

## CURRENT APPROACH TO THE TREATMENT OF TYPE 2 DIABETES

The therapeutic approach to patients with type 2 diabetes has changed profoundly in recent years. According to new approaches lower glycemic control targets as well as early onset of insulin and combination therapies instead of the traditional gradual therapy were adopted. Two current (IDF and ADA/EASD) approaches widely accepted in the treatment of type 2 diabetes, are summarized below, and moreover the SEMT approach is described in detail.

### 9.1 THE IDF AND THE ADA/EASD RECOMMENDATIONS

#### 9.1.1 The IDF Recommendations

“Global Partnership Group in the Treatment of Type 2 Diabetes”, established by IDF Europe in 2005 to improve the compliance of patients with type 2 diabetes to therapy and to reduce the morbidity and mortality due to diabetes by decreasing A1C, has recommended to treat type 2 diabetes earlier and more aggressively. Accordingly;

- to achieve a target A1C of  $\leq 6.5\%$  within the first six months of treatment,
- to start OAD combinations, and insulin therapy if needed in patients with baseline A1C  $>9\%$ ,
- to start OAD monotherapy based on the underlying pathology (insulin secretagogue or insulin sensitizer) in patients with baseline A1C  $<9\%$ ,
- to add a second OAD or an insulin if A1C goal has not been achieved after three months.

#### 9.1.2 The ADA/EASD Recommendations

“The Guide for Management of Type 2 Diabetes”, published by the ADA and the EASD in 2006, summarized the treatment algorithm to be undertaken for patients with type 2 diabetes;

- to keep a target A1C of  $<7\%$ , fasting glycemia of 70-130 mg/dL and postprandial peak glycemia of  $<180$  mg/dL.
- to start metformin (if no contraindication) simultaneously with lifestyle modification in newly diagnosed type 2 diabetes patients.
- to add either a sulfonylurea, a TZD or basal insulin to treatment if a target A1C has not been achieved within 2 to 3 months.
- to add a third OAD or switch to intensive insulin therapy if a second-line treatment is insufficient.
- to switch to basal-bolus insulin therapy if glycemic control has not been achieved.
- to start a treatment with insulin in patients with baseline A1C of  $>8.5\%$  and severe hyperglycemia symptoms.
- ADA/EASD recommends using medications with proven efficacy and safety in long-term experience (sulfonylureas and basal insulin) or alternatively somewhat new drugs with less sufficient experience (pioglitazone and exenatide) as second-line therapy if metformin plus lifestyle modifications fails and emphasizes to give the priority to the former in 2009 recommendations. Intensive insulin is recommended as the third line therapy in case second-line therapy is insufficient.

## 9.2 SEMT TREATMENT ALGORITHM IN PATIENTS WITH TYPE 2 DIABETES

In the light of current approaches and also taking into account the realities of our country, SEMT Diabetes Study Group has been identified "Type 2 Diabetes Treatment Algorithm". This algorithm is shown in Figure 9.1. The outlines of this algorithm are summarized below in terms of glycemic control targets and treatment choice.

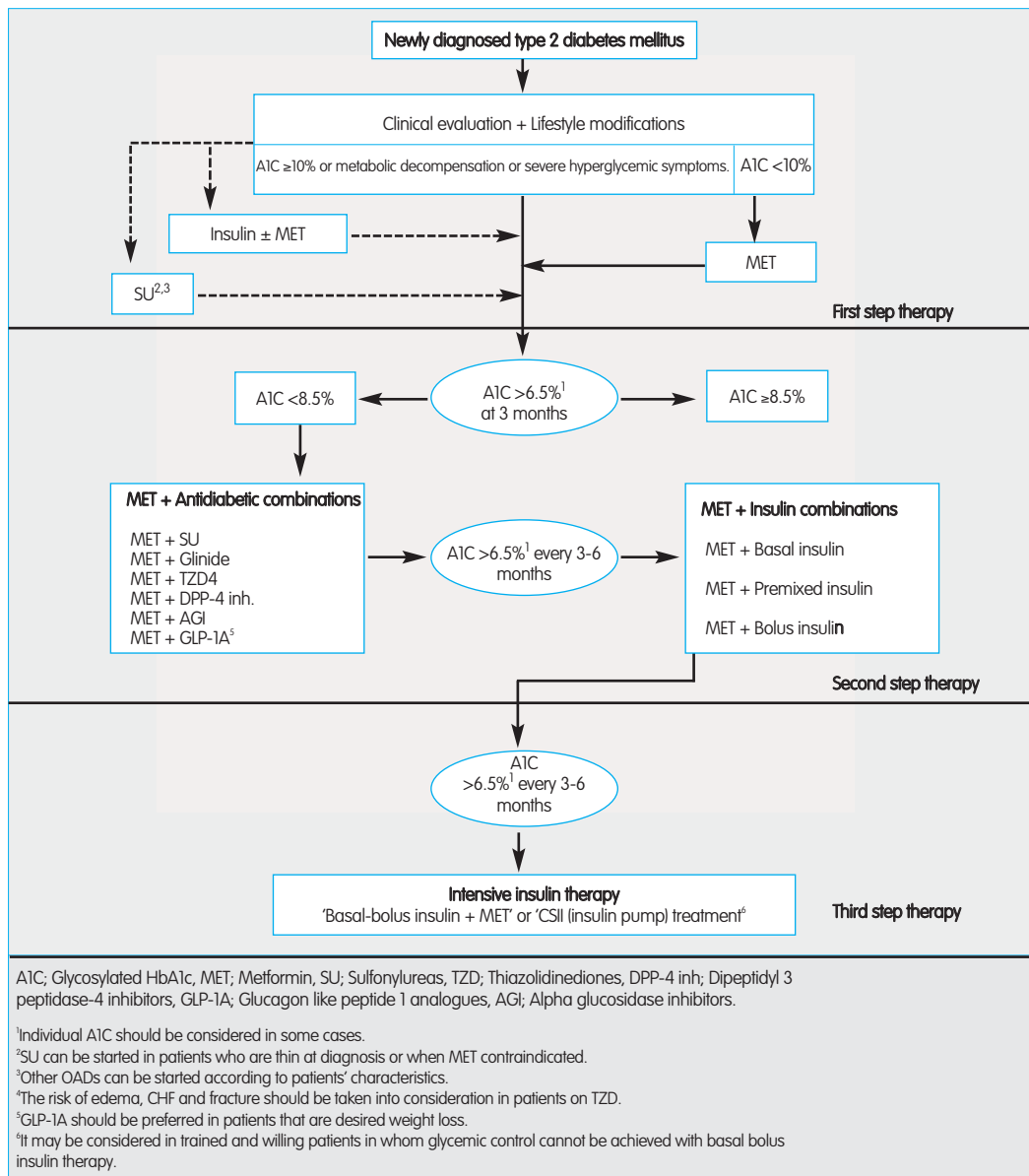


Figure 9.1 Treatment algorithm for patients with type 2 diabetes

### 9.2.1 Targets of Glycemic Control

- Glycemic targets should be tailored to the individual with type 2 diabetes and consideration given to individual characteristics and clinical situation.
- If there is not a special condition that increases the risk of hypoglycemia or the life expectancy is long enough, therapy in most individuals with type 2 diabetes should be targeted to achieve an A1C  $\leq 6.5\%$  in order to reduce the risk of microvascular complications. However, A1C goal can be identified as 6% in special conditions (e.g. high risk pregnancy) and in patients with good compliance unless they experience severe hypoglycemia.
- The benefits of a lower A1C should not increase the risk of hypoglycemia and mortality particularly in patients at high risk of CVD.

Targets of glycemic control should be set higher in patients with low life expectancy and those at high risk of hypoglycemia.

- In general, new arrangements should be made if A1C >6.5% and the patient's individual glycemic targets are not achieved.
- A1C should be measured in every 3 months until it reaches to a target level, and then every 3 to 6 months.
  1. The objective is to achieve and maintain glycemic targets near to normal levels.
  2. Principally FPG and preprandial PG levels should be desired to achieve glycemic control targets, and preprandial and FPG levels should be kept 70-120 mg/dL.
  3. If FPG and preprandial PG targets cannot be maintained or A1C is >6.5% in spite of meeting the targets, then postprandial PG control becomes necessary. Postprandial PG is measured 2 h (1 h in a pregnant) after the first bite of a meal. Postprandial PG should be <140 mg/dL. Postprandial PG measurement may have different timing in patients who perform carbohydrate counting or use insulin pump.
  4. Patients with type 2 diabetes also should be educated with a multi-disciplinary approach about their diseases. Education should aim to inform and empower the patient about self-management of diabetes, to gain skills for SMBG, and to share the responsibility with healthcare providers.

## 9.2.2 Treatment Preference

In the selection of anti-hyperglycemic treatment, glucose-lowering effect as well as extra-glycemic effects, safety, tolerability and cost characteristics of drugs should be taken into consideration. Necessary changes in treatment and dose adjustments should be made at appropriate time to achieve target A1C identified to an individual patient within first 6-12 months. Treatment of type 2 diabetes should be performed in three steps:

### A. First Step Treatment

Considering its long-term safety and relatively low-cost, and if there is no contraindication, metformin is indicated for use in patients diagnosed with type 2 diabetes as concomitant therapy to lifestyle modifications. Lifestyle modifications should be implemented at all stages of treatment.

- Initially FPG should be measured three days per week and then SMBG should be administered as the selected drugs required. The frequency of SMBG should be increased, based on the changes in treatment, initiation of insulin, and dose titration.
- Weight loss (at least 4 kg or 5% of body weight) is essential for positive impact on CV problems, HT, and dyslipidemia frequently accompanying to diabetes.
- A nutritionally balanced diet, and regular physical activity for overweight and obese people should be implemented to achieve a healthy body weight, unfortunately these attempts are insufficient in the long term.
- At first line metformin treatment is initiated 500 mg twice daily, and in patients with gastrointestinal discomfort 500 mg once daily and is titrated weekly in 500 mg increases to a 1000 mg twice daily in one to two months (maximum total daily dose of metformin is 3000 mg).
- The sulfonylureas are an alternative if metformin is contraindicated or not tolerated, particularly in thin patients, in those who have severe symptoms of hyperglycemia, and when a rapid response is required. Long-acting sulfonylureas like glibenclamide should not be preferred.
- In some cases other OAD (such as glinides and alpha-glucosidase inhibitors) can be initiated as the first line treatment according to patient characteristics and physician's experience.
- In patients with initial A1C  $\geq 10\%$ , and in those with severe hyperglycemia symptoms and metabolic decompensation the therapy should be initiated with insulin. In fact some patients, as in this case, are likely to have previously undiagnosed type 1 diabetes, while others are type 2 diabetes patients with severe insulin deficiency. Insulin therapy should be initiated with preferably a basal-bolus regimen or at least a pre-mixed insulin, and metformin should be added if possible.

### B. Second Line Treatment

When glycemic goals cannot be reached or maintained new drugs should be added to the treatment or new treatment modalities should be initiated in short time.

- If glycemic targets are not achieved and A1C is >6.5% within 3 months of lifestyle modification and 2000 mg/day metformin use, another pharmaceutical agent should be initiated.
- The second drug should be chosen according to the individual characteristics, and the cost-effectiveness along with the efficacy and safety of a particular drug should be taken into account. Metformin should be continued in the second line therapy as long as there is no contraindication.

- The drugs with proven long-term efficacy (insulin, sulfonylureas) should be preferred primarily in second line therapy.
- Insulin is the most effective therapeutic choice in the second line therapy. Especially if A1C  $\geq 8.5\%$  insulin (preferably a basal insulin) should be considered. The risk of hypoglycemia and weight gain should be taken into account. The algorithm for insulin therapy in patients with type 2 diabetes is summarized in Figure 9.2. Insulin therapy should be intensified if basal insulin is insufficient. Alternatively a premixed human or analogue insulin can be used.
- If A1C is  $>6.5\%$  but  $<8.5\%$ , a second OAD (sulfonylurea, glinide, TZD, DPP-4 inhibitor, alpha-glucosidase inhibitor or GLP-1 analogue) can be added to the treatment.
- A sulfonylurea is the cheapest option and more effective than a TZD. The risk of hypoglycemia and weight gain should be taken into account. Long-acting sulfonylureas such as glibenclamide have a greater risk of hypoglycemia.
- The risk of hypoglycemia with TZDs is lower than sulfonylureas, and the long-term efficacy is higher than that. But because TZD group of drugs are associated with increased risk of edema, congestive heart failure, and fractures, patients taking TZD in addition to metformin in the second line therapy should be followed carefully.
- Glinides, alpha-glucosidase inhibitors or DPP-4 inhibitors can also be used for postprandial glycemia control. But in general the cost and gastrointestinal side effects with the second group should be taken into account.
- Although the risk of hypoglycemia with incretin-based drugs (GLP-1 agonists, DPP-4 inhibitors) is lower than insulin and sulfonylureas, their efficiency is lower than these medications. However, the high cost and insufficient evidence regarding the long-term efficacy and side effects restrain widespread use of these agents. DPP-4 inhibitors may be beneficial as they do not cause weight gain, and are used orally.
- If the physician has sufficient experience a GLP analogue, exenatide can be used in patients for whom weight loss is desired. But the high cost and the absence of sufficient evidence regarding the long-term efficacy and side effects prevent its widespread use. It should not be used in obese children and adolescents under 18 years of age with type 2 diabetes. If weight loss obtained with exenatide is less than expected, the treatment should be discontinued. In addition, patients should be followed for the risk of pancreatitis.
- If A1C is  $>6.5\%$  within 3 to 6 months using metformin together with a second OAD (or GLP-1A), or individual glycemic targets are not met, insulin treatment should be initiated immediately.

### C. Third line Treatment

If A1C is  $>6.5\%$  within 3 to 6 months after using a basal or a mixed insulin, or individual glycemic targets are not met insulin treatment should be intensified.

- Intensive insulin treatment consists of basal-bolus multiple daily injections (See Chapter 8.2).
- Insulin pump (SCII) treatment may be considered among educated and motivated young patients in whom glycemic control cannot be achieved with basal-bolus insulin, and in those who have flexible lifestyle.
- If A1C is  $<8.5\%$  a third antidiabetic drug can be added. But in this case the treatment cost rises, and the effectiveness of treatment is lower than insulin. Moreover, the treatment is generally become insufficient within relatively short time..

### 9.2.3 Insulin Therapy in Type 2 Diabetes

Intensification of insulin therapy is summarized in the algorithm (Figure 9.2).

- Getting started with insulin therapy in type 2 diabetes basal insulin therapy is preferred.
- In some patients with high insulin requirements a second dose of basal insulin, or pre-mixed human insulin analogue may be necessary starting from the beginning of the treatment.
- Basal insulin regimen consists of either NPH insulin at night or long-acting analogue insulin (glargine, detemir) at night, in the evening or in the morning at a dose of 0.1-0.2 IU/kg. Since long-acting insulin analogues (glargine, detemir) have lower risk of symptomatic hypoglycemia and hypoglycemia at night, they may be preferred instead of NPH in patients with this type of risks.
- The dose is increased by 2 IU every 3 days until FPG levels are  $\leq 120$  mg/dL (it may be increased by 4 IU when FPG is  $>180$  mg/dL).
- If hypoglycemia occurs or if FPG is  $<70$  mg/dL in patients using insulin at night, the insulin dose is reduced 4 IU (if insulin dose is more than 60 IU it is decreased by 10%). The insulin dose in the evening or at night should be reduced if FPG is  $<100$  mg/dL in elderly patients with coronary problems or dementia.
- Basal-bolus insulin regimen should be preferred in patients with high basal insulin requirements ( $>0.5$  IU/kg/day).
- If A1C is measured  $>6.5\%$  three months after start of basal insulin therapy, 4 IU rapid or short-acting insulin is initiated at noon, in the evening or at night according to PG level, and the daily dose is increased by 2 IU every 3 days until PG reaches  $\leq 120$  mg/dL.

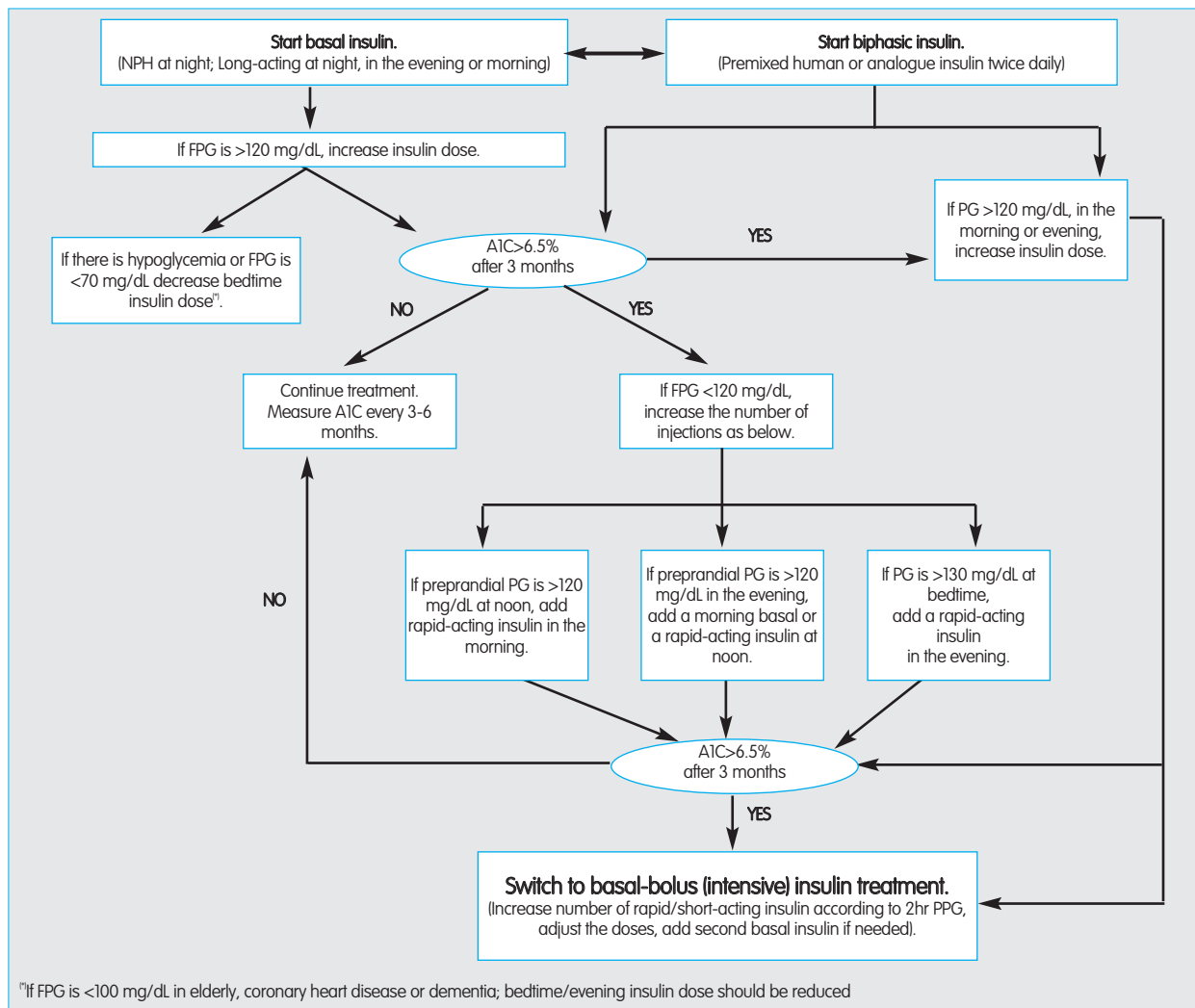


Figure 9.2 Insulin therapy in type 2 diabetes

### 9.2.4 Type 2 Diabetes Treatment in Special Circumstances

■ If A1C is over 6.5% a second dose of basal insulin can be added. Alternatively the number of rapid-acting analogue (aspart, glulisine and lispro) can be increased depending on the 2hr postprandial PG levels.

■ Insulin secretagogues (sulfonylureas or glinides) should be discontinued once a rapid or a short-acting insulin is commenced.

■ Insulin therapy is recommended to be used in combination with an insulin sensitizer, preferably metformin. Intensive insulin therapy combined with TZDs has been shown to increase the risk of edema and congestive heart failure. However, a TZD (preferably pioglitazone) can be added to therapy for short-term in patients requiring very high doses of insulin until the insulin resistance is relieved. These patients should be monitored closely.

Insulin therapy should be preferred concomitantly with lifestyle modifications in patients with uncontrolled diabetes and increased catabolism as details shown below.

■ FPG >250 mg/dL, at any time PG >300 mg/dL or A1C >10%

■ In the presence of ketonuria

■ If there are serious diabetes symptoms (e.g. polyuria, polydipsia, weight loss)

In these patients OAD can be added to therapy after the symptoms have resolved, and even the insulin therapy can be discontinued at that time.

#### Comorbidities accompanying to type 2 diabetes

The problems accompanying to type 2 diabetes, particularly dyslipidemia and hypertension, should be treated aggressively and in accordance with the current guidelines to achieve success. This is also important to reduce the risk of microvascular complications.

**SEMT RECOMMENDATIONS FOR TREATMENT OF TYPE 2 DIABETES**

1. *If there is no contraindication metformin should be initiated concomitantly with lifestyle modifications in newly diagnosed type 2. Diabetes patients [For obese patients: Class A, Level 1A evidence (1); for non-obese patients: Class D, evidence-based consensus].*
  - *The treatment can be initiated with a sulfonylurea in patient with symptoms of hyperglycemia, who is asthenic or cannot tolerate metformin (Class D, evidence-based consensus).*
  - *Insulin therapy should be preferred concomitantly with lifestyle modifications in patients with hyperglycemia symptoms and A1C>10%.*
2. *Glycemic targets must be individualized, taking into consideration the risk of hypoglycemia (Class D, evidence-based consensus).*
  - *The majority of the patients should aim for an A1C target of  $\leq 6.5\%$  (Class D, evidence-based consensus).*
3. *If glycemic control has not been achieved at the end of 3 months another OAD or insulin should be added to the treatment.*
  - *The necessary changes in treatment and dose adjustments should be made to achieve patient-specific A1C target within 6 to 12 months (Class D, evidence-based consensus).*
4. *Pharmacological treatment regimens of type 2 diabetes patient should be individualized taking into consideration the degree of hyperglycemia and the specifications of the antihyperglycemic agents (effectiveness, side effects, contraindications, risk of hypoglycemia, and cost) presence of diabetes complications or comorbidities, and patient preferences (Class D, evidence-based consensus).*
5. *When basal insulin is used, long-acting analogues may be considered instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia [Class A, Level 1A evidence (2)].*
6. *The following agents (listed in alphabetical order), should be considered to lower postprandial BG levels:*
  - *Alpha-glucosidase inhibitors [Class B, Level 2 evidence (3)]*
  - *DPP-4 inhibitors [Class A, Level 1 evidence (4-6)]*
  - *Glinides [Class B, Level 2 evidence (7,8)]*
  - *Premixed insulin analogues [Class B, Level 2 evidence (9,10)]*
  - *Rapid-acting insulin analogues [Class B, Level 2 evidence (11-13)]*
7. *All individuals with type 2 diabetes using insulin or insulin secretagogues should be counseled about the recognition and prevention of drug-induced hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed (Class D, evidence-based consensus).*

## REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
2. DeVries JH, Lindholm A, Jacobsen JL, et al; Tri-Continental Insulin Aspart Study Group. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with type 1 diabetes. *Diabet Med* 2003;20:312-8.
3. Zinman B, Tildesley H, Chiasson JL, et al. Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes* 1997;46:440-3.
4. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care* 2002;25:439-44.