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Issues in the treatment of type 2 diabetes; Sulfonylureas, metformin, and troglitazone

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This is the third of six reports on the International Diabetes Federation (IDF) meeting held in Helsinki, Finland, in July 1997. It deals with the treatment of type 2 diabetes.

Issues in the Treatment of Type 2 Diabetes

George Alberti, Newcastle, U.K., discussed the timing of treatment of type 2 diabetes. Factors to be addressed in determining when to begin treatment are quality of life, prevention of complications, and prevention of disability once complications develop. The goal of preventing diabetic complications rather than achieving glycemic control per se should determine when treatment is initiated. Diabetic complications include a two- to fivefold increased incidence of heart disease, stroke, and peripheral vascular disease, as well as neuropathy, gangrene and amputation, retinopathy and cataract formation, and hypertension and nephropathy. In the U.K. Prospective Diabetes Study (UKPDS), at initial presentation 20–26% of diabetic patients had retinopathy, 3–7% had evidence of peripheral neuropathy, 1–4% had increased serum creatinine, 19–36% had hypertension, 19% had an abnormal electrocardiogram, 7–13% had abnormal peripheral pulses, and 2% had evidence of a prior myocardial infarction; in addition, 16–20% of the men had experienced impotence. Overall, half of the patients had some evidence of micro- or macrovascular disease. Extrapolating backward from retinopathy data, once can estimate that on average type 2 diabetes begins 9–12 years prior to diagnosis. In developing countries, late diagnosis is even more common. Of rural Tanzanians with diabetes, 90% do not know they have it, and mortality is 17–26% per year, 10 times greater than that in comparable European diabetic populations. Alberti concluded that earlier intervention is needed.

A number of environmental factors contribute to type 2 diabetes. There is evidence that low birth weight is associated with increased risk of subsequent diabetes, as well as with increased risk of obesity, hypertension, and other features of the insulin resistance syndrome, suggesting that an improvement in maternal nutrition during pregnancy might help to prevent diabetes. Measures to prevent obesity, including changing dietary caloric content and composition, as well as encouraging physical activity among those living in cities, would also be important. A high-yield strategy for identifying individuals at risk would be to evaluate individuals over age 45 who are overweight or have a history of cardiovascular disease (CVD) or a family history of diabetes. Specific ethnic groups should be targeted, such as those from India, where the prevalence of type 2 diabetes increases from 1.3% in rural areas to 6% in cities; migrant Indian communities such as those in South Africa and in the Fiji islands having diabetes prevalences of 11–13%. Alberti reminded the audience of the new criteria for diagnosis of diabetes, fasting glucose >126 mg/dl (7 mmol/l) or 2-h post–75-g glucose >200 mg/dl (11.1 mmol/l). Early diagnosis can be effective, with a Tanzanian study showing a considerable decrease in the rate of onset of diabetes with lifestyle modification. Alberti was reluctant to recommend pharmacotherapy in general for prevention of type 2 diabetes, stating pointedly that "obviously the United States feels you should, [but] I think you shouldn't," and that "drugs with a long history of safety" should be the only ones used.

Several early diabetes treatment studies are underway. Holman et al. (abstract 58) reported on the Early Diabetes Intervention Trial. (Abstract numbers are from Abstracts of the 16th International Diabetes Federation Congress, Helsinki, 20–25 July 1997, *Diabetologia* 40 [Suppl. 1]:A1–A722.) In this trial, 668 self-referred subjects have been randomly assigned to double-blind treatment with acarbose, metformin, both, or placebo. Goals of the study will be to determine whether classification by fasting glucose level, HbA_{1c} level, or glucose tolerance test results best predicts which subjects will progress to diabetes and to assess whether early treatment with acarbose or metformin therapy can delay this progression. Yamada et al. (abstract 767) described the Japan Diabetes Complications Study, a 6-year prospective trial in which 2,066 type 2 diabetic subjects have been randomly assigned to intensive lifestyle modification or conventional treatment.

Cull et al. (abstract 1366) addressed the efficacy of using a single therapeutic agent to treat patients with established type 2 diabetes. For the 5,102 patients with newly diagnosed type 2 diabetes enrolled in the UKPDS and prospectively followed during treatment with diet, glyburide, chlorpropamide, insulin, or, for obese patients, metformin monotherapy, good glycemic control was obtained in only a minority. At 3 years, about half of pharmacologically treated patients had HbA_{1c} <8% and 40% had HbA_{1c} <7%. At 6 and 9 years, however, only 35–38% and 16–21% had HbA_{1c} <8%, suggesting that the use of multiple agents needs to be considered if glycemic control is to be maintained. One wonders whether this study, designed to show whether glycemic control is of value in type 2 diabetes, can hope to show a benefit of intervention if only a minority of enrolled patients achieved adequate control.

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Abbreviations: CVD, cardiovascular disease; IDF, International Diabetes Federation; Kir, potassium inward rectifier; SU, sulfonylurea; SUR, sulfonylurea receptor subunit; TGZ, troglitazone; UKPDS, U.K. Prospective Diabetes Study.

Sulfonylureas

In a symposium on new treatments for hyperglycemia at the IDF meeting, Pierre LeFèbvre, Liège, Belgium, reviewed the stages in the life of a new drug that were originally proposed by Wortheimer in 1971. The first stage is "discovery," during which use is low. This leads to a period of "enthusiasm," with increasing use, until the drug encounters its "first failures," when usage decreases to a level of "initial stabilization." Some drugs may then encounter a "disappointment" stage, with markedly decreased use, after which there can be another period of "reappraisal," followed by "final stabilization." Such a cycle describes the history of the sulfonylureas (SUs), discovered by chance in 1942 by Janbon in France, with a period of initial enthusiasm followed by the realization that not all patients with diabetes respond to these agents. After the University Group Diabetes Program (UGDP) report (1) appeared there was a marked dip in usage and finally a reappraisal of usage patterns. This product "life cycle" clearly applies to many agents used in the treatment of diabetes, and advances in the field may again increase the importance of the SUs and related agents.

In a symposium on new treatments for hyperglycemia, Erol Cerasi, Jerusalem, Israel, further discussed SU treatment. He commented that type 2 diabetes is a disease of relative, but quite definite, insulin deficiency, so that the use of insulin secretagogues is appropriate. The fall in basal insulin levels after a period of SU treatment, rather than being evidence of a supplementary decrease in insulin resistance, is merely an appropriate response to lower levels of fasting glucose. The insulin response to glucose, although improved with SUs, is not corrected to levels seen in nondiabetic subjects. There may, in addition, be peripheral effects of SUs. Gliclazide increases glucose uptake during a hyperinsulinemic hyperglycemic clamp, and some studies show increased basal glucose uptake with this agent. Glimepiride has been shown to increase both GLUT1 and GLUT4 transporter activity. Overall, however, Cerasi doubted that this is an important effect. Another consequential question is whether there are adverse cardiac effects of SUs, as first suggested by the UGDP studies (1). There is prominent SU receptor expression in cardiac muscle. Animal studies of the effects of glyburide show increased vascular resistance, decreased blood flow, interference with the protective phenomenon of postischemic vasodilatation, and evidence of increased ischemic damage, although there may be a beneficial antiarrhythmic effect. In humans, there is also evidence of increased systemic vascular resistance, decreased postischemic vasodilatation, and decreased diazide-induced vasodilatation. Several studies do, however, show actual decreases in CVD mortality with SU treatment. Clearly, it will be important to address the issues of whether SUs show effect during acute ischemia and whether they change the progression of acute myocardial infarction. Given the high CVD frequency in type 2 diabetes, we must consider which end points should be studied to best analyze this. In a study further suggesting a cardiac action of SUs, Ayvaz et al. (abstract 1246) noted that thallium, used for myocardial perfusion scanning, acts via K_{ATP} channels, which are closed under physiological conditions and open with hypoxia or ischemia. These authors showed that the ^{201}Tl washout rate decreased to 63% of basal levels in 10 patients newly diagnosed with diabetes who started on SU treatment, suggesting that this agent contributes to relative closing of myocardial K_{ATP} channels.

Frances Ashcroft, Oxford, U.K., discussed the mechanism of action of SUs. There are two general types of insulin secretagogues: potentiators, such as the hormones glucagon, glucagon-like peptide-1, vasoactive intestinal polypeptide, and cholecystokinin, the neurotransmitter acetylcholine, and the amino acid arginine; and initiators, including nutrients such as glucose and leucine and the SUs. All of the initiators act by inhibiting K_{ATP} channels. Glucose, on entering the cell, is metabolized, leading to increased ATP and decreased ADP levels, which inhibit the K_{ATP} channels. SUs act directly at a receptor site to similarly decrease activity of these channels. This depolarizes the cell membrane, increasing Ca^{2+} entry and setting in motion a process that leads to insulin secretion. Thus, the K_{ATP} channel plays a central role in insulin secretion. Mutations affecting this channel can cause diabetes or hypoglycemic states. Glucokinase and mitochondrial mutations that prevent ATP generation leave K_{ATP} channels open, preventing Ca^{2+} entry and causing decreased insulin secretion. Such mutations are among the causes of maturity-onset diabetes of the young syndromes, which respond well to SU treatment. Conversely, neonatal hyperinsulinemic hyperglycemia is due to mutations causing the K_{ATP} channel to remain closed, leading to unrestricted Ca^{2+} entry and insulin secretion.

The K_{ATP} channel is composed of the pore-forming potassium inward rectifier (Kir) 6.2 subunit and the larger SU receptor subunit (SUR) 1, which displays high SU affinity and has two sequences showing nucleotide binding. The pore-forming unit has two transmembrane domains linked by a sequence that lines the potassium channel. When expressed, four SUR1 and four Kir 6.2 units link together to form the actual transporter, the Kir subunits around the central channel and the SUR1 subunits arranged at the outer circumference. Ashcroft described studies (some presented by Gribble et al. [abstract 11]) in which the K_{ATP} channel was expressed and reconstituted in *Xenopus* oocytes. Microelectrode recordings were used to analyze its properties, particularly addressing the question of which are intrinsic to Kir and which to SUR1, information that is potentially useful in designing new therapeutic approaches to stimulating insulin secretion. A truncated Kir protein was produced that allowed K^+ currents similar to those of the overall complex and was found to respond to ATP. Coexpression of truncated Kir 6.2 with SUR1 increased sensitivity to ATP 10-fold, allowed partial response to ADP, and allowed response to SU. The mechanism of ATP inhibition of Kir 6.2 appears to be direct, and, interestingly, does not distinguish well between ATP and ADP. Mutations in SUR1 abolish activation by ADP, which presumably attaches to the nucleotide-binding domains of this protein. Finally, coexpression of either intact or truncated Kir 6.2 with SUR1 greatly increased the response to metabolic regulation by glucose.

The oocyte preparation was used to investigate the pharmacology of the K_{ATP} channel. Tolbutamide was found to interact with two separate binding sites on the receptor complex, with the lower-affinity site apparently on Kir 6.2 itself. Ashcroft suggested that the imadazolines such as phentolamine might induce insulin secretion by acting at this site. She also noted that different subunits exist in different tissues. The Kir 6.2/SUR1 complex is found in the β-cell and in brain. A combination of Kir 6.2 with a different protein, SUR2A, is found in cardiac and skeletal muscle, and Kir 6.2, as well as a related protein, Kir 6.1, is found in combination with SUR2B in smooth muscle. Both the cardiac and β-cell complexes are activated by ATP, while SUs have much less effect on Kir 6.2 / SUR2 sys-

tems. Further studies will be important in addressing differences among SUs and in developing non-SU insulin secretagogues. In work showing the power of using *Xenopus* oocytes for expression of cloned β-cell K_{ATP} channels, Gribble et al. (abstract 401) investigated the mechanism of action of the commonly used quinoline methanol antimalarial drug mefloquine and the chemically related drug halofantrine on β-cells. Both drugs closed K_{ATP} channels. In a potentially important related presentation, Heron et al. (abstract 10) described endosulfine, an endogenous ligand for the SU receptor, which exists as α and β forms. The α form was shown to inhibit binding of the SU glyburide both to rat cortex and to islet β-cell membranes.

Nishimura et al. (abstract 425) described a pathway of glucose-induced insulin secretion that is independent of K_{ATP} channels, does not involve detectable elevation of intracellular calcium, and is dependent on protein kinase C activation. This suggests that new classes of pharmacological insulin secretagogues may await discovery. Laffranchi et al. (abstract 426) presented data suggesting that nitric oxide could also be involved in the insulin secretory pathway. Gross et al. (abstract 521) reported on *Citrullus colocynthis* Schrad, a fruit traditionally used in Morocco and other Mediterranean countries in antidiabetic medications. Several fruit extracts were shown to act to increase insulin secretion in the isolated rat pancreas. Jeppesen et al. (abstract 529) studied stevioside, a glycoside contained in the leaves of *Stevia rebaudiana* Bertoni, which is used in the traditional treatment of diabetes in Brazil. The agent was shown to lower glucose levels and had an insulin-secretory action in a type 2 diabetic rat model.

Metformin

Other presentations at the meeting dealt with metformin treatment of type 2 diabetes. Bernardo Wajchenberg, São Paulo, Brazil, discussed the effects of this agent. Decreased glycemia appears to be primarily due to falls in hepatic glucose production. There are also antiatherogenic effects, which appear to be independent of the changes in glycemia and include improved fibrinolysis, decreased platelet aggregation, increased erythrocyte deformability, decreased lipid incorporation into vessel walls, decreased arterial wall smooth muscle cell growth, and restoration of arterial vasodilation.

Perrielloet al. (abstract 33) compared metformin plus insulin with SU plus insulin treatment of obese and nonobese patients with type 2 diabetes. In the nonobese group, metformin treatment gave similar glycemic control, but with lower insulin doses and with a weight gain of 0.4 vs. 3.0 kg. In the obese patients, there was a 2.3 vs. 1.0 kg weight loss and HbA_{1c} was 7.4 vs. 8.2%.

Johansen (abstract 1222) presented a meta-analysis of 8 randomized controlled trials comparing metformin with placebo and 11 comparing it with SUs. The weighted mean differences between placebo- and metformin-treated groups were 3.1 mmol/l in fasting blood glucose and 1.3% in glycosylated hemoglobin. Body weights were not different. SUs and metformin lowered blood glucose equally, but weight was 3 kg lower after metformin treatment.

Robinson et al. (abstract 1353) reported that 19 patients with insulin-treated type 2 diabetes and poorly controlled blood glucose levels showed a fall in HbA_{1c} of 0.9% with the addition of metformin at a dose of 1 g twice daily for 12 weeks. Zapecka-Dubno et al. (abstract 1244) reported that metformin decreased fasting and glucagon-stimulated amylin levels by about 1.0 pmol/l, while glyburide increased levels by the same amount, suggesting an additional mechanism for the decreased insulin resistance seen with metformin treatment. Ruggiero et al. (abstract 1218) showed that in vitro metformin decreased glycoxidation of albumin by the dicarbonyl compounds glyoxal and methylglyoxal by 30 and 50%, suggesting that metformin may directly decrease AGE formation.

Troglitazone

Troglitazone (TGZ) treatment was another topic at the meeting. The Troglitazone Study Group (abstract 178) presented a study of 93 patients with type 2 diabetes who were randomly assigned to TGZ in doses of 0, 100, 200, 400, or 600 mg daily for 6 months. Basal hepatic glucose production was unaffected by TGZ except with the 600-mg dose. Insulin-mediated glucose disposal was increased by 45% with doses of 400 and 600 mg.

Kawamori et al. (abstract 1203) administered 30 mg pioglitazone or placebo to 30 patients with type 2 diabetes. Insulin-stimulated hepatic glucose uptake increased from 28.53 to 59.35% and peripheral glucose uptake increased from 8.23 to 9.20 $mg \cdot kg^{-1} \cdot min^{-1}$. Foot et al. (abstract 1209) compared 18 nondiabetic subjects treated with 200 mg TGZ or placebo for 13 days. Insulin levels decreased with treatment. Buysschaert et al. (abstract 1229) studied 259 patients treated with SU. After 16 weeks, HbA_{1c} and fasting glucose were 8.2% and 11.5 mmol/l with placebo, 7.7% and 10.4 mmol/l with 100 mg TGZ, and 7.4% and 9.2 mmol/l with 200 mg TGZ daily. Kench and Beranek (abstract 1215) analyzed the safety profile of TGZ in 1,066 patients studied in Europe for up to 16 weeks. Drug-related adverse events were reported in 27% of TGZ- and 27% of placebo-treated patients, with drug-related serious adverse events in 1% of each group.

References

1. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes mellitus. II. Mortality results. *Diabetes* 19 (Suppl. 2):789–830, 1970