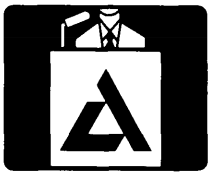
Policy Statement



The UGDP Controversy

AMERICAN DIABETES ASSOCIATION

The first report from the University Group Diabetes Program (UGDP) on the use of diet, insulin, and tolbutamide in treatment of maturity-onset diabetes was presented at the annual scientific meeting at the American Diabetes Association (ADA) in June 1970 and published soon thereafter.[1] Controversy regarding the findings preceded its presentation and was recognized in the original statements on the UGDP report released by the ADA.[2,3] Unusual attention was directed to the first report of the UGDP because of the pioneering nature, ambitious scope, and magnitude of the study and because of the surprising conclusion that a relationship might exist between cardiovascular mortality and use of the sulfonylurea drug, tolbutamide.

Since 1970, further reports from the UGDP[4–6] as well as critiques of the initial and subsequent reports have been presented.[7–13] Despite these and other published material, no broad agreement has developed within scientific circles regarding the conclusions of the UGDP study or its significance as a guide to the medical community, except the suggestion that dietotherapy should be the basis of treatment for the patient with maturity-onset diabetes. Indeed, much disagreement has arisen on how pertinent the findings of the UGDP study are to individual physicians who advise diabetic patients. It is no surprise that an awareness of this disagreement between physicians has spilled over into the nonscientific press whose writings have added confusion and not a little consternation to interested consumers who must read of professional disputations without benefit either of the historical-scientific background or of the basic data. A real consumer uncertainty also has involved physicians and other health advisers who do not specialize in diabetes care, yet who are expected to advise diabetic patients.

During the years since the initiation of the UGDP study and its reports, advances in knowledge have occurred about the nature of diabetes, about the influence of metabolic control on microvascular complications, about the adverse effect of obesity on diabetes, and about the meaning of cardiovascular risk factors. Thus, it is clear that obese diabetics must lose weight, and for this a restricted calorie intake is the key mode of therapy. It has become clearer that careful control of blood glucose levels favorably affects microvascular problems.[14] Cardiovascular risk factors are more precisely defined now, and the distinction between juvenile-onset (insulin-dependent) and maturity-onset (noninsulin-dependent) diabetes is receiving broad acceptance.

Physicians have responded to these newer attitudes by adopting therapeutic maneuvers different from those extant in 1961 when the UGDP study was started. Today, neither insulin nor oral hypoglycemic agents would be given initially to asymptomatic diabetic patients in whom a dietary trial had not been pursued. Cigarettes are interdicted and lower fat diets are emphasized. Hypertension is controlled. Attention to normalizing fasting and postprandial blood glucose levels by appropriate adjustments of therapeutic modalities is a more common practice. Regular physical activity is encouraged. Thus, the management of maturity-onset diabetes has significantly advanced since 1961. The American Diabetes Association recognizes these advances and submits that advice pertinent in 1970 based on a study initiated in 1961 would be incomplete in 1979.

Reappraisal of some of the existing UGDP data with a stricter definition of patient selection,[15] as well as reports by others,[16] has again suggested that some of the inferences from the UGDP reports deserve restudy and modification. This is especially true in view of the reanalyses by the Biometric Society in 1975[17] and by the 1978 report of the Food and Drug Administration (FDA)[18] of some of the pooled final data, neither of which dealt exhaustively with the primary data from the 12 participating centers. For example, neither study analyzed in detail (nor examined in the light of newer knowledge) the appropriateness of patient inclusion in the study, the specifics on follow-up management of patients in the study, and the cumulative effect of dropout and crossover between treatment groups on continuing morbidity and mortality.

In addition, both review groups, though impeccable in makeup of participants, did fail to include any number of eminent diabetologists who could have added clinical wisdom and perspective to the panels. As a result, neither of these reports has slackened the disputations which surround the UGDP study.

Because of the continuing controversy over the UGDP study, because of the voiced concerns about the UGDP conclusions by many experienced diabetologists, because of the newer therapeutic attitudes toward maturity-onset diabetes, and especially because of the personal concerns of the affected diabetic people themselves, it is appropriate that the American Diabetes Association reassess its position concerning the UGDP reports. The timing of this reassessment has been made appropriate by the recent publication of the FDA audit analysis and the reopening of the comment period.

The following statements reflect the current viewpoints of the ADA toward the UGDP study and the controversy surrounding it.

(1) The scientific literature does not reflect a clear consensus on the interpretation of the UGDP findings.

(2) The recent audit by the FDA has reassured the ADA only so far as its analyses were carried. Data on only 159 participants out of 1027 of the UGDP study were addressed. No review of the primary clinical data or follow-up analysis on morbidity and mortality of the remaining 868 patients has been undertaken as yet. Clinical data from the 12 centers were not systematically examined.

(3) Significant differences do exist between the therapeutic designs of the UGDP protocol initiated in 1961 and the medical strategies commonly applied in 1979 by physicians with respect to the management of maturity-onset diabetes. Thus, the UGDP protocol used only one sulfonylurea drug, tolbutamide, at a single, fixed daily dosage. Neither tolbutamide nor other sulfonylureas were used in variable doses as is common practice. Of course, daily insulin dosage was varied in only one of the two study groups using insulin. More aggressive attempts at achieving weight control in the obese patient are pursued today, and attention to biochemical control of blood glucose levels is the rule irrespective of whether an oral hypoglycemic agent or insulin is used in addition to diet. These actions often require more frequent patient-physician encounters than were part of the standard UGDP protocol.

(4) It is proper that resolution of the controversies about the UGDP findings and their clinical significance be pursued within the medical community from data published in refereed scientific journals. It is distressing to read hyperbole in publications—comments that generally polarize rather than clarify the issues.

(5) The patient-physician interaction should continue to be the primary arena of decision-making regarding the appropriate therapy for the individual diabetic patient whether that therapy is diet alone, diet plus insulin, or diet plus an oral sulfonylurea.

(6) The unique nature and size of the UGDP study, its multicentered base, the time now elapsed from the inception of the study, and the previously proposed governmental decisions concerning the nature of professional advice that physicians should give their diabetic patients suggested that access to and review of data from the 12 centers of the UGDP should be carried out by ad hoc review groups that would include clinical diabetologists. However, the magnitude of the task in time, money, and manpower lessens the feasibility of this approach and the likelihood of a successful outcome and, therefore, renders it impractical at this time.

(7) Sufficient uncertainty now prevails regarding the UGDP data on sulfonylureas to warrant reconsideration of any restrictive governmental actions based on the initial findings of the UGDP study. At this time, we oppose any formal governmental restrictions on use of the sulfonylurea agents that are based on the initial interpretations of the UGDP findings until newer analyses, some of which are already available,[19] can be evaluated.

From these foregoing viewpoints, the American Diabetes Association recommends that:

(1) only data presented in refereed scientific publications concerning the UGDP be given professional credence;
(2) physician judgement on management of the maturity-onset diabetic patient should be based on an assessment of all therapeutic information available, including
   (a) data on known cardiovascular risk factors,
   (b) data on the positive influence of metabolic control of the diabetic state on vascular disease,
   (c) data pointing to the clear importance of dietotherapy in the obese diabetic patient,
   (d) data emphasizing the importance of regular physical activity,
   (e) data on objective reports in the scientific literature which pertain to the UGDP study, and
   (f) data on objective reports in the scientific literature which relate to the long-term use of the sulfonylureas.
(3) physicians continue to emphasize dietotherapy as the prime form of treatment for maturity-onset diabetes with appropriate use of an oral sulfonylurea or insulin only after diet therapy alone has clearly failed to achieve desired therapeutic goals. The choice of a sulfonylurea or insulin will be left to the judgement of the physician after discussion with the patient;
(4) until a review of all newer data which relate to the UGDP findings has been completed, any formal recommendations on the use of tolbutamide in maturity-onset diabetes that are based on the initial

findings of the UGDP study should be held in abeyance; and

(5) a package insert be developed by the ADA and the FDA for the professional and consumer community which will recognize the state of the art regarding therapy of maturity-onset diabetes current to 1979. This insert should offer physicians data and references from various studies that impinge on the modern management of maturity-onset diabetes including the use of diet, insulin, and the oral sulfonylurea drugs in achieving acceptable goals of diabetes control. Emphasis on avoiding cardiovascular risk factors should also be included.

Furthermore, the ADA comments with reference to prospective multicentered clinical studies that

(1) despite the controversies surrounding the UGDP study, well planned and executed multicentered clinical trials should continue to be supported by appropriate governmental agencies because this is the only mechanism by which certain clinical problems in diabetes can be properly studied;

(2) when such multicentered clinical trials occur in the future, provision should be made at the inception of the study for monitoring of the study by an independent referee(s) who is not a collaborating participant(s); and

(3) the activities of the independent referees would enhance the perception by the medical community on the significance of the findings by the study group.

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REFERENCES

[1] Klimt, C. R., Knatterud, G. L., Meinert, C. L., and Prout, T. E.: The University Group Diabetes Program: A study of the effect of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. I. Design, methods and baseline characteristics. II. Mortality results. Diabetes *19* (Suppl. 2): 474–830, 1970.

[2] Initial Statement on Treatment of Diabetes by the American Diabetes Association. Diabetes *19*: 527, 1970.

[3] Ricketts, H. T.: Editorial Statement on University Group Diabetes Program (UGDP) by the American Diabetes Association. Diabetes *19* (Suppl. 2): iii–v, 1970.

[4] University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. III. Clinical implications of UGDP results. J.A.M.A. *218*: 1400–1410, 1971.

[5] Knatterud, G. L., Meinert, C. L., Klimt, C. R., et al.: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. V. Evaluation of phenformin therapy. Diabetes *24* (Suppl. 1): 65–184, 1975.

[6] Knatterud, G. L., Klimt, C. R., Levin, M. E., et al.: University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VII. Mortality and selected non-fatal events with insulin treatment. J.A.M.A. *240*: 37–42, 1978.

[7] Editorial Statement. Are anti-diabetic drugs dangerous? Br. Med. J. *4*: 444, 1970.

[8] Feinstein, A. R.: Clinical biostatistics. VIII. An analytic appraisal of the University Group Diabetes Program (UGDP) Study. Clin. Pharmacol. *12*: 167–191, 1971.

[9] Prout, T. E., Knatterud, G. L., Meinert, C. L., et al.: The UGDP controversy: clinical trials versus clinical impressions. Diabetes *21*: 1035–1040, 1972.

[10] Feinstein, A. R.: Clinical biostatistics. XXXV. The persistent clinical failures and fallacies of the UGDP study. Clin. Pharmacol. *19*: 78–93, 1976.

[11] Feinstein, A. R.: Clinical biostatistics. XXXVI. The persistent biometric problems of the UGDP Study. Clin. Pharmacol. *19*: 472–485, 1976.

[12] Cornfield, J.: The University Group Diabetes Program: A further statistical analysis of the mortality findings. J.A.M.A. *217*: 1676–1687, 1971.

[13] Seltzer, H. S.: A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). Diabetes *21*: 976–979, 1972.

[14] Cahill, G. F., Etzwiler, D. D., and Freinkel, N. F.: Blood glucose control in diabetes. Diabetes *25*: 237, 1976.

[15] Kilo, C., Williamson, J. R., Choi, S. C., and Miller, J. P.: Refuting the UGDP conclusion that insulin treatment does not prevent vascular complications in diabetes. IV. International Symposium on Early Diabetes. Camerini, R., Ed. In press.

[16] Carlstrom, S., Persson, G., and Schuster, B.: Anti-diabetic treatment in the prevention of cardiovascular disease of subjects with borderline glucose tolerance. Diabetes *24* (Suppl. 2): 414, 1975 (Abstr.).

[17] Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. J.A.M.A. *231*: 583–608, 1975.

[18] Food and Drug Administration (FDA) analysis of UGDP study. Fed. Reg. *48* (220): 52732–52734, 14 November 1978.

[19] Williamson, J. R., and Kilo, C.: Comments on the UGDP, the FDA audit of the UGDP, and proposed labeling changes for oral hypoglycemic agents—a common sense look at the UGDP. Testimony submitted to Bureau of Drugs, FDA on 20 December 1978.