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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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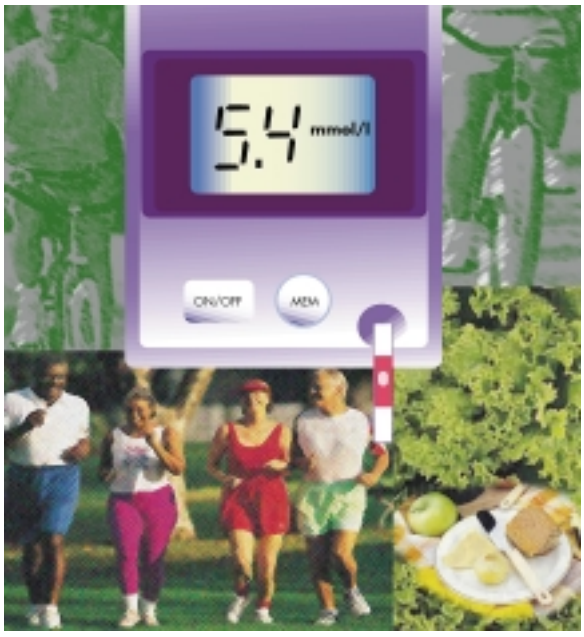
MANAGEMENT OF TYPE 2 DIABETES

Diabetes mellitus is a common disease affecting approximately 5 % of the population.[1] Type 2 diabetes (non-insulin-dependent diabetes mellitus) accounts for 85-90 % of patients with diabetes mellitus.[2] Patients with diabetes have an approximately threefold risk for all cardiovascular diseases [3, 4] and their relative risk of death from all causes is increased by 75%. [5,6]

What is the evidence that improved glucose control leads to a decrease in complications of type 2 diabetes?

As yet there is no conclusive evidence that improved glucose control with oral agents leads to a decrease in the complications of type 2 diabetes. There is some evidence that improved glucose control delays the onset of complications in type 2 diabetes. In a cohort study of 114 patients followed for 5 years, the incidence of progression of retinopathy increased linearly as a function of the HbA_{1C} level: 2% in those with HbA_{1C} less than 0.070 and 62% in those with HbA_{1C} greater than 0.090.[7] In a randomised secondary prevention intervention trial of diabetic patients (majority type 2 diabetes) who had suffered an MI, those who had intensive insulin treatment had an absolute reduction of mortality of 11% (44% vs 33%) compared to the regular therapy group after 3.4 years of follow-up.[8] In a randomised trial of 110 patients with type 2 diabetes, those who received multiple insulin injections had an absolute reduction in the progression of retinopathy of 24%, and of nephropathy of 20%, after 6 years of follow-up, when compared with a conventional therapy group.[9] Preliminary results of a large prospective randomised trial, that is examining the relationship of glucose control to complications of diabetes in type 2 diabetics, show an improvement in HbA_{1C} levels in patients who received treatment, whether with sulfonylurea, metformin or insulin.[10]

In contrast, there is strong evidence that near-normalisation of blood glucose levels with insulin can delay the development and progression of retinopathy, nephropathy, and neuropathy of patients with type 1 diabetes mellitus (IDDM). [11]



What are the new criteria for the diagnosis of diabetes mellitus?

- Fasting glucose*7.0 mmol / L.* and/or
- 2 hour post 75 g glucose load*11.1 mmol / L.* and/or
- Symptoms of diabetes plus a single random glucose *11.1 mmol / L.

* In the absence of symptoms, a second test should be done to confirm the diagnosis.

The development of diabetic retinopathy and nephropathy mainly occurs when the fasting glucose is 7.8 mmol/L or greater.[12,13] However, fasting glucose levels of greater than 6.0 mmol/ l are associated with a higher incidence of cardiovascular disease.[12,13] This information led the Canadian and American Diabetes Associations to develop new, lower criteria for the diagnosis of diabetes.[14,15]

What are the risk factors for diabetes?

The risk factors for diabetes are age (≥45 years), family history (first degree relative with diabetes), high-risk ethnic group (aboriginal, Asian, Pacific Islander, Hispanic, African), obesity (BMI ≥ 27 kg/m2), history of gestational diabetes or macrosomic infant (≥4.5 kg), hypertension, coronary artery disease.

What is the evidence for non-drug therapies?

There is good evidence that diet and exercise can delay the onset of type 2 diabetes in persons at risk. In one intervention trial 577 subjects with impaired glucose tolerance (a lesser degree of hyperglycemia) were randomized to control, diet, and exercise groups. Over a 6-year period, 67% of the control group but only 41 to 43% of the intervention groups developed type 2 diabetes, an absolute risk reduction of approximately 25%.[16] In several well designed, large scale cohort studies, with follow-up of 6 to 14 years, there was a relative decrease of 30 to 50% in the development of type 2 diabetes among those who exercised regularly compared to those who were sedentary.[17,18,19] This result was found in both men and women, and obese and non-obese subjects.

Weight loss, restricted diets, and exercise have all been advocated for the treatment of type 2 diabetes. Exercise, as an adjunct to diet, leads to increased weight loss and prevention of weight gain among patients with type 2 diabetes. There is some inconsistency, but **most studies have demonstrated the effectiveness and feasibility of exercise over the long term in treating type 2 diabetes.[20,21]**

There is evidence that a variety of dietary interventions and weight loss work in the short term in the treatment of type 2 diabetes. However, the evidence of longer-term intervention trials suggests that diet alone does not improve glucose control or reduce morbidity in type 2 diabetes.[22]

What drug therapies have been shown to lower blood glucose?

A controlled trial of 2520 patients comparing diet alone with diet plus chlorpropamide, glyburide, insulin, or metformin found all the drugs equally good at lowering glucose and better than diet alone.[23] In this study, patients had significant weight gain on sulfonylurea or insulin therapy (a mean of 5 kg and 7 kg, respectively) but not on metformin therapy (1 kg weight gain). Hypoglycemic reactions over a 6-year period were 17 and 27 % for sulfonylurea and insulin respectively, but only 5 % for metformin. **In this study glucose control deteriorated steadily over time in patients on all types of therapy,** whether diet, sulfonylurea, metformin, or insulin because of decreasing B-cell function. After 4 to 5 years of therapy, HbA_{1C} levels returned to higher values than existed before therapy was initiated.[22] Sulfonylureas, metformin, and insulin all reduce mean levels of HbA_{1C} by between 0.7% and 0.8% over diet alone.[22] Troglitazone reduces HbA_{1C} by 0.5% compared to diet alone.[24] Acarbose reduces HbA_{1C} by 0.55% to 0.9%.[25, 26]

Modes of action:

Sulfonylureas increase insulin secretion and potentiate insulin action on the liver and peripheral tissues.

Metformin decreases hepatic glucose production, increases glucose uptake and possibly decreases appetite.

Alpha glucosidase inhibitors slow the absorption of carbohydrates.

Troglitazone decreases insulin resistance.

Table 1: Oral Drug Therapies

Class	Generic Name	Trade Name	Daily Dose Range in mg	Average Daily Cost Range*
Sulfonylurea	Glyburide	Diabeta®, Euglocon®, generic	1.25 – 20.0	$0.02 - $0.28
	Tolbutamide	Orinase®, Mobenol®, generic	500 – 2000	$0.03 - $0.12
	Chlorpropamide	Diabinese®, generic	100 – 500	$0.05 - $0.08
	Gliclazide	Diamicron®	40 – 320	$0.20 - $1.60
Biguanide	Metformin	Glucophage®, generic	500 – 3000	$0.13 - $0.78
Alpha Glucosidase Inhibitors	Acarbose	Prandase®	75 – 300	$0.36 - $0.99
Thiazolidinedione	Troglitazone**	Rezulin®	200 – 400	$2 .00 - $4.00***

* Average price in BC (1997 Pharmacare data)
** Not yet available in Canada
*** Estimate based on current US price

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Table 2: Choice of Oral Medication

Drug	Advantages	Disadvantages
Biguanide (metformin)	• May assist in weight loss. • Useful in obese patients. • Little hypoglycemia.	• GI symptoms: diarrhea, nausea, vomiting, metallic taste. • Danger of lactic acidosis in patients with renal or hepatic dysfunction. *
Sulfonylurea (glyburide,gliclazide, chlorpropamide, tolbutamide)	• Better tolerated than other oral agents.	• Weight gain. • Hypoglycemia (less with tolbutamide[27]).
Acarbose	• Little hypoglycemia.	• GI side effects.
Troglitazone		• Lowers blood glucose less than other agents. • Expensive. • **Concern about hepatotoxicity led to removal from the market in the UK**

*Adjust dose based on creatinine clearance.

Conclusions

- Exercise and diet are effective in preventing type 2 diabetes.
- Exercise and weight loss are effective in treating type 2 diabetes, but weight loss is difficult to maintain.
- Sulfonylureas, metformin, and insulin are equally efficacious in improving glucose control in type 2 diabetes.
- The effectiveness of intensive insulin treatment in delaying the onset of complications of diabetes has been established for type 1 and to lesser extent for type 2 diabetes.

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