Increased Resting Metabolic Rates in Obese Subjects with Non-insulin-dependent Diabetes Mellitus and the Effect of Sulfonylurea Therapy

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SUMMARY

Obese subjects with non-insulin-dependent diabetes mellitus (NIDDM) lose weight soon after diagnosis and tend to gain weight during hypoglycemic therapy. One explanation for these weight shifts is the change in caloric loss from glycosuria. We compared 24 obese Pima Indians with NIDDM to 24 Pima Indians with normal glucose tolerance to determine whether resting metabolic rate changes may be an additional factor influencing the weight shifts. The diabetic and nondiabetic subjects were equally obese, body fat 38 ± 1% versus 37 ± 1% (mean ± SEM), respectively, as determined by densitometry. In the morning after an overnight fast, resting metabolic rate (RMR) was measured by indirect calorimetry. The mean RMR of the diabetic subjects, 32.9 ± 0.5 kcal/day · kg fat-free mass (FFM), was 5% higher than that of the nondiabetic subjects, 31.4 ± 0.5 kcal/day · kg FFM ($P < 0.05$). In nine of the diabetic subjects, 6 wk of tolazamide therapy was associated with reductions in mean FPG, 253 ± 16 to 144 ± 14 mg/dl ($P < 0.01$), mean daily urine glucose loss, 128 ± 26 to 11 ± 4 g ($P < 0.01$), and mean RMR, 31.9 ± 0.8 to 30.2 ± 0.6 kcal/day · kg FFM ($P < 0.04$). Weight of the subjects was maintained constant from beginning to end of therapy (106.5 ± 9.6 versus 108.1 ± 9.9 kg) by decreasing daily calorie intake from 3070 ± 103 to 2784 ± 163 kcal ($P < 0.01$). We conclude that RMRs of obese, NIDDM subjects are increased compared with the RMRs of equally obese, nondiabetic subjects and that tolazamide therapy that decreases FPG reduces RMR in obese subjects with NIDDM. DIABETES 1986; 35:1–5.

Obese subjects lose weight within 2 yr after the diagnosis of non-insulin-dependent diabetes mellitus (NIDDM).[1] Although this weight loss may result from caloric restriction, this explanation seems unlikely, since most obese subjects are unable to maintain reduced body weights with diet therapy.[2] Urinary caloric loss due to glycosuria is probably a more important cause of negative caloric balance and weight loss in these patients. Another possible contributing cause of weight loss in untreated, obese diabetic subjects may be increased resting metabolic rates, as recently observed in lean, insulin-dependent diabetic subjects (IDDM).[3]

The results of the University Group Diabetes Program (UGDP) study showed that subjects with NIDDM gain weight during insulin therapy.[4] Similarly, Chan et al. have shown that insulin-treated, obese, alloxan-diabetic rodents gain weight due to reduced glycosuria and increased "energy efficiency."[5] The data of the UGDP study[4] also showed that subjects with NIDDM gain weight during oral sulfonylurea therapy, and Gelderman et al.[6] reported that phenformin treatment of five subjects for 2 wk was associated with weight gain. However, not all investigators have observed weight gain in obese diabetic subjects during oral sulfonylurea therapy.[7]

In our study, we tested the hypothesis that obese, NIDDM subjects have increased resting metabolic rates as another mechanism of weight loss during onset of their disease, and that sulfonylurea therapy decreases the elevated resting metabolic rates and could result in weight gain if caloric intake is unchanged during treatment.

MATERIALS AND METHODS

Subjects. Southwestern American Indians were admitted to the Phoenix Clinical Research Center for study. Written, informed consent was obtained from all subjects. Blood was drawn for complete blood count, liver function tests, blood urea nitrogen, creatinine, electrolytes, calcium, total protein, and albumin after an overnight fast. Forty-eight subjects who had normal physical examinations and fasting blood test results were entered into the study. None of the subjects had

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taken any medicines for the preceding month. After at least 2 days of a diet containing a minimum of 200 g of carbohydrate, an oral glucose tolerance test (OGTT) was performed.[8] Each subject's glucose tolerance was classified according to the National Diabetes Group Criteria.[8] Twenty-four subjects (7 males, 17 females) had NIDDM. These subjects were closely matched for sex, body weight, and degree of obesity (see below) with subjects who had normal glucose tolerance.[8] Characteristics of the 48 subjects are listed in Table 1. The diabetic subjects were slightly older than the nondiabetic subjects, but the groups were otherwise similar in body weight, height, and degree of obesity.

Body composition. The percent body fat of each volunteer was estimated by underwater weighing, as previously described by others.[9] Briefly, each subject entered a tank of water kept at 35°C, sat in a canvas chair suspended from a scale, and his/her weight was recorded after a full, forced expiration while completely submerged. Simultaneously, the subject breathed into a spirometer (Warren E. Collins Co., Braintree, Massachusetts) so that the residual lung volume could be estimated by helium dilution. The body density and percent body fat were calculated according to the equation of Keys and Brozek.[10]

Determination of postabsorptive endogenous glucose production rates. After the OGTT and at 0600 h after an overnight fast, an intravenous (i.v.) catheter was placed in an antecubital vein for infusion of 3-^{3}H-glucose. Another catheter was inserted retrograde in a dorsal vein of the opposite arm, and that arm was placed in a warming box heated to 70°C for withdrawal of arterialized venous blood. The 3-^{3}H-glucose was given as a primed (30 μCi)-continuous infusion (0.3 μCi/min) for 180 min. Blood was drawn for determination of plasma glucose, insulin, and 3-^{3}H-glucose specific activity at 150, 160, 170, and 180 min.

Plasma free fatty acid (FFA) concentrations. Three blood samples were drawn for determination of plasma FFA concentrations during the last 30 min of the 3-^{3}H-glucose infusion and again on another morning. The blood was drawn into iced tubes containing EDTA and diethyl *p*-nitrophenyl phosphate (1.1 mg/ml, Sigma Chemical Co., St. Louis, Missouri).

Indirect calorimetry. During the last 60 min of the 3-^{3}H-glucose infusion, a clear-plastic ventilated hood was placed over the subject's head. Room air was drawn through the hood and the flow rate was measured by a pneumotachograph (Gould, Cleveland, Ohio). A constant fraction of expired air was withdrawn and analyzed for oxygen and carbon dioxide content. The oxygen analyzer was a zirconium cell analyzer and the carbon dioxide analyzer was an infrared analyzer (Applied Electrochemistry, Sunnyvale, California). The analyzers and flowmeter were connected to a desktop computer (Hewlett-Packard, Palo Alto, California) that recorded continuous, integrated calorimetric measurements every 5 min for the last hour of the 3-^{3}H-glucose infusion. Protein oxidation during the tests was estimated from the urinary urea production rate. Mean substrate oxidation and energy expenditure rates were calculated from the equations of Lusk[11] for the last 40 min of the test.

Effect of tolazamide therapy. We determined the effect of oral tolazamide (Tolinase, Upjohn Co., Kalamazoo, Michigan) therapy on resting energy expenditure in nine (four males, five females) of the subjects with NIDDM (mean age of 30 ± 4 yr, mean height 162.6 ± 2.2 cm, and mean percent body fat of 37 ± 2% before treatment). No subjects had been treated with oral hypoglycemic agents or insulin for 1 mo before the study and all subjects remained on the metabolic ward for the duration of the studies. After at least 10 days of a weight-maintaining diet, each subject's resting energy expenditure was determined as described in the paragraph above. On the following morning, oral tolazamide therapy was begun. To achieve maximal hypoglycemic effect, the dose was gradually increased the first week up to a maximum dose of 500 mg twice daily. Glycemic control was monitored by plasma glucose determinations (fasting and before the evening meal) every second day for the first week and twice each week thereafter. A 24-h urine collection for determination of daily glucose excretion was done before and during the sixth week of therapy. During the sixth week of therapy, the resting energy expenditure was again determined after an overnight fast and before the morning dose of tolazamide.

During the study, the body weights of the subjects were measured each morning and were corrected for the weight of their hospital clothes. Caloric intake was increased or decreased to maintain constant body weight by monitoring trends in body weight changes over 3-day intervals.

All meal portions were weighed before serving and the caloric content of each meal was calculated from the United States Department of Agriculture (USDA) food tables. Patients were instructed to eat all of their food and to eat noth-

TABLE 1
Subject characteristics and fasting plasma glucose, insulin, and free fatty acid concentrations

	Nondiabetic subjects (N = 24)		Diabetic subjects (N = 24)	
	Mean ± SEM	Range	Mean ± SEM	Range
Age (yr)	26 ± 1	18–39	32 ± 2*	19–54
Height (cm)	161.9 ± 1.5	150.3–176.0	162.7 ± 1.7	149.0–176.5
Weight (kg)	94.5 ± 3.7	67.0–132.3	95.6 ± 3.7	66.6–135.6
Body fat (%)	37 ± 1	28–50	38 ± 1	26–49
Fasting glucose (mg/dl)	91 ± 2	79–106	219 ± 13*	118–318
Fat-free mass (kg)	59.2 ± 2.3	40.5–80.7	59.4 ± 2.3	41.3–82.7
Fasting free fatty acid (μeq/L)†	378 ± 21	225–575	480 ± 31*	282–774

*Significantly different between groups, $P < 0.05$.
†Fasting free fatty acid concentrations were available in 23 nondiabetic and 21 diabetic subjects.

TABLE 2
Endogenous glucose production rate, glucose oxidation rate, lipid oxidation rate, and resting energy expenditure

	Nondiabetic subjects (N = 24)		Diabetic subjects (N = 24)	
	Mean ± SEM	Range	Mean ± SEM	Range
Energy expenditure (kcal/day · kg FFM)	31.4 ± 0.5	27.2–35.2	32.9 ± 0.52*	27.1–37.4
Endogenous glucose production rate‡ (mg/min · kg FFM)	2.54 ± 0.07	1.84–3.16	3.83 ± 0.27†	2.15–6.02
Glucose oxidation rate (mg/min · kg FFM)	1.87 ± 0.16	0.3–3.56	1.65 ± 0.12†	0.65–2.71
Lipid oxidation rate (mg/min · kg FFM)	1.11 ± 0.06	0.47–1.86	1.34 ± 0.05†	0.90–1.78

*Significant difference between groups, $P < 0.05$.
†Significant difference between groups, $P < 0.0001$.
‡Endogenous glucose production rate was determined on only 15 diabetic subjects.

ing more. At the end of each meal period, food trays were examined for uneaten food to monitor compliance.

Data calculation and analyses. The appearance rate (Ra) of glucose in plasma was calculated from the 3-^{3}H-glucose specific activities by using Steele's steady-state equations.[12] Plasma glucose concentrations were determined by the glucose-oxidase method using a glucose analyzer (Beckman Instruments, Fullerton, California). Plasma insulin concentrations were determined by the Herbert modification[13] of the radioimmunoassay of Yalow and Berson.[14] Tritiated glucose specific activity in blood samples was determined after precipitating protein with perchloric acid as described by others.[15] Concentrations of free fatty acids were measured using the microfluorometric method of Miles et al.[16]

The data are expressed as the mean ± standard error of the mean (SEM). All statistical analyses were calculated by using the Statistical Analysis System (SAS Institute, Cary, North Carolina). Comparisons of meaned data between nondiabetic and diabetic groups were by unpaired *t*-tests and comparisons of mean data of diabetic subjects before and after oral sulfonylurea therapy were made by paired *t*-tests.

RESULTS

The mean fasting plasma glucose (FPG) and free fatty acid (FFA) concentrations were significantly higher in the diabetic than in the nondiabetic subjects (Table 1); the mean resting energy expenditure was 5% higher in the diabetic than in the nondiabetic subjects ($P < 0.05$, Table 2). The mean rates of endogenous glucose production and lipid oxidation were significantly higher, and the glucose oxidation rate significantly lower, in diabetic compared with nondiabetic subjects (Table 2).

Effect of tolazamide therapy (Table 3). Oral tolazamide therapy for 6 wk was associated with a significant decrease in the mean FPG concentration and daily glucose excretion in the nine diabetic subjects. There was also a ~5% reduction in the mean resting expenditure ($P < 0.04$). Body weight after therapy did not change significantly, but there was a significant reduction in daily weight-maintenance calories. There were no significant correlations between the changes in resting energy expenditure and FPG, daily glucose excretion, or daily weight-maintaining calories.

DISCUSSION

This study has shown that obese, NIDDM subjects have higher rates of resting energy expenditure than do equally obese, nondiabetic subjects. These data are similar to results reported by Nair et al. in lean, IDDM subjects.[3] Ravussin et al.[17] also compared the resting energy expenditure of 12 obese subjects who had abnormal glucose tolerance or NIDDM with the resting energy expenditure of 7 obese subjects who had normal glucose tolerance. They observed a 5% higher resting energy expenditure in the glucose-intolerant group, but the difference was not statistically significant. The similar results in their study and ours suggest, however, that an increased rate of resting energy expenditure is common in subjects with NIDDM.

Increased resting energy expenditure may be another mechanism, in addition to caloric losses due to glycosuria, for weight loss in untreated, obese subjects with NIDDM.[1] A 5% higher resting energy expenditure might result in a net daily caloric deficit of about 100 kcal/day, or 3000 kcal/mo. If one pound of human body fat is equivalent to 3500 kcal,[18] this caloric deficit might result in a 10-lb loss of body fat per year. However, resting energy expenditure accounts for only about 70% of 24-h energy expenditure and, if the thermic effect of food or exercise is reduced in obese subjects with NIDDM, the 24-h energy expenditure may be unchanged.

TABLE 3
Comparison of body weight, fasting plasma glucose concentration, caloric intake, and resting energy expenditure before and after tolazamide therapy in nine subjects with NIDDM

	Before therapy (Mean ± SEM)	After therapy (Mean ± SEM)
Body weight (kg)	106.5 ± 9.6	108.1 ± 9.9
Fasting plasma glucose (mg/dl)	253 ± 16	144 ± 14*
Urinary glucose loss (g/24h)	128 ± 26	11 ± 4*
Resting energy expenditure (kcal/day · kg FFM)	31.9 ± 0.8	30.2 ± 0.6†
Weight-maintenance caloric intake (kcal/day)	3070 ± 103	2784 ± 163*

*Significant difference between before and after therapy, $P < 0.01$.
†Significant difference between before and after therapy, $P < 0.04$.

Thus, the potential for changes in daily energy expenditure to contribute to weight loss in obese subjects with NIDDM will not be completely known until 24-h energy expenditure is measured in these patients. Regardless of its possible effect on body weight, elevated resting energy expenditure is indicative of altered resting metabolism in obese subjects with NIDDM.

Increased rates of energy expenditure could result from one or several mechanisms: (1) increased protein turnover, (2) increased sympathetic nervous system activity, (3) increased substrate cycling, or (4) abnormal mitochondrial oxidative-phosphorylation. Nair et al.[3] reported increased rates of protein synthesis and catabolism in poorly controlled IDDM subjects. These increases may also occur in NIDDM subjects, but no data are available. There also are no findings that demonstrate increased activity of the sympathetic nervous system in NIDDM subjects. Increased substrate cycling in NIDDM has been reported by Efendic et al.[19] These authors observed an increased rate of cycling of glucose—through glucose-6-phosphate, fructose-6-phosphate, and glucose-6-phosphate— and back to glucose. Stevensen et al.[20] observed increased rates of glucose recycling through the Cori cycle[21] in diabetic dogs, and 20 yr ago Reichard et al.[22] reported preliminary evidence of increased rates of glucose recycling through the Cori cycle in diabetic humans. Increased plasma concentrations of gluconeogenic precursors[23] and increased rates of hepatic uptake of gluconeogenic precursors in subjects with NIDDM have also been reported.[24]

These findings provide further indirect evidence of increased rates of the Cori cycle in these diabetic patients. It is also possible that there is a causal association between the increased endogenous glucose production rate and resting metabolic rate observed in the obese diabetic subjects in this study. Increased glucose production rates probably reflect elevated rates of gluconeogenesis, an energy-costly process. Thus, as previously theorized by Ravussin et al.,[17] an increased rate of gluconeogenesis may contribute to the higher increased resting energy expenditure of subjects with NIDDM.

As we have previously suggested,[25] the mechanism for increased gluconeogenesis in these subjects may be partly a result of increased FFA concentrations that occur with decreasing plasma insulin concentrations and in vivo "insulin resistance." Increased FFA concentrations may also be associated with higher resting energy expenditure by another mechanism. As recently reviewed by Himms-Hagen,[26] FFAs have been postulated to "uncouple" mitochondria so that the ratio of heat produced to ATP production is increased. The increased FFA concentrations and lipid oxidation rates observed in the obese diabetic subjects in this study are consistent with such a mechanism.

In this study, the mean resting energy expenditure of diabetic subjects was reduced after 6 wk of oral tolazamide therapy. Similarly, Ravussin et al.[17] reported that weight loss in obese subjects with abnormal glucose tolerance or NIDDM was associated with reduction of elevated rates of energy expenditure. One mechanism for the reduction in resting energy expenditure after therapy with either weight loss or oral hypoglycemic agents is the decreased endogenous glucose production rates, and presumably decreased rates of gluconeogenesis.[27,28] Rates of protein turnover or sympathetic nervous system activity may also be decreased. Reductions in plasma FFA concentrations with therapy[29] may be the mechanism-lowering rates of gluconeogenesis and may also result in normalized mitochondrial function. Finally, it is possible that there is an independent effect of reduced caloric intake to reduce resting energy expenditure in the subjects in our study and in the weight reduction study by Ravussin et al.[17]

As previously discussed, however, in addition to changes in resting energy expenditure, unmeasured changes in the thermic responses to meals and exercise might have also contributed to changes in net daily energy expediture after sulfonylurea therapy. Thus, the effect of tolazamide therapy on 24-h energy balance remains unknown. The mean weight-maintenance caloric intake of our subjects treated with tolazamide decreased by 286 kcal/day. The mean caloric requirement might have been expected to decrease by 100 kcal/day due to a 5% reduction in resting energy expenditure and to decrease another 470 kcal/day due to reduced glycosuria, for a total of 570 kcal/day less energy requirements. This discrepancy between the expected and measured reduction in caloric requirements is probably due to the errors of the methods, in particular the measurement of caloric intake. Regardless of the discrepancy, it is apparent that, during diabetic therapy, caloric requirements decrease by at least two mechanisms, a reduced resting energy expenditure and decreased glycosuria. Of these, reduced glycosuria appears to be quantitatively more important than changes in resting energy expenditure in determining changes in caloric requirements.

In summary, the resting energy expenditure of the obese NIDDM subjects studied was higher than that of equally obese, nondiabetic subjects, and was reduced after 6 wk of oral sulfonylurea therapy. We conclude that, in addition to urinary caloric loss from glycosuria, increased resting energy expenditure is potentially another mechanism for weight loss in obese NIDDM subjects. Also, reduced glycosuria and possibly reduced resting energy expenditure may result in weight gain if caloric intake is not concomitantly decreased during diabetic therapy.

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