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Short-term Treatment of Glucose Intolerance in Middle-aged Subjects by Diet, Exercise and Sulfonylurea

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ABSTRACT

In a screening survey of women and men 47-54 years old for detection of glucose intolerance (GI), with 75 g oral glucose tolerance tests (OGTT), 25 subjects with GI were randomly selected for a therapeutic trial for normalization of the GI. A control group of 18 GI subjects was chosen randomly from the same health survey and given no treatment for 5-10 months; no significant changes in OGTT variables, body mass index, blood pressure or blood lipids were found in this group during follow-up.

The treatment group was given advice concerning a low-sucrose, low-fat, high-fiber and energy-restricted (when overweight) diet and also concerning exercise - single-handed (16 subjects) or in an exercise group (9 subjects). The GI improved in the 25 treated subjects after 6 months of this therapy. Thus the total area under the glucose curve and the 1-h and the 2-h glucose values had decreased, the mean 2-h glucose value was restored to normal (<7.0 mmol$\cdot l^{-1}$) and 48 % of the treated subjects had a normal 2-h glucose value. Body mass index, systolic blood pressure, serum cholesterol and serum triglycerides were also reduced at the follow-up.

The 6-month result was similar in the subgroup of nine GI subjects who followed the dietary advice and exercised in a group for at least one hour per week during at least three months. Physical working capacity was increased, although non-significantly.

Glipizide, 1.25 mg daily, was added at breakfast to ten GI-subjects who still had pathological 2-h glucose values after 6 months of dietary and exercise treatment. After a further 6 months of treatment of these 10 subjects, the total glucose area and the 2-h glucose value were reduced, while the mean 2-h glucose value had not required the normal level. Body mass index was unchanged. Another four subjects in this subgroup now showed a normal 2-h glucose value.

In conclusion, the 2-h glucose value was restored to normal in totally 64 % of all treated GI subjects after short-term treatment with a diet, exercise and, in some cases, added glipizide.

INTRODUCTION

Subjects with glucose intolerance (GI) run an increased risk, 20-60 % per ten years, of developing manifest diabetes mellitus (6,13,14,16,17,20). The Whitehall study concerning males (7,8) and the Bedford study concerning females (11) have shown that among GI subjects the mortality from ischemic heart disease is increased independent of other factors than blood glucose, although this has not been verified by the International Collaborative Group (21). In a long-term study in Lund (18), the rates of post-exercise pathological ST changes at ECG and plethysmographic changes in the legs were higher in GI subjects than in controls. We have recently found that obese GI subjects have a higher rate of hypertension than obese subjects with normal glucose tolerance, even at comparable levels of overweight (3). Blood glucose levels have been found to be correlated to blood pressure, independently of factors such as age and body mass index, at the Whitehall and the Bedford studies (10).

In view of the probability that GI might constitute a considerable risk factor for the development of manifest diabetes and for cardiovascular disease, this study was undertaken to investigate the effect of diet, physical activity and sulfonylurea treatment in a short-term treatment trial in middle-aged female and male subjects with GI. All GI subjects were diagnosed at a recent health survey according to the WHO criteria (24). The diagnostic criteria have previously been variable, and the treatment of detected GI subjects often arbitrary. Few similar studies have been performed concerning GI (2,5,12,20,22).

MATERIAL AND METHODS

At a health survey intended to cover 1 170 middle-aged females and males, 47-54 years old, living in the city of Uppsala, the participation rate was 70 % after one mailed invitation (443 females and 376 males). The rate of manifest diabetes mellitus was 1.5 %, of which cases 1.2 % were diagnosed prior to the survey and not tested, and 0.3 % were detected at the survey. The rate of GI as the result of two consecutive 75 g oral glucose tolerance tests (OGTTs) and according to the WHO criteria was 6.2 % (31 females and 20 males). The following WHO criteria were used for a diagnosis of GI (venous whole blood glucose values) (24):

Fasting glucose <7.0 mmol·l^{-1} and 2-h glucose 7.0-$<$10.0 mmol·l^{-1} at two consecutive OGTTs. (Subjects with fasting glucose <7.0 at both, 2-h glucose 7.0-$<$10.0 at the first and 2-h glucose 10.0-12.0 mmol·l^{-1} at the second OGTT were classified as GI subjects).

OGTT was performed in the morning after ten hours of fasting according to WHO recommendations. A load of 75 g of anhydrous glucose in 300 ml of water was drunk over a period of 5 min. Venous whole blood values were measured at 0-h and at 2-h in the first screening OGTT and then at 0-h, ½-h, 1-h and 2-h in all subsequent OGTTs by a glucose oxidase technique (Yellow Spring Instrument Model 23 AM). The total area under the glucose curve, AUC-G ($mmol \cdot h \cdot l^{-1}$), was calculated by the trapezoidal rule.

Blood pressure (BP) was measured in the sitting position and the diastolic pressure was recorded at the Korotkoff fifth-phase sound. It was read to the nearest 5 mm Hg. Body mass index (BMI) was calculated as height/weight^2 ($kg \cdot m^{-2}$), and expressed as relative BMI (%) as described by the Society of Actuaries (15) and West (23) based on a standard BMI of 20.6 $kg \cdot m^{-2}$ in females and 22.1 $kg \cdot m^{-2}$ in males. The patients were weighed with clothing but without shows and an assumed clothing weight of 1 kg was subtracted. Obesity was defined as relative BMI $\geq$120 %.

Serum cholesterol (range 2.6-7.1 $mmol \cdot l^{-1}$), serum triglycerides (range 0.23-1.70 $mmol \cdot l^{-1}$) and serum liver enzymes (ASAT, upper limit <0.7 $\mu kat \cdot l^{-1}$; ALAT, upper limit <0.7 $\mu kat \cdot l^{-1}$) were measured by an auto-analyzer.

A simple questionnaire was administered to all treated GI subjects at the end of the trial. They were asked to express positive, indifferent or negative feelings concerning the invitation to the health examination, information on the diagnosis of GI and advice concerning diet and exercise.

In subjects treated in a special exercise group, a submaximal exercise test on a bicycle ergometer was performed before and after the treatment period. Work of submaximal intensity lasting 6 min was carried out, and the mean heart rate during the last 2 min of work at the submaximal load was used for calculating physical working capacity (ml oxygen $\cdot kg^{-1} \cdot min^{-1}$) (25).

Randomization of treatment and control groups

At the start of the treatment trial 46 of the 51 GI subjects had been detected, and they were divided into a treatment group of 26 subjects and a control group of 20 subjects by a consecutive randomization procedure. One subject in the treatment group and two in the control group did not want to undergo the follow-up OGTT and were excluded from the study. Thus the study comprised 25 subjects in the treatment group (19 females and 6 males) and 18 in the control group (8 females and 10 males), and their clinical characteristics are presented in Table 1. There was no significant differences concerning age, BMI, systolic and diastolic BP, blood glucose values during OGTT, serum cholesterol or serum triglycerides between the two groups at the start of the study. By chance the sex distribution was uneven.

Table 1. Clinical characteristics at the start of the study in subjects with glucose intolerance; treatment and control groups. Values are mean ± SD.

	Treatment group	Control group
Number of subjects	25	18
Age (years)	51.4 ± 2.0§	51.4 ± 2.1
Relative body mass index (%)	138.5 ± 24.3§	136.9 ± 17.6
Systolic blood pressure (mm Hg)	149.8 12.9§	150.6 ± 12.4
Diastolic blood pressure (mm Hg)	89.0 ± 6.1§	91.9 ± 6.0
Venous whole blood glucose ($mmol \cdot l^{-1}$)		
0-h level	5.0 ± 0.7§	5.1 ± 0.8
½-h "	8.7 ± 1.1§	8.6 ± 1.4
1-h "	10.6 ± 1.2§	10.4 ± 1.4
2-h "	8.5 ± 1.5§	8.7 ± 1.7
AUC-G (total area under the glucose curve, $mmol \cdot h \cdot l^{-1}$)	17.7 ± 1.8§	17.8 ± 2.5
Serum cholesterol ($mmol \cdot l^{-1}$)	6.1 ± 1.4§	6.0 ± 1.0
Serum triglycerides ($mmol \cdot l^{-1}$)	2.25 ± 1.12§	2.64 ± 1.02

Non-paired Student's t-test: § non-significant, $p>0.05$

Control group: None of the 18 control GI subjects were informed about their diagnosis during the trial, and they were not given any advice concerning diet or exercise. OGTT was performed at the start and at the follow-up after 5-10 months.

Treatment group I: The 25 participating subjects were informed that they were glucose intolerant but that they did not have diabetes, and that they might be at risk of developing diabetes later. Initially they were all given dietary advice by the investigator - fewer plain sugar products, less fat, more fiber, and energy restriction (when overweight). Usually the relative proportion of protein in the diet was 15-20 %, of fat 30-35 % and of carbohydrates 50 % (maximally 5 % plain sugars). The energy content was usu-

ally 2 000 kcal per day (8.4 MJ) when non-obese and 1 500 kcal per day (6.3 MJ) when obese. They were also all instructed to increase their physical activity during leisure, either single-handed or by participating in a special exercise group. Attempt was made to find physical exercise suited to the individual wishes (walking, jogging, cycling, swimming). OGTT was performed at the start of the trial and after 6 months of treatment.

Treatment group Ia: Nine of all 25 treated GI subjects, 8 females and one male, agreed to participate in an exercise group, under the guidance of a physiotherapist, for one hour per week and with instructions to train at home for another hour per week during at least three months. The training consisted of jogging and gymnastics of light and medium intensity with relaxation periods; more intensive exercise was not performed until the last part of the training period. This subgroup received further dietary advice on three occasions, including individual counselling, by a dietician. OGTT was performed at the start and at the follow-up after 6 months of treatment.

Treatment group Ib: Thirteen of the subjects in treatment group I were found to still be glucose intolerant, with 2-h blood glucose values of 7.0-<10.0 $mmol \cdot l^{-1}$, at the follow-up OGTT after 6 months of treatment with diet and exercise. Ten of them (9 females and one male) accepted to be given 1.25 mg of glipizide per day half an hour before breakfast and were recommended to continue the dietary and physical training regimen as during the previous 6 months. They were asked to report signs of hypoglycemia. Another OGTT was performed 4-6 months after the start of the glipizide treatment, as follow-up. Drug compliance was assessed at an interview.

Statistical analysis

Student's t-test (two-tailed test) was used for comparison of means, and significance levels were tested at the 0.05, 0.01 and 0.001 levels. T-test levels are given in the following. As Wilcoxon's signed rank test is independent of the degree of normal distribution of the data, every comparison of paired means was also tested by this method at the 0.05, 0.02 and 0.01 levels. A rank test level is only given in the exercise group 1a, since significance levels were the same with both tests in all other comparisons of means. The chi-square test (X^2) with Yates' correction was used for comparison of proportions, and Pearson's coefficient was used for correlations (4).

RESULTS

Treatment group I versus control group

Blood glucose values during OGTT at the start and after 6 months of diet and exercise in all 25 treated GI subjects and after 5-10 months in all untreated control GI subjects are presented in Fig. 1. It is seen that the glucose values at the 1-h and the 2-h levels improved ($p<0.001$) in the treated group and that the mean 2-h glucose value was restored to normal in this group (<7.0 mmol·l^{-1}). No significant changes in blood glucose were observed in the control group.

Fig. 2a and 2b show the mean values of the total glucose areas (AUC-G), systolic and diastolic BP, relative BMI, serum cholesterol and serum triglycerides in the 25 treated and the 18 untreated subjects at the start of the trial and at the follow-up. The mean AUC-G (11 %), 2-h blood glucose (21 %), systolic BP (5 %), relative BMI (5.2 %), serum cholesterol (7.5 %) and serum triglycerides (14.7 %) decreased significantly in the treatment group, while no significant changes occurred in the control group.

Forty-eight per cent of the treated GI subjects (5 males and 7 females) had a 2-h blood glucose value within normal limits (<7.0 mmol·l^{-1}) at follow-up, compared with 22.2 % of the controls (1 male and 3 females) ($p>0.05$).

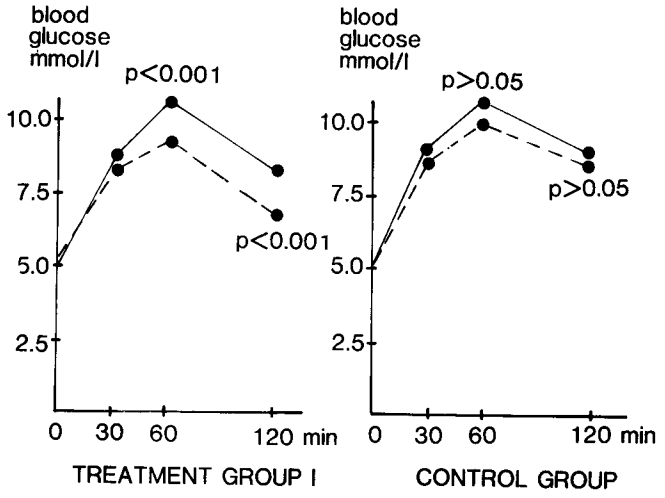

Fig. 1. Mean blood glucose values during 75 g oral glucose tolerance tests in 25 subjects with glucose intolerance (GI) before (whole line) and after (dashed line) 6 months of treatment with diet and exercise and in 18 GI subjects before (whole line) and after (dashed line) 5-10 months without treatment.

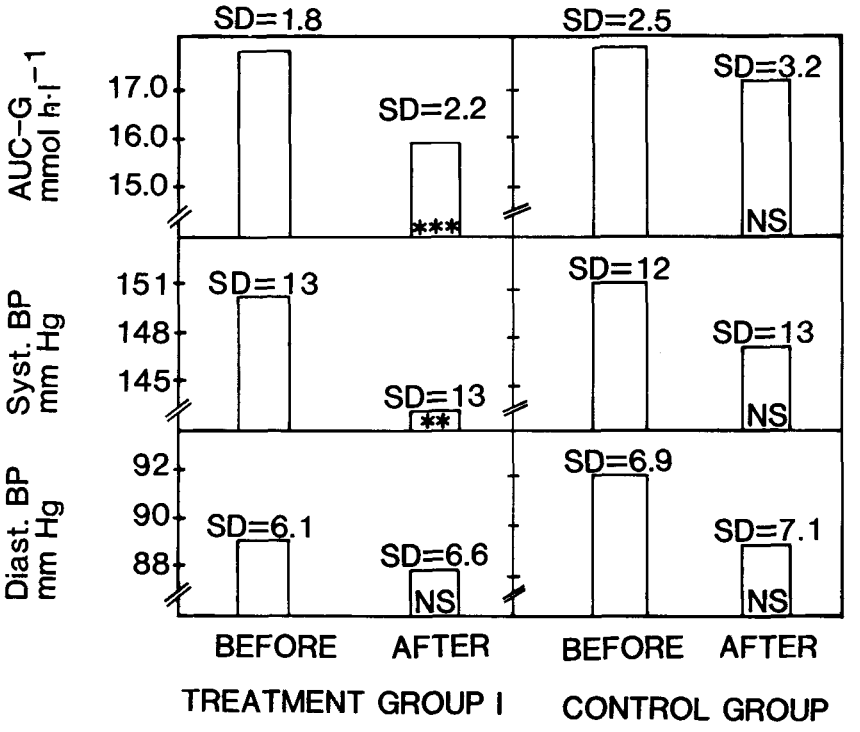

Fig. 2a. Comparison of the total area under the glucose curve (AUC-G) and the systolic and diastolic blood pressures (BP) at the start and end of the study period. The treatment group comprised 25 middle-aged subjects with glucose intolerance (GI) treated with diet and exercise for 6 months (group I). The control group comprised 18 middle-aged GI subjects without treatment for 5-10 months. Each bar represents mean ± SD, significance levels of differences between the two groups are shown within the bars (*** $p<0.001$, ** $p<0.01$; NS = not significant $p>0.05$). The mean AUC-G in six non-obese subjects with normal glucose tolerance at a 75 g OGTT was 10.9 ± 1.2 $mmol \cdot h \cdot l^{-1}$.

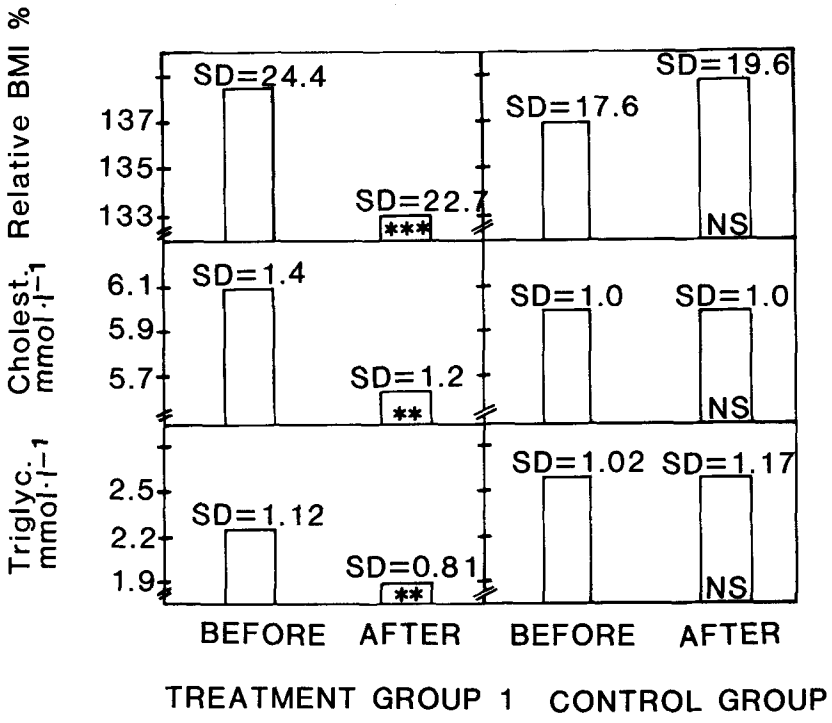

Fig. 2b. Comparison of relative body mass index (BMI), serum cholesterol and serum triglycerides at the start and end of the study period. The treatment group (group I) comprised 25 middle-aged subjects with glucose intolerance (GI) treated with diet and exercise for 6 months. The control group comprised 18 middle-aged GI subjects without treatment for 5-10 months. Each bar represents mean ± SD, significance levels of differences between the two groups are shown within the bars (** $p<0.01$, *** $p<0.001$; NS = not significant $p>0.05$).

Treatment group Ia

The blood glucose values during OGTT at the start of the trial and at the follow-up after 6 months of diet and physical training in the nine subjects of group Ia are given in Fig.3. These subjects exercised for at least one hour per week during at least 3 months of the treatment period. The mean AUC-G was 17.4 mmol·h·l^{-1} at the start and 15.7 mmol·h·l^{-1} at the follow-up 6 months later ($p<0.05$, signed rank test; $p> 0.05$, t-test), a decrease of 10 %. The mean 2-h blood glucose value was reduced by 21 % at follow-up ($p<0.01$) and was normalized (<7.0 mmol·l^{-1}); four subjects had a normal 2-h glucose at this time. The mean systolic BP was reduced by 8.4 % and the mean diastolic BP by 3.3 % at follow-up; thus BP was 155/91 mm Hg at the

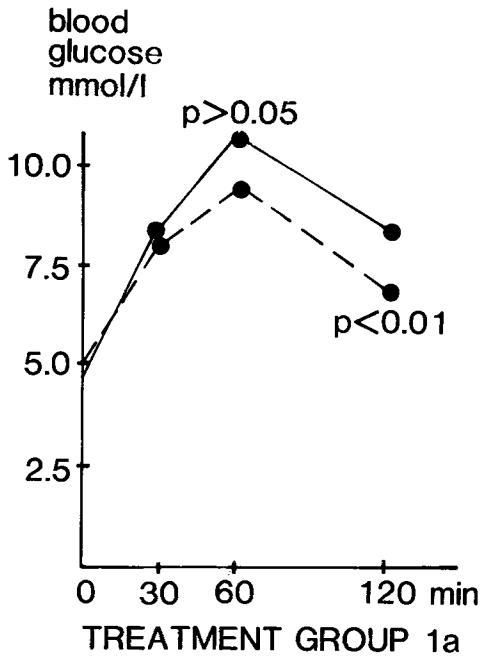

Fig. 3. Mean blood glucose values during 75 g oral glucose tolerance tests in 9 subjects with glucose intolerance participating in an exercise group for one hour weekly and treated with dietary regimen for 6 months (treatment group Ia).
Whole line = before treatment
Dashed line = after 6 months of treatment

start and 142/88 mm Hg at follow-up ($p<0.001/<0.05$). The mean relative BMI was reduced by 5.7 % at follow-up, 132.4 % compared with 138.1 % at the start ($p<0.001$). There was a slight increase in physical working capacity by 6.9 % at follow-up in seven tested subjects ($p<0.05$, one-tailed t-test; $p>0.05$, two-tailed t-test).

Treatment group Ib

The blood glucose values during OGTT in the 10 subjects of group Ib at the start and at the end of the glipizide treatment period are presented in Fig. 4. The mean 2-h glucose value decreased by 10 % ($p<0.05$) but did not regain the normal level of <7.0 $mmol \cdot l^{-1}$. A further four subjects had a normal 2-h value after the addition of glipizide. The mean AUC-G decreased from 17.4 $mmol \cdot h \cdot l^{-1}$ at the start to 15.6 $mmol \cdot h \cdot l^{-1}$ at the end of the glipizide period, i.e. by 10 % ($p<0.05$). The mean relative BMI was unchanged during this period (138.2 % before and 138.5 % after glipizide treatment, $p>0.05$).

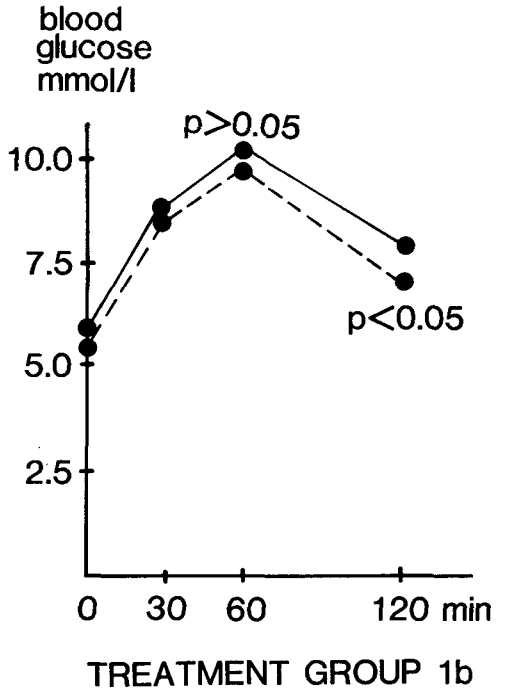

Fig. 4. Mean blood glucose values during 75 g oral glucose tolerance tests in 10 subjects with glucose intolerance treated with diet, exercise and 1.25 mg of glipizide daily for 4-6 months (treatment group Ib).
Whole line = before treatment
Dashed line = after 4-6 months of treatment

It was found that the 2-h blood glucose value became normal in 12 of all 25 treated GI subjects after 6 months of diet and exercise and in a further four subjects after addition of glipizide for another 6-month period -totally 64 % of all treated subjects ($p<0.05$, compared with the control group).

Comments on the state of health of the subjects and the feasibility of the trial

None of the GI subjects had pancreatic disease. One of the treated GI subjects had been operated on for duodenal ulcer. None reported a high alcohol intake. One treated female and one control male had a serum ASAT or ALAT value of >0.7 microkat·l^{-1}.

In a questionnaire answered by the treated subjects, 96 % reported positive feelings concerning the invitation to the health examination. To receive information about the diagnosis of GI was reported as preferable to not being aware of the condition by 88 % and negative by 12 %. Advice about the diet and exercise was experienced as positive and valuable by 84 %.

There was no report of serious symptoms of hypoglycemia during glipizide treatment. One subject complained of dizziness and hunger initially on a few occasions and was excluded, since she refused to attend the follow-up.

Correlations between OGTT parameters

The correlation between the 2-h blood glucose value and AUC-G in all 117 OGTTs performed during this study was $r = 0.79$ ($p<0.001$).

DISCUSSION

Since glucose intolerance is proposed as a risk factor both for the development of manifest diabetes and for cardiovascular disease, and since glucose intolerance seems to be related to hypertension, appropriate treatment of glucose intolerance might be of value as a preventive measure.

In the present study an unselected group of subjects with GI, detected in a sample representative of a middle-aged urban Swedish population, was given advice concerning a dietary regimen and exercise. The main purpose of this study was to see if changes of diet and exercise in GI subjects might normalize the blood glucose values. The trial was carried out at a primary care unit, using available resources with the guidance of the author, a dietician and a physiotherapist. At the follow-up after 6 months of treatment, both OGTT variables, body mass index, blood pressure and blood lipids were significantly improved. Concerning differences between sexes, more males than females showed a normalized 2-h glucose value at the follow-up. The overwhelming majority of the participants had a positive attitude to being informed about the diagnosis of GI and to these therapeutic measures. Untreated GI controls showed no change in any of the variables at the follow-up.

In a special subgroup of 9 treated GI subjects who exercised according to a special program guided by a physiotherapist at least once a week for at least 3 months, there were similar significant improvements in all the above-mentioned variables at the follow-up. An increase in physical working capacity was seen, although insignificant. Thus, the main finding of this study was that GI can be , at least initially, normalized when the detected GI subjects are given advice concerning diet, exercise and GI as a risk factor.

There have previously been few reports on improvement of a borderline diabetic state by short-term energy restriction or weight loss, and the methods and diagnostic criteria at glucose tolerance tests have varied (9,17). However, Saltin et al (19) report successful results of dietary advice and physical training in 48 middle-aged GI males with normoglycemics as controls. OGTT was restored to normal in 25 GI subjects who were given dietary advice

and two weekly exercise sessions during a period of 6-12 months, and it improved in 12 GI males given dietary advice alone and in 11 GI males participating in an exercise group for 3 months. The mean body weight was decreased and the working capacity improved, even in the diet-treated group. Björntorp et al (1) report on five severely obese GI subjects, three females and two males, who were trained physically 3 times per week under the guidance of a physiotherapist for 2 months. Maximal oxygen consumption increased slightly in only three patients after the treatment period. Glucose tolerance did not change. Fasting plasma insulin, as well as the sum of insulin values, decreased at IVGTT but not at OGTT at follow-up.

In the present study glipizide was added in a low dose in those GI subjects who had been unsuccessfully treated with a diet and exercise for 6 months. Nearly all glipizide-treated subjects were females. The OGTT variables decreased after glipizide therapy, although the mean 2-h blood glucose was still above normal, and the body mass index was not affected by the drug. Further four subjects were normalized. But this result might have been obtained by the continued regimen of diet and exercise instead of by added SU, and cannot be used for evaluation of SU-treatment of GI.

Other sulfonylureas have mostly been used previously for the treatment of glucose intolerance. Tolbutamide was used in a long-term study in Lund (20). At the ten-year follow-up, none of the tolbutamide-treated subjects had developed manifest diabetes, compared with 13 % of the diet-treated and 29 % of the untreated subjects. The dose was 0.5 g t.i.d. No case of myocardial infarction or intermittent claudication had occurred in the tolbutamide-treated GI subjects and the rate of pathological ECG changes was close to that in the normoglycemic control group, while most cases of cardiovascular disease were found in the untreated and diet-treated GI subjects (18). In three other long-term studies, the Bedford study (12), the study of Stowers (22) and the study of Feldman (5), sulfonylurea therapy did not appear to affect diabetes morbidity. In the present study a "modern" sulfonylurea in a low dose was used. In another glipizide trial, 23 GI subjects were treated with 2.5 mg of glipizide daily. At a follow-up after three years, the mean width of the muscle capillary basement membrane had decreased to a level similar to that in normal subjects, whereas the width in 18 untreated GI subjects was increased at follow-up (2).

In summary, middle-aged subjects with GI detected at a health survey were given short-term treatment with diet and exercise. It was found that the glucose tolerance was improved in the treated GI subjects, and half of them showed a normal 2-h post-load blood glucose value after 6 months, compared with 22 % of untreated GI controls. Blood pressure and blood lipids were also reduced in the treated GI subjects. When glipizide in a low dose was added

in subjects resistant to treatment with diet and exercise alone, totally two-thirds of the treated GI subjects achieved a normal 2-h glucose value.

In accordance with WHO, glucose intolerance or impaired glucose tolerance was preferred as a diagnostic concept rather than latent or chemical diabetes in this study. Since GI is a risk factor for the development of manifest diabetes and probably of cardiovascular disease, detected GI subjects should not be left untreated. It was found here that advice concerning diet and exercise with supporting guidance by a physician and a dietician was appropriate as treatment of GI. Although some of the GI subjects were also treated with glipizide, it cannot be concluded from the present results that glipizide should be used for the treatment of GI.

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