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CONTROVERSIAL ISSUE

Trade-offs in Treatment Alternatives for Non-Insulin-dependent Diabetes Mellitus

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THE COST associated with the care of patients who have non-insulin-dependent diabetes mellitus (NIDDM) have been estimated at nearly 14 billion dollars per year. Over 80% of these patients are cared for by primary care physicians rather than endocrinologists or diabetologists.[1] Their providers are faced with a complex, and perhaps ambiguous, set of treatment alternatives that include the use of insulin therapy, prescription of sulfonylurea agents, diabetic diets and weight loss, and patient education. The choice among these alternatives is complex because the costs, risks, and benefits of the alternatives have not been well defined.

In this paper, we review the alternatives with emphasis on patient factors that have often been neglected in the diabetes literature. We consider traditional views of treatment benefits and side effects, and discuss patient factors.

THE UNIVERSITY GROUP DIABETES PROGRAM CONTROVERSY

Substantial epidemiologic data suggest that prolonged elevation of blood glucose is correlated with complications in a variety of organ systems.[2] However, the assumption that reductions in blood glucose are associated with reductions in the probabilities of these complications has been more difficult to demonstrate in humans. The best available evidence was provided by the large and controversial University Group Diabetes Program (UGDP), a cooperative randomized clinical trial involving 12 medical centers. In this program, 823 patients were randomly assigned to five treatment groups. Two groups received insulin injections, one on a variable-dosage schedule and the other on a standard-dosage schedule. The third group received tolbutamide — an oral hypoglycemic agent — while the fourth group received placebo. The fifth group was assigned to take phenformin, but this part of the study was discontinued after complications were observed early in its course. All groups were given a special diet.

After eight years, the mortality status of 818 of the original 823 patients was determined. Those randomly assigned to receive tolbutamide had a significantly *increased* probability of death due to cardiovascular diseases in comparison with the placebo group. The two insulin groups did not differ significantly from the placebo group. The UGDP study touched off a variety of controversies. Various authors suggested that there were methodologic flaws associated with the randomization, the dependability of the outcome measures, the uniformity of protocols across centers, and a variety of decisions that were made throughout the project.[3-5] By 1971, statisticians were calling for moratoriums on reanalyses of the UGDP data. Indeed, when the final results were published in 1982, most observers had already made up their minds about the credibility of the study.

Since the publication of the UGDP results, several related studies have been reported. Davidson[1] argued that at least six studies failed to support the UGPD conclusions. Perhaps the most important of these was the prospective study conducted in Bedford, England. This trial showed no adverse consequences of tolbutamide, but also failed to show long-term benefits.[6] A related prospective study demonstrated an initial positive effect on survival associated with tolbutamide use, but this effect had diminished by the fourth year of follow-up.[7] Several studies (reviewed by Davidson) considered different treatment approaches in non-randomized studies. The results of these studies tended not to suggest a toxic effect of sulfonylurea medications. However, they consistently showed higher mortality rates in insulin-treated patients, probably because insulin treatment is a proxy for severity of disease.

The benefits of various treatment approaches for NIDDM remain ambiguous. Although hyperglycemia is clearly a risk factor, it has not been clearly established that alternative treatment approaches improve survival and reduce disease complications. Evidence fails to confirm the UGDP finding of increased cardiovascular death in the tolbutamide condition. However, evidence that chronic use of sulfonylurea agents prevents death and complications is also absent.

The UGDP controversy affected the use of oral agents. Prescriptions for these medications rose in the years prior to the publication of the UGDP findings, then sharply fell to a low in 1979. However, the use of oral hypoglycemic agents has sharply increased since 1980. By 1986, these drugs accounted for about 1% of all prescriptions, or about 21.5 million orders.[8] Many of the recent prescriptions for oral hypoglycemic medications have been for "second-generation" com-

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pounds. These have the convenient property of not having been evaluated in the UGDP study. Although the newer agents are more effective in reducing blood sugar, their value in reducing complications remains to be demonstrated.

SIDE EFFECTS

A choice among the treatment alternatives for NIDDM must consider risks and benefits. Insulin therapy is considered by many to be appropriate for treatment of late stages of NIDDM. The side effects of insulin therapy include delayed local skin reactions, insulin allergies, insulin-induced lipoatrophy, and lipohypertrophy. Furthermore, symptomatic hypoglycemia is a common occurrence with insulin therapy, particularly when the goal is to obtain tight control.

Although the side effects are well documented, their rates are less well established. Early studies suggested that delayed local skin reactions occurred in as many as 50% of patients who used older, impure insulin preparations. The comparable figure with current regimens is variable across studies. Insulin allergies occur in only about 0.1% of all cases.[1] Subtle side effects of insulin treatment are not as well documented. However, patients often complain that insulin serves as an appetite stimulant and may be associated with undesired weight gain. The Diabetes Control and Complications Trial (DCCT) group recently confirmed clinical observations that Type I NIDDM patients who were aggressively treated with insulin gained more weight than did patients adhering a standard regimen.[9]

Davis and colleagues[10] evaluated psychosocial adjustment for insulin-using and non-insulin-using NIDDM patients. They found that those using insulin reported more adjustment problems, including more problems controlling their condition, more social problems, and greater perceived risk of complications. However, since the patients were not randomly assigned to condition, insulin use may have indicated greater disease severity.

The prevalence of side effects of sulfonylurea agents has been estimated to be 5%, with reactions necessitating discontinuation of therapy apparent in 1–2% of all patients. The most common side effects are gastrointestinal and cutaneous. Some investigators have reported disulfiram-like reactions, although they are rare. Prevalence rates for these reactions have ranged from 1% to 33% of those taking chlorpropamide. These compounds may also cause inappropriate secretion of antidiuretic hormone. As a result, serum sodium levels may become abnormally low and result in headaches, lethargy, stupor, and seizures.[11]

It is often assumed that dietary therapy, which is the cornerstone of NIDDM management, is without risk. Two aspects of dietary therapy are important. First, it is widely believed that diets high in fiber and complex carbohydrate will improve glucose tolerance. The second aspect of dietary therapy is directed toward weight management.

One of the complications with weight loss protocols is that sustained weight reduction has been difficult to achieve.[12] This has been compounded by recent evidence suggesting that repeated cycles of weight loss and regain may do harm. In one animal study, rats assigned to a protocol of repeated cycles of weight gain and weight loss reduced the rate at which weight was lost and increased the rate at which weight was regained during each repeated cycle of food deprivation and ad lib feeding.[13] In other words, repeated cycles of weight loss and regain may stimulate metabolic efficiency. In studies of adolescent wrestlers, for example, those who repeatedly lost weight prior to matches had significantly lower mean metabolic rates than those who did not go through voluntary weight reduction cycles.[14]

Henry et al.[15] reported impressive results of very-low-calorie diets for obese NIDDM patients. Newer approaches to these diets have alleviated earlier concerns aggravated by deaths associated with liquid protein diets reported to the FDA.[16] However, the maintenance of weight loss in the study of Henry et al, was strikingly poor, and obtaining dietary compliance is difficult. Ary and colleagues[17] reported that medication compliance is more commonly obtained than are recommended changes in diet or exercise. Although short-term weight loss has been achieved in many studies, permanent weight loss has rarely been reported. The ultimate consequences of short-term weight loss are not entirely clear. However, there is growing concern that repeated cycles of weight loss and regain may have metabolic consequences.

OTHER ASPECTS OF DIABETES CARE

Comprehensive diabetes care involves a variety of other options. For example, the American Diabetes Association recommends that third parties reimburse for outpatient educational and nutritional counseling. Yet the evidence that patient educational programs result in better patient outcomes is not firmly established. For instance, Kaplan and Davis[18] reviewed the 13 studies that were used to support the ADA policy statement. They found that only two of these studies compared a treatment group with a control group, and patients were not randomly assigned in either study. Although it has been argued that outpatient diabetes educational programs are cost-effective, only four of the studies supporting the ADA position actually accounted for program costs. Upon close inspection, it appeared that many of these programs increased rather than decreased health care expenditures. The impacts of the programs upon diabetes control were inconsistent across studies, and few of the studies considered any functional outcome or comprehensive measure of patient health status.[18]

Since we frequently make the assumption that care is good, we further assume that the more care patients receive, the better their outcomes will be. Community programs in diabetes often measure their success by the number of service units delivered. Yet the relationship between service and outcome is unclear. In one study, Anderson and colleagues[19] evaluated the care given by community physicians in Michigan in 1980–1981 and again in 1985. During the interval, physicians increased their use of modern management techniques such as oral medications, multiple injections, and self-monitoring of blood glucose. Despite increased care, there was no consequent improvement in the mean glycosylated hemoglobin values of the patients. Although dissemination of modern management methods is important, success should be judged by improved outcomes, not just increased service.

Other innovations in diabetes care, such as home glucose monitoring, may not be fulfilling their promise in terms of patient outcomes. For example, Wing and colleagues[20] did not observe a consistent relationship between home glucose monitoring and patient outcomes in NIDDM groups. Home glucose monitoring may be a problem for patients. For example, Mazze et al.[21] found that nearly three-fourths of patients asked to keep self-monitoring records of blood glucose failed to report the values accurately. Many studies have reported problems with compliance. This innovative aspect of care may create significant burdens without necessarily producing clear benefits.

The preceding review suggests that choices among treatment alternatives are complex. The benefits of each treatment alternative are not definitively established. Although each alternative may be associated with side effects, few studies have measured these side effects or have provided systematic guidelines for evaluating benefits versus side effects. The target of treatment is typically improved glucose tolerance. Yet we cannot say with certainty that improved glucose tolerance, particularly for the marginally affected NIDDM patient, will result in less mortality or morbidity or better quality of life. Modern treatments are often a nuisance for patients, but the literature rarely documents patient attitudes toward their care or patient preferences for alternatives.

THE PATIENT'S ROLE

Clinical articles often make the paternalistic assumption that physicians are entitled to make treatment decisions for their patients. Despite a growing consensus that patients should be involved in decisions affecting their health care,[22] recent studies suggest that patients rarely report being advised of their options regarding surgical procedures.[23] This failure to inform is all the more indefensible in diabetes care because many interventions affect quality of life in addition to life expectancy. Determining potential benefit requires the integration of patient utilities and the assessment of various outcomes weighted by their probabilities.

PATIENT FACTORS IN DIABETES

The published literature tells us remarkably little about patient preferences for different treatment modalities. Many studies have attempted to predict compliance among NIDDM patients. Yet these studies tend to focus on demographic and personality characteristics used to "diagnose" the non-complier. Little consideration is given to the effects of the treatment on the patients and their life-styles. For example, a recent paper concerning insulin-dependent diabetes mellitus (IDDM) patients evaluated discontinuation of continuous subcutaneous insulin infusion (CSII) therapy. The authors focused on demographic characteristics, mental illness, and cigarette smoking, all of which were poor predictors of dropping out of treatment. However, the most common reason for terminating treatment was that it was uncomfortable, that it caused irritation, or that there was an infection at the infusion site.[24] Several studies have reported that patients are more likely to drop out of treatment if they have poor outcomes.[25] "Noncompliance" might mean that the treatment is not working or that it is creating new problems. It is interesting that there is essentially no literature evaluating the nuisance factor of using sulfonylurea medications. A MEDLINE search crossing sulfonylurea compounds with patient compliance revealed only five papers published in the last 20 years.

Social learning theory suggests that situational factors play a more important role in determining compliance behavior then do dispositional or demographic characteristics. Social environment and specific health beliefs may be good predictors of compliance.[26] Other studies have demonstrated that diabetic adults deviate from their regimens when they become a nuisance. Open-ended questions suggest that common reasons for dietary non-adherence include eating out in restaurants or being in social situations where food offers are difficult to refuse.[17]

Occasionally, changes in regimens may have other consequences. For example, diabetic patients are not allowed to operate commercial motor vehicles if they take insulin. They may gain commercial certification if their condition is stabilized by either diet or a combination of diet and oral hypoglycemic drugs.[27] A diabetic adult can get a commercial pilot's license if his or her condition is controlled by diet but use of insulin or oral medications is grounds for disqualification.[28]

There are now a few published examples of patient coparticipation in the decision process. In one study, adults who had IDDM were asked to describe their requests. There was a significant correlation between the

TABLE 1

Summary of Risks and Benefits of Three Approaches to Management of Non-Insulin-dependent Diabetes Mellitus

	Benefits	Risks	Unknown*
Insulin	Improved control of blood sugar (probable) Reduced symptomatic hyperglycemia (probable)	Delayed local skin reaction (rare) Insulin resistance (occasional) Lipoatrophy (probable) Symptomatic hypoglycemia (probable) Lifestyle interference (probable) Weight gain (probable) Compliance failure (probable)	Reduced mortality Reduced complications Improved quality of life
Sulfonylureas	Improved control of blood sugar (probable in short run, moderately probable in long run)—failure in 15–20% Reduced symptomatic hyperglycemia (probable)	GI disturbance (occasional) Skin reactions (rare) Disulfiram-like reactions (rare) Cholestatic jaundice (rare) Dilutional hyponatremia (rare) Compliance failure (25%/year probable) Increased chance of drug interactions	Reduced mortality Reduced complications Improved quality of life
Dietary treatment	Improved control of blood sugar (probable with significant, long-term weight loss) Favorable alteration of blood lipid profile (probable)	Poor long-term compliance (probable) Sense of failure with weight regain (probable) Alteration of metabolic rate, making future weight loss more difficult (possible)	Reduced mortality Reduced morbidity Improved quality of life

*Current data do not allow an evaluation of the impact of treatment upon morbidity, mortality, or quality of life for any treatment alternative.

perceived fulfillment of these requests and perceived health status and a nonsignificant trend suggesting a relationship between request fulfillment and reduced glycosylated hemoglobin.[29] In another experimental study, Greenfield and associates[30] randomly assigned NIDDM patients to a control condition or to a 20-minute session designed to improve information-seeking during physician encounters. In comparison with controls, those experiencing the intervention were twice as effective in eliciting information from their physicians and eventually achieved lower glycosylated hemoglobin values. Patients can productively contribute to therapeutic decisions, and the time has come to activate them in the treatment decision process.

SUMMARY

In order to evaluate the choice among alternatives quantitatively, a formal decision model must be developed. Yet the literature does not currently include the information required to develop this model. Data tell us very little about what factors should be considered in the choice of treatment for NIDDM patients. Table 1 summarizes some of the advantages and disadvantages of insulin, sulfonylureas, and dietary treatments. Insulin may have the greatest effect upon blood glucose, but may also be associated with the greatest likelihood of nuisance for the patient. At the other extreme, dietary treatment may be safe, but may have a low probability of achieving long-term blood glucose control. There is remarkably little in the literature that considers nuisance factors for the patient, minor but persistent side effects, or the likelihood of other physical changes such as weight gain. We know even less about how to integrate preferences for benefits and side effects into a comprehensive decision.

Although some profiles of laboratory results clearly dictate a treatment protocol, there is considerable variability in the treatment options for a large number of NIDDM patients. Consider, for example, the patient who has a fasting blood glucose of 250 mg/dl but no symptoms. There may be several treatment alternatives. Yet the chances of therapeutic success could be influenced by the patient's concern about being dependent upon medication, willingness to comply with life-style changes, and fear of using needles. We suggest that the patient must be active in negotiating the choice of treatment, and that patient preferences for expected outcomes, side effects, and nuisance factors need to be considered.

We are unable to simulate the impact of oral hypoglycemic agents, insulin, or diet upon health outcomes. The data on the effects of these treatments on life expectancy and diabetic complications have not been well established. Thus, Table 1 shows as unknown the effect of each treatment on mortality, complications, and quality of life. Blood glucose is often cited as an outcome of diabetes care. Blood glucose is important because it correlates with life expectancy or quality of life either currently or at some point in the future, yet blood glucose is not a health outcome. Although reductions in blood glucose are presumed to result in better health outcomes, data do not firmly establish this inference.

In order to develop a comprehensive decision model, we need research that will allow the quantification of treatment benefits and all side effects. The side effects should include inconvenience and psychologi-

cal symptoms, such as fear and anxiety. Labeling effects and changes in self-image should also be considered. A comprehensive model, we believe, will be a step toward improved well-being and greater satisfaction for NIDDM patients.

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