Weight Loss in Severely Obese Subjects Prevents the Progression of Impaired Glucose Tolerance to Type II Diabetes

A longitudinal interventional study

STUART D. LONG, BS
KEVIN O'BRIEN, PHD
KENNETH G. MACDONALD, JR., MD
NANCY LEGGETT-FRAZIER, RN
MELVIN S. SWANSON, PHD
WALTER J. PORIES, MD
JOSÉ F. CARO, MD

OBJECTIVE — To determine if weight loss may prevent conversion of impaired glucose tolerance (IGT) to diabetes, because weight loss reduces insulin resistance. The prevalence of IGT in the U.S. population is estimated at 11.2%, more than twice that of diabetes. Furthermore, because an oral glucose tolerance test is needed for its detection, most of these patients are undiagnosed. Screening for IGT would be meaningful if progression to diabetes could be delayed or prevented.

RESEARCH DESIGN AND METHODS — For an average of 5.8 years (range 2–10 years), 136 individuals with IGT and clinically severe obesity (>45 kg excess body weight) were followed. The experimental group included 109 patients with IGT who underwent bariatric surgery for weight loss. The control group was made up of 27 subjects with IGT who did not have bariatric surgery. The criteria of the World Health Organization was used to detect IGT and diabetes in this population. The main outcome measure of this nonrandomized control trial is the incidence density, or number of events (development of diabetes) divided by the time of exposure to risk.

RESULTS — Of the 27 subjects in the control group, 6 developed diabetes during an average of 4.8 ± 2.5 years of postdiagnosis follow-up, yielding a rate of conversion to diabetes of 4.72 cases per 100 person-years. The 109 individuals of the experimental group were followed for an average of 6.2 ± 2.5 years postbariatric surgery. Based on the 95% confidence interval of the comparison group, we would expect to find that between 22 and 36 subjects in the experimental group developed diabetes over the follow-up period. Only 1 of the 109 experimental-group patients developed diabetes, resulting in a conversion rate of the experimental group of only 0.15 cases per 100 person-years, which is significantly lower ($P < 0.0001$) than the control group.

CONCLUSIONS — Weight loss in patients with clinically severe obesity prevents the progression of IGT to diabetes by >30-fold.

From the Departments of Medicine and Surgery, East Carolina University, Greenville, North Carolina; and the Department of Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania.

Address correspondence and reprint requests to José F. Caro, MD, Department of Medicine, Jefferson Medical College of Thomas Jefferson University, 1025 Walnut Street, Philadelphia, PA 19107.

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IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization; NDDG, National Diabetes Data Group; FPG, fasting plasma glucose; CI, confidence interval.

Impaired glucose tolerance (IGT) is a new diagnostic category coined by the National Diabetes Data Group (NDDG) in 1979 (1) and adopted by the World Health Organization (WHO) in 1980 (2). Individuals included in this category are those whose fasting plasma glucose (FPG) concentration is less than the level diagnostic of diabetes (140 mg/dl) and whose 2-h glucose concentration after a 75-g oral glucose tolerance test (OGTT) is between normal and diabetic values (140 to 200 mg/dl. Thus, to diagnose IGT, an OGTT needs to be performed, a procedure rarely used in today's clinical practice.

This new diagnostic category is important for several reasons. The prevalence of IGT in the U.S. population 20–74 years of age is high, being estimated at 11.2% by the WHO criteria and estimated at 22.8% in the oldest age group (3). Furthermore, subjects with IGT are at higher risk for the development of macrovascular disease (4,5) and type II diabetes (6–14). A longitudinal study of the natural history of IGT found that approximately one-fourth developed type II diabetes at 5 years and two-thirds at 10 years, with one-third reverting to normal (6).

As established previously, the prevalence of type II diabetes and IGT is increased by obesity (3). Although short-term improvement in glucose tolerance by caloric restriction (15) or weight loss (13) has been shown in individuals with IGT, the long-term impact of these interventions on the development of clinical diabetes is unknown. This is an important issue because, as indicated by the NDDG (1), a case for detection of IGT in the general population should rest on our ability to intervene, and possibly prevent, the progression to clinical diabetes. Herein, we demonstrate that weight loss does prevent the progression of IGT to type II diabetes.

RESEARCH DESIGN AND METHODS

— From 1 February 1980 to 31 October 1991, 168 individuals with

Table 1—*Baseline characteristics of the subjects with IGT*

	Experimental group	Control group	*P* value
n	109	27	
Age (years)	36 ± 8	37 ± 10	0.68
Sex (M/F %)	14/86	11/89	0.72
Race (black/white %)	17/83	15/85	0.83
BMI (kg/m^2)	48 ± 8	51 ± 9	0.15
Alcohol consumption (%)	18	25	0.43
Smoking (%)	26	38	0.20
BP (mmHg)			
sBP	132 ± 17	136 ± 14 (26)	0.30
dBP	85 ± 11	84 ± 9 (26)	0.68
FPG (mM)	6.0 ± 0.7	6.1 ± 0.7	0.46
2-h glucose (mM)	9.2 ± 0.8	9.0 ± 0.8	0.32
Fasting plasma insulin (pM)	231 ± 164 (58)	228 ± 132 (22)	0.93
2-h insulin (pM)	1217 ± 751 (55)	1133 ± 705 (22)	0.65
Follow-up (years)	6.2 ± 2.5	4.8 ± 2.5	0.01

Data are means ± SD. The number of subjects studied was 109 for the experimental group and 27 for the control group unless indicated in parentheses.

clinically severe obesity (45 kilos over the 1983 median weight of the Metropolitan Life Insurance Tables) were diagnosed as IGT per WHO criteria during their preoperative evaluation (2) for gastric bypass surgery. Of these individuals, 167 were found eligible for the operation and 130 underwent the operation. Of the 130 individuals, 109 have had a minimum of 2 years postoperative blood glucose follow-up; these subjects make up the experimental group of this study. A total of 37 individuals did not undergo surgery, 27 of whom have had at least 2 years of follow-up. These subjects did not undergo surgery because of personal choice or other nonmedical reasons. These subjects did, however, agree to be followed in a manner similar to the experimental group and therefore provide an adequate control group.

Each patient underwent a thorough medical and laboratory evaluation, an interview with a psychologist, and several evaluations to measure mental health, physical and role functioning, economic status, and education levels, as described previously in detail (16). Each patient had a 75-g OGTT as recommended by the WHO (2). The diagnostic criteria for IGT was that of the WHO (2). Postoperative care and follow-up visits have been described elsewhere (16) and included a minimum of nine visits the first year, two visits the second year, and yearly visits thereafter. Once a gastric bypass operation is performed, an OGTT is of undefined diagnostic value, and is also unacceptable to the patient because of the dumping syndrome. Therefore, the follow-up data are based on the presence or absence of diabetes as defined by the WHO, i.e., an FPG concentration >140 mg/dl on two occasions or a random plasma glucose reading >200 mg/dl plus classical symptoms of diabetes. This approach underestimates the rate of conversion to diabetes because it would not identify those patients with an FPG concentration <140 mg/dl and a 2-h plasma value past 75 g OGTT >200 mg/dl. However, identical diagnostic criteria was used for the control group. The glucose assay was performed by the hexokinase method on an Abbott Spectrum instrument (North Chicago, IL). Insulins were performed using an INCstar kit (Stillwater, MN).

Statistical analysis

The statistical analysis was conducted using the SAS software with graphics performed using Plot-It (17). Descriptive statistics, such as means, standard deviations, counts of events, and totals, were calculated for the comparison and experimental groups. A Student's *t* test for independent samples was used to compare various characteristics between the two groups. Pearson's χ^2 was used to test for differences between binary variables. The incidence densities (events divided by time of exposure to risk), incidence density ratios, and tests of hypothesis were calculated as discussed by Kleinbaum et al. (18). Confidence intervals (CI) (95%) were conducted under an exponential model, following the approach given by Kalbfliesch et al. (19).

RESULTS — Table 1 summarizes the baseline characteristics of the experimental and the control groups.

Patients with IGT make up 31.1% of the total cohort of patients with clinically severe obesity that was entered in the study from 1980 to 1991. Of the remaining patients, 27.2% have type II diabetes and 41.7% have normal OGTT, as per the WHO diagnostic criteria (2). The prevalence of IGT in this obese population is more than double that of the general population (2), but similar to that of other obese populations (6).

Figure 1*A* shows the means ± SE of the FPG in the experimental group before surgery and the FPG and/or random plasma glucose of the same patients after surgery. Figure 1*B* shows the percentage of excess body weight lost during the 10 years of follow-up. The numbers in parentheses represent the data from the patients at that point of follow-up. The closed circles represent the entire group except for one patient, represented by open circles, who developed type II diabetes at year 3 of follow-up.

A statistically significant decrease in plasma glucose occurs ($P < 0.0001$ at 3 months to 0.0048 at 10 years) throughout the duration of the study that usually pre-

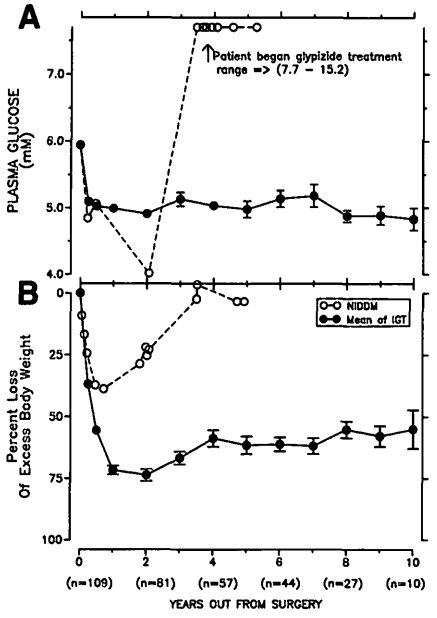

Figure 1—*The means ± SE of the FPG before gastric bypass and the FPG and/or random plasma glucose after surgery is shown* (A). *SE bars are not displayed if they are smaller than the symbol. The entire group* (●) *except for the single patient who developed type II diabetes* (○) *is represented. The percentage of body weight is shown* (B). *Numbers in parentheses represent data from the patients at that point of follow-up.*

cedes maximum weight loss. This occurred also in the only subject that subsequently developed type II diabetes. This individual did not have any preoperative characteristics different from the group and failure to lose weight is likely the major reason for the conversion to type II diabetes.

In contrast to this extraordinarily low rate of progression from IGT to diabetes in the experimental group, 6 of the 27 subjects in the control group developed type II diabetes during an average 4.8 ± 2.5 years of follow-up. The diagnosis of type II diabetes was established in one patient during year 1, in one patient during year 2, in two patients during year 3, in one patient during year 4, and in one patient during year 6. The control group did not lose weight during the follow-up period. None of the preoperative characteristics disclosed in Table 1 were different between the control group with or without diabetes.

Table 2 shows the statistical differences in conversion from IGT to diabetes between the experimental group and the control group. Also included are data from seven longitudinal studies (6–11,14) on the natural history of conversion from IGT to diabetes.

The rate of conversion to diabetes in our comparison group is 4.72 cases per 100 person-years, which is identical to the average incidence rate of the seven previous studies summarized in Table 2.

In contrast, the conversion rate of the experimental group is only 0.15 cases per 100 person-years. Thus, the incidence density ratio of the experimental group indicates a >30-fold decrease in the risk of developing NIDDM after weight loss.

CONCLUSIONS— We report that weight loss prevents the development of type II diabetes in an extremely high-risk population for the disease. Individuals with IGT who did not lose weight developed type II diabetes at a rate of 4.72 cases per 100 person-years, which is similar to that reported previously by others (6–11,14) and is summarized in Table 2. In contrast, loss of ~50% of excess body weight resulted in a significant reduction in the conversion rate to type II diabetes to a low of 0.15 cases per 100 person-years.

Though type II diabetes is a genetic disease, the phenotype is influenced by other factors, such as obesity, sedentary lifestyle, and aging. Although not all patients with IGT develop diabetes, and some reverse spontaneously to normal, IGT provides a unique patient population to test preventive therapy—either with weight loss, exercise, or preferably both.

IGT in obesity is mainly the result of a reduction of insulin action (21). The resulting hyperglycemia then signals increased insulin secretion, initiating a cycle

Table 2—*Conversion from IGT to diabetes*

Study	Incidence of NIDDM (patient years)	Incidence rate (100 person-years)	95% CI Lower	95% CI Upper	Incidence ratio	*P* value
Experimental group	1/682	0.15	0.05	0.24	1.00	
Control group	6/127	4.72	3.46	5.98	31.47	<0.0001
Reference number						
14	19/1938	0.98	0.83	1.13	6.53	<0.0001
7	14/255	5.49	4.53	6.45	30.13	<0.0322
11	5/91	5.49	3.89	7.10	36.60	<0.0001
8	48/2506	1.92	1.73	2.10	12.80	<0.0010
6	118/1267	9.31	8.75	9.87	62.07	<0.0001
5	27/1020	2.65	2.31	2.98	17.67	<0.0001
10	3/57	5.26	3.28	7.25	35.07	<0.0001

Patient years is the sum of individual total years from the point of initial IGT diagnosis. Individual years were truncated by one of three events: date last seen by physician, date of NIDDM diagnosis, date of death. Incidence ratios and *P* values were compared with the experimental group.

leading to β-cell unresponsiveness to glucose, insulin exhaustion, and then diabetes. Weight loss may contribute to breaking this cycle because obesity itself is a common cause of insulin resistance with multiple cellular defects—most of which are reversible after proper treatment (22).

The patient population in our study, and the method used for weight loss, are neither representative of the majority of obese subjects nor of the optimal treatment modality. Of the 34 million obese adults in America, between 3 and 7 million are severely obese, exceeding their ideal body weight by >45 kg. Our study includes only severely obese subjects. The morbidity and mortality rates of these patients present a difficult problem to health providers because of the high rate of medical treatment failures. The earlier surgical procedures, such as jejunoileal bypass, were associated with unacceptable complications and have been abandoned. Previously, the National Institutes of Health consensus conference (23) on bariatric surgery indicated that the newer surgical procedures, such as gastric bypass and vertical banded gastroplasty, are more appropriate procedures. The method used for weight reduction in our study is gastric bypass surgery. Some changes in the gastrointestinal tract that alter insulinotropic hormones and the rate of nutrient absorption might account for the decrease in progression to diabetes rather than any effect of weight loss per se. Therefore, it should be established that less obese individuals with IGT are able to prevent or delay their conversion to type II diabetes by weight loss using less invasive therapeutic procedures. Although we believe this will be the case, new data need to be generated to test this hypothesis. For now, we have made a case for the detection of IGT in demonstrating the success of intervening to block the progression to clinical diabetes.

Diabetes is a major health problem costing 150,000 American lives and >$20 billion each year. Accordingly, methods to prevent the disease should be a top public health priority.

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