of 23.8 years (range: 19.4-28.1). On average, it took 12.9 years (range: 12.2-13.5) to progress from a background retinopathy to lesions requiring treatment. Mean HbA1c +/- SD was 7.8 +/- 1.5% over a period of 30 years. In order to compare HbA1c levels with different methodologies between 1986 and 2015, each HbA1c level was first expressed in a percentage according to the actual upper normal limit (6.2%). While it could have been expected to observe a higher prevalence of retinopathy, this study described by far the lowest prevalence comparing to similar studies, probably due to a good average HbA1c over 30 years.

Reversal of Incipient Diabetic Retinopathy with Improved Glycemic Control

In three children with the features of Mauriac syndrome we have shown ocular complications characterized by increased capillary permeability at fluorescein angiography [22]. In one of these patients, a 14-year-old girl, fluorescein leakages disappeared after eight months of adequate diabetic control as measured by HbA1c [44]. Unfortunately, during the following year, she did not adhere to good control for psychologic reasons, and HbA1c increased to 12%. Simultaneously, fluorescein leakages reappeared. This is illustrated by figure 3 (A to D).



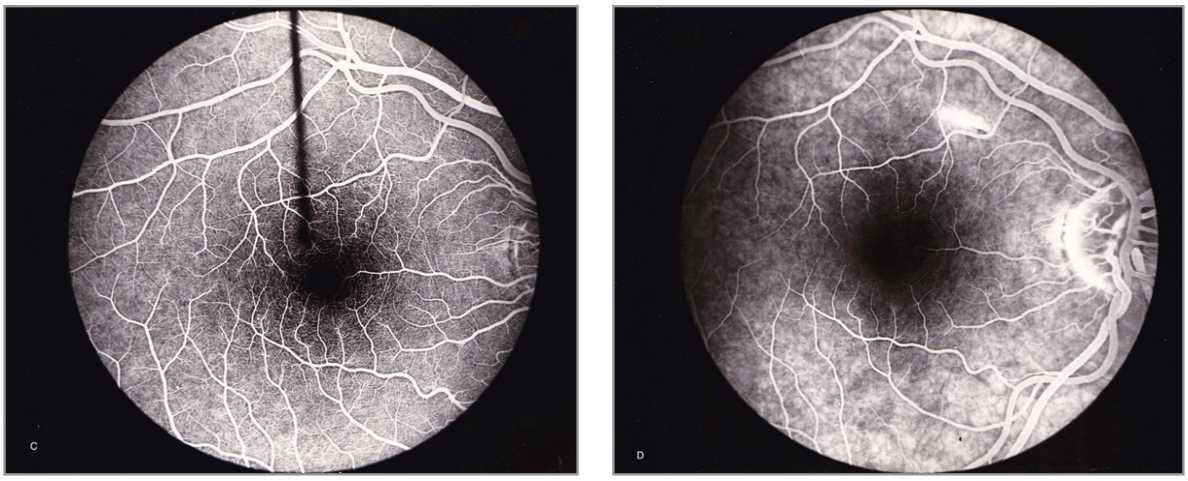


Figure 3: A: Right eye of a 14-year-old girl presenting with Mauriac syndrome (I.B.). The red-free photograph is apparently normal. B. Same patient (I.B.) at the same age. Fluorescein angiography (venous phase). Appearance of fluorescein leaks mainly in the perimacular and peripapillary areas.
C. Same patient (I.B.) one year later, at 15 years old. Fluorescein angiography (arteriovenous time); normalization, disappearance of fluorescein leaks (also at the late time not illustrated here). Clinically, this corresponds to a clear improvement in metabolic control.
D. Same patient (I.B.), one year later, at 16 years old. Fluorescein angiography (venous time). Significant leaks of fluorescein. Clinically, degradation of the degree of metabolic control. For psychological reasons, HbA1c increased to 12%.

Rapid Change from a Long Period of Poor Control to Good Metabolic Control Can Worsen Diabetic Retinopathy

However, one should not rush to achieve good metabolic control in long-term poorly balanced diabetic patients, as retinopathy can worsen significantly. We have published an observation showing the appearance of a very serious macular edema rapidly decreasing vision, in a 14-year-old child, when his degree of control was quickly normalized after 11 years of major glycemic imbalance [45]. Fortunately, this condition regressed thanks to the injection of massive doses of dexamethasone. We suggested that this edema was due to a vasculopathy at the level of the optic disc, characterized by a transient rupture of the hematoretinal barrier, inducing leaks in and around the optic nerves.

Key Points

Screening for diabetic retinopathy should be done from puberty, after more than 3 years of diabetes, by a very sensitive method such as fluorescein angiography including photographs at late times, what is essential for seeing fluorescein leaks, but rarely done in practice. It can highlight fluorescein leaks, resulting from a functional disorder that can precede the appearance of microaneurysms which are irreversible lesions. Fluorescein leaks can be reversible by improving HbA1c. On the other hand, one should not improve HbA1c too quickly in a patient who has had very poor glycemic control for a long period, as there is a risk of worsening retinopathy.

2. Neuropathy

Clinical and Subclinical Neuropathy

Clinical neuropathy is rarely described in children. We diagnosed it, by a very careful clinical examination carried out by a neurologist (distal muscle weakness, sensory disorders, patellar areflexia and decrease or absence of Achilles reflex), in 11% of young diabetics, aged 14.5 ± 4.7 years, with a duration of diabetes of 7.1 ± 4.5 years, whose average HbA1c was 134% compared to the upper normal limit [46]. However, a conscientious clinical examination remains subjective.

Since the 1980s, our team has carried out a series of electrophysiological studies in diabetic children and adolescents in order to try to highlight early subclinical neurological abnormalities, before the appearance of well-known irreversible lesions in adults [44-50]. They include EEG, peroneal and femoral motor nerve conduction velocity, sympathetic skin response, heart variability and statistical spectral analysis, afferent nerve action potential and cerebral somatosensory evoked potential.

Electroencephalogram (EEG): Minimal Abnormalities Related to Hypoglycemic comas and Retinopathy

Minor hypoglycemic manifestations, even frequent ones, do not influence the EEG [47]. The relationship between the beginning abnormalities of retinal capillaries and EEG abnormalities may be due to the fact that both retinal and cerebral capillaries have "zonulae occludentes" which become permeable in case of hyperglycemia, which explains the retinal leaks of fluorescein described above.

Motor Conduction Velocities in the Lower Limbs, Distal and Proximal

The determination of motor conduction velocity is a technique more easily used routinely in the screening of subclinical neuropathy than sensitive conduction [46, 48-50]. We measured the peroneal motor nerve conduction velocity (PMNCV) in 61 children and adolescents aged 7 to 22 years, with a duration of diabetes from 1 to 15 years [49].

In 36% of patients, the PMNCV was below the normal average minus 2 standard deviations. Furthermore, in 16% of subjects, half of whom have a normal PMNCV, but the muscle action potential presents late components, which reveals a slowdown in motor conduction in only a few fibers. This is therefore a very early stage of dysfunction. This means that a normal PMNCV can mask the involvement of a limited number of nerve fibers. The VCMSPE is negatively correlated with the HbA1c level.
The slowing down of the PMNCV is an early, rapid, and reversible functional disorder, dependent on glycemic control, before

irreversible lesions appear (demyelination, neuronal loss). In poorly balanced patients, subclinical neuropathy can occur from the onset of diabetes because of initial hyperglycemia, which is different from retinopathy. In conclusion, being easy to measure and sensitive, the use of VCMSPE should be done annually from the onset of diabetes.

Key Points

The measurement of peroneal motor conduction velocity is a technique more easily used routinely in the screening of subclinical neuropathy than sensitive conduction. If PMNCV is normal, late components reveal a slowdown in motor conduction in only a few fibers. A slowing down is reversible by improving HbA1c.

3. Nephropathy

Markers of Early Glomerular and Tubular Dysfunction: An Exercise Test did not Give more Information than at Rest

In 1976, in a preliminary study, later confirmed, we showed that there could be an abnormal urinary excretion of micro-albumin and β2-microglobulin in diabetic adolescents, at rest as well as during maximum effort on a cycle ergometer [51, 52]. To determine whether protein excretion during exercise is an earlier sign of renal dysfunction in diabetic adolescents than the basal measurements, urinary creatinine, total proteins, albumin, and ß2-microglobulin were studied before, immediately after, and 30 min after exercise until exhaustion on a bicycle ergometer in a group of 21 adolescent diabetic boys (Albustix negative) and in a comparable control group.

Among the 21 diabetic subjects, 11 had an incipient retinopathy diagnosed by fluorescein angiography. Urinary output of creatinine was similar in diabetic and in nondiabetic groups, and did not vary during exercise. At rest, the urinary output of total proteins, albumin, and ß2-microglobulin was significantly higher in diabetic subjects than in controls. These data suggest that the subclinical proteinuria of diabetes is of mixed origin, being both glomerular and tubular.

An exercise test leading to exhaustion did not give any additional information other than the basal excretion. There was no difference between diabetic subjects with early retinal vascular changes and those free from all retinopathy. These two complications can appear independently of each other and must be searched for simultaneously.

Fasting measurements are fortunately easier in routine.

Under the Influence of Training, Both Albumin and β2-Microglobulin Excretion were Reduced

Physical exercise triggers, within 30 minutes, a proteinuria linked to the intensity of the effort rather than its duration, which disappears within 24 hours following the cessation of effort according to a logarithmic curve, with a half-life of about 1 hour [53]. We investigated the effect of regular physical training on the urinary excretion of micro-albumin and β2-microglobulin in diabetic children, aged 11 to 18 years, with an average duration of diabetes of 11 years, who participated in a sports holiday camp (6 hours of sport per day) for 15 days. After 2 weeks of training, both micro-albuminuria and β2-microglobulinuria decreased by half for the same effort load, compared to the starting situation [54]. Whether this effect is beneficial in the case of nephropathy at stages 2 and 3 remains an open question.

Other Potential Markers of both Glomerular and Tubular Dysfunction: Urinary Transferrin and Acid Glycoaminoglycans

We have studied other markers of both glomerular and tubular dysfunction [32, 33].

It has been proposed that the determination of urinary transferrin (protein very similar to albumin in molecular weight (90,000 vs 69,000), and shape, but with a higher isoelectric point. Protéins with high isoelectric point are filtered more easily through the glomerular barrier. In a study including 105 unselected patients with a median age of 16 years, a median diabetes duration of 8 years and mean HbA1c of 7.4% (upper normal limit: 6.1%), we concluded that urinary transferrin excretion contributed less than micro-albuminuria as a marker of early renal dysfunction.

Acid glycoaminoglycans (GAG) are incorporated within the glomerular membrane. Their negative charges prevent the transfer of macromolecules through the membrane. Therefore, we tried to answer the following question: would GAG excretion be an earlier marker of glomerular dysfunction than micro-albuminuria? In a study including 101 unselected patients with a mean age of 17 years, a mean diabetes duration of 8 years and a mean HbA1c of 7.4% (upper normal limit: 6.1%), we found a slightly elevated micro-albuminuria in 5 patients (5%) and a higher GAG excretion rate in 6 other patients (6%). The independent predictive value of GAG as an early marker of glomerular dysfunction should be confirmed in a prospective study.

Key Points

During the earlier phases of type 1 diabetes, subclinical abnormalities of renal function might be detected by sensitive methods screening for micro-albuminuria and β2-microglobulinuria. Using our methodology, an exercise test leading to exhaustion does not give any additional information to measurements obtained in the resting condition which is easier.

4. Markers for Subclinical Complications

Lipoprotein (a): not a Marker

This genetically determined lipoprotein has a structural homology with plasminogen, and could be a link between the lipid and coagulation disorders observed in diabetic subjects. However, its role as a genetic marker predictive of micro and macrovascular complications is controversial. In our experience, high levels of lipoptotein (a) in diabetic children and adolescents are not markers for subclinical complications [55].

Oxidative Stress: Reduction of GPX, GRD Activities and Vitamin C levels: Not a Marker in Practice

Endothelial dysfunction, a forerunner of diabetic angiopathy, is present early in the course of childhood diabetes. The mechanism is not clear, but oxidative stress has been proposed as one of the putative mechanisms of vascular injury in diabetes. It results from the balance between the different antioxidant defenses, non-enzymatic (vitamins C, E or A, free radical scavengers) and enzymes (red cell superoxide dismutase-SOD, red cell glutathione peroxidase-GPX, glutathione reductase-GRD) and free radical production.

We measured some biological parameters that play a role in the defense against the toxicity of oxidative radicals (plasma vitamins C and E, glutathione peroxidase, glutathione reductase, and erythrocyte superoxide dismutase) in 119 diabetic patients aged 17.0 ± 7.0 years, with a diabetes duration of 8.2 ± 6.4 years, and whose HbA1c is 6.7 ± 1.5% (upper normal limit: 5.5%) [56, 57].

There is a decrease in glutathione peroxidase (in subjects with subclinical neuropathy), glutathione reductase (related to the age of the patients and the duration of diabetes) and vitamin C (in those with subclinical nephropathy, perhaps due to increased renal leakage), indicating the existence of oxidative stress in young diabetics [58].

We were unable to demonstrate a relationship between antioxidant parameters and HbA1c, but it should be noted that the average HbA1c level of our patients is not very elevated. High levels of vitamin E are measured in the least well-balanced patients, and consequently with hyperlipemia, due to the increase in the transport capacity of this vitamin.

The question of preventive antioxidant treatment does not have an absolute answer [58]. Contrary to some assertions, glycemic variability does not increase oxidative stress.

Oxidized LDL and Autoantibodies to Oxidized LDL: Not Markers

As qualitative changes in lipoproteins, following their oxidation by free radicals, can play an important role in the development of micro- and macro-angiopathy, we decided to study autoantibodies against oxidized LDL cholesterol and total antioxidant status, as well as levels of vitamins A and E, in 110 young diabetics in relation to lipoproteins, HbA1c, and subclinical complications [60].

In conclusion, in our diabetic patients with fairly good glycemic control, we were unable to demonstrate any abnormalities in lipid peroxidation or total antioxidant status, even in those with subclinical complications.

Highly Sensitive CRP (hs-C-Reactive Protein): Marker for Subclinical Complications before the CT/HDL Ratio

An inflammatory process is involved in the development of atherosclerosis. The measurements of acute phase proteins, particularly C-reactive protein produced by the liver, are interesting. Highly sensitive CRP (hs-CRP) measurements have been developed to detect small but significant and reproducible increases.

We tried to determine if high levels of hs-CRP exist in young diabetics and if a relationship can be found between plasma lipids and subclinical complications [61]. Patients were classified into 2 groups: A, without subclinical complication; B, with at least one subclinical complication. The levels of hs-CRP were significantly higher in the 126 diabetic patients compared to the 52 control subjects (2.6 ± 4 mg/L vs 0.7 ± 0.7 mg/L; $p < 0.001$). This difference persists when comparing the controls with the 81 patients in group A (2.0 ± 3.1; $p < 0.01$) and the 45 in group B (3.6 ± 5.1; $p < 0.001$).

The levels of hs-CRP were correlated with total cholesterol, the total cholesterol/HDL-cholesterol ratio, and LDL-cholesterol for the 2 groups of patients. The correlations with triglycerides, age, and duration of diabetes were only significant in group A. Multivariate analysis shows that only age, the CT/HDL-c ratio, and hs-.CRP are independent predictors of risk of complications. The hs-CRP has the highest Odds ratio.

In conclusion, hs-CRP levels are 3 times higher in young diabetics without complications (currently, but later some will develop) than in controls and 5 times higher in diabetic subjects with at least one subclinical complication. The dosage of hs-CRP therefore seems to be an interesting indicator of the risk of developing complications; next comes the CT/HDL-c ratio.

Key Points

In practice, the most interesting predictive marker of subclinical complications is the dosage of hs-CRP, before the CT/HDL-c ratio. Obviously, a part from any infection.

5. Other Subclinical Complications

Increase in the Glycolytic Activity of Red Blood Cells: Linked to Glycemic Control

In young diabetic subjects, we have demonstrated an overconsumption of glucose by erythrocytes correlated both with concomitant glycemia and total HbA1 (total glycated hemoglobin), an increase in the activity of phosphofructokinase, a negative relationship between ATP (Adenosine Tri-Phosphate) and glycemia, and a positive relationship between 2,3 DPG (Di-Phospho-Glycerate) and HbA1 [62].

The increase in 2,3 DPG compensates for the greater affinity of HbA1 for oxygen. In conclusion, there is an increase in the glycolytic activity of red blood cells which need more energy to balance their metabolic balance. Glycolytic activity and concentrations of ATP and 2,3 DPG are linked to the degree of short- and medium-term control. Since disturbances in erythrocyte function are implicated, among other things, in the genesis of microangiopathy, it seems prudent to require excellent metabolic control in young diabetic patients, also from this point of view.

Low Serum Erythrocyte Magnesium Content (EMC): Related to Glycemic Control

Magnesium levels, EMC, magnesium in urine, and HbA1c were measured in 118 type 1 diabetic patients aged 19 ± 8 years, with a duration of diabetes of 11 ± 8 years, and in 96 controls [63]. The conclusion is that magnesium levels and EMC are lower in diabetic subjects. Hypomagnesemia is related to age, duration of diabetes, poor metabolic control, and the presence of subclinical complications. EMC is negatively correlated with urinary magnesium, related to microalbuminuria and ß2-microglobulinuria. The increase in Mg clearance due to hyperglycemia has also been confirmed. Therefore, it is necessary to look for Mg depletion in young diabetics and consider a replacement treatment in addition to aiming to decrease HbA1c.

Low T3 Syndrome: Related to Glycemic Control

We conducted a study on subclinical thyroid abnormalities in a group of 64 diabetic children aged 13.8 ± 4.2 years, with a diabetes duration of 5.6 ± 3.9 years, compared to a control group of the same age [64]. Only the concentrations of triiodothyronine (T3) are statistically lower in diabetic children than in controls; they are negatively correlated with HbA1c levels, but also with concomitant blood glucose. This suggests that brief changes in blood glucose could influence T3, probably through its action on T4-5' deiodinase. On the other hand, the concentrations of TSH (Thyroid Stimulating Hormone), T4 (thyroxine) and rT3 (reverse T3) are not different in young diabetics compared to controls.

Key Points

These three other subclinical complications can be avoided by maintaining good HbA1c levels.

It is necessary to look for Mg depletion in young diabetics and consider a replacement therapy.

The study of thyroid function in diabetic patients should use serum measurements of TSH and free T4, not T3.

Quality of life, Alexithymia and HbA1c

The Better the Glycemic Control, the Better the Well-being

The treatment aims to achieve the best possible glycemic control, therefore the HbA1c closest to normal values. However, therapeutic constraints should not impair quality of life. This is why we tried to objectively measure the well-being of our fully autonomous patients aged 14 to 38 years (average: 21), thanks to a questionnaire [65].

The average age at the onset of diabetes was 10 years, the average duration of diabetes, 12 years. The annual HbA1c of the 100 patients, a quarter of whom are of Moroccan origin, is 7.3%. The general well-being of women is slightly less than that of men, due to a greater tendency towards depression.

The age of the patients, the duration of diabetes, the frequency of insulin injections and self-monitoring of blood glucose, the existence of subclinical complications have no influence on well-being. On the other hand, well-being is inversely proportional to HbA1c levels: the higher the HbA1c, the more anxiety and depression increase while simultaneously energy and positive well-being decrease.

Influence of Family Cohesion and Maternal Alexithymia on HbA1c

Thanks to a constructive collaboration with prof. Olivier Luminet, head of the Psychology Department of the Catholic University of Louvain (UCL), we studied the "emotional skills and family functioning: links with glycemic control and quality of life of young type 1 diabetics" (title of the PhD thesis of Marie Housiaux).

Alexithymia is a difficulty in identifying, differentiating and expressing one's emotions, or sometimes those of others. The first study included 45 Belgian families with at least one type 1 diabetic child aged six to 18 years (25 girls and 20 boys) [66]. Parents completed demographic questionnaires about themselves and their children. Family cohesiveness (FACES-III) and parental alexithymia (TAS-20) were assessed. Hierarchical regression analyses show that the mother's perception of family cohesion predicts the number of severe hypoglycemic events over in the last 12 months.

Parents' demographic variables ($p < 0.001$) and maternal alexithymia ($p < 0.05$) were found to be predictors of the number of hospitalizations for hyperglycemia in the last 12 months. As for HbA1c, only two parental demographic variables were significant predictors (marital and professional status, $P < 0.01$ and $P < 0.05$, respectively). In conclusion, the maternal perception of family cohesiveness and maternal alexithymia have an impact on glycemic control in children and adolescents with diabetes.

The second study included 45 type 1 diabetic children, aged 8-12 years (24 girls and 21 boys [67]. Participants completed a sociodemographic questionnaire and provided medical information on their diabetes, HbA1c values, and the number of severe hypoglycemic episodes and hospitalizations for hyperglycemia, were collected for the previous 12 months (3 months for severe hypoglycemia). Alexithymia characteristics were measured by means of the Alexithymia Questionnaire for children. Hierarchical regression analyses confirmed that both demographic (marital status and parental education; $p < 0.05$) and medical (duration of diabetes and daily self-monitoring of blood glucose frequency; $p < 0.01$) variables were associated with HbA1c levels.

More important one alexithymia factor (difficulty describing feelings) was found to be an additional predictor over and above the other variables ($p < 0.01$), explaining an additional 12% of the total variance in HbA1c levels. The present study show, for the first time, that children who have difficulties in expressing their feelings to others are more at risk of poor glycemic control Difficulties describing feelings to others still predicts glycemic control up to 24 months later in children with type 1 diabetes [68].

Key Points

Well-being is inversely proportional to HbA1c levels. Children who have difficulty expressing their emotions to others are more at risk for glycemic control (up to 12% more HbA1c), even in the long term. A psychological variable (alexithymia) influences a physical variable (HbA1c). Such a complementary diagnostic tool is helpful for identifying, at the onset of diabetes treatment, those who are most at risk of poor glycemic control and then allowing the implementation of tailor-made interventions for their specific needs.

Genetics and Immunology in DT1

Speculation on the Existence of a Gene on Chromosome 6 Involved in the Differentiation of Beta Cells

In 1993, we have reported on a female neonate with diabetes mellitus and methylmalonic acidaemia, who died at age 16 days [69]. Using immunocytochemistry, electron microscopy and in situ hybridisation, we were unable to demonstrate any insulin cells in the pancreatic islets. Methylmalonic acidemia was caused by a methylmalonyl coenzyme A mutase apoenzyme defect. The metabolic crisis of the methylmalonic acidemia aggravated the diabetes and may explain the failure of insulin therapy. Our results suggest that the infant suffered from a congenital absence of beta cells associated with a genetically transmitted mutase apoenzyme defect.

In this patient, serotyping of the HLA antigens, DNA typing of HLA-B and HLA class II loci, study of polymorphic DNA markers of chromosome 6, and cytogenetic analysis demonstrated paternal isodisomy, involving at least a 25-centiMorgan portion of the chromosome pair that encompasses the MHC [70]. ID probably caused methylmalonic acidemia by duplication of a mutated allele of the corresponding gene on the chromosome 6 inherited from the father. It is also very likely that ID was etiologically related to the agenesis of beta cells and consequent insulin-dependent diabetes mellitus in our patient. We thus speculate on the existence of a gene on chromosome 6 involved in beta cell differentiation.

From a practical standpoint, the detection of uniparental isodisomy of chromosome 6 in patients with neonatal diabetes may help identify a subgroup of patients in whom the disorder has a different pathogenicity and prognosis [71].

Differences in HLA-DQ Status in Different Ethnic Groups but not Immune Markers

The aim of this retrospective study was to compare genetic (HLA-DQ) and immune markers in a large population of

type 1 diabetic children and adolescents (452 patients aged 0.1-17.5 yr at diagnosis) residing in the same environment, but of different ethnic origin: European Caucasians (EC), Moghrabin Caucasians (MC), Black Africans (BA) and of Mixed Origin (MO) [72]. HLA-DQ genotyping, diabetes-associated autoantibodies, organ-specific autoantibodies, and other markers of autoimmunity were studied.

The proportion of the different ethnic groups was: 55% EC, 35% MC, 6% BA, and 4% MO. Between these four groups, there were no significant differences concerning age, HbA1c, presence of diabetic ketoacidosis, random C-peptide level at diagnosis and 2 yr later. The two most frequent haplotypes were DQA1*0501-DQB1*0201 and DQA1*0301-DQBI*0302 with a significant higher prevalence in MC and EC ($p = 0.002$ and 0.03, respectively). The high-risk heterozygous genotype DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201 was more frequent in EC than in MC, whereas the homozygous genotype DQA1*0501-DQB1*0201/DQA1*0501-DQB1*0201 was more prevalent in MC ($p = 0.019$). These susceptible genotypes were more frequent in youngest patients ($p = 0.003$). Diabetes-associated autoantibodies, organ-specific autoantibodies, and other immune markers did not statistically differ between ethnic groups.

Genetic and Immunological Predisposition to Diabetic Ketoacidosis (DKA) at Diagnosis

DKA is the leading cause of morbidity and mortality in children with type 1 diabetes. Little is known about the association between genetic and immunological markers and the risk for DKA at onset of T1D. The aim of this retrospective study was to create a model foreseeing the onset of DKA in newly diagnosed patients [73]. It included 532 T1D children (aged <18 years at diagnosis) recruited in our hospital, from 1995 to 2014. DKA and its severity were defined according to the criteria of ISPAD [74]. Genetic risk categories for developing T1D were defined according to the Belgian Diabetes Registry [75].

Overall 42% of patients presented DKA at diagnosis. This study outlined the major risk of DKA at diagnosis for younger children (<3 years) and for those belonging to ethnic minorities. Children carrying neutral genotypes had a 1.5-fold increased risk of DKA at diagnosis than those with susceptible or protective genotypes, a paradoxical observation not previously reported. Only solitary positive IA-2A increased the risk of DKA at diagnosis. The proposed model could help to predict the probability of DKA in 70% of newly diagnosed cases.

This was the first reported implication of IA-2A positivity and neutral genotypes predisposing to DKA at diagnosis regardless of its severity.

Autoimmune Thyroid, Celiac and Addison's Diseases Related to HLA-DQ Types in Young Patients with Type 1 Diabetes

In 831 patients with T1D we looked for autoantibodies (Ab) to thyroid, celiac and adrenal disease [76]. One hundred and twenty-three (14.8%) have positive thyroid Ab (antithyroid peroxydase and/or thyroglobulin antibodies). The risk of developing thyroid Ab was increased in girls (HR 2.3; 95% CI 1.6 - 3.2, $p < 0.0001$).

Thirty-three (3.9%) patients had positive endomysium Ab. Adrenal Ab were detected in 5 patients. The DQA*0301-DQB*0301 haplotype was more frequent in patients with thyroid Ab; DQA*1301-DQB*302 and DQA*501-DQB*201 in patients with endomysium Ab. All patients with adrenal Ab were positive for DQA*301-DQB*302.

Figure 4 shows the cumulative incidence for autoantibodies to thyroid apparition from diabetes diagnosis, according to gender.

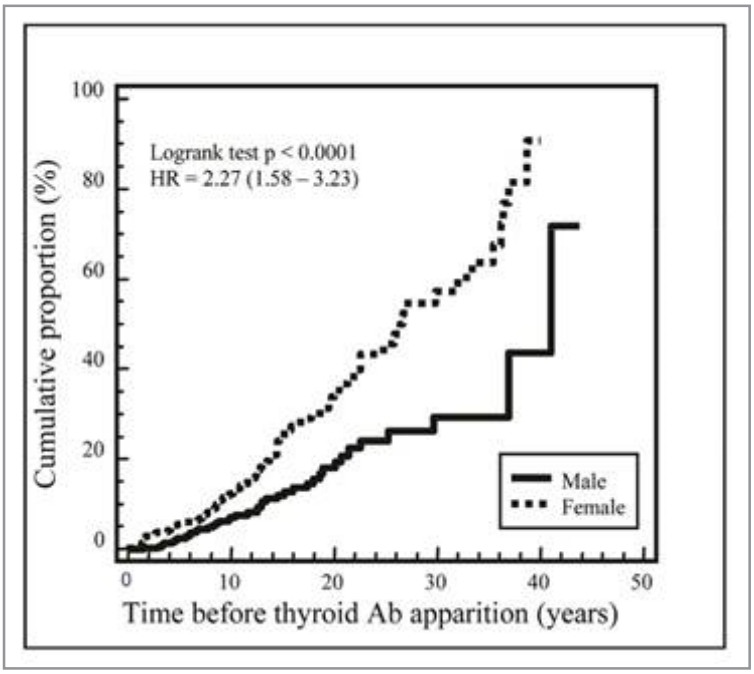


Figure 4: Cumulative incidence for autoantibodies to thyroid apparition from diabetes diagnosis, according to gender.

Evolution of Diabetes-associated Autoantibodies and of C-peptide Since the onset of Type 1 Diabetes

The objective was to investigate the immunological markers associated with beta cell autoimmunity (islet cell autoantibodies = ICA, antibodies to insulin = IAA, glutamic acid decarboxylase = GADA, and protein tyrosine phosphatase = IA-2A) and the residual insulin secretion (as measured by the C-peptide levels) from the onset of diabetes, their evolution over time and their relationship with gender, age, HbA1c, IAA at diagnosis and HLA-DQ genotypes [77].

The study included 636 patients with T1D aged from 0.2 to 28.3 years at diagnosis, with a follow-up of 1.4 to 25.3 years. Among the 636 patients, 5.4% were negative for all autoantibodies at diagnosis, 11.8% were positive for 1 autoantibody, 22.5% for 2 autoantibodies, 31.8% for 3 autoantibodies and 28.6% were positive for the 4 autoantibodies. A nearly total disappearance of ICA was observed after 5 years, of GADA after 7 years and of IA-2A after 8 years. The susceptible genotype 0301-0302/0501-0201 was more prevalent in patients with multiple autoantibodies and at a younger age at diagnosis. The most frequent autoantibody among the patients was ICA.

IAA and ICA were more frequent in younger patients at diagnosis and GADA in older patients. Male gender, younger age, higher HbA1c and the presence of autoantibodies (especially of ICA) at diagnosis were related to lower C-peptide levels. Male gender, older age, and positivity of IAA at diagnosis were correlated with longer persistence of ICA. Male gender was also correlated with longer persistence of GADA. Older age, lower HbA1c and positivity of IAA at diagnosis, as well as 0301-0302/0301-0302 genotype, were associated with longer persistence of IA-2A. During the long follow-up of this study (25 years), there was an association between the evolution of the autoantibodies and age, gender, HbA1c, C-peptide, positivity of IAA at diagnosis and HLA-DQ genotype (only for IA-2A). In conclusion:

1. the evolution of beta cell autoantibodies was influenced by age, gender, HbA1c, C-peptide at diagnosis, positivity of IAA at diagnosis, HLA-DQ genotype (only for IA-2A);
2. the evolution of C-peptide was influenced by the presence of autoantibodies at diagnosis, age, gender and HbA1c at diagnosis.

Figure 5 illustrates the evolution of C-peptide and beta cell autoantibodies according to time. Positivity for GADA and IA-2A persisted longer than ICA. C-peptide decreases more rapidly than the antibodies.

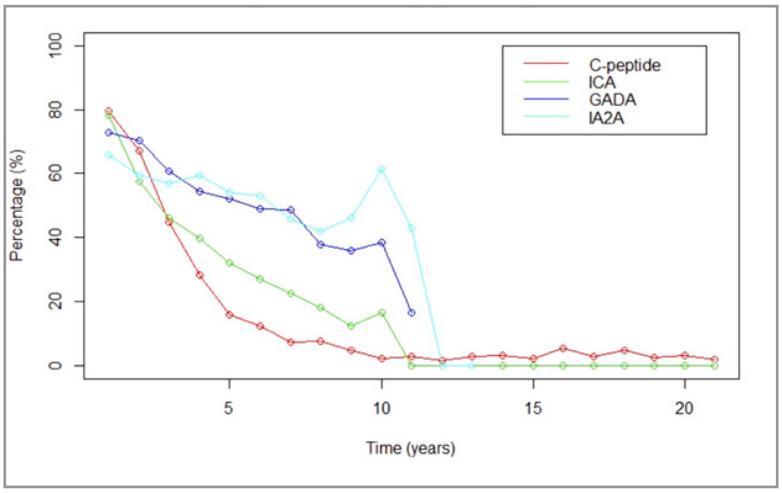


Figure 5: Evolution of C-peptide and beta cell autoantibodies according to time.

(Pre)Type 2 Diabetes and MODY: Pediatric Diabetology Future

Type 2 diabetes mellitus (T2D) is no longer a disease only of adults. In some American locations and populations, incidence and prevalence of T2D are much higher than those of type 1 diabetes, because of increased calorie and fat intake, and decreased exercise [78]. The increasing prevalence of T2D in the United States has closely paralleled the increase in childhood obesity noted there, but now across the Western world. Besides obesity, the other youth risk factors for T2D are: ethnicity, family history, puberty, female, metabolic syndrome, acanthosis nigricans and polycystic ovary syndrome. Any feature or condition associated with insulin resistance/hyperinsulinemia should alert to screen youth at increased risk for (pre)T2D.

In 2009, during our study, only 7 patients out of 483 diabetic children under the age of 18 were diagnosed with Type 2 diabetes (DT2), accounting for 1.44% of the cohort. Differential diagnosis must be conducted with monogenic diabetes or MODY (Maturity Onset Diabetes of the Young), particularly MODY-2, caused by a mutation in the glucokinase gene on chromosome 7, and MODY-3, resulting from a mutation in the hepatocyte nuclear factor-1α gene on chromosome 12. By definition, these are non-ketotic diabetes cases that typically manifest early (usually before age 25) and exhibit autosomal dominant inheritance.

MODY cases constitute 2 to 3% of all diabetes cases. They may present with mild fasting hyperglycemia (ranging from 110 to 140 mg/dL) and hyperglycemia following an oral glucose test (less pronounced in MODY-2 compared to MODY-3). In 2009, in our hospital, the diagnosis of MODY was confirmed in 7 patients aged 9 to 16 years, representing 1.44% of the population of diabetic children under 18 years old.

Key Points

The detection of uniparental isodisomy of chromosome 6 in patients with neonatal diabetes may help identify a subgroup of patients in whom the disorder has a different pathogenicity and prognosis HLA-DQ genotypes are different in ethnic groups residing in Belgium but not immune markers.

Earlier diagnosis through genetic and immunological screening of high-risk children could decrease DKA incidence at diabetes onset. Type 1 diabetic patients should be screened annually for thyroid autoimmunity, mainly in girls, and celiac disease. The residual insulin secretion is lower in males, at a younger age, with the presence at diagnosis of higher HbA1c and of ICA. As long as a residual secretion of endogenous insulin persists, glycemic control is easier. With increasing obesity, type 2 diabetes is no longer a disease only of adults. Differential diagnosis must be conducted with monogenic diabetes or MODY.

Chimeras and Hermaphrodites Imagined by Félicien Rops or Biotech Art

In order to conclude this review on a more playful and cultural note, I will quote Félicien Rops, a brilliant artist, lithographer, engraver, painter, and letter writer. He was born in Namur, Belgium, in 1833, and passed away in Essonnes near Paris, France, in 1898. His inventiveness led him through various artistic movements, from realism to symbolism. Rops created unique "living" beings: chimeras, hermaphrodites, and more [79].

In genetics, a chimera is an organism formed from two or more genetically distinct populations of cells. It's an animal or person that contains a "mosaic" of two (or more) genetic backgrounds within a single body. Chimera formation typically results from the fusion of two very early embryos. Each cell retains its original DNA.

For example, the fusion of a goat embryo and a sheep embryo results in a chimera known as a "geep" (from the English term). It's essential not to confuse this with a hybrid "geep," which arises from the sexual reproduction cross between a goat and a sheep. In the latter case, each cell contains genetic material from both parents. In human dizygotic twins, chimerism can occur through placental anastomoses. The hematopoietic marrow of one twin may become colonized by cells from the other, sometimes even replacing it entirely. This can lead to intriguing scenarios, such as an adult woman with male XY blood.

Transgenesis involves introducing exogenous DNA into an individual. This process occurs by adding DNA or a chromosome fragment to a fertilized egg. The outcome can be that all cells carry the additional genetic material, or prior cell divisions before insertion into the genome result in only some tissues containing it. Such an individual is termed a chimeric transgenic because they harbor two types of cells: those with and without the transgene. Gene therapy encompasses three aspects: gene silencing, gene replacement, and gene editing, where mutations are modified using nucleases.

In January 1888, Paul Verlaine (1844-1896), a poet from Paris, asked Rops to design the frontispiece for a poetic collection titled "Parallèlement." Rops engraved "La Shynge" (Figure 6), a chimera—a woman with androgynous features, part lion, part bird…

Figure 6:"La Shynge", a chimera—a woman with androgynous features, part lion, part bird

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