Implications of the United Kingdom Prospective Diabetes Study

AMERICAN DIABETES ASSOCIATION

Diabetes is a metabolic disorder primarily characterized by elevated blood glucose levels and by microvascular and cardiovascular complications that substantially increase the morbidity and mortality associated with the disease and reduce the quality of life. Type 1 diabetes is characterized by total reliance on exogenous insulin for survival and comprises ~10% of all cases of diabetes. The more prevalent form of diabetes, called type 2, comprising 90% of all people with diabetes, is characterized by insulin deficiency and/or insulin resistance.

An association between the complications of diabetes and elevated blood glucose levels was postulated in the early part of this century. However, only in the last 3 decades has a substantial body of animal experimental studies and human observational studies and clinical trials directly linked hyperglycemia with the development of diabetic complications (1). Some of these studies have also demonstrated that treatment that lowers blood glucose reduces the risks of diabetic retinopathy, nephropathy, and neuropathy.

Notable are the results of the Diabetes Control and Complications Trial (DCCT) (2) and the similarly designed but smaller Stockholm Diabetes Intervention Study (3). These studies showed unequivocally in type 1 diabetes that lowering blood glucose delayed the onset and slowed the progression of microvascular complications. Risk reductions for various outcomes ranged from 35 to 75%. Secondary analyses in these studies showed strong relationships between the risks of developing these complications and glycemic exposure over time. Moreover, there was no discernable glucose threshold, i.e., there was a continuous reduction in complications as glycemic levels approached the normal range. Improved glycemic control was also associated with reduced cardiovascular events in the DCCT, but the difference was not statistically significant. Perhaps this was because the population studied was young adults and therefore the event rate was very low.

Many of the observational studies also support a correlation between glycemic control and diabetic complications in patients with type 2 diabetes, but until now, there have been only three randomized controlled trials attempting to test the benefit of lowering blood glucose on the incidence of complications. The first of these studies was the University Group Diabetes Program (UGDP), which showed no benefit of glycemic control in new-onset type 2 diabetic patients (4). However, in the UGDP, there were only 200 subjects in each treatment group, HbA_{1c} was not available as a reliable method for measuring chronic glycemia, and the difference in glucose control between the most intensively treated group and the other treatment groups was only a fasting plasma glucose of ~30 mg/dl (1.7 mmol/l). Of note, a major concern emanating from the UGDP was the observation that the sulfonylurea agent (tolbutamide) and a biguanide (phenformin) used to reduce hyperglycemia were associated with increased cardiovascular mortality. The suspicion that glucose lowering with oral agents in patients with type 2 diabetes may actually be harmful has persisted since publication of the UGDP data in 1970.

The second controlled trial in type 2 diabetes was only recently reported (5). This small study conducted in 110 lean Japanese subjects showed that multiple insulin injections resulting in better glycemic control (HbA_{1c} = 7.1%) compared with conventional treatment (HbA_{1c} = 9.4%) significantly reduced the microvascular complications of diabetes. The extent of the risk reduction in this Japanese study was similar to that in the DCCT, thereby supporting the hypothesis that glycemic control is important in both types of diabetes.

The third trial in type 2 diabetes was a pilot study that randomized 153 men to intensive or conventional therapy (6). Despite a 2% absolute HbA_{1c} difference in glycemic control between the two groups, the trial reported no significant difference in cardiovascular events (when adjusted for baseline characteristics) in a follow-up period of only 27 months.

With this background, we now have the results of the largest and longest study on type 2 diabetic patients that has ever been performed (7–10). The United Kingdom Prospective Diabetes Study (UKPDS) recruited 5,102 patients with newly diagnosed type 2 diabetes in 23 centers within the U.K. between 1977 and 1991. Patients were followed for an average of 10 years to determine *1*) whether intensive use of pharmacological therapy to lower blood glucose levels would result in clinical benefits (i.e., reduced cardiovascular and microvascular complications) and 2) whether the use of various sulfonylurea drugs, the biguanide drug metformin, or insulin have specific therapeutic advantages or disadvantages. In addition, patients with type 2 diabetes who were also hypertensive were randomized to "tight" or "less tight" blood pressure control to ascertain the benefits of lowering blood pressure and to ascertain whether the use of an ACE inhibitor (captopril) or β-blocker (atenolol) offered particular therapeutic advantages or disadvantages.

SUMMARY OF THE MAIN RESULTS AND CONCLUSIONS OF THE UKPDS

- The UKPDS results establish that retinopathy, nephropathy, and possibly

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Abbreviations: DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study.

neuropathy are benefited by lowering blood glucose levels in type 2 diabetes with intensive therapy, which achieved a median HbA_{1c} of 7.0% compared with conventional therapy with a median HbA_{1c} of 7.9%. The overall microvascular complication rate was decreased by 25%.

- These results materially increase the evidence that hyperglycemia causes, or is the major contributor, to these complications. Epidemiological analysis of the UKPDS data showed a continuous relationship between the risks of microvascular complications and glycemia, such that for every percentage point decrease in HbA_{1c} (e.g., 9 to 8%), there was a 35% reduction in the risk of complications.
- The results demonstrate that the risks of complications can be significantly lowered even in the range of hyperglycemia where HbA_{1c} levels are <8.0%. There was no evidence of any glycemic threshold for any of the microvascular complications above normal glucose levels (i.e., HbA_{1c} >6.2%).
- These results confirm previous conclusions that lowering blood glucose would be beneficial based on observational studies, pathological studies, and on three randomized clinical trials: the DCCT, the Stockholm Diabetes Intervention Study, and the Japanese study.
- No significant effect of lowering blood glucose on cardiovascular complications was observed. A 16% reduction (which was not statistically significant, P = 0.052) in the risk of combined fatal or nonfatal myocardial infarction and sudden death was observed.
- Epidemiological analysis showed a continuous association between the risk of cardiovascular complications and glycemia, such that for every percentage point decrease in HbA_{1c} (e.g., 9 to 8%), there was a 25% reduction in diabetes-related deaths, a 7% reduction in all-cause mortality, and an 18% reduction in combined fatal and nonfatal myocardial infarction. Again, no glycemic threshold for these complications above normal glucose levels was evident.
- The highest average annual incidence of major hypoglycemic events was 2.3% of patients per year in those receiving insulin therapy.
- The study showed that lowering blood pressure to a mean of 144/82 mmHg significantly reduced strokes, diabetes-related deaths, heart failure, microvascular complications, and visual loss.
- Epidemiological analysis showed a continuous relationship between the risk of all the above outcomes and systolic blood pressure. There was no evidence of a threshold for these complications above a systolic blood pressure of 130 mmHg.

The results of the UKPDS and its implications for the treatment of type 2 diabetes will now be discussed in the format of pertinent questions and answers. This discussion also reflects the position of the American Diabetes Association on the UKPDS findings.

QUESTION 1: How was the UKPDS conducted?

The design of the UKPDS was explicit and was directed by prespecified protocols with appropriate randomization of patients. Laboratory and clinical tests were performed by accepted methodologies, and all end points were satisfactorily documented. The large number of patients and their heterogeneity provide great assurance that the results should apply to the U.S. population of men and women with type 2 diabetes.

The UKPDS was originally designed as a straightforward randomized clinical trial comparing the effects of an "intensive treatment policy" with four pharmacological monotherapies, versus a diet control group, on the cardiovascular and microvascular complications of type 2 diabetes. The three main original monotherapies to which all patients were randomized were chlorpropamide, glyburide, and insulin. In the subgroup of overweight subjects, metformin as monotherapy was compared with the control group and to the other three pharmacological agents.

The primary and major question of the study was whether lowering blood glucose was beneficial. Therefore, the treatment goal in all the intensive pharmacotherapy groups was a fasting plasma glucose (FPG) level <6.0 mmol/l (108 mg/dl), and the treatment goal in the conventional diet control group was an FPG level <15 mmol/l (270 mg/dl). These widely different treatment targets were meant to insure attainment of adequate glycemic separation to test the main hypothesis. However, it became apparent that none of the oral pharmacological monotherapies were capable of maintaining the intensive treatment goal, and therefore adequate glycemic separation from the control group might be jeopardized. Thus, combination therapy was used, mixing insulin or metformin with sulfonylureas, as well as crossing over patients into the alternate pharmacological treatment groups. The final main "intention to treat" comparison was between intensive therapy, which now included all patients originally assigned to insulin and sulfonylurea drugs, and conventional therapy, which included all patients originally randomized to diet treatment.

It must also be noted that the diet group could likewise not be kept pure. When patients in this group exceeded an FPG level of 15 mmol/l (270 mg/dl), they were also treated with the same pharmacological agents used in the other groups. Ultimately, 80% of the patients in the diet group required one or more of the same pharmacological agents for which this group was to serve as the control. Thus, all effects of each of the pharmacological treatment groups were confounded by crossovers, making it difficult to discern specific drug effects. For example, of the total person-years of treatment in the control group, 58% were spent on the original diet treatment only, 25% on a sulfonylurea alone or in combination with other drugs, 12% on metformin, and 15% on insulin. In the obese subgroup, metformin was administered alone or in combination with other drugs for 82% of person-years to those assigned to it and for 10% of person-years to those in the obese control group.

On the one hand, these drug crossovers make the ultimate differences in efficacy observed between the intensive and conventional groups all the more impressive. On the other hand, the prevalence of treatment crossovers and additions reduces our confidence in the differences observed, or not detected, among the various pharmacological agents. Of note, the main analysis performed by the UKPDS is identical to the analysis performed in the DCCT. In both studies, intensive treatment designed to achieve near normal glycemia with whatever means necessary was compared with conventional therapy.

QUESTION 2: What has the UKPDS contributed to our understanding of the biology of diabetic complications?

The UKPDS results confirm and extend previous evidence supporting the hypothesis that hyperglycemia and its sequelae are a

major cause of the microvascular complications of diabetes. The risk gradient in the UKPDS for late microvascular events was very similar to that seen in the DCCT for early microvascular events. This indicates that the presence of hyperglycemia is a toxic state whether it occurs early or late in life and irrespective of its underlying cause.

The UKPDS also demonstrated by epidemiological analysis that cardiovascular outcomes were consistently associated with hyperglycemia in a manner similar to the relationship between microvascular complications and hyperglycemia. Nonetheless, the UKPDS did not prove definitively that intensive therapy that lowered blood glucose levels reduced the risk of cardiovascular complications compared with conventional therapy. Thus, the role of hyperglycemia in cardiovascular complications is still unclear.

QUESTION 3: What level of glucose or blood pressure control do the UKPDS results suggest should be achieved in patients with type 2 diabetes?

The median HbA_{1c} levels achieved in both the conventionally treated group (7.9%) and the intensively treated group (7.0%) are lower than the present average HbA_{1c} in type 2 diabetic patients in the U.S. (~8.5–9.0). These differences most likely reflect the fact that patients were enrolled in the UKPDS on diagnosis, whereas the HbA_{1c} levels usually achieved in the general population reflect diabetes of mixed durations.

A significant reduction in complications was achieved with intensive therapy that lowered HbA_{1c} levels to a median of 7.0% over 10 years when compared with conventional treatment that achieved a median HbA_{1c} of 7.9%. Furthermore, on epidemiological analysis, there was no evidence of any glycemic threshold above a normal HbA_{1c} level of 6.2%. Therefore, the results of the UKPDS mandate that treatment of type 2 diabetes include aggressive efforts to lower blood glucose levels as close to normal as possible.

The results of the UKPDS blood pressure study also indicate that aggressive treatment of even mild-to-moderate hypertension is beneficial. Moreover, continued reduction of blood pressure into the normal range resulted in fewer complications. Hence, blood pressure should be kept below 130/85 mmHg, as previously recommended by the American Diabetes Association and others.

QUESTION 4: What are the risks of aggressive glucose or blood pressure control?

In the UKPDS, at the glycemic levels achieved, a small fraction of patients had a major episode of hypoglycemia regardless of the pharmacological therapy used, and one patient died from hypoglycemia over the 27,000 patient-years of intensive therapy. Thus, the risk of hypoglycemia should not discourage attaining HbA_{1c} levels approaching normal.

As mentioned above, the UGDP study raised concerns that treatment with sulfonylurea agents may increase cardiovascular events or death. However, the UKPDS found no increase in the rates of myocardial infarction or diabetes-related deaths when participants treated intensively with sulfonylurea drugs were compared with those treated conventionally.

Some but not all previous observational studies have suggested that plasma insulin levels may be associated with increased cardiovascular disease risk. However, the UKPDS showed no increase in cardiovascular events or mortality in patients assigned insulin therapy, even though their fasting plasma insulin levels were higher than those of the conventionally treated patients. Thus, the beneficial effects of intensive glucose control with insulin or sulfonylurea agents outweigh their purported risks.

QUESTION 5: What differences were observed between the various forms of intensive therapy?

In the main trial, there were no significant differences with regard to diabetic complications or adverse cardiovascular events between therapy with insulin and with sulfonylurea drugs. The strength of this conclusion is somewhat attenuated by the frequency with which drug crossovers and additions occurred for the purpose of achieving blood glucose targets. Patients randomized to sulfonylurea drugs remained on them ~80% of the time (with a fraction treated with alternate therapies), and patients randomized to insulin remained on it ~75% of the time. It is again worth noting that no increase in cardiovascular events or death was observed with either insulin or sulfonylurea drugs—this despite the fact that both agents led to greater weight gain and higher plasma insulin levels than in the conventional group. This observation gives some additional reassurance that insulin should not be held culpable for atherosclerotic events and that sulfonylurea drugs should not be held responsible for lethal cardiovascular toxicity. In that regard, physicians who have been greatly concerned with the possibility of these serious adverse effects should feel considerably less constrained in using these agents for their valuable blood glucose–lowering benefits, such as saving vision.

QUESTION 6: What were the role and results of metformin therapy in the UKPDS?

This topic requires individual discussion because of the different ways in which metformin was used and the conflicting results observed in each instance. The initial UKPDS design included assignment of obese patients to metformin as well as to the other intensive therapies and conventional therapy. Patients initially assigned to intensive therapy with metformin had decreased risks of combined diabetes-related end points, diabetes-related deaths, all-cause deaths, and myocardial infarction compared with the conventionally treated patients. These risks were significantly reduced by about one-third ($P < 0.0023$–0.017). The beneficial effect on cardiovascular disease is in contrast to the failure of insulin or sulfonylurea treatment to reduce cardiovascular outcomes when compared with conventionally treated obese patients. This difference between drugs may possibly relate to the absence of weight gain with metformin and/or to some beneficial effects of metformin on the insulin resistance syndrome. Surprisingly, no significant decrease in microvascular complications was observed with intensive metformin therapy or with combined insulin/sulfonylurea intensive therapy in the obese subjects. This inconsistency, along with drug crossovers between the treatment groups and the lesser numbers of patients in the subgroups, creates uncertainty regarding the overall beneficial effect of metformin on obese patients.

Late in the study, 537 obese and normal-weight patients originally assigned to sulfonylurea therapy who failed to maintain blood glucose in the designated target range

were randomly assigned to continue sulfonylurea therapy alone or to have metformin added. In this substudy, an intention-to-treat analysis showed that the group assigned to combined metformin/sulfonylurea therapy had a 96% increase in diabetes-related deaths ($P < 0.039$) and a 60% increase in all-cause death ($P < 0.041$), compared with the patients assigned to continue maximal doses of sulfonylurea drugs alone. However, to keep the FPG level <15 mmol/l (270 mg/dl) and the patients asymptomatic, metformin was given to 25% of the patients initially randomized to receive sulfonylurea drugs alone. Additionally, the lack of a placebo control and the inability to employ masking in this substudy also call these detrimental effects into question.

In an attempt to reconcile the beneficial effects observed when metformin was used in obese subjects, with the detrimental effects observed when metformin was added to maximum sulfonylurea therapy, the results of the two substudies were combined in a meta-analysis. We believe this analytical approach does not resolve the discrepancy in the results with metformin, that is, it does not provide assurance that the combination is safe or prove that it is unsafe.

If there is some specific mechanism of adverse interaction between metformin and sulfonylurea drugs, this can only be definitely determined in a new, appropriately designed, randomized, placebo-controlled trial. Until such a trial is concluded, we do not recommend any change in the current guidelines for the use of metformin as monotherapy or in combination with sulfonylurea drugs.

QUESTION 7: What were the effects of blood pressure control?

"Tight blood pressure control," as achieved in the UKPDS, significantly reduced the risks of virtually all cardiovascular and microvascular outcomes, with risk reductions ranging from 24 to 56%. A 21% reduction seen in myocardial infarction was not significant ($P = 0.13$). The type and number of adverse effects seen with "tight blood pressure control" (mean 144/82 mmHg) or "less tight blood pressure control" (mean 154/87 mmHg) were not different from those generally reported in the literature.

The UKPDS also compared antihypertensive treatment with an ACE inhibitor to that with a β-blocker. Both drugs were about equally effective in lowering blood pressure, although patients on β-blockers had slightly better blood pressure control (a 1-mmHg systolic and 2-mmHg diastolic improvement). Neither drug was superior to the other in any outcome measured, including diabetes-related deaths, myocardial infarction, and all microvascular end points. Also, there were no significant differences in microalbuminuria or proteinuria. However, because of the low prevalence of nephropathy in the population studied, it is unclear whether there were sufficient events to observe a protective effect of either drug on the progression of nephropathy. We conclude that both drugs used to reduce hypertension are equally effective and safe, and either can be used with great benefit to treat uncomplicated hypertension in patients with type 2 diabetes.

Of note, conventionally and intensively treated blood glucose study patients had equal benefit from blood pressure lowering. Likewise, the tightly and less tightly controlled blood pressure study patients had equal benefit from blood glucose lowering. Thus, both hyperglycemia and hypertension should be vigorously treated when they occur together with an expectation that reductions in microvascular and cardiovascular outcomes will be additive.

QUESTION 8: Is tight control contraindicated in any group of type 2 diabetic patients?

Patients with type 2 diabetes are usually diagnosed at an age when the likelihood of having comorbid conditions increases. Competing comorbidities such as hypertension and dyslipidemia can lead patients and physicians toward emphasizing the treatment of one problem over another. In most cases, however, this does not have to occur, and the results of the UKPDS at least support the premise that equal attention to diabetes and hypertension can be accomplished.

Older type 2 diabetic patients have a shorter life expectancy from time of diabetes diagnosis by virtue of their age and their risk or presence of cardiovascular disease. Thus, it has been argued that the benefits of glycemic control that are realized over time may be preempted by earlier adverse outcomes of other diseases. But since patients in the UKPDS entered the study at an age equivalent to the average age of diagnosis in the U.S., vigorous treatment to prevent the complications of diabetes from the time of diagnosis is clearly warranted given the UKPDS results. In addition, because the UKPDS confirmed that a substantial proportion of newly diagnosed patients (~50%) already have some early evidence of diabetic complications, such disturbing findings should provide an even greater impetus to aggressive intervention.

Finally, it is important to note that kidney failure is much more common in the U.S. than in the U.K., because the U.S. has larger minority populations who develop type 2 diabetes earlier in life and have worse average blood glucose control. There may also be a genetic susceptibility to kidney disease in some ethnic populations in the U.S. Because the UKPDS reported significant reductions in the risk of developing kidney disease and in the risk of its progression, the results are particularly important for the prevention of diabetic renal disease in the U.S. population.

QUESTION 9: Are the results of the UKPDS achievable for most people with diabetes?

In theory and practice the answer is yes. Although the UKPDS was a clinical research trial, subjects were enrolled and managed in a wide variety of community clinics. The professionals conducting the study and directing care were very knowledgeable about diabetes, but the overall treatment program was not unusually sophisticated or complex. Patients enrolled in the UKPDS started with an HbA_{1c} level of 9.1%. The conventional treatment group achieved a 10-year median HbA_{1c} level of 7.9%, and the group treated intensively with readily available glucose-lowering agents achieved a median HbA_{1c} level of 7.0%. Perhaps the most important ingredient leading to therapeutic success was persistence.

It should be acknowledged that there is an increase in blood glucose levels with increasing duration of type 2 diabetes—an upward trend noted in both the conventional and intensive treatment groups of the UKPDS. The ability to prevent or at least retard this rise may be facilitated by recently approved glucose-lowering drugs that were not available to the UKPDS. Both the success and the difficulties of the UKPDS should stimulate further development of new treatments and combinations that can successfully manage hyperglycemia in type 2 diabetes.

QUESTION 10: Are there other major unanswered questions in the treatment of diabetes?

The UKPDS and the DCCT have answered the question of whether blood glucose control is beneficial for people with type 1 and type 2 diabetes. It definitely is. However, both trials enrolled patients before serious microvascular complications had developed.

The benefits of achieving normal blood glucose levels are not known in those who already have more advanced complications. Also, the risk of hypoglycemia may be greater in such patients. Thus, additional studies would be desirable on the risks and benefits in people with diabetes who have more advanced complications.

Neither study gave a definitive answer to the question of whether glucose control reduces the risk of cardiovascular disease. Both studies showed trends in reducing the risk of cardiovascular events, but these trends were not statistically significant. Several observational studies, including the results of the epidemiologic analyses of UKPDS data, have shown strong associations between blood glucose control and the risk of cardiovascular disease morbidity (heart attacks, strokes, and amputations) and all-cause mortality. However, these studies do not prove that high blood glucose causes these complications and that intensive treatment to lower glucose would reduce the risk.

Fortunately, the patients in both the DCCT and the UKPDS are enrolled in long-term follow-up studies that will determine whether the initial period of intensive treatment prevents cardiovascular complications by comparison with the initial period of conventional treatment. Other studies would also be desirable to establish the risks and benefits of glucose control in patients who already have cardiovascular disease. Such risks and benefits may well be different from those characteristic of earlier stages in the natural history of diabetes.

CONCLUSIONS — The UKPDS has provided strong support for the American Diabetes Association's position that vigorous treatment of diabetes can decrease the morbidity and mortality of the disease by decreasing its chronic complications. The results show that lowering blood glucose reduces the incidence of microvascular complications in type 2 diabetes as it does in type 1 diabetes. In addition, lowering blood pressure reduces the incidence of cardiovascular complications as it does in nondiabetic individuals, and also leads to further reduction in the severity of microvascular complications. Although the UKPDS did not establish directly any effect of lowering blood glucose on cardiovascular complications, the use of insulin, sulfonylureas, or metformin (and perhaps metformin in combination with sulfonylureas) does not appear to increase the risk of cardiovascular events. Therefore, nothing should stop practitioners from pursuing the American Diabetes Association's goals for glycemia and blood pressure. The UKPDS is another landmark diabetes study proving the value of metabolic control. It is time for all health professionals to treat diabetes aggressively. It is also time for patients to take their diabetes with utmost seriousness. And it is incumbent upon the health care system to provide the necessary resources for both to be successful. Compromise or acceptance of a disadvantageous and dangerous status quo in people with diabetes should not be tolerated any longer.

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