EFFECT OF CONVENTIONAL THERAPY ON THE DEVELOPMENT AND PROGRESSION OF COMPLICATION IN NONINSULIN DEPENDENT DIABETES MELLITUS (NIDDM)

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ABSTRACT :

Chaiyapak V. Effect of Conventional Therapy on the Development and Progression of Complications in Noninsulin Dependent Diabetes Mellitus (NIDDM). (Region 7 Medical Journal 1996 ; 3 : 321-326).

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There are accelerated macrovascular and microvascular complications in patients with NIDDM. I examined whether conventional therapy with the goal of maintaining blood glucose concentrations close to the normal range (< 160 mg/dl) could decrease the frequency and severity of these complications.

A total of 767 patients with NIDDM were followed for less than 5 years, between 5 and 10 years, and more than 10 years, and the appearance and progression of complications were assessed regularly. Good blood glucose control reduced the progression of PVD, nephropathy, PDR, and neuropathy, but increased CHD and CVD ($P < 0.05$ only over 10 years follow-up with CHD). This increased risk should be avoided by keeping preprandial blood glucose above 120 mg/dl especially in patients of old age group.

NIDDM is the more common form of diabetes. It is characterized by chronic hyperglycemia without insulin deficiency. There is increased hepatic glucose output in the presence of hyperglycemia and insulin. Insulin resistance exists for many years' duration for which the pancreas can initially compensate but eventually fails. The insulin resistance can be partly decreased with weight loss or sulfonylurea or insulin therapy. There is accelerated macrovascular disease, such as peripheral vascular disease, coronary artery disease, stroke, and microvascular disease, such as retinopathy, nephropathy and neuropathy. The Diabetes Control and Complications Trial Research Group (DCCT) has clearly shown that the microvascular complications of insulin dependent diabetes mellitus can be delayed or prevented by good glucose control.[1] The effective level of control (average blood glucose 150 mg/dl) in the DCCT study should be applied to the patients with NIDDM. I report a study to determine the effect of good glucose control on the development and progression of complications in NIDDM.

Material and Method

A total of 767 patients were examined from 1981 through 1995, (range of follow-up, 0.5 to 14 years), 223 males and 534 females. They were divided into 3 groups, less than 5 years, 5 to 10 years, and over 10 years follow-up. Each group was subdivided into good and bad diabetes control. The criteria of good control included the absence of symptoms attributable to glycosuria or hyperglycemia, the maintenance or change toward ideal bodyweight, freedom from severe or frequent hypoglycemia, and preprandial blood glucose 160 mg/dl or elow, in average. The base-line characteristics of the study patients are shown in Table 1.

Conventional therapy consisted of ducation about diet and exercise, sulfonyl urea, metformin, insulin, and their combinations. The dosage was adjusted according to the results of preprandial blood glucose in order to fulfil the criteria of good control. The trial design and methods to detect base-line omplications have been described elsewhere.[2-6] These complications are shown in Table 2. Thereafter the complications were to be recorded if new event of hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, nephropathy, retinopathy, cataract, or pulmonary tuberculosis occured, or there was progression in severity. Rising of blood pressure under treatment, more frequent ischemic attacks, increased urinary albumin excretion, development of proliferative retinopathy after previous background retinopathy, new amputations, all of these indicated progression in severity of complications. The incidence of new and progressive complications is demonstrated in Table 3. Chi-square test was used for comparisons of variables.

Table 1 Base-Line characteristics of 767 patients

Follow up		< 5 yr		5-10 yr		> 10 yr	
		n	%	n	%	n	%
Age (yr)	13-19	1	0.27	1	0.38	1	0.74
	20-29	5	1.35	1	0.38	0	0
	30-39	20	5.42	22	8.36	9	6.67
	40-49	70	18.97	54	20.53	27	20.0
	50-59	116	31.44	103	39.16	67	49.63
	60-69	128	34.69	68	25.86	26	19.35
	70 up	29	7.86	14	5.32	5	3.7
Male		104	28.18	80	30.42	49	36.3
Female		265	71.82	183	69.58	86	63.7
Good Control		100	27.1	77	29.28	24	17.78
Bad Control		269	72.9	186	70.72	111	82.22
Diet		13	3.66	13	4.81	1	0.7
Sulfonyl urea		185	52.11	111	41.11	42	29.58
Sulfonyl urea + Metformin		115	32.39	111	41.11	67	47.18
Metformin		1	0.28	1	0.37	0	0
Sulfonyl urea &/or Metformin + Insulin		9	2.54	9	3.33	8	5.6
Insulin		32	9.0	25	9.26	24	16.9

Table 2 Base-line complications in 767 patients with NIDDM (%)

Follow up	< 5 yr		5-10 yr		> 10 yr	
	G (n - 100)	B (n - 269)	G (n - 77)	B (n - 186)	G (n - 24)	B (n - 111)
Hypertension	15.0	13.01	18.18	13.98	20.83	19.82
CHD	0	2.23	5.19	1.61	0	1.8
CVD	1.0	0.37	0	1.08	0	0
PVD	1.0	0.37	0	1.08	0	0
Nephropathy	4.0	3.72	3.9	8.06	0	5.41
Retinopathy	1.0	1.12	1.3	4.3	0	2.7
neuropathy	1.0	0.74	1.3	0.54	8.33	1.8
Cataract	2.0	1.49	1.3	1.08	0	0
TBc	2.0	2.23	2.69	3.23	4.17	5.41

G = Good diabetes control
B = Bad diabetes control
CHD = Coronary heart disease
CVD = Cerebrovascular disease
PVD = Peripheral vascular disease
Tbc = Pulmonary tuberculosis

Table 3 The effect of good against bad diabetes control on the progression of complication in NIDDM (%)

Follow up	< 5 yr		5-10 yr		> 10 yr	
	G (n - 100)	B (n - 269)	G (n - 77)	B (n - 186)	G (n - 24)	B (n - 111)
Hypertension	8.0	9.67	12.99	15.58	12.5	18.02
CHD	4.0	3.72	14.29	11.29	37.5	18.92
CVD	1.0	1.49	3.9	2.15	12.5	7.12
PVD	0	2.97	0	3.76	0	5.41
Nephropathy	2.0	7.43	3.9	6.99	12.5	13.51
BDR	1.0	1.86	2.6	3.23	16.67	9.91
PDR	1.0	2.23	1.3	3.76	0	3.6
neuropathy	0	4.09	3.9	9.68	0	8.11
Cataract	8.0	8.92	16.88	9.14	20.83	18.92
TBc	0	1.49	1.3	2.15	8.33	8.11

BDR = Background retinopathy
PDR = Proliferative retinopathy

Results

There were no significant differences in baseline characteristics of patients with NIDDM in each group. More than 90% of the patients were in the over- 40 age group.

Coronary heart disease was found more frequently in the good glucose, 5-10 years follow-up group (5.19 percent, vs. 1.61 percent ; $P < 0.05$) (Table 2). There were no significant differences in the incidence of other macrovascular disease, such as peripheral vascular disease, stroke, and microvascular disease, such as nephropathy, retinopathy, neuropathy, and other disease, such as hypertension, cataract, pulmonary tuberculosis, in both good and bad glucose control group.

After completion of study, only 27%, 29% and 17% of the patients in each group (< 5 yr, 5-10 yr, > 10 yr follow-up respectively) were effectively controlled by conventional therapy. The patients in the effective therapy group had a higher incidence of progression of coronary heart disease than did those in the bad diabetes control group. But only the > 10 year follow-up group had significant difference ($P< 0.05$)

Good diabetes control reduced cerebrovascular and peripheral vascular complications except cerebrovascular disease in the 5-10 yr follow-up and in the > 10 yr follow-up. But all differences were not significant ($P > 0.05$).

Albuminuria developed in fewer patients in

good glucose control group than in bad glucose control group. The differences were not statistically significant ($P > 0.05$)

The risk of background and proliferative retinopathy was reduced by good diabetes control except in the > 10 yr follow-up group which the reverse was true but without statistical significant ($P > 0.05$).

Good diabetes control also reduced the appearance of clinical neuropathy in every follow-up groups without significant difference ($P > 0.05$).

Hypertension, cataract, and pulmonary tuberculosis progressed independently on the difference of control.

Discussion

Good blood glucose control in conventional therapy of patients with NIDDM slowed the progression of peripheral vascular disease, nephropathy, proliferative retinopathy, and neuropathy. But it worsened coronary heart disease and cerebrovascular disease. All the results were not statistically significant except in the > 10 year follow-up group complicated with coronary heart disease.

The DCCT conclusively demonstrated in IDDM that intensive diabetes management, with the goal of lowering blood glucose concentrations to as close to the normal range as possible, delayed the onset and slowed the progression of clinically important retinopathy, nephropathy, and neuropathy, by a range of 35 to more than 70 percent but did not show a significant change in macrovascular disease.[1] Both the American Diabetes Association and the American Association of Clinical Endocrinologists recommended that the levels of control shown effective in the DCCT study be applied to the patients with NIDDM. This application was criticized in two reviews.[7,8] They concluded that intensive therapy would likely have a similar impact on the microvascular and neurological complications of diabetes in patients with NIDDM as intensive therapy had in patients with IDDM. Added caution should be exercised with NIDDM patients at higher risk for adverse complications of intensive therapy and/or with lower potential benefit, such as the elderly who represented over 90 percent of NIDDM patients in this study and elsewhere.[6,9] The DCCT research group advised caution in the use of therapies other than diet that were aimed at achieving euglycemia in patients with NIDDM.

There is currently no evidence that pharmacologic intervention with either oral hypoglycemic agents or insulin reduces the prevalence or progression of atherosclerosis in patients with NIDDM. In unpublished data from the Veterans Administration Cooperative Study Diabetes Mellitus Group, intensive glucose control after the initial onset of vascular disease was associated with increased new vascular events of five to six times those patients not treated intensively.

The risk of severe hypoglycemia was three times higher with intensive insulin therapy.[1] Subclinical hypoglycemia might present in good diabetes control group in this study and aggravate the progression of coronary heart disease and cerebrovascular disease. Blood glucose of diabetes patients in old age group should not be allowed to fall below 120 mg/dl in order to avoid the potential for the

treatment to cause or exacerbate underlying cardiovascular disease or cerebrovascular disease. This study confirms with the other study that good blood glucose control, although not so extensive as that of the DCCT, can reduce the microvascular complications of retinopathy, nephropathy, and neuropathy.[1,10] Intensive therapy may further increase this benefit, but the risk-benefit ratio may be less favorable in patients in old age group and in patients with advanced complications, such as end-stage renal disease or cardiovascular or cerebrovascular disease.

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