

Effects of Exercise on the Metabolic Changes in Diabetes Mellitus

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To study the metabolic and hormonal effect of muscular exercise on severe diabetics and to establish the biochemical criteria for physical exercise treatment for diabetic patients, paper questionnaires concerning daily physical exercise were answered by 225 diabetic patients, and treadmill exercise tests were performed after oral administration of 100g glucose in 2 severe diabetics. In both patients, fasting blood sugar levels were approximately 300 mg/dl. One patient was ketotic (basal levels 2.5—3.5 mM/l) and another was non-ketotic (0.2—0.4 mM/l).

73 (32.5%) of the patients participated in physical exercise treatment every day and 92 (40.9%) of them did it irregularly, while 60 (26.6%) of them did not practice special physical exercise. Most of the patients did not know how to do the exercise.

The rise of blood glucose and FFA in response to treadmill exercise is similar in ketotic and non-ketotic patients. In the ketotic diabetic exercise led to an additional rise in ketone body and glucagon levels, but not in non-ketotic. Therefore, exercise was a stressor, and a hypercaloraemic state induced further hypercaloraemia for the ketotic patient.

After treatment for one month, blood glucose and FFA concentrations fell during and after exercise. In the well-controlled diabetic ketone body levels changed little from those of the resting state during and after exercise.

It is concluded that (1) one-third of the diabetic patients did not participate in physical exercise treatment chiefly because of loss of patient education (2) in ketotic insulin deficient diabetic patients, even non-strenuous exercise can induce severely disadvantageous consequences, in contrast to the possible beneficial effects of exercise in well-controlled diabetics.

Physical exercise has been considered beneficial in the treatment of diabetes for many years.^{1,2)} In fact, the therapeutic use of exercise was advocated as early as 600 B. C. by the Indian doctor Sushruta;³⁾ the therapeutic usefulness of physical activity for diabetes was widely recognized by the physicians of the 18th century.⁴⁾ Since then numerous studies have shown that in diabetics exercise reduces the insulin requirements,^{5,6)} and improves glucose tolerance;⁷⁾ therefore, exercise is effective in well-controlled diabetic patients. In poorly

controlled, especially, ketotic diabetic patients, however, physical exercise results in more pronounced hyperglycemia, hyperlipidemia and hyperketonemia.⁸⁻¹⁰⁾

In 1970 the University Group Diabetes Program¹¹⁾ questioned the long-term cardiovascular safety of oral-hypoglycemic agents. The results of the study, of course, have stirred much controversy.¹²⁾ But it must be stated that the American Diabetes Association has vouched for the results of U. G. D. P. study.¹³⁾

The patients with maturity-onset diabetes

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can often be controlled by diet and physical exercise.¹⁴⁾ As for diet there have been many regimens for diabetics. The Japan Diabetic Society has already edited special diet exchange tables which have been used clinically.¹⁵⁾ But with regards to exercise there have been no authorized program and biochemical criteria of indication for diabetic patients.¹⁶⁾

In the present study, treadmill exercise tests after oral administration of 100g of glucose were undertaken to examine the effects of physical exercise on the metabolic changes in severe diabetic patients. In addition, these studies were designed to establish the biochemical criteria for exercise treatment for diabetic patients.

Procedures and Methods

Patients Since 1958 more than three thousand patients have been registered at the special clinic for diabetics at the Department of Internal Medicine, Nagoya University Hospital. Among them 225 patients were randomly selected and given a paper questionnaire concerning daily physical exercise.

Two male severe diabetic patients were examined. One patient was ketotic (44 yrs old, 160 cm, 56 kg) and the other was non-ketotic (54 yrs old, 169 cm, 58 kg). No specific treatment had been administered before the studies. There was no history or evidence of liver disease. No patients had signs or symptoms of peripheral vascular disease. The studies were carried out at the Research Center of Health, Physical Fitness and Sports and Department of Internal Medicine, School of Medicine, Nagoya University, Nagoya. The nature, purpose and possible risks involved in this study were carefully explained to the

patients prior to obtaining their consent to participate.

Procedures The studies were started at 9.00 AM following an overnight fast of 12 to 14 hours. 100g oral glucose tolerance test (O-GTT) was performed and from 30 to 60 min. following injection of 100g glucose treadmill exercise (70 m/min.) was performed (ex-GTT) by the patient on the next day of O-GTT. Blood samples were collected from the antecubital vein at basal condition and repeated at timed intervals for three hours after the ingestion of glucose for the analysis of glucose, free fatty acid (FFA), acetoacetate, 3-hydroxybutyrate, immunoreactive insulin, C-peptide and glucagon. The ketotic patient was admitted to the Department of Internal Medicine, Nagoya University Hospital. He was treated first by insulin injection and finally oral hypoglycemic agents (glibenclamide 2.5 mg/day). One month afterward, when his diabetes became well-controlled, 100g O-GTT and ex-GTT were again performed.

Analytical Methods Venous blood samples were immediately transferred into several chilled tubes; one portion was put into 20% perchloric acid for deproteinization and the neutralized supernatant was assayed for 3-hydroxybutyrate and acetoacetate on the same day. Another portion was transferred into tubes containing EDTA-Na₂ and Trasylol, and centrifuged; plasma samples were frozen for subsequent analysis of glucagon levels. From a third portion of blood, serum was obtained for analysis of FFA levels; the remainder of the serum was frozen in separate portions for subsequent radioimmunological hormone assays. Additional samples of whole blood were

processed for determination of glucose concentrations. Glucose was determined in whole blood by the method of Hoffman,¹⁷⁾ using a Technicon autoanalyser. 3-hydroxybutyrate and acetoacetate were analyzed in whole blood using enzymatic techniques.¹⁸⁾ Plasma FFA was measured according to the method of Laurell.¹⁹⁾ Insulin, C-peptide and glucagon were determined in plasma by radioimmunoassay.²⁰⁾

1. Present condition of exercise treatment in out-patient clinic.

Percentage distribution of obesity in relation to exercise treatment is shown in Figure 1. Among 225 out-patients, 73 (32.5%) of them practice physical exercise treatment regularly every day and 92 (40.9%) of them did special physical exercise irregularly. Therefore, approximately 70 percent of the out-patients did physical exercise treatment. Sixty (26.6%) of them, however, did not do any special physical exercise treatment, because most of them did not know how to do the exercise. The per-

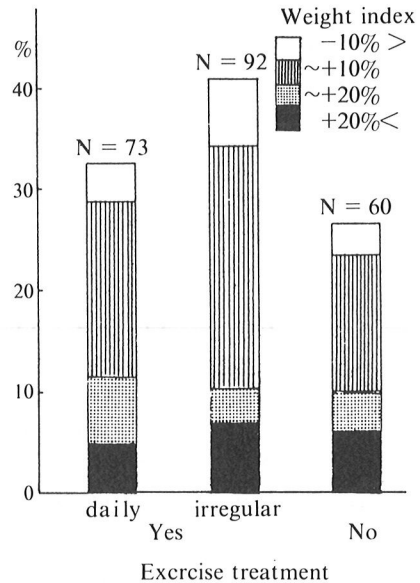


Figure 1. Percentage distribution of obesity in relation to exercise treatment (N = 225)

centage of obese patients tended to be lower in the daily-group (15.1%) than in the no-group (21.7%) but the comparison didn't show any statistical significance.

2. Effect of exercise on the metabolic condition in severe diabetic patients.

The metabolic effects of physical exercise are

Table 1. Effects of exercise on the blood sugar, F.F.A. and ketone body concentrations after oral administration of 100g glucose.

	ketotic diabetics						non-ketotic diabetics						
	0	30	60	70	120	(min) 180	0	30	60	70	120	(min) 180	
Blood sugar (mg/dl)	O-GTT	320	456	680		808	664	330	408	492		504	642
	ex-GTT	372	512	712	808	760	776	300	384	468	510	570	552
F.F.A. (μEq/l)	O-GTT	599	619	485		470	391	940	839	738		821	833
	ex-GTT	639	661	828	611	461	533	622	820	1070	1186	802	913
Total ketone bodies (mM/l)	O-GTT	2.47	2.32	2.37		1.88	1.61	0.45	0.32	0.21		0.14	0.15
	ex-GTT	3.28	3.73	3.11	3.45	3.30	2.40	0.38	0.38	0.22	0.32	0.20	0.16

Exercise was performed from 30 to 60 minutes after ingestion of 100g glucose.

Table 2. Effects of exercise on the insulin, C-peptide and glucagon concentrations after oral administration of 100g glucose.

		ketotic diabetics						non-ketotic diabetics					
		0	30	60	70	120	(min) 180	0	30	60	70	120	(min) 180
Insulin (μ U/ml)	O-GTT	3.5	5.0	4.0		5.0	7.0	3.5	2.0	1.5		2.0	3.0
	ex-GTT	5.0	6.0	6.5	4.5	3.5	7.0	4.0	4.5	6.0	6.5	5.0	5.0
C-peptide (ng/ml)	O-GTT	2.1	1.8	2.1		2.6	2.8	3.0	3.3	4.1		3.4	3.7
	ex-GTT	2.3	2.8	3.0	3.0	3.1	2.1	3.6	4.2	4.5	4.8	5.2	4.9
Glucagon (pg/ml)	O-GTT	155	164	183		181	184	255	288	295		275	372
	ex-GTT	128	156	200	170	165	148						

Exercise was performed from 30 to 60 minutes after ingestion of 100g glucose.

summarized in Table 1 and 2. Fasting blood sugars of both patients were approximately 300 mg/dl. The rise of blood glucose in response to treadmill exercise is similar in ketotic and non-ketotic patients. FFA values also increased after exercise in both patients. In the diabetic subject with ketosis in the resting state, exercise elicited a rise in total ketone bodies, while total ketone bodies kept low levels during and after exercise in the non-ketotic diabetic. In both ketotic and non-ketotic patients, concentrations of insulin and C-peptide remained low level. Exercise did not have any influence on them. Glucagon level in the ketotic patient increased after exercise.

3. Comparison of the metabolic changes before and after treatment in the ketotic patient.

In Figure 2, the effect of exercise on blood glucose, plasma free fatty acid, and total ketone body concentrations after oral administration of 100g glucose are shown. Before treatment treadmill exercise was accompanied by a significant rise in blood glucose concentration. In contrast, after treatment

blood glucose levels in the well-controlled diabetic patient fell during and after exercise.

Before treatment FFA concentration rose approximately 20% with treadmill exercise and total ketone body levels also slightly increased after exercise. After treatment FFA concentration declined progressively following ingestion of glucose and exercise caused FFA levels to fall further. In the well-controlled diabetic the total ketone body concentrations changed little from the resting state during and after exercise.

The effect of exercise on plasma insulin, C-peptide and glucagon concentrations after oral administration of 100g glucose are depicted in Figure 3. Before treatment, insulin and C-peptide values remained at a low level and physical exercise did not produce any effects. Exercise was accompanied by a slight rise in glucagon concentration. After treatment insulin and C-peptide concentrations increased after oral glucose, and the glucagon curve also normalized. There were no significant differences between insulin, C-peptide, and glucagon concentrations of O-GTT and those of ex-GTT.

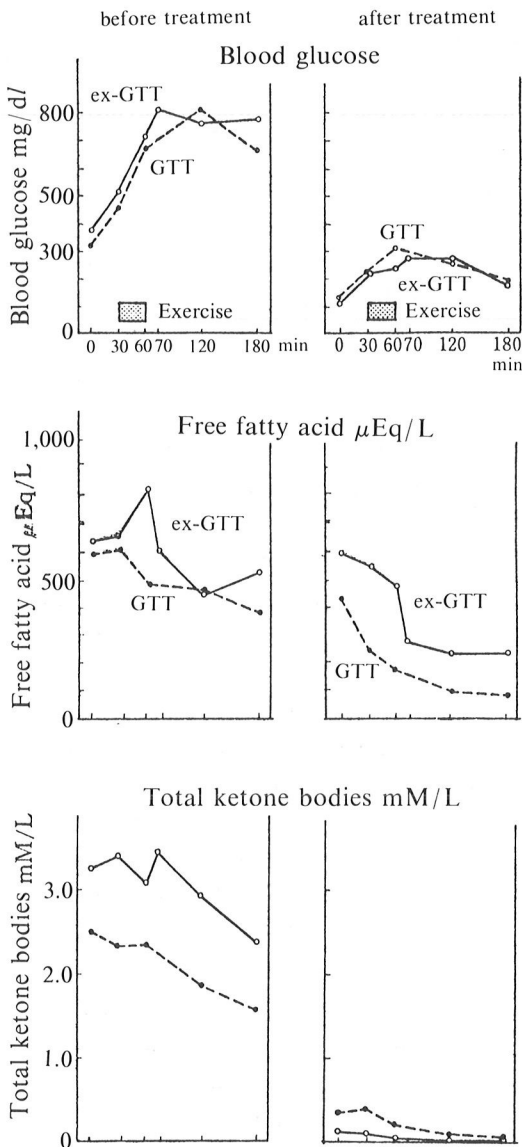


Figure 2. Effect of exercise on blood glucose, plasma free fatty acid and total ketone body concentrations following ingestion of 100g of glucose in a severe diabetic patient

Discussion

Impaired glucose tolerance is a well documented consequence of absolute bed rest

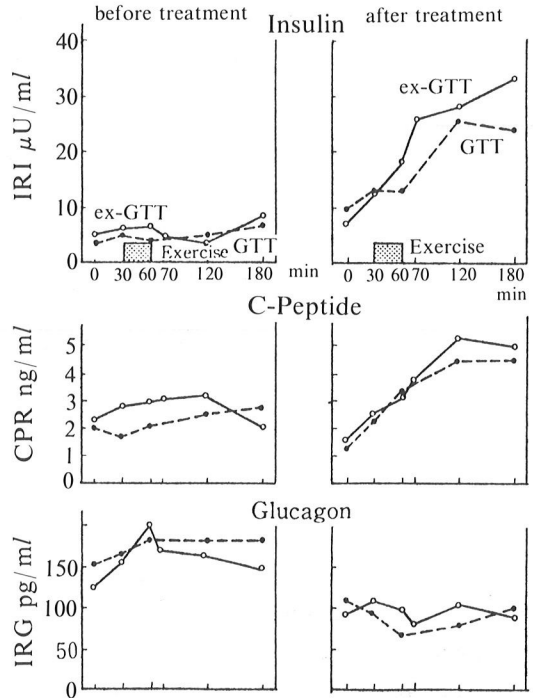


Figure 3. Effect of exercise on plasma insulin, C-peptide and glucagon concentrations following ingestion of 100g of glucose in a severe diabetic patient.

in man.²¹⁾ Nowadays, physical activity in the treatment of diabetes mellitus is generally recommended in medical textbooks and in teaching programs for patients.^{14, 22)}

The results of this study demonstrate, first, that most diabetic patients perform the physical exercise treatment but they do not practice it properly. The questionnaire shows that they do not know how to do so. Therefore, physicians should teach the diabetic patients. However, it is very difficult to do so, because there have been no definite biochemical criteria for exercise treatment of diabetes mellitus.^{16, 23)}

Second, this study shows that the hormonal and metabolic effects of mild exercise in insulin-deficient diabetes are dependent on the patient's state of metabolic control. In

particular, exercise induced a fall of blood glucose in well-controlled patients, but a further rise of glucose levels in ketotic diabetics.

The hormonal response to exercise in healthy subjects is characterized by a fall in plasma insulin and a rise in plasma glucagon. The decrease in insulin concentration during heavy exercise is noteworthy since hypoinsulinemia then occurs in spite of a modest rise in the blood glucose level²⁴⁾ — suggesting that an inhibition of insulin secretion is possibly mediated by the adrenergic nervous system.²⁵⁾ Norepinephrine is also emphasized as a major ketogenic hormone in man.²⁶⁾ On the other hand, physiologic levels of glucagon can stimulate lipolysis and cause hyperketonemia and hyperglycemia in man;²⁷⁾ insulin antagonizes the lipolytic and ketogenic effects of glucagon more effectively than the hyperglycemic effect.²⁸⁾ Further under appropriate conditions, physiologic levels of growth hormone can augment lipolysis and ketonemia in man.²⁹⁾ Vasopressin and angiotensin II also can stimulate hepatic glycogenolysis *in vivo*, and thereby could contribute to the glucagon depletion and hyperglycemia of diabetes, at least in severe acute ketoacidosis.^{30,31)} By using the hepatic and femoral venous catheter techniques, Wahren *et al.*^{1, 8)} have demonstrated that splanchnic glucose output rises during exercise to a similar extent in both diabetics and controls, while uptake of gluconeogenic substrate is markedly higher in diabetics; exercise in diabetic patients with mild ketosis is associated with a rise in blood glucose and FFA levels as well as augmented splanchnic ketogenesis and peripheral uptake of ketone bodies.

It has been suggested that the metabolic effects of exercise on diabetic patients can be

masked by an increased absorption of subcutaneously injected insulin induced by muscle contractions and/or concomitant circulatory changes.^{32,33)} Although no insulin was injected after treatment in this study, blood glucose levels were lower during ex-GTT than O-GTT. By contrast, before treatment, in accordance with the previous studies of Wahren *et al.*^{1,8)} and Berger⁹⁾ *et al.*, increases of blood glucose, FFA and ketone bodies were observed in the ketotic patient during exercise. For the ketotic patients, exercise becomes a stressor and the hypercaloraemic state induces further hypercaloraemia.^{10, 34)} Therefore, exercise treatment is contra-indicated for ketoacidotic patients.^{8, 10)} On the basis of animal experiments,³⁵⁾ Berger *et al.*^{9, 37)} have demonstrated that in the complete absence of insulin, glucose fails to increase during muscle contraction, suggesting that insulin may exert a permissive effect on exercise-induced glucose uptake. They have also suggested that the potential blood glucose lowering effects of physical exercise in diabetics — similar to the stimulation of muscle glucose uptake by contraction — is dependent upon the presence of small amounts of insulin, and that in insulin deficiency the exercise-induced increase in splanchnic glucose production cannot be balanced by an appropriate increase in peripheral glucose uptake.^{9, 35)}

Data from other laboratories in pancreatectomized dogs³⁶⁾ and on glucose uptake of contracting muscles in insulin deprived juvenile diabetes³⁷⁾ strongly support this hypothesis.

Krebs³⁴⁾ has indicated that metabolic changes after exercise in well-trained athletes are significantly different from those of untrained subjects. Improvement of both cardiovascular and respiratory functions as well as the

decrease in lipoprotein moieties and the increase in high density lipoprotein (HDL) levels induced by physical training might protect against the development of atherosclerosis and coronary heart disease —such a long-term effect of physical activity would be of particular importance for diabetics because more than half of all diabetic patients die of angiopathy such as cerebral apoplexy and coronary heart disease,^{39, 40)} Already, field work has shown the existence of such a preventive effect of physical training with respect to the incidence of cardiovascular issue in non-diabetic populations.³⁸⁾ Further investigation with regards to long-term effect of physical exercise treatment on diabetes mellitus in addition to acute metabolic effect is required.

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