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Type 2 Diabetes: An Overview

Harold E. Lebovitz

Type 2 diabetes is a heterogeneous disorder. Clinical expression of the disorder requires both genetic and environmental factors. One theory concerning its etiology is that it is the result of the evolution of a thrifty genotype that had survival benefits in the past but is detrimental in the current environment. An opposing theory is that it represents an adult metabolic response to fetal malnutrition. Hyperglycemia in type 2 diabetes results from absolute or relative insulin deficiency. Most often relative insulin deficiency is attributable to an inability to adequately compensate for insulin resistance. Insulin resistance may be caused by a variety of genetic or metabolic factors. The most common etiological factor in insulin resistance is central obesity. Insulin resistance is associated with a cluster of metabolic abnormalities that include glucose intolerance, hypertension, a unique dyslipidemia, a procoagulant state, and an increase in macrovascular disease. Clinical intervention studies have demonstrated that reduction in the chronic microvascular and macrovascular complications of type 2 diabetes requires treatment of hyperglycemia to achieve hemoglobin A1c <7.0%, blood pressure ≤130/80 mmHg, and plasma LDL-cholesterol ≤2.6 mmol/L (≤100 mg/dL). Oral antihyperglycemic agents increase endogenous insulin secretion, decrease insulin resistance, or lower postprandial plasma glucose rise by delaying absorption of complex carbohydrates. Long-term glycemic control in type 2 diabetes requires progressive, stepwise, combination treatment with oral agents and eventually combination treatment with oral agents and insulin.

Type 2 diabetes as defined by the new classification of the American Diabetes Association (ADA)[1] is a confusing entity *(1)*. The ADA describes it as the most common form of diabetes, occurring with increasing frequency with age, usually associated with insulin resistance and always with either relative or absolute insulin deficiency and not generally requiring insulin treatment for survival. However, this phenotypic description describes a wide variety of genotypes, which range from specific monogenic entities such as maturity-onset diabetes of youth (MODY) to polygenic metabolic disturbances (classic type 2 diabetes). In the ADA classification, when a specific etiology has been established for a phenotype, it is removed from the type 2 category and placed in the "other specific types" category (Table 1), although it may be clinically indistinguishable from type 2 diabetes. From pathophysiologic and treatment perspectives, this classification schema has limited value.

Genetics and Environment

Hyperglycemia in type 2 diabetes is always a consequence of insulin deficiency *(2)*. Insulin deficiency causes reduced insulin-mediated glucose uptake from muscle, exaggerated glucose production from the liver, and increased free fatty acid mobilization from adipose tissue *(3)*. The result initially is postprandial hyperglycemia, which later is followed by fasting hyperglycemia. Insulin resistance *(4)*, whether genetic or acquired, can contribute to the development of type 2 diabetes by increasing the requirements for insulin, thus leading to insulin insufficiency in those individuals whose β cells have limited secretory reserve.

A type 2 diabetic phenotype can develop in individuals with normal insulin sensitivity who have a monogenic defect that impairs β-cell function *(5)* (Table 2) or in individuals who have any one of many polygenic disorders in which obesity, insulin resistance, and impaired β-cell insulin secretory function are part of the altered metabolic state. Monogenic defects have been described in those individuals who previously had been identified by clinical features as having a form of non-insulin-dependent diabetes mellitus that was characterized by mild to moderate insulin secretory deficiency, an autosomal dominant form of inheritance, and onset of diabetes at less than 25 years of age in some family members. This subtype of diabetes is referred to as MODY. It is a heterogeneous disorder, and abnormalities in five genes

SUNY-Downstate Medical Center, 450 Clarkson Ave., Box 1205, Brooklyn, NY 11203. Fax 718-447-1558; e-mail hlebovitz@IBM.net.

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[1] Nonstandard abbreviations: ADA, American Diabetes Association; MODY, maturity-onset diabetes of youth; UKPDS, United Kingdom Prospective Diabetes Study; and HbA_{1c}, hemoglobin A1c.

Table 1. Etiologic classification of diabetes mellitus.[a]

Type 1 diabetes (β-cell destruction, usually lending to absolute insulin deficiency)
Type 2 diabetes (etiology unknown, with varying degrees of insulin resistance and insulin secretory defects)
Other specific types
Genetic defects of β-cell function
Genetic defects in insulin action
Diseases of exocrine pancreas
Endocrinopathies
Drug- or chemical-induced
Infections
Uncommon forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes
Gestational diabetes mellitus

[a] From the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus *(1)*.

have been identified to date (Table 2). The point mutation of the specific gene varies among families. MODY accounts for <5% of diabetic patients. Type 2 diabetic patients with polygenic defects account for ~85% of diabetic patients.

Environmental factors can influence the clinical expression of monogenic disorders and are frequently necessary for the clinical expression of the polygenic disorders. An example of this interaction is seen in Pima Indians. Those who reside in Arizona are in an environment that fosters high calorie diets and minimal physical activity. They are quite obese and have an extremely high prevalence of type 2 diabetes *(6)* (Table 3). Another tribe of the Pima Indians lives in the mountains of northern Mexico. Their lifestyle consists of intensive physical activity and low-calorie diets. Their body weight is close to the ideal and their prevalence of type 2 diabetes is approximately the same as the general Mexican population *(6)* (Table 3).

It has been speculated that polygenic forms of type 2 diabetes are the consequence of having evolved a thrifty genotype from ancient times when the food supply was scarce and physical activity for survival was high. In our modern society, this thrifty genotype is a disadvantage and leads to obesity, insulin resistance, and type 2 diabetes *(7)*.

An opposing view to the polygenic theory of the pathogenesis of type 2 diabetes is provided by some recent studies that have demonstrated that individuals with a low birth weight have a higher prevalence of obesity, insulin resistance, and type 2 diabetes in adult life than those who had a normal birth weight. These data have led to an alternative hypothesis that insulin resistance and type 2 diabetes are the consequences of fetal malnutrition *(8)*.

At present, it is clear that both genetic and environmental factors are important in the development of the type 2 diabetic phenotype. The type 2 diabetic phenotype consists of many genotypes. The polygenic type 2 diabetic phenotype is likely to be very heterogeneous, and it is not unexpected that genetic analyses to date have given disparate results and no consistent pattern of abnormalities. In the monogenic type 2 diabetic phenotypes, the clinical course of the disease is also dependent on environmental interactions.

Insulin Resistance and Obesity

Insulin resistance is present and precedes the development of type 2 diabetes in the majority of patients *(9)*. The insulin resistance can be related to genetic abnormalities in a few individuals, but in most it appears to be related to obesity and in particular to central or visceral obesity *(10)*. After hyperglycemia is present an additional component of insulin resistance occurs that is caused by the effects of hyperglycemia itself (glucose toxicity or desensitization) *(11)*.

Insulin resistance as defined by the euglycemic insulin clamp, the Bergman minimal model, the fasting plasma insulin, or the Homeostasis Model Assessment model is an impairment of that function of insulin that causes the normal glucose uptake by muscle and/or restraint in glucose production by the liver *(12)*. The degrees to which other actions of insulin are normal or resistant in type 2 diabetes are not clear. Insulin effects on ovarian androgen production and lipogenesis among others appear not to be resistant *(13)*.

Our own data and those of many other investigators suggest that the insulin resistance in many type 2 diabetic patients is the result of an increase in visceral adiposity *(14)*. Visceral obesity rather than subcutaneous or total obesity is independently correlated with insulin resistance. It has been hypothesized that the direct release of free fatty acids and/or other products from visceral

Table 2. Known monogenic forms of diabetes characterized by impaired β-cell function.

Type	Gene	Chromosome	Defect
MODY 1	Hepatic nuclear factor-4α	20q	Progressive β-cell failure
MODY 2	Glucokinase	7p	↓[a] Glucose regulated insulin secretion
MODY 3	Hepatic nuclear factor-1α	12q	Progressive β-cell failure
MODY 4	Insulin promoter factor 1	13q	↓ Development of pancreas ↓ Glucose stimulation of insulin gene transcription
MODY 5	Hepatocyte nuclear factor-1β	17cen-q	Progressive β-cell failure + renal disease
MIDD	t-RNA Leu(UUR)	Mitochondrial genome	↓ ↓ Glucose-regulated insulin secretion + deafness

[a] ↓, decreased; ↓ ↓, substantially decreased.

Table 3. Pima Indians: Mexico and Arizona.[a]

	Women		Men	
	Mexico	Arizona	Mexico	Arizona
Body mass index, kg/m^2	25.1	35.5[b]	24.8	30.8[b]
Systolic blood pressure, mmHg	114	117	127	130
Diastolic blood pressure, mmHg	73	72	77	79
Cholesterol, mg/dL	149	168[c]	143	181[b]
Diabetes prevalence, %	10.5	37	6.3	54

[a] From Ravussin et al. *(6)*.
[b] $P < 0.0001$.
[c] $P < 0.01$.

adipose tissue into the portal circulation and the liver may be an important mechanism in causing insulin resistance. On the other hand, there are recent data to indicate that subcutaneous and visceral adipose tissue stromal cells respond differently metabolically to agents that affect insulin action, such as the thiazolidinediones *(15)*.

In longitudinal studies, insulin resistance appears to lead to the development of impaired glucose tolerance. The progression from impaired glucose tolerance to type 2 diabetes is related to decreasing β-cell insulin secretion because insulin resistance does not appear to worsen substantially unless hyperglycemia with glucose toxicity supervenes *(16)*.

Insulin resistance leads to type 2 diabetes only if there is an associated inability of the β-cell to compensate for the insulin resistance with appropriate hyperinsulinemia. The majority of obese individuals are insulin resistant, but only a small fraction progress to type 2 diabetes.

The Insulin Resistance Syndrome

Numerous epidemiologic and clinical studies have presented evidence that several metabolic, cardiovascular, and anthropometric factors consistently cluster together. These factors include the following: insulin resistance, hyperinsulinemia, glucose intolerance, central obesity, hypertension, a unique dyslipidemia (high plasma triglycerides, low plasma HDL-cholesterol, and an increase in the proportion of small dense LDL particles in the plasma), increased plasma plasminogen activator inhibitor 1, and an increased risk of atherosclerotic disease *(9)*. Stern *(9)* has made the distinction between the components of the syndrome and the outcome measures of the syndrome, the outcome measures being the development of type 2 diabetes and atherosclerotic disease.

Much controversy exists concerning the pathogenesis of the syndrome and the interrelationship among the various components of the syndrome as well as the relationship between the various components of the syndrome and the outcome measures. There are racial differences in these relationships *(17)*.

Type 2 diabetes is preceded by insulin resistance, hyperinsulinemia, the unique dyslipidemia, and obesity in 75–85% of the patients. The unique dyslipidemia and the development of type 2 diabetes are highly correlated with insulin resistance and hyperinsulinemia in almost all studies. The relationship between hypertension and insulin resistance is more controversial. Although some studies have shown a close association, others, particularly those in individuals of African origin or obese individuals, show little or no relationship. The obesity is a cause of insulin resistance rather than a consequence.

The relationship between insulin resistance and/or hyperinsulinemia with accelerated atherosclerosis appears to be more of an association rather than a causal relationship. Epidemiology studies have been evenly split between those that show a correlation between plasma insulin concentrations and the development of coronary heart disease in nondiabetics and those that do not. Definitive longitudinal data on the relationship between insulin resistance and either coronary artery disease or carotid artery intimal and medial thickening are lacking. Intervention studies with insulin treatment of type 2 diabetic patients, including the University Group Diabetes Program study of the 1960s and the recently completed United Kingdom Prospective Diabetes Study (UKPDS), have not shown any increase in coronary artery or any other macrovascular disease *(18)*. A reasonable conclusion is that insulin itself is unrelated to accelerated atherosclerosis. Insulin resistance is questionable, but the other components of the insulin-resistance syndrome (hypertension and dyslipidemia) are clearly related to the increased macrovascular disease seen in the type 2 diabetic patient.

Intervention Studies in Type 2 Diabetic Patients

Several recent intervention studies have provided evidence that intensive pharmacologic treatment of the metabolic abnormalities of type 2 diabetic patients reduces the long-term complications of the disease. The UKPDS on type 2 diabetic patients was a randomized placebo-controlled trial in which 4209 newly diagnosed patients were followed for a mean of 11 years on a conventional treatment regimen (diet plus small doses of oral antihyperglycemic agents if necessary) or an intensive treatment regimen (sulfonylureas, metformin, or insulin) of glycemic control *(18)*. The endpoints measured were clinical microvascular and macrovascular complications. The results of the study are listed in Tables 4 and 5.

An intensive policy of glycemic control with insulin or sulfonylureas produced a median hemoglobin A1c (HbA_{1c}) of 7%, whereas the conventional policy patients had a median HbA_{1c} of 7.9% (Table 4). This 0.9% difference in median HbA_{1c} over the 11 years produced a 12% reduction in all diabetes-related complications and a 25% reduction in microvascular complications. There was no statistically significant reduction in myocardial infarctions. No significant benefits or detriments were noted from insulin vs sulfonylurea treatment other than that hypoglycemia was more common with insulin treatment

Table 4. Glucose control study results in UKPDS.[a]

	Risk reduction,[b] %	P
Any diabetes-related endpoint	12	0.03
Diabetes-related deaths	10	NS[c]
Myocardial infarction	16	0.052
Microvascular disease	25	0.01
Stroke	NS	NS

[a] From the UK Prospective Diabetes Study Group *(18)*.
[b] Risk reduction achieved by intensive glucose control policy (median HbA_{1c}, 7.0%) compared with conventional glucose control policy (median HbA_{1c}, 7.9%).
[c] NS, not significant.

and that sulfonylurea inadequacy of treatment was greater than that for insulin treatment in years 6–11.

A small randomized overweight population treated with metformin (342 patients) did show a significant reduction in diabetes-related deaths and myocardial infarctions when compared with a conventionally treated overweight type 2 population (411 patients; Table 5) *(19)*. A point of interest in that analysis was the median HbA_{1c} decrease in the metformin group compared with the conventional group (0.6%), which was no greater than that achieved with insulin or sulfonylureas in the overweight group (1293 patients). Only the metformin group, however, showed a statistically significant decrease in macrovascular events. The metformin results were complicated by a second study in which metformin or placebo was added to a sulfonylurea failure group some 7.1 years after therapy was initiated. After a median treatment time of 6.6 years, a significantly higher mortality was noted in the metformin-added group. A number of secondary analyses were carried out on that second study, and they have suggested that the data in this later study were flawed. Although the initial randomized study suggested that metformin treatment in the overweight patient might have advantages over the other treatments, it is probably necessary to reproduce those results in another study; at the same time it would be useful to prove that the late-combination study was indeed invalid and that the results were attributable to random chance.

Regardless of that controversy, the UKPDS unequivocally showed that improved glycemic control reduces microvascular complications in type 2 diabetic patients.

The UKPDS also incorporated a study of blood pressure control within their larger glycemic control study. This study started in 1987, and 1148 patients were recruited and randomized to tight blood pressure control and less tight blood pressure control *(20)*. The tight blood pressure control group maintained a mean blood pressure of 144/82 mmHg and the less tight maintained a mean of 154/87 mmHg. Table 6 shows the significant risk reductions in diabetes-related deaths, heart failure, stroke, and microvascular disease achieved by tight blood pressure control. Although the UKPDS study did not show a statistically significant reduction in myocardial infarctions, the Hypertension Optimal Therapy Study recently reported that reducing the diastolic blood pressure from ≤90 mmHg to ≤80 mmHg reduced major cardiovascular events, including myocardial infarctions in type 2 diabetic patients by 51% *(21)*.

The impact of lowering plasma LDL-cholesterol in type 2 diabetic patients has been studied in secondary prevention but not primary prevention studies. The Cholesterol and Recurrent Events study showed that type 2 diabetic patients treated with pravastatin to lower their plasma LDL-cholesterol from a mean of 1.39 g/L to ~1.0 g/L reduced recurrent coronary events over a 6-year period by 23% *(22)*. This risk reduction was equivalent to that observed in the nondiabetic subjects who had had a previous myocardial infarction. The impact of lowering LDL-cholesterol to 1.0 g/L on reducing recurrent coronary events in type 2 diabetics has far reaching clinical significance. It is well established that myocardial infarctions occur at rates two- to fourfold higher in diabetics than in nondiabetics and cause a 50–70% higher mortality. Haffner et al. *(23)* have not only confirmed this increased risk of myocardial infarction in Finnish type 2 diabetic patients, they have also shown that a type 2 diabetic without any previous evidence of coronary artery disease has the same risk of having a myocardial infarction over a 7-year period as a nondiabetic who has already had one myocardial infarction (Table 7) *(23)*. They raised the interesting hypothesis that prevention of a myocardial

Table 5. Effect of metformin treatment in overweight type 2 diabetics.[a]

	Risk reduction,[b] %	P
Any diabetes-related endpoint	32	0.002
Diabetes-related deaths	42	0.02
Myocardial infarction	39	0.01
Microvascular disease	29	NS[c]
Stroke	41	NS

[a] From the UK Prospective Diabetes Study Group *(19)*.
[b] Risk reduction compared with conventionally-treated overweight type 2 diabetic patients: UKPDS results. Median HbA_{1c} in metformin-treated patients, 7.4%, and in conventionally-treated patients, 8.0%.
[c] NS, not significant.

Table 6. UKPDS intensive blood pressure control study results.[a]

	Risk reduction,[b] %	P
Any diabetes-related endpoint	24	0.005
Diabetes-related deaths	32	0.02
Myocardial infarction	21	NS[c]
Microvascular disease	37	0.009
Stroke	44	0.01
Heart failure	56	0.004

[a] From the UK Prospective Diabetes Study Group *(20)*.
[b] Risk reduction is for tight control (144/82 mmHg) vs less tight control (154/87 mmHg).
[c] NS, not significant.

Table 7. Incidence of cardiovascular events during a 7-year follow-up of type 2 diabetic and nondiabetic subjects.[a]

	Prior myocardial infarction			
	Type 2 diabetic subjects		Nondiabetic subjects	
	Yes	No	Yes	No
Myocardial infarction (fatal or non-fatal), events/100 person-years	7.8	3.2	3.0	0.5
Strokes (fatal or non-fatal), events/100 person-years	3.4	1.6	1.2	0.3
Cardiovascular deaths, events/100 person-years	7.3	2.5	2.6	0.3

[a] From Haffner et al. *(23)*.

infarction in a type 2 diabetic without clinical evidence of coronary artery disease represents the same clinical problem as preventing recurrent coronary disease in a nondiabetic who has already had a myocardial infarction.

From these intervention studies, one must conclude that intensive glycemic, blood pressure, and lipid management are essential for the prevention of chronic complications in type 2 diabetic patients.

Current Management of Glycemic Control in Type 2 Diabetic Patients

Effective treatment of hyperglycemia in type 2 diabetic patients requires recognition of several key elements. Of utmost importance is an understanding of the mechanism by which each available pharmacologic agent reduces hyperglycemia *(24–28)*. The concomitant effect of each antihyperglycemic agent on cardiovascular risk factors should be an important consideration *(29)*. The potential serious side effects of each agent need to be evaluated in the particular clinical setting that it is to be used. Matching the patient's clinical characteristics and profile of metabolic abnormalities with the pharmacologic profile of the agents to be used assures the safest and most effective outcome.

A treatment regimen must be designed to achieve specific target goals. These target goals will depend on the age of the patient, the years of anticipated survival, other concomitant illnesses, and the patient's willingness to comply with specific treatment regimens. The chronic complications of type 2 diabetes evolve over many years and are dependent on the degree of glycemic control over those many years. Intensive management is indicated for those who are likely to benefit from it. More conservative management is indicated for those in whom the long-term reduction of chronic complications is not a goal.

Type 2 diabetes is a progressive metabolic disorder characterized by increasing β-cell failure with time. Treatment regimens that depend on some quantity of endogenous insulin secretion become less effective as the duration of type 2 diabetes increases. Treatment for hyperglycemia in type 2 diabetic patients usually progresses from lifestyle intervention, which ranges from dietary management and increased physical activity to addition of a single oral antihyperglycemic agent (monotherapy) to combinations of oral antihyperglycemic agents and, finally, to combinations of oral antihyperglycemic agents with insulin *(30)*. This stepwise, progressive, combination therapy is essential if the target glycemic goal of a $HbA_{1c} \leq 7\%$ is to be achieved and maintained.

The characteristics of the currently available antihyperglycemic agents are listed in Table 8. They include agents that reduce hyperglycemia through three major mechanisms: increasing insulin secretion, decreasing insulin resistance, and decreasing postprandial plasma glucose rises by delaying digestion of complex carbohydrates. As monotherapy for the ordinary type 2 diabetic patient, insulin secretogogues and metformin appear to have the greatest effect in decreasing hyperglycemia. The thiazolidinedione troglitazone and the α-glucosidase inhibitors have unique effects that make them useful as monotherapy in some patients.

When it becomes necessary to use combinations of oral agents to achieve the target glycemic goal, combining an agent that increases insulin secretion with one that decreases insulin resistance is usually the most effective. There are, however, some data to indicate that combination therapy with metformin and troglitazone (Rezulin),

Table 8. Characteristics of antihyperglycemic agents.

			Effects on glycemia	
Generic name	Trade name	Mechanism of action	FPG,[a] mg/L	HbA_{1c}, %
Repaglinide	Prandin	↑ Insulin secretion	↓ 500–780	↓ 1.5–2.5
Sulfonylureas	Amaryl Glucotrol XL Glynase	↑ Insulin secretion	↓ 500–750	↓ 1.5–2.5
α-Glucosidase inhibitors	Precose Glyset	Delays digestion and absorption of complex carbohydrates	↓ 200–300	↓ 0.5–1.0
Metformin	Glucophage	Insulin sensitizer (liver > muscle)	↓ 500–750	↓ 1.5–2.5
Thiazolidinedione	Rezulin (Troglitazone)	Insulin sensitizer (muscle > liver)	↓ ~400	↓ 0.6–1.0

[a] FPG, fasting plasma glucose; ↑, increased; ↓, decreased.

Table 9. Effects of antihyperglycemic agents on cardiovascular risk factors.[a]

	Insulin secretogogues	α-Glucosidase inhibitors	Metformin	Troglitazone
Body weight	↑[b] 4–5 kg	↓ 0.8 kg	↓ 1–2 kg	↑ 1–6 kg
Blood pressure	0	0	0	±
Plasma triglycerides	0	0	↓ 4–5%	↓ 15–20%
Plasma LDL-cholesterol	0	0	↓ 4–5%	↑ 10–15%
Plasma HDL-cholesterol	0	0	0	↑ 10%
Lipoprotein(a)			↓	↑
Procoagulant state	±	0	↓	↓
Insulin resistance	0	±	↓	↓
Plasma insulin	↑	↓	↓	↓

[a] From Lebovitz *(29)*.
[b] ↑, increase; ↓, decrease; 0, no effect; ±, no consistent effect.

both of which are insulin sensitizers, is quite effective in improving glycemic control. It is thought that this combination is effective because metformin is more effective in reducing insulin resistance in the liver and troglitazone is more effective in reducing it in the muscle.

The known effects of the various oral antihyperglycemic agents on factors that may influence cardiovascular risk are listed in Table 9. The major effects relate to body weight, lipid profiles, and procoagulant states. Insulin secretogogues as well as insulin itself usually produce 4- to 5-kg weight gain when effective as antihyperglycemic agents. Troglitazone when used as monotherapy is associated with a small weight gain, but when combined with insulin or sulfonylureas, it is associated with a sizeable weight gain. Metformin therapy usually is associated with a small weight loss. α-Glucosidase inhibitor treatment may also be associated with a small weight loss. Metformin is the only antihyperglycemic agent that has been shown to have a beneficial effect on the plasma lipid profile. The data with troglitazone and its beneficial or detrimental effects on the plasma lipid profile are not interpretable at the present time because plasma LDL-cholesterol and lipoprotein(a) increase, but plasma triglycerides decrease and plasma HDL-cholesterol increases.

The major serious side effects of the oral antihyperglycemic agents must be recognized and contraindications and monitoring guidelines followed explicitly. Sulfonylureas and insulin have the major side effect of severe hypoglycemia. Sulfonylurea treatment should be used with great caution in individuals over 65 years of age who are frail, forget to eat, or have significant cardiovascular or renal disease. The new insulin secretogogue repaglinide can be used in patients with impaired renal function. Metformin can lead to lactic acidosis in patients with impaired renal function or symptomatic congestive heart failure. Metformin almost never causes lactic acidosis in type 2 diabetic patients if the prescribing guidelines are followed. Troglitazone treatment is associated with a 1.8–2.0% incidence of significant increases of hepatic enzymes. A number of deaths (~30) and several liver failures requiring liver transplantation have occurred in troglitazone-treated patients. This idiosyncratic response may be minimized by monthly monitoring of liver enzymes and discontinuing the drug when liver enzyme concentrations exceed the upper limit of normal.

After 5–10 years of clinically recognized type 2 diabetes, a majority of patients will need insulin administration as a part of their therapeutic regimen to maintain target glycemic control. Initially, a dose of intermediate-acting insulin at 2200 may be added to the combination of oral antihyperglycemic agents during the day. Eventually, many patients will require insulin administration two or three times a day. At that stage, a combination of insulin and an orally administered insulin sensitizer seem to give the best glycemic control with the best cardiovascular risk profile and minimal serious side-effects.

If blood pressure is higher than 130/85 mmHg or the plasma lipid profile is not in the range considered appropriate for the patient, pharmacologic interventions for these disturbances must be pursued with the same vigor as controlling the glycemia.

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