A Three-Day Insulin-Induced Normoglycemia Improves Carbohydrate Oxidation in Type 2 Diabetic Subjects

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Two months of a better glycemic control improve carbohydrate oxidation in type 2 diabetes. However, this benefit is uncertain for a shorter duration. We tested the effect of 3 days of normoglycemia induced by an insulin infusion. Ten type 2 diabetic subjects (body mass index [BMI], 30.0 ± 1.1; glycosylated hemoglobin [HbA_{1C}], 10.1 ± 0.5) were studied twice, before and after normal glucose levels were maintained by a 72-hour intravenous insulin infusion. Indirect calorimetry was performed 1 hour before (basal) and during the 3 hours after (postprandial) the ingestion of a standard meal (carbohydrates, 72 g; fat, 21 g; protein, 32 g), at noon. Carbohydrate storage was calculated as ingested carbohydrate – (postprandial glycosuria + suprabasal postprandial carbohydrate oxidation). After normoglycemia, glucose and triglyceride levels were decreased (basal glucose, 13.8 ± 1.1 mmol/L to 8.8 ± 0.5; postprandial, 14.9 ± 0.9 to 11.0 ± 0.5; basal triglycerides, 2.2 ± 0.1 mmol/L to 1.6 ± 0.2; postprandial, 2.7 ± 0.2 to 1.9 ± 0.2; all $P < .01$), C peptides were unchanged. Glycosuria (before, 0.30 mg/kg/min) was abolished after normoglycemia. Basal carbohydrate, lipid, protein oxidation, and energy production rates were unchanged. Postprandial carbohydrate oxidation was increased after normoglycemia (before, 1.33 ± 0.38 mg/kg/min; after, 1.77 ± 0.42; $P < .05$). Lipid oxidation and plasma free fatty acids (FFA) tended to be more suppressed by the meal after normoglycemia (not significant [NS]). Carbohydrate storage (before, 67,5 ± 4.6 g; after, 65.7 ± 3.6; NS) and diet-induced thermogenesis did not change after normoglycemia. Short-term insulin-induced normoglycemia improves the postprandial oxidation of carbohydrates, but not their storage.

CHRONIC HYPERGLYCEMIA deteriorates insulin secretion and the peripheral effects of insulin.[1] The improvement of plasma glucose, by any means (insulin, diet) may therefore help to treat type 2 diabetes. This glucotoxicity concept leads to propose short-term intensive insulin therapy to type 2 diabetic subjects with secondary failure of oral antidiabetic agents, which is widely performed in France.[2-4]

Improvement of insulin secretion, peripheral glucose uptake, and endogenous glucose production have been reported in type 2 diabetics after 2 to 4 weeks of subcutaneous insulin-induced normoglycemia.[5-7] Although it seems attractive to reduce these delays, this may be limited because hyperglycemia has an immediate positive effect on glucose uptake, which partly compensates for the insulin resistance of type 2 diabetes.[8,9] Beneficial effects of 3-day interventions based on fasting[10] have, however, been reported.

In 10 obese, poorly controlled, type 2 diabetic subjects, we have studied the effect of a 3-day normoglycemia induced by an intravenous insulin infusion on carbohydrate oxidation and storage after a mixed meal.

MATERIALS AND METHODS

Subjects

A total of 10 type 2 diabetic subjects participated in the study. Their age was 56 ± 3 years. They were overweight (body mass index [BMI], 30.0 ± 1.1) and poorly controlled (postabsorptive glycemia, 13.8 ± 1.1 mmol/L; glycosylated hemoglobin [HbA_{1C}], 10.1% ± 0.5%, measured by high-performance liquid chromatography [HPLC]) despite maximal doses of oral antidiabetic medications: all subjects were on glibenclamide, 15 mg/d, 8 were on metformin, 2,550 mg/d (2 did not take medication because of digestive intolerance). They were on these treatments for at least 3 months before admission, and they continued throughout the study. In all subjects, the absence of intercurrent disease that could have influenced glucose control was verified by a medical interview, physical examination, and a biologic check-up (hemogram, erythrocyte sedimentation rate, urine bacteriology, and electrocardiogram). All subjects gave written informed consent for the study, which was approved by an ethical comittee.

Experimental Protocol

Lunch tests were performed from 11 AM to 3:30 PM before and after 72 hours of normoglycemia. Respiratory exchanges were monitored from 11 AM to noon and from 12:30 to 3:30 PM. From noon to 12:30 PM, the subjects ingested the same mixed meal that contained 72 g carbohydrates, 21 g fat, and 32 g proteins.

The insulin infusion began at the end of the first lunch test and was continued for 72 hours; the second lunch test was performed the day after the infusion was stopped. Human regular insulin was infused intravenously with an electric syringe (Havard Instruments, Les Ullis, France). The insulin infusion rate was adjusted every 2 hours according to capillary glucose assessment, with an objective of 5.5 mmol/L. Plasma glucose levels were controlled after 24 hours (6.7 ± 0.5 mmol/L), 48 hours (6.0 ± 0.6 mmol/L), and 72 hours (5.5 ± 0.5 mmol/L) of insulin infusion.

Respiratory Exchange Measurements

Continuous indirect calorimetry was performed with a Deltatrac metabolic monitor (Datex, Lyon, France). Results were cumulated at 1-hour intervals. Calculations were performed as proposed by Ferrannini[11]: $GOx = 4.55\ V_{CO_2} - 3.21\ \dot{V}_{O_2} - 2.87$ NU; $LOx = 1.67\ (\dot{V}_{O_2} - V_{CO_2}) - 1.92$ NU; $EPR = 3.91\ \dot{V}_{O_2} + 1.10\ V_{CO_2} - 3.34$ NU. When respiratory quotient greater than 1 was found, Gox was calculated as: $GOx = 1.34 V_{CO_2} - 6.49$ NU. Carbohydrate storage after the lunch was calculated as: ingested carbohydrates – (glycosuria + suprabasal carbohydrate oxidation during the 3 hours after the lunch).

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Analytical Procedures

Plasma glucose[12] and FFA[13] concentrations were determined enzymatically. C peptides were measured by radioimmunoassay (RIA). Urinary nitrogen (U_N) was defined as the sum of urinary urea, creatinine, and uric acid N, determined using routine, semiautomated methods: U_N (mmol · min^{-1}) = (2 × u_{urea}) = (3 × U_{cr}) + (4 × $U_{uric\ acid}$).

Results are presented as means ± SEM. Comparisons were performed by 1-way analysis of variance (ANOVA) followed by paired *t* test. $P < .05$ was considered significant.

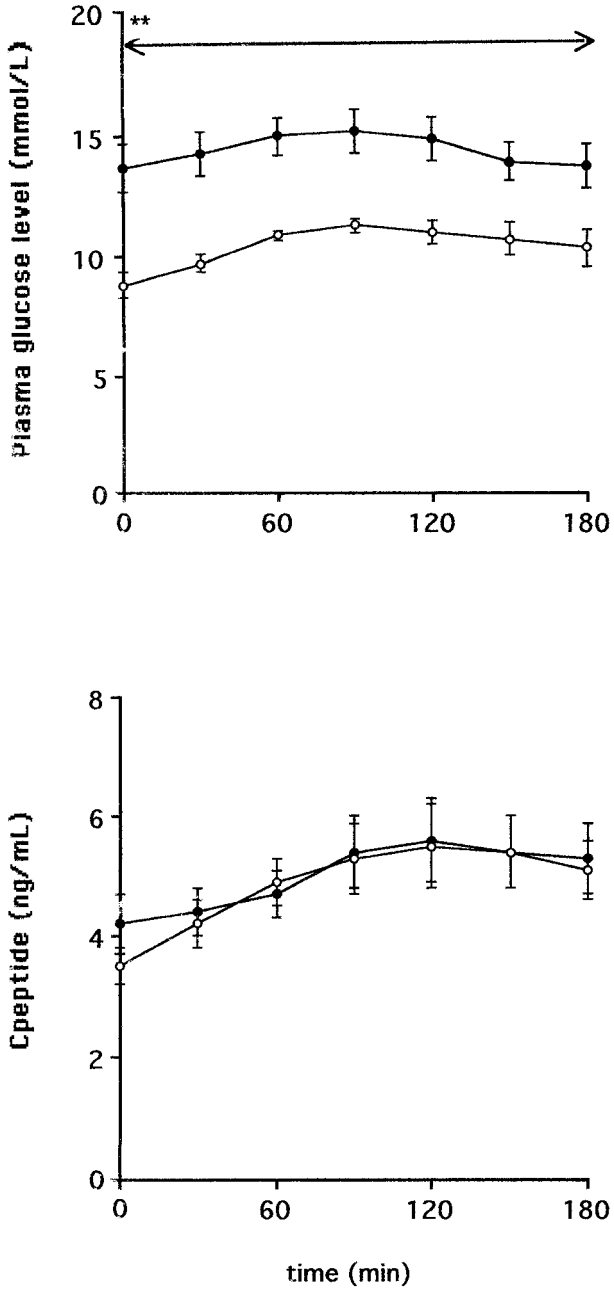

Fig 1. Time course of plasma glucose (mmol/L) and C peptide (ng/mL) levels before and after the lunch test. (●) Before and (○) after 72 hours of normoglycemia. **$P < .01$ between the 2 lunch tests.

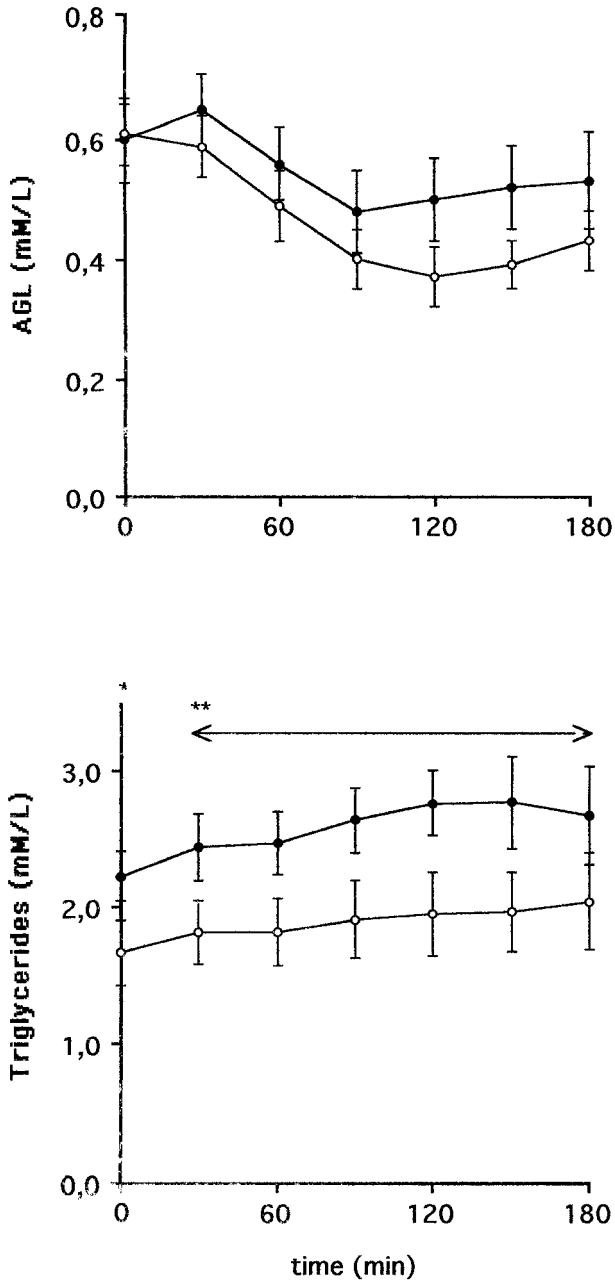

Fig 2. Time course of plasma FFA and triglyceride levels (mmol/L) before and after the lunch test. (●) Before and (○) after 72 hours of normoglycemia. **$P < .01$ between the 2 lunch tests.

RESULTS

Metabolites

As shown in Fig 1 and Table 1, plasma glucose levels were lowered after normoglycemia ($P < .01$ between meals for all times). The postprandial glycemic excursion was more pronounced after normoglycemia: plasma glucose values were higher after than before lunch, whereas the difference hardly reached significance before normoglycemia (peak at time 90 minutes, 15.2 ± 0.9 mmol/L; $P = .06$ *v* time 0 minute, 13.8 ±

1.0). C peptide did not differ between both meals, although its postprandial excursion was more pronounced after normoglycemia: values were significantly higher than basal ($P < .01$) as soon as 30 minutes after lunch, whereas significance was reached only 90 minutes after lunch before normoglycemia. Glycosuria was abolished after normoglycemia.

As shown in Fig 2, normoglycemia reduced plasma triglycerides at all times without influencing the postprandial triglyceride excursion. FFA values were identical before both meals, their postprandial suppression was significant only after normoglycemia ($P < .05$ *v* time 0 minute at time 6O minutes, and $P < .01$ thereafter), wheras it was not before normoglycemia. At time 120 minutes, FFAs were at 0.50 ± 0.07 mmol/L before and 0.37 ± 0.05 mmol/L after normoglycemia ($P = .08$).

Substrate Oxidation

Respiratory quotients did not differ significantly before and after normoglycemia. As shown in Fig 3, their postprandial values were higher after normoglycemia. Total glucose oxidation was identical before meals; its postprandial excursion only occured after normoglycemia, and values of the second and third postprandial hours were significantly higher after normoglycemia ($P < .05$ *v* same periods before normoglycemia). Postprandial cumulative glucose oxidation was higher after normoglycemia (before, 0.0 ± 5.5 g; after, 5.9 ± 3.6; $P < .05$) (Fig 4). Carbohydrate storage was similar before and after normoglycemia (before, 67.5 ± 4.6 g; after, 65.7 ± 3.6, NS). Energy production rates, diet-induced thermogenesis, lipid, and protein oxidation did not differ before and after normoglycemia.

DISCUSSION

In 10 poorly controlled type 2 diabetic patients, 72 hours of insulin-induced normoglycemia allowed an approximate 5 mmol/L decrease of plasma glucose levels before and after lunch and a significant increase of postprandial carbohydrate oxidation.

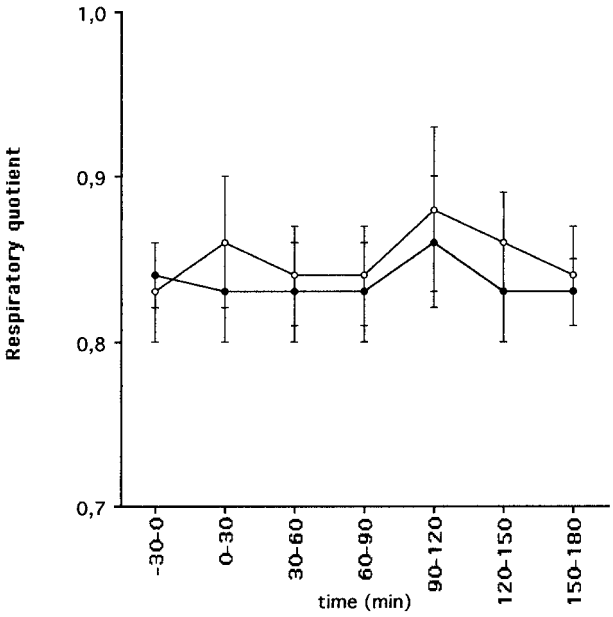

Fig 3. Time course of respiratory quotients before and after the lunch test. (●) Before and (○) after 72 hours of normoglycemia.

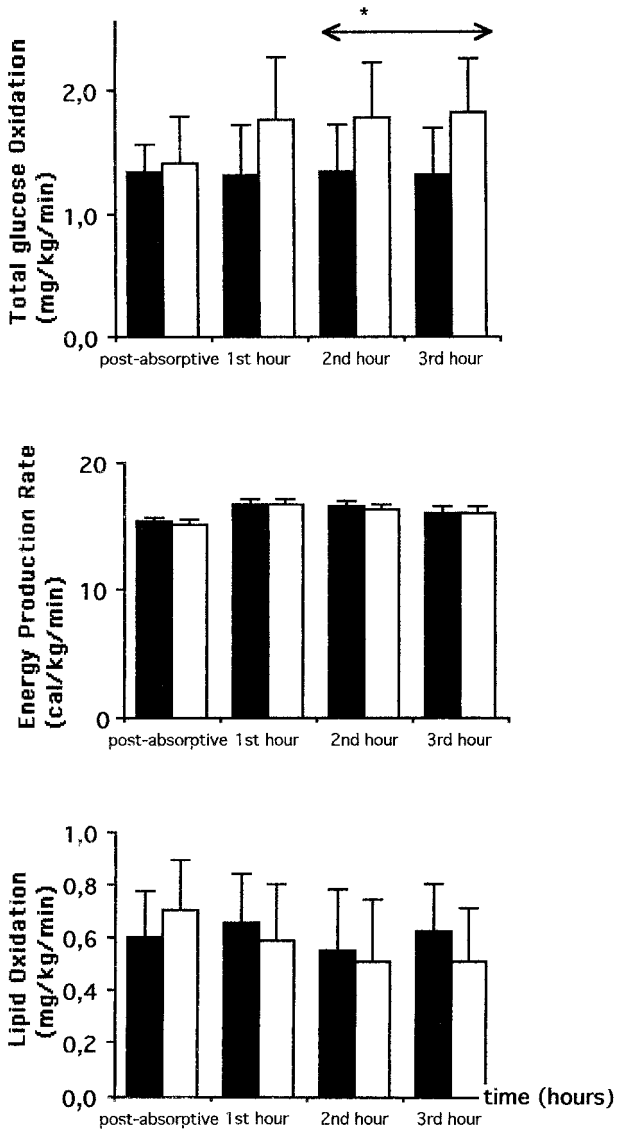

Fig 4. Time course of total glucose oxidation, lipid oxidation (mg/kg/min), and energy production rates (cal/kg/min) before and after the lunch test. (■) Before and (□) after 72 hours of normoglycemia. *$P < .05$ between the 2 lunch tests.

Carbohydrate oxidation is abnormally regulated in type 2 diabetes. At the postabsorptive state, values usually do not differ from those of normal subjects[14,15]; however, this is obtained through compensatory hyperglycemia: when diabetic subjects are studied at the same plasma glucose level as controls, their postabsorptive glucose oxidation rate is 25%[16] to 40%[17] reduced. Identical postabsorptive values despite less 5 mmol/L plasma glucose, as we found, is already an improvement. After an oral[14,15] or intravenous[16,17] glucose challenge, rates of carbohydrate oxidation are reduced in type 2 diabetic subjects.

Table 1. Pre- and Postprandial (time 120 minutes) Metabolite Concentrations and Substrate Utilization Rates (time 60 to 120 minutes and cumulated values on 3 postprandial hours for carbohydrate storage).

	Before Normoglycemia		After Normoglycemia		*P* Value*	
	Postabsorptive	Postprandial	Postabsorptive	Postprandial	Postabsorptive	Postprandial
Glycemia (mmol/L)	13.8 ± 1.1	14.9 ± 0.9	8.8 ± 0.5	11.0 ± 0.5	<.01	<.01
C peptide (ng/mL)	4.2 ± 0.5	5.6 ± 0.7	3.5 ± 0.3	5.5 ± 0.7	NS	NS
Triglycerides (mmol/L)	2.2 ± 0.1	2.7 ± 0.2	1.6 ± 0.2	1.9 ± 0.2	<.05	<.01
FFA (mmol/L)	0.60 ± 0.07	0.50 ± 0.07	0.61 ± 0.05	0.37 ± 0.05	NS	NS
Glycosuria (mg/kg/min)	0.28 ± 0.09	0.30 ± 0.12	0	0.02 ± 0.01	<.01	<.01
Gox (mg/kg/min)	1.33 ± 0.23	1.33 ± 0.38	1.40 ± 0.38	1.77 ± 0.42	NS	<.05
Lox (mg/kg/min)	0.60 ± 0.17	0.55 ± 0.23	0.70 ± 0.19	0.51 ± 0.23	NS	NS
Pox (mg/kg/min)	0.92 ± 0.30	1.24 ± 0.27	0.60 ± 0.08	0.88 ± 0.09	NS	NS
Postprandial glucose oxidation (g)		0.0 ± 5.5		5.9 ± 3.6		<.05
Carbohydrate storage (g)		67.5 ± 4.6		65.7 ± 3.6		NS
Energy production rate (cal/kg/min)	15.3 ± 0.2	16.5 ± 0.4	15.1 ± 0.3	16.2 ± 0.4	NS	NS

Abbreviation: NS, not significant.
*After *v* before normoglycemia.

The quick postprandial improvement we observed was not at all assured according to previously published data. Because hyperglycemia compensates for the deficient glucose uptake and oxidation,[18] its correction may decrease glucose oxidation for the short term. Felber et al[10] indeed found a marked impairement in carbohydrate oxidation in 6 obese diabetic subjects after a 3-day fast with a glycemic reduction similar to ours. However, starvation is well known to decrease glucose oxidation, even when it deteriorates glucose tolerance as observed in normal subjects.[19] Gougeon[20] reported that normalization of glycemia for 8 days in 7 type 2 diabetic subjects improved carbohydrate storage, not oxidation (however, +16%, NS) of a meal test. This may be due to the effect of preprandially injected insulin on glucose storage, and it should be noted that the respiratory quotient was higher before and all along the meal tests despite approximately 5 mmol/L lower glucose levels. Our results are in agreement with those from Boden et al,[14] but 2 months on a fiber diet was necessary to improve carbohydrate oxidation in the 9 subjects they studied, whereas 3 days were sufficient with intravenous insulin, which seems quite encouraging.

The mechanism of the improved carbohydrate oxidation needs comment. The effects of insulin-induced normoglycemia (more glucose oxidized, similar glucose storage) were opposed to those of starvation as reported by Felber et al[10] in type 2 diabetics or Fery et al,[19] and to the effects of a lipid infusion on the disposal of oral glucose,[21,22] increased glucose storage, and reduced glucose oxidation. In all of these situations, the availibility of lipid substrates is increased, as demonstrated by higher levels of FFA and higher rates of lipid oxidation. According to the Randle's cycle hypothesis, this reduces glucose oxidation through inhibition of pyruvate dehydrogenase.[23] The effect on carbohydrate storage is more controversial, as it depends on the plasma glucose level,[24] the route of glucose administration,[25] and the duration of the lipid challenge.[26] The better suppression of postprandial lipid metabolism as we observed therefore surely played a critical role in the improved carbohydrate oxidation. A more pronounced glycemic and C peptide excursion after normoglycemia also favored carbohydrate oxidation. The fact that glucose storage did not improve after normoglycemia may be due to a strong splanchnic storage component (that is not influenced by lipid modifications[25]) to the lower glycemia (hyperglycemia preferly stimulates nonoxidative glucose disposal[27]), or this defect may simply be more resistant in type 2 diabetic subjects. Our estimation of carbohydrate storage is indirect, the effects of normoglycemia on splanchnic glucose metabolism are not evaluable without a tracer approach: reduction of splanchnic glucose uptake and less suppressed endogenous glucose production may occur, they would imply a higher nonoxidative glucose disposal after normoglycemia that we could not detect. However, the fact that diet-induced thermogenesis, which is mainly due to the energetic cost of nutrient storage, was not modified by normoglycemia, also argues for a stable carbohydrate storage.

Improved glycemic control led to a slight insignificant reduction of energy production rate (-0.25 cal/kg/min) and to the abolition of glycosuria (-1.20 cal/kg/min), which represent a 5,200 kcal benefit for 1 month (mean body weight, 81.8 ± 4.6 kg). This is quite similar to the 0.600 kg/month fat accumulation on insulin therapy in healthy type 2 diabetic patients as we previously reported.[28]

A 3-day insulin-induced normoglycemia is sufficient to improve postprandial carbohydrate oxidation in poorly controlled type 2 diabetic subjects. The clinical interest of attaining short-term glucose control by insulin in type 2 diabetic patients remains questionable, but long-term results reported by other investigators[4] also suggest this therapeutic approach must not be neglected.

REFERENCES

1. Yki-Järvinen H: Glucose toxicity. Endocrine Rev 13:415-431, 1992

2. Valensi P, Moura I, Le Magouarou M, et al: Short term effects of continuous insulin infusion treatment on insulin secretion in non-insulin-dependent overweight patients with poor glycemic control despite maximal oral anti-diabetic treatment. Diabetes Metab 23:51-57, 1997

3. Meyer L, Grulet H, Guerci B, et al: Short term intensive insulin

therapy in insulin-requiring diabetes: Effectiveness and factors predicting success. Diabetes Metab 23:75-79, 1997

4. Dupuy O, Mayaudon H, Palou M, et al: Optimized transient insulin infusion in uncontrolled type 2 diabetes: Evaluation of a pragmatic attitude. Diabetes Metab 26:371-375, 2000

5. Scarlett JA, Gray RS, Griffin J, et al: Insulin treatment reverses the insulin resistance of type II diabetes mellitus. Diabetes Care 5:353-363, 1982

6. Garvey WT, Olefsky JM, Griffin J, et al: The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 34:222-234, 1985

7. Gormley MJJ, Hadden DR, Woods R, et al: One month's insulin treatment of type II diabetes: The early and medium term effects following insulin withdrawal. Metabolism 35:1029-1036, 1986

8. Revers RR, Fink R, Griffin J, et al: Influence of hyperglycemia on insulin's in vivo effects in type II diabetes. J Clin Invest 73:664-672, 1984

9. Capaldo B, Santoro D, Riccardi G, et al: Direct evidence for a stimulatory effect of hyperglycemia per se on glucose disposal in type II diabetes. J Clin Invest 77:1285-1290, 1986

10. Felber JP, Meyer HU, Curchod B, et al: Effect of a 3-day fast on glucose storage and oxidation in obese hyperinsulinemic diabetics. Metabolism 30:184-189, 1981

11. Ferrannini E: The theorical basis of indirect calorimetry: A review. Metabolism 37:287-301, 1988

12. Bergmeyer HV: Methods of Enzymatic Analysis. New York, NY, Academic, 1974

13. Laville M, Riou JP, Beylot M, et al: Measurement of free fatty acids by an enzymatic method. Lyon Méd 249:67-70, 1983

14. Boden G, Ray TK, Smith RH, et al: Carbohydrate oxidation and storage in obese non-insulin-dependent diabetic patients. Diabetes 32: 982-987, 1983

15. Féry F, Melot C, Balasse EO: Glucose fluxes and oxidation after an oral glucose load in patients with non-insulin-dependent diabetes mellitus of variable severity. Metabolism 42:522-530, 1993

16. Henry RR, Thorburn AW, Beerdsen P, et al: Dose-response characteristics of impaired glucose oxidation in non-insulin-dependent diabetes mellitus. Am J Physiol 261:E132-140, 1991

17. Golay A, De Fronzo RA, Ferrannini E, et al: Oxidative and non-oxidative glucose metabolism in non obese type 2 (non insulin dependent) diabetic patients. Diabetologia 31:585-591, 1988

18. Henry RR, Gumbiner B, Flynn T, et al: Metabolic effects of hyperglycemia and hyperinsulinemia on fate of intracellular glucose in NIDDM. Diabetes 39:149-156, 1990

19. Fery F, D'Atellis NP, Balasse EO: Mechanisms of starvation diabetes: A study with double tracer and indirect calorimetry. Am J Physiol 259:E770-777, 1990

20. Gougeon R: Thermic and metabolic responses to oral glucose in obese subjects with non-insulin-dependent diabetes mellitus treated with insulin or a very-low-energy diet. Am J Clin Nutr 64:78-86, 1996

21. Kruszynska YT, Mulford MI, Yu JG, et al: Effects of nonesterified fatty acids on glucose metabolism after glucose ingestion. Diabetes 46:1586-1593, 1997

22. Rigalleau V, Beylot M, Pachiaudi C, et al: Mechanisms of glucose intolerance during triglyceride infusion. Am J Physiol 275: E641-E648, 1998

23. Randle PJ, Kerbey AL, Espinal JC: Mechanisms decreasing glucose oxidation in diabetes and starvation: Role of lipid fuels and hormones. Diabetes Metab Rev 4:623-38, 1988

24. Felley CP, Felley EM, Van Melle GD, et al: Impairement of glucose disposal by infusion of triglycerides in humans: Role of glycemia. Am J Physiol 256:E747-E752, 1989

25. Rigalleau V, Binnert C, Minehira K, et al: In normal men, free fatty acids reduce peripheral, but not splanchnic glucose uptake. Diabetes 50:727-732, 2001

26. Bonadonna RC, Zych K, Boni C, et al: Time dependence of the interaction between lipid and glucose in humans. Am J Physiol 257: E49-E56, 1989

27. Ferrannini E, Locatelli L, Jéquier E, et al: Differential effects of insulin and hyperglycemia on intracellular glucose disposition in humans. Metabolism 38:459-465, 1989

28. Rigalleau V, Delafaye C, Baillet L, et al: Composition of insulin-induced body weight gain in diabetic patients: A bio-impedance study. Diabetes Metab 25:321-328, 1999