

Non-insulin Dependent Diabetes-The Past, Present and Future

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Abstract

Diabetes, known since antiquity, has been defined by glycosuria. In 1886, when Minkowski demonstrated that pancreatectomized dogs developed diabetes, the islets of Langerhans became a focus of the search for an active principle culminating in the discovery and the isolation of insulin in 1921 by Banting, Best and Collip. In 1959, the radioimmunoassay of Yalow and Berson solidified the concept of insulin resistance in non-insulin dependent diabetes (NIDDM). In 1971, the insulin receptor was defined as a cell surface protein that initiated the insulin signal transduction cascade.

Today, we know that NIDDM accounts for at least 90% of all diabetes worldwide and involves approximately 100 million people. The microvascular complications of NIDDM are the same as for insulin dependent diabetes (IDDM) and are related to the intensity and duration of hyperglycaemia. Further, it is clear from the Diabetes Control and Complications Trial (DCCT) that all microvascular complications can be reduced with intensive control of the blood glucose. Macrovascular disease is also accelerated in NIDDM, including both hypertension and dyslipidemia. The major risk factors for NIDDM are age, obesity, physical inactivity, and genetic background. The earliest feature seen in individuals destined to develop NIDDM is insulin resistance, but for hyperglycaemia to ensue there must be a defect in insulin secretion. Thus, insulin resistance defines the prehyperglycaemic phase of NIDDM, but varying degrees of insulin secretory deficiency define the hyperglycaemic phase. Macrovascular risk occurs throughout the lifetime of the individual, whereas microvascular risk ensues with the inception of hyperglycaemia.

Tomorrow, we will understand more clearly whether lifestyle changes, such as diet and exercise, or new classes of drugs, can delay or prevent NIDDM. Clinical trials are now beginning to test whether impaired glucose tolerance (IGT) can be delayed or prevented from moving to overt NIDDM,

The genetics of NIDDM are under intense study. Mutations in the insulin receptor lead to NIDDM in a small number of patients, and mutations in the glucokinase gene lead to maturity onset diabetes of the young (MODY). Work is now underway to study other candidate genes as well as work on positional cloning techniques to identify diabetes genetic loci. The hormone Leptin has just been discovered and is a major regulator of body weight.

In summary, the most important new emphasis on the treatment of NIDDM is the recognition of the importance of hyperglycaemia and our ability to both treat and possibly prevent this metabolic perturbation. This joins the longer-term emphasis on cardiovascular risk reduction from both treatment and prevention of hypertension and dyslipidemia.

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Diabetes-The Past

The earliest descriptions of diabetes go back 5000 years to Egypt, then to Greece and to India. These descriptions defined the cardinal features of the disease as we know it today, i.e. polydipsia, polyphagia, and polyuria. This descriptive phase lasted for many years, but in the 19th century it was joined by more discreet scientific inquiries. The first was by Claude Bernard, where quantitative measures of glucose were made, and the role of the liver in forming glucose from glycogen was discovered. Bernard introduced the concept of "internal secretion," but a number of years lapsed before the relevance of the pancreas to glucose metabolism was established. Minkowski and Von Mering car-

ried out the seminal experiment that proved the relationship of the pancreas to diabetes. This work provided the basis for the discovery of insulin by Banting, Best, Macleod, and Collip in 1921. Nineteen ninety-six marks the 75th anniversary of this monumental discovery.

The dramatic effect of insulin on the metabolic features of the disease permitted the complications of the disease to emerge and, thus, non-insulin dependent diabetes has become one of the most important chronic diseases worldwide. The introduction of radioimmunoassay and the measurement of insulin in plasma began to clearly define the concepts of insulin deficiency and insulin resistance. In the late 1960s and early 1970s, the mechanism of insulin biosynthesis was eluci-

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dated with the discovery of proinsulin. This led to the discovery of the insulin gene, and insulin became the first pharmaceutical produced by the biotechnology industry. This was followed by the discovery of the cell surface receptor for insulin and the insulin receptor gene. Genetic studies have demonstrated mutation in the insulin receptor gene that led to insulin resistance and rare forms of non-insulin dependent diabetes. Substrates of the insulin receptor have now been defined and attempts are being made to describe the general phenomenon of insulin resistance in molecular terms.

Non-insulin Dependent Diabetes (NIDDM)–The Present

The process of biomedical research means that the present encompasses the past. It is clear, however, that at the present time the pace of discovery has been markedly accelerated. There have been three general areas of advancement that will be further considered that have had a major impact on our understanding of NIDDM as a major worldwide chronic disease and that has allowed for a better understanding of how to best manage patients. These areas of inquiry, epidemiology, pathogenesis, and treatment have demonstrated many common features of NIDDM as it presents worldwide.

Epidemiology

In the United States there are approximately eight million people with diagnoses of diabetes and approximately 95 per cent have NIDDM. Since only half of these patients are diagnosed, the number of diabetic patients is approximately 16 million. Further, it is clear that the prevalence of diabetes is proportional to age and, therefore, the number of diabetics is increasing as the population ages. In addition, the prevalence of NIDDM is greater in subsets of the population. With respect to the Caucasian population, the rate of NIDDM is 1.5 times greater in African Americans, two-fold greater in Hispanic Americans, and four-fold greater in native Americans (Table I).

Just as different ethnic populations have a different prevalence of NIDDM in the United States, the same is true for the Pacific region. For instance, the age-sex adjusted prevalence of NIDDM in Singapore is 7.5 for

Chinese and 14.7 for Malaysians. Further, there is an enormous range of values going up to 42 per cent for Micronesians in Nauru. This value is similar to the highest prevalence of NIDDM in the world, found in the Pima Indians in the United States.²

When one considers both the microvascular and macrovascular complications of diabetes, the health impact is enormous (Table II). For instance, cardiovascular disease is markedly increased in the diabetic, and diabetes is the leading cause of new cases of blindness, the most common cause of end-stage renal disease, and accounts for 54 000 cases of non-traumatic amputation annually.

Two other major trends have emerged. It is clear that the prevalence of diabetes increases in the same ethnic population as they move from a rural environment to an urban environment. A further trend has been shown in the Japanese as they move from Hiroshima to Hawaii, and then from Hawaii to Seattle, Washington. Thus, there are a number of environmental factors at work leading to an increased prevalence of NIDDM.

Thus, there are a number of worldwide demographic factors leading to an increased prevalence of NIDDM. These factors include: ageing of the population, rural to urban migration, and movement of Asian populations to the United States.

Risk Factors for the Development of NIDDM

Studies of population groups have demonstrated a number of important risk factors that are associated with the development of NIDDM. Again, risk factors have a similar trend worldwide. The most extensive groups of longitudinal studies of both genetic and environmental factors related to NIDDM have been carried out over the past 30 years in the Pima Indians of Arizona in the United States. This population has the highest prevalence of NIDDM in the world. A summary of these risk factors is shown in Table III.³

The strongest risk factor is familial. The offspring of two diabetic parents in this population has a similar risk of developing NIDDM as identical twins. There is considerable evidence to suggest that this results from

TABLE I: NON-INSULIN DEPENDENT DIABETES (NIDDM) IN THE UNITED STATES'

• Approximately 7.8 million with diagnosed diabetes in the United States in 1993
• 90 to 95 per cent have NIDDM
• Incidence: 625 000 cases annually
• Prevalence:
• 1.3 per cent at age 18 to 44
• 6.2 per cent at age 45 to 64
• 10.4 per cent at age equal to or greater than 65

TABLE II: HEALTH IMPACT OF NON-INSULIN DEPENDENT DIABETES IN THE UNITED STATES

• Cardiovascular disease 2 to 4 times more common
• Cardiovascular disease present in 75 per cent of diabetes-related deaths
• Stroke: 2 to 6 times more common
• Leading cause of new cases of blindness in adults greater than age 30
• 24 000 new cases of blindness annually
• Most common cause of end-stage renal disease
• Approximately 15 000 new cases of renal failure per year
• Approximately 40 000 people with diabetes in the end-stage renal disease programme
• 54 000 non-traumatic amputations annually

TABLE III: RISK FACTORS FOR NON-INSULIN DEPENDENT DIABETES (NIDDM)

- Parental NIDDM
- Obesity (especially central obesity or visceral obesity)
- Physical inactivity
- Diabetic intrauterine environment
- Nulliparity and menstrual disorder
- Formula feeding
- Low birth weight

Presented by Dr. Peter H Bennett in the Banting Lecture of the American Diabetes Association, June 1996.³

polygenic traits rather than a shared common environment. Other very strong risk factors include obesity and low physical activity. Again, these same risk factors exist in other population groups. For instance, in a Japanese population studied in Seattle, there is a strong correlation with body mass index but, in addition, there is a strong association with abdominal obesity or visceral adiposity.”

Pathogenesis

For the purpose of understanding the pathogenesis of NIDDM, it is useful to separate the pathogenic features that lead to underlying metabolic conditions from those features that lead to hyperglycaemia. The earliest feature discovered thus far is insulin resistance. Thus, patients with the greatest degree of insulin resistance are at the greatest risk for developing NIDDM. This is usually measured by glucose clamp techniques, but is probably already evident in hyperinsulinaemic children destined to develop NIDDM. During this metabolic phase of the disease, insulin resistance dominates, the patient is hyperinsulinaemic, and hepatic glucose output is normal. The next discernible phase is impaired glucose tolerance (IGT). At this phase, the patient remains generally hyperinsulinaemic, but now a low insulin response to a rapid glucose infusion becomes an additional risk factor.⁵ With time, insulin resistance remains constant, but overall insulin response to glucose diminishes. As the insulin response decreases, increased hepatic glucose output ensues and the patient develops hyperglycaemia.

There is considerable evidence that a variety of biochemical events resulting from hyperglycaemia lead to microvascular complications.⁶ Thus, it is possible to separate the general features of the metabolic pre-hyperglycaemic phase of the disease from the hyperglycaemic phase where the patient becomes at risk for microvascular complications.

Treatment

There are two fundamental goals of treatment in NIDDM. They are an attempt to ameliorate the accelerated macrovascular disease and to prevent or postpone the microvascular component of the disease.

The cardiovascular macrovascular component must be treated by modifying all of its known risk factors. The two major issues in NIDDM are the treatment of hypertension and dyslipidemia with either lifestyle modification of diet and exercise or with appropriate drugs. An equally important issue is the prevention and/or cessation of smoking cigarettes. Clearly, control of blood pressure and plasma lipids will favourably affect cardiovascular risk. It has not yet been clearly demonstrated that treatment of hyperglycaemia will decrease cardiovascular risk, but it is clear that hyperglycaemia is a major cardiovascular risk factor. Further, the Diabetes Control and Complications Trial (DCCT) has clearly demonstrated that control of the blood glucose will decrease the microvascular risk of retinopathy, nephropathy and neuropathy (Table IV).⁶ There is early evidence to suggest that this is also true in NIDDM.⁷ This is all consistent with the idea that the mechanisms by which hyperglycaemia leads to microvascular complications are the same in insulin dependent diabetes (IDDM) and in NIDDM.

Thus, the goal of treatment in NIDDM and IDDM should be the same, and that is to maintain the glycosylated haemoglobin concentrations to as near normal as possible. Furthermore, this goal is easier to achieve in NIDDM inasmuch as the blood glucose is not as labile as in IDDM. Even mild hyperglycaemia should be treated and treated as early as possible. This is based on the idea that the complications of diabetes are a function of the duration and intensity of hyperglycaemia and the demonstration that any decrease in glycosylated haemoglobin values, even if not to normal, will markedly decrease microvascular risk.*

While lifestyle changes involving diet and exercise are very important and should always be pursued, most patients with mild to moderate NIDDM will require some form of drug to achieve normalisation of blood glucose. There are a variety of options that can be utilised and a general approach is outlined in Table V. The major point of emphasis is not the particular therapeutic agent, but the goal of achieving near or normal glycaemia. In the United States, approximately 40 per cent of NIDDM patients will require insulin therapy to achieve near or normal glycaemia.

Finally, there is, fortunately, another set of options for treating the microvascular complications of diabetes independent of control of hyperglycaemia. Thus, laser photocoagulation has a major effect in preventing pro-

TABLE IV: SUMMARY OF THE DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT)⁵

Intensive Therapy	Reduced Clinically Meaningful:
• Retinopathy	76 per cent
• Nephropathy	34 to 57 per cent
• Neuropathy	60 per cent

TABLE V: GENERAL STRATEGY FOR TREATMENT OF NIDDM

Goal 1	Normalise all cardiovascular risk such as obesity, hypertension, dyslipidemia, and smoking
Goal 2	Attempt to achieve as near normal blood glucose values as possible. (a) Careful attention to diet and physical activity is required for all degrees of hyperglycaemia, but is likely to be effective in achieving the goal in only the mildest cases. (b) Oral agents: A variety of oral agents are available such as the sulfonylurea class of drugs, metformin, and acarbose. These drugs are approved in most countries and should first be used as single agents, but when not completely effective can be combined, such as the combination of a sulfonylurea and metformin. Other agents that have been effective such as the troglitazone class of drugs are approved in some countries but will likely be useful in the future. These drugs either singularly or in combination are likely to be effective in mild to moderate hyperglycaemia, but in more severe cases, i.e., plasma glucose >200 mg/100 ml, they are unlikely to achieve the goal and insulin therapy is required.
Goal 3	When either retinopathy or nephropathy occur in spite of the best attempts at metabolic control, then photocoagulation and the administration of angiotensin converting enzyme inhibitors should be used.

NIDDM: non-insulin dependent diabetes

liferative retinopathy.⁹ In addition, a recent clinical trial has demonstrated that Captopril, an angiotensin converting enzyme inhibitor, will decrease by 50 per cent the progression of diabetic nephropathy to end-stage renal disease. This effect occurs independent of the drug's effect on controlling blood pressure.¹⁰

Since approximately 20 per cent of NIDDM patients already have microvascular complications of the disease at the time of diagnosis, it is critical that mild diabetes be treated as soon as possible. The specific mode of therapy is not the critical issue in either mild, moderate or severe hyperglycaemia, but the goal of near or normal glycaemia is critical. Studies are in progress to determine whether intensive therapy will affect macrovascular disease, but this may be very difficult to demonstrate objectively because of the nature of the process and the limitation on the size of the studies.¹¹ While some concern has been raised about intensive therapy of NIDDM with insulin, because of cardiovascular risk associated with insulin resistance and hyperinsulinaemia, no additional cardiovascular risk has been shown for diabetic patients treated with insulin.

The Future

Based on the major thrust of diabetes research today, it can be expected that progress will be made in the future in many areas, but two specific areas deserve emphasis. The first is a more complete understanding of the aetiological basis of NIDDM and, second, the mechanisms to prevent the disease.

Aetiology

It is best to think of NIDDM as a collection of aetiological

conditions that lead to the phenotypic expression of hyperglycaemia. Thus, in this case, we are talking about the aetiology of the metabolic condition that precedes hyperglycaemia. At this point in time, we can specify only a small number of aetiologies. The first is at the initial site of insulin action. Insulin must bind to its cell surface receptor in order to initiate its complex metabolic effects. Thus, mutations in the proinsulin gene may lead to a relatively inactive insulin and NIDDM. The insulin receptor is a heterodimeric protein on the cell surface that binds insulin by way of its alpha subunit and transduces its effect by way of autophosphorylation of the beta subunit. Mutations of the insulin receptor lead to insulin resistance and result in the Type A syndrome of NIDDM. Likewise, autoantibodies to the insulin receptor may block insulin action and lead to the Type B syndrome of NIDDM. Other mitochondrial genetic mutations result in NIDDM. Furthermore, in maturity onset diabetes of the young (MODY), mutations of the glucokinase gene, as well as several other mutations, alter the islets secretory response to glucose and result in NIDDM. All of these conditions collectively do not define more than 2 per cent of the aetiological basis of NIDDM. Based on the strong genetic predisposition in NIDDM, it is generally assumed that the common forms of the disease have a polygenic basis.

These multiple, possibly interacting genes, are being sought in two primary ways. The first is the pursuit of candidate genes such as those mentioned, i.e. insulin, the insulin receptor, and glucokinase. There are obviously a number of other metabolic enzymes or intracellular regulatory proteins involved in the insulin signaling cascade to be considered. Thus far, no unique protein has emerged as a candidate for the aetiology of the common form of NIDDM.

A second line of pursuit is positional cloning. In this technique, one looks for loci by scanning the entire human genome that may be associated with NIDDM. While several loci have been identified, no specific genes have as yet been elucidated by this approach.

The third important technique being pursued is to look for homologues in the genes of man known to cause a defect in animal models. The most important success of this technique thus far has been the discovery of the hormone leptin and its receptor, which is clearly involved in obesity and possibly in diabetes.

We are in an early stage with all of these studies and much can be anticipated in the future.

Prevention

Because of the tremendous progress in understanding the pathogenetic events and risk factors for NIDDM, we have great promise in being able to prevent or delay the expression of hyperglycaemia well before we un-

derstand the aetiologic basis of the disease.

The National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health is, therefore, inaugurating the largest randomised controlled primary prevention trial of NIDDM ever undertaken. The trial is based on efforts to modify insulin resistance and epidemiologic data from several longitudinal studies that have shown that lifestyle changes can modify the occurrence of NIDDM.

The study will enroll approximately 4000 patients into four clinical arms: (a) a generally healthy lifestyle group receiving usual diet and exercise recommendations; (b) intensive diet and exercise group; (c) metformin group; and (d) troglitazone group. The goal of the study will be to see if any or all of these manoeuvres can prevent or delay the progression of impaired glucose tolerance to diabetes as determined by the World Health Organization (WHO) criteria. The groups will be further followed for the advent of fasting hyperglycaemia. The results of this study will have a major impact on the screening of high risk patients for more specific primary preventive measures.

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