Slower Activation of Insulin Action in Upper Body Obesity

Gianni Biolo, Gabriele Toigo, and Gianfranco Guarnieri

To determine the influence of body fat distribution on kinetic aspects of insulin action, we have monitored the rate of increase of glucose infusion during 6-hour hyperinsulinemic (40 mU/m^2/min) euglycemic clamps in 10 patients with upper body obesity (body mass index [BMI], 41 ± 3 kg/m^2; waist-to-hip ratio [WHR], >1.00 for men and >0.85 for women), 12 patients with lower body obesity (BMI, 40 ± 2 kg/m^2; WHR, <1.00 for men and <0.85 for women), and 5 control subjects (BMI, <30 kg/m^2; WHR, <1.00 for men and <0.85 for women). In all subjects, glucose infusion rate (GIR) to maintain euglycemia increased during the clamp studies to achieve maximal, steady state values after the fourth to fifth hour. During the first 2 hours of clamp, mean GIR ($GIR_{20\text{-}120min}$) (traditional approach to assess insulin sensitivity) was lower ($P < 0.05$) in the upper body obesity group than in the lower body obesity group (2.12 ± 0.14 and 3.03 ± 0.33 mg/kg per min, respectively). In contrast, the maximal steady-state GIR (GIR_{MAX}) (calculated as mean GIR during the sixth hour of clamp) was similar in the upper body and in the lower body obesity groups (4.48 ± 0.45 and 4.57 ± 0.36 mg/kg per min, respectively). Control subjects exhibited higher values of both $GIR_{20\text{-}120min}$ and GIR_{MAX} (5.57 ± 0.67 and 7.05 ± 0.59 mg/kg per min, respectively) than those of both groups of obese patients. The time to reach half-maximal GIR ($T_{1/2}$) was greater ($P < .05$) in the upper body obesity (94 ± 12 min) than that in the lower body obesity (41 ± 5 min) and in the control group (30 ± 5 min). In pooled subjects, BMI correlated with GIR_{MAX} (n = 27, $R = -.75$, $P < .001$), but not with $T_{1/2}$ ($R = .21$). Similarly, whole body percent fat mass, as assessed by bioelectrical impedance analysis, correlated with GIR_{MAX} (n = 16, $R = -.79$, $P < .001$), but not with $T_{1/2}$ ($R = .10$). In contrast, WHR closely correlated with $T_{1/2}$ (n = 27, $R = .78$, $P < .001$), but not with GIR_{MAX} ($R = .11$). We conclude that upper body obesity is associated with a slower rate of activation of insulin action on glucose metabolism, whereas total body adiposity selectively affects the maximal, steady-state insulin effect.

INSULIN ACTION IN VIVO is characterized by a physiologic delay between the increase in plasma insulin concentration and the onset of the hormone effects on glucose metabolism.[1-4] Rate-limiting steps of insulin action in vivo involve trans-endothelial passage of insulin from plasma into interstitial space[5-7] and unidentified postreceptorial events.[7-9]

Insulin sensitivity can be currently quantitated in vivo by the euglycemic hyperinsulinemic clamp technique.[10] The method involves determining the amount of glucose to be infused to maintain basal plasma glucose levels during constant insulin infusion. Because of the slow onset of insulin action, it takes 3 to 5 hours of constant physiologic hyperinsulinemia to achieve steady-state insulin effects on glucose disposal.[1] Obesity and non–insulin-dependent diabetes mellitus are characterized by both reduced steady-state insulin-mediated stimulation of glucose utilization and slower-than-normal rate of onset of insulin action.[2,9,11] We have recently shown that, for the same degree of obesity, hypertension was associated with a slower rate of activation of insulin action on glucose metabolism, whereas the maximal steady state insulin effects were not affected by elevated blood pressure.[12] Thus, steady-state defects of insulin action and delayed onset of insulin effect may represent distinct mechanisms of insulin resistance.

It is now recognized that an upper body fat distribution is more closely associated with the development of metabolic abnormalities, including hypertension, insulin resistance, and hyperinsulinemia, than is a lower body distribution of fat.[13] It is not known, however, whether body fat distribution affects the kinetic aspects of insulin action (ie, rate of activation and steady-state insulin action). We have determined in subjects with moderate or severe obesity the relative influence of upper body fat deposition, as assessed by the waist-to-hip ratio (WHR), and of total adiposity, as assessed by the body mass index (BMI), and by bioelectrical impedance analysis, on the rate of activation and steady-state insulin action during prolonged euglycemic hyperinsulinemic clamp studies.

MATERIALS AND METHODS

Subjects

Twenty-two Caucasian obese patients (BMI, >30 kg/m^2) and 5 Caucasian control subjects (BMI, <30 kg/m^2) gave informed written consent to participate in the study (Table 1). Twelve obese subjects exhibited a lower body distribution of adiposity, defined as a WHR lower than 1.00 for men and lower than 0.85 for women. Ten obese subjects had upper body obesity, defined as a WHR greater than 1.00 for men and greater than 0.85 for women. Right arm blood pressures were taken with a standard mercury sphygmomanometer using cuffs of appropriate size. Eleven patients had systemic hypertension as defined by a mean of 3 blood pressure measurements greater than 140 mm Hg systolic and/or greater than 90 mm Hg diastolic. Hypertensive patients were present in all groups: 7 and 6 in the upper and lower body obesity groups, and 1 in the control group. Diastolic blood pressure tended to be greater in the upper body obesity than in the lower body obesity group. Body composition was determined in 16 subjects (males/females = 2/14) using bioelectric impedance (Akern, Firenze, Italy).[14] Percent body fat correlated with values of BMI ($R = .88$, $P < .001$). A complete medical work-up was performed to exclude secondary forms of obesity and hypertension. Eighteen patients had impaired tolerance to a 75-g load of oral glucose according to the criteria set by the National Diabetes Data Group.[15] Renal and liver function were normal. All patients were free of medications. Volunteers were hospitalized at least 2 days before the study at the Istituto di Clinica Medica, Ospedale di Cattinara, Trieste, Italy. For at least 2 days before the study, subjects were fed a weight maintenance diet containing 55% carbohydrate, 30%

From the Department of Clinical, Morphological, and Technological Sciences, Division of Internal Medicine, University of Trieste, Trieste, Italy.

Submitted August 16, 1999; accepted May 11, 2000.

Address reprint requests to Gianni Biolo, MD, Clinica Medica, University of Trieste, Ospedale di Cattinara, I-34149, Trieste, Italy.

0026-0495/01/5001-0025$10.00/0
doi:10.1053/meta.2001.17726

Table 1. Characteristics of Subjects

	Controls (N = 5)	Lower Body Obesity* (N = 12)	Upper Body Obesity† (N = 10)
Age (yr)	45 ± 5	46 ± 4	45 ± 4
Gender (male/female)	1/4	4/8	4/6
BMI (kg/m^2)	26 ± 2	40 ± 2‡	41 ± 3‡
Waist circumference (cm)	81 ± 4	111 ± 5‡	124 ± 7‡
WHR	0.80 ± 0.04	0.86 ± 0.02	0.98 ± 0.04‡§
Systolic blood pressure (mm Hg)	136 ± 2	147 ± 4	149 ± 6
Diastolic blood pressure (mm Hg)	78 ± 2	88 ± 3	96 ± 3‡§

*Lower body obesity is defined as WHR <1.00 for men and <0.85 for women.

†Upper body obesity is defined as WHR >1.00 for men and >0.85 for women.

‡$P < .05$ *v* controls.

§$P < .05$ *v* lower body obesity.

fat, and 15% protein. Subjects were studied after an overnight 12-hour fast. Studies were approved by the competent Authority of the University of Trieste.

Experimental Design

Euglycemic hyperinsulinemic clamp studies[10,12] were begun at 8:00 AM. All infusions were administered through an indwelling polyethylene catheter placed into an antecubital vein. Blood samples were taken from an indwelling catheter placed in a wrist vein of the opposite hand that was kept in a warming device to ensure arterialization of venous blood. A primed-constant infusion of regular insulin (Actrapid; Novo Industry, Copenhagen, Denmark) was started and continued for 6 hours at the rate of 40 mU/m^2/min. Priming infusion was administered as previously described.[10,12] Whole blood glucose concentrations were measured in samples obtained at 5- to 10-minute intervals. Blood glucose levels were maintained constant at baseline throughout the study period by infusing 20% dextrose solution at a variable rate adjusted according to glucose measurements.

Analysis

Whole blood glucose concentrations were measured immediately after blood drawing using glucose oxidase paper strips (One Touch; Lifescan, Milpitas, CA) and a portable glucometer (One Touch II, Lifescan). During the study, precision of blood glucose determinations was evaluated every 30 minutes using a calibrated paper strip. Mean and standard deviation of 22 determinations of glucose concentrations from the same heparinized blood sample were 85.2 mg% and 1.8, respectively. Plasma insulin was measured by radioimmunoassay.

Calculation and Statistical Analysis

During the hyperinsulinemic clamp study, the rate of glucose infusion required to maintain euglycemia was calculated at the end of each 10-minute interval and served as an overall measure of insulin action on glucose metabolism. Overall insulin sensitivity was calculated according to the traditional approach, in nonsteady-state conditions, as mean glucose infusion rate between 20 minutes and 120 minutes of the clamp study ($GIR_{20\text{-}120min}$).[10] Maximal glucose infusion rate (GIR_{MAX}) was calculated during the sixth hour of the clamp study after achievement of steady state for glucose infusion. Rate of activation of insulin action ($T_{1/2}$) was calculated by estimating the time to reach half-maximum rate of glucose infusion after the start of insulin administration. Epidemiologic evidence indicates that insulin action in vivo is normally distributed in populations.[16] All data are expressed as mean ± SEM. Comparisons among upper and lower body obese patients and control subjects were made using analysis of variance, repeated measures analysis of variance, and Newman-Keuls post hoc test. Regression analysis was performed according to standard methods. Results were considered to be statistically significant at values of $P < .05$.

RESULTS

The 2 groups of obese subjects with high and low WHR had similar postabsorptive values of plasma glucose (88 ± 4 *v* 92 ± 5 mg/dL, respectively) and insulin (18 ± 3 *v* 14 ± 5 μU/mL, respectively) concentrations. In the control group, postabsorptive values of plasma glucose and insulin concentrations were 84 ± 5 mg/dL and 11 ± 4 μU/mL, respectively. During the clamp, insulin concentrations increased to high physiologic levels in both groups and were maintained constant until the end of the study. In the high WHR group, insulin concentrations were 98 ± 8, 104 ± 6, 105 ± 5, 101 ± 7, 114 ± 6, 110 ± 6 μU/mL for 1, 2, 3, 4, 5, and 6 hours of the clamp, respectively. In the low WHR group, insulin concentrations were 94 ± 7, 100 ± 5, 98 ± 6, 110 ± 6, 108 ± 5, 112 ± 7 μU/mL for 1, 2, 3, 4, 5, and 6 hours, respectively. In the control group, insulin concentrations were 92 ± 4, 98 ± 5, 97 ± 6, 100 ± 7, 95 ± 4, 102 ± 5 μU/mL for 1, 2, 3, 4, 5, and 6 hours of the clamp, respectively. In all subjects, blood glucose levels were maintained within a range of ±6 mg/dL the individual basal values.

Figure 1 shows the time course of mean GIR during the 6-hour clamp studies in the control subjects and in the patients with upper and lower body obesity. Steady-state, maximal values of GIR to maintain euglycemia were achieved by the fifth hour of clamp and were maintained during the sixth hour. The kinetics of insulin action are shown in Table 2. $GIR_{20\text{-}120min}$, the traditional assessment of overall insulin sensitivity, was greater in the lower body than in the upper body obese patients and further increased in the control subjects.

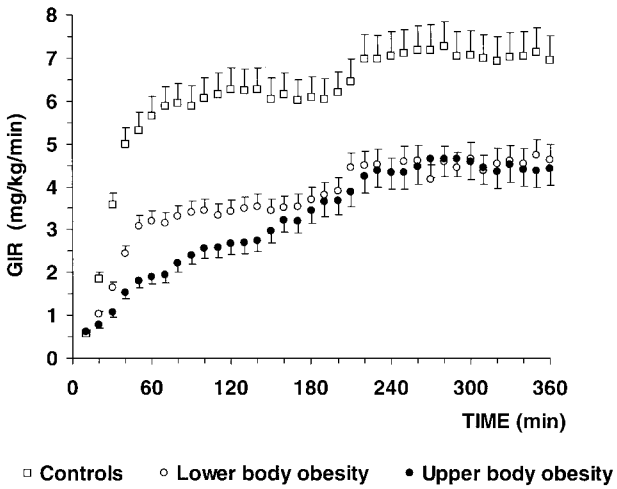

Fig 1. Time-course of GIR during 6-hour euglycemic hyperinsulinemic (40 mU/m^2/min) clamp in control subjects and in patients with upper body obesity (WHR > 1.00 for men and >0.85 for women) and lower body obesity (WHR < 1.00 for men and <0.85 for women).

Table 2. Kinetics of Insulin Action

	Controls (N = 5)	Lower Body Obesity* (N = 12)	Upper Body Obesity† (N = 10)
$GIR_{20\text{-}120min}$ (mg/kg/min)	5.57 ± 0.67	3.03 ± 0.33‡	2.12 ± 0.14‡§
GIR_{MAX} (mg/kg/min)	7.05 ± 0.59	4.57 ± 0.36‡	4.48 ± 0.45‡
$GIR_{20\text{-}120min}/GIR_{MAX}$	0.79 ± 0.06	0.66 ± 0.04	0.50 ± 0.04‡§
$T_{1/2}$ (min)	30 ± 5	41 ± 5	94 ± 12‡§

*Lower body obesity is defined as WHR <1.00 for men and <0.85 for women.

†Upper body obesity is defined as WHR >1.00 for men and >0.85 for women.

‡$P < .05$ *v* controls.

§$P < .05$ *v* lower body obesity.

GIR_{MAX} was similar in the 2 groups with lower and upper body obesity, whereas the control group exhibited greater values of GIR_{MAX} than both groups of lower and upper body obese patients. During the first 2 hours of the clamp study, the fractional activation of insulin action, ie, $GIR_{20\text{-}120min}/GIR_{MAX}$, was lower in the upper body obese patients than in the lower body obese patients and in the control group. $T_{1/2}$ was significantly greater ($P < .01$) in the high WHR group compared with the low WHR patients and the control group.

Table 3 presents the results of simple Pearson's correlation coefficients between kinetic parameters of insulin action with several selected variables for all of the subjects. BMI correlated with GIR_{MAX} and with $GIR_{20\text{-}120min}$, whereas it did not correlate with $T_{1/2}$. Waist circumference correlated with all kinetic parameters of insulin action: $GIR_{20\text{-}120min}$, GIR_{MAX}, $T_{1/2}$. WHR correlated with $GIR_{20\text{-}120min}$, but not with GIR_{MAX}. WHR closely correlated with $T_{1/2}$ (Fig 2). The close correlation between $T_{1/2}$ and WHR was present in both subgroups of male and female obese patients (Fig 2). $T_{1/2}$ closely correlated with the values of diastolic blood pressure, but not with the values of systolic blood pressure. In 16 patients (female/male: 14/2) with mean BMI of 36 ± 2 kg/m^2 (range, 22 to 55) body composition was assessed by bioelectrical impedance analysis. Percent body fat (mean, 51% ± 2%; range, 42% to 59%) significantly correlated with GIR_{MAX} ($R = -.79$; $P < .001$) and with $GIR_{20\text{-}120min}$ ($R = -.62$, $P < .01$), but not with $T_{1/2}$ ($R = -.10$).

DISCUSSION

The insulin resistance of obesity, as assessed by the glucose clamp technique, is characterized by both steady-state defects of insulin action and kinetic abnormalities of the onset of insulin effects.[2,9] The kinetic defect in obesity involves a delayed trans-endothelial passage of insulin[4-7] and undefined abnormalities in postreceptorial events.[7-9] In this study, we provide evidence of a selective association between body fat distribution and the rate of onset of insulin action on glucose metabolism. We found that patients with upper body obesity (ie, high WHR) exhibited a slower rate of increase in glucose infusion during euglycemic hyperinsulinemic clamp compared with obese subjects with similar BMI, but with a lower distribution of body fat (ie, low WHR). In contrast, at the end of the clamp studies, the absolute magnitude of the steady-state insulin effects on glucose metabolism were similar in the 2 groups.

During the clamp studies, glucose infusion rate to maintain euglycemia was progressively increased and maximal steady-state values achieved 4 to 5 hours after the start of the clamping. The maximal steady-state insulin effect was calculated during the sixth hour of the study (GIR_{MAX}). The rate of onset of insulin action on glucose metabolism was expressed as time to achieve half-maximal rate of glucose infusion ($T_{1/2}$). Overall insulin sensitivity was assessed using a traditional approach during the first 2 hours of the clamp ($GIR_{20\text{-}120min}$). By such traditional approach, overall insulin sensitivity was, as expected, higher in the lower body obesity than in the upper body obesity group and further increased in the control subjects. In contrast, the maximal steady-state insulin effect was influenced by the degree of obesity, but not by body fat distribution. Kinetic analysis during the clamp indicates that the rate of onset of insulin action was slower in the upper body obese patients than those in the lower body obesity and in the control groups.

In this study, we have used both comparisons of means of 3 samples and regression analysis to determine the relationships between WHR and BMI and kinetic parameters of insulin

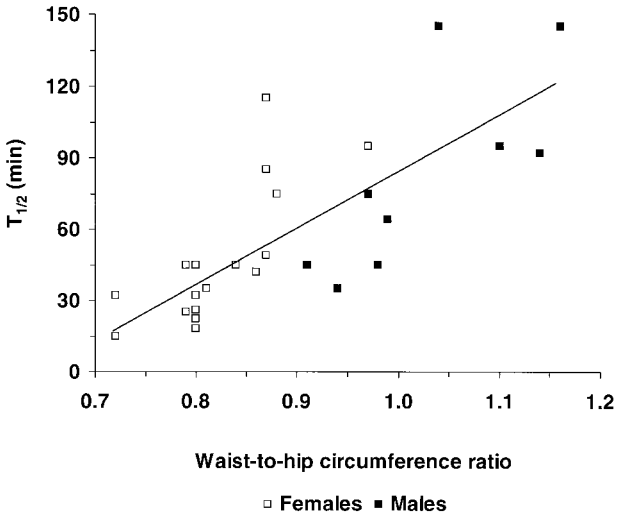

Fig 2. The relationship between individual values of WHR and delay of activation of insulin action, calculated as time required to achieve half-maximal GIR ($T_{1/2}$) in male (n = 9; $R = .77$; $P < .05$) and female (n = 18; $R = .78$; $P < .001$) obese subjects. Results of pooled subjects are shown in Table 3.

Table 3. Summary of Pearson Correlation Coefficients of Kinetics of Insulin Action With Selected Variables

Parameter	$GIR_{20\text{-}120min}$	GIR_{MAX}	$T_{1/2}$
BMI	−0.69*	−0.75*	0.21
Waist circumference	−0.74*	−0.57†	0.51†
WHR	−0.54†	0.11	0.78*
Systolic blood pressure	−0.36	−0.28	0.28
Diastolic blood pressure	−0.60†	−0.37	0.66*

*$P < .001$.

†$P < .01$.

action. The results of the 2 statistical methods were in agreement. We found that WHR correlated with $T_{1/2}$ (61% of the variance) in both men and women, but not with GIR_{MAX}. On the other hand, BMI was related to GIR_{MAX} (56% of the variance), but not to $T_{1/2}$. Waist circumference, which is proportional to both abdominal fat accumulation and whole body adiposity,[17] correlated with both $T_{1/2}$ (26% of the variance) and GIR_{MAX} (32% of the variance). Overall insulin sensitivity, as assessed by $GIR_{20\text{-}120min}$, was influenced by WHR, BMI, and waist circumference.

In a physiologic setting, a kinetic defect in insulin action is functionally more important than a steady-state impairment of the hormone effect.[18] After a meal, insulin concentration increases and decreases in about 2 to 3 hours and, in this time interval, maximal insulin effects cannot be achieved. Thus, postprandial metabolic changes appear to be largely dependent on the kinetics of onset of insulin action. The relationship between kinetics of onset of insulin action and WHR found in this study may account for the fact that upper body obesity was statistically associated with greater metabolic abnormalities than a lower body distribution of body fat.[13]

Although the mechanisms responsible for the association between a high WHR and a slower onset of insulin action cannot be elucidated by our study, certain inferences are possible. WHR is an anthropometric approximation of the visceral versus the peripheral accumulation of adipose tissue. Evidence indicates that visceral obesity is associated with hypertension, type 2 diabetes, dyslipidemia, and a higher prevalence of cardiovascular diseases.[13] An increased free fatty acid (FFA) output into the portal vein to the liver could contribute to such greater metabolic abnormalities in visceral obesity.[19,20] In fact, FFA has been shown to reduce hepatic insulin clearance,[21] enhance hepatic glucose production,[22] impair muscle glucose disposal,[23] raise vascular resistance and blood pressure,[24] enhance alpha-adrenoreceptor sensitivity,[25] and inhibit nitric oxide synthase activity.[26] Some of these mechanisms acting at the levels of the endothelial barrier and target cells may explain the greater insulin-resistance and possibly the kinetic defect associated with abdominal obesity. In addition, some endocrine abnormalities often associated with abdominal obesity, such as increased cortisol and androgen secretion, may contribute to the kinetic defect of insulin action.[13] Finally, it should be noted that WHR may contain more information than body fat distribution because the hip circumference includes a measurement of the large muscle groups in the gluteal region. A high WHR may therefore be associated with a relative decrease in skeletal muscle mass, which is a major contributor of insulin-mediated glucose disposal. There may also be an effect dependent on muscle mass distribution. Chowdhury et al[27] have recently shown that a greater ratio of upper to lower body muscle mass distribution was associated with increased metabolic risk factors for type 2 diabetes and cardiovascular disease. There is also an association between insulin resistance and a higher than normal component of the white, fast twitch, glycolytic fibers at the expense of the red, slow twitch, oxidative fibers.[28] The latter may predominate in the large, lower-body, postural muscles and contribute to improving the kinetics of insulin action in subjects with low WHR.

Whatever the link between WHR and the timing of onset of insulin action might be, the mechanisms of a kinetic defect in insulin action on glucose metabolism have been thoroughly described in an experimental dog model of chronic hyperinsulinemia.[7] In this study, trans-endothelial insulin transport was impaired and was responsible for one third of the kinetic defect, while slower intracellular mechanisms of glucose disposal were responsible for the remaining two thirds.

One of the main findings of this study was the link between the steady-state defect of insulin action and total body adiposity expressed either as BMI or as percent body fat by bioelectrical impedance analysis. Thus, the steady-state defect in insulin action appears to be proportional to the excess body fat relative to lean body mass, whereas the rate of onset of insulin action was influenced by body fat distribution. These results suggest that the onset of insulin action and the steady-state insulin effects are distinct determinants of overall insulin sensitivity and may represent different mechanisms of insulin resistance.

We have previously shown that in obesity the presence of hypertension was associated with a selective alteration of the kinetics of onset of insulin action, whereas the steady-state insulin effect was not affected by the presence of hypertension.[12] In the present study, the subjects with upper body obesity tended to have higher diastolic blood pressure levels than the subjects with lower body obesity. Furthermore, $T_{1/2}$ closely correlated with both values of WHR and diastolic blood pressure. Different mechanisms may account for the link between elevated blood pressure and kinetic defects in insulin action. The metabolic abnormalities associated with abdominal obesity, such as increased FFA and greater insulin resistance and hyperinsulinemia, may directly increase blood pressure levels.[13,24-26,29,30] On the other hand, essential hypertension is associated with endothelial dysfunction,[31] which may impair trans-endothelial transport of insulin and delay the onset of insulin action.

During hyperinsulinemic glucose clamps, the rate of glucose infusion to maintain euglycemia reflects simultaneous changes of both glucose uptake and production.[19] In the present study, we did not assess the contributions of hepatic glucose production to the kinetic defect of insulin action on glucose metabolism. However, it is likely that defective insulin-mediated glucose disposal largely accounted for the overall kinetic abnormality of insulin action found in this study. In fact, evidence from previous studies indicates that, in contrast to stimulation of glucose disposal, the rate of suppression of hepatic glucose production by insulin was normal in obese subjects,[2,9] non–insulin-dependent diabetic patients,[9,11] and experimental chronic hyperinsulinemia.[7]

In conclusion, important aspects of the insulin-resistance syndrome, such as upper body fat deposition and obesity-associated hypertension, are characterized by a selective alteration of the rate of onset of insulin action. The steady-state insulin effects are not influenced by upper body obesity or hypertension, but are inversely determined by total body adiposity, which in turn, does not influence the timing of insulin action.

REFERENCES

1. Doberne L, Greenfield MS, Schulz B, et al: Enhanced glucose utilization during prolonged glucose clamp studies. Diabetes 30:829-835, 1981
2. Prager R, Wallace P, Olefsky JM: In vivo kinetics of insulin action on peripheral glucose disposal and hepatic glucose output in normal and obese subjects. J Clin Invest 78:472-481, 1986
3. Freidenberg GR, Suter SL, Henry RR, et al: Delayed onset of insulin activation of insulin receptor kinase in vivo in human skeletal muscle. Diabetes 43:118-126, 1994
4. Miles PDG, Levisetti M, Reichard D, et al: Kinetics of insulin action in vivo: Identification of rate-limiting steps. Diabetes 44:947-953, 1995
5. Yang YJ, Hope ID, Ader M, et al: Insulin transport across capillaries is rate limiting for insulin action in dogs. J Clin Invest 84:1620-1628, 1989
6. Freidenberg GR, Suter SL, Henry RR, et al: In vivo stimulation of insulin receptor kinase in human skeletal muscle: Correlation with insulin-stimulated glucose disposal during euglycemic clamp studies. J Clin Invest 87:2222-2229, 1991
7. Miles PDG, Li S, Hart M, et al: Mechanisms of insulin resistance in experimental hyperinsulinemic dogs. J Clin Invest 101:202-211, 1998
8. Ciaraldi TP, Molina JM, Olefsky JM: Insulin action kinetics in adipocytes from obese and non-insulin-dependent diabetes mellitus subjects: Identification of multiple cellular defects in glucose transport. J Clin Endocrinol Metab 72:876-882, 1991
9. Nolan JJ, Ludvik B, Baloga J, et al: Mechanisms of the kinetic defect in insulin action in obesity and NIDDM. Diabetes 46:994-1000, 1997
10. De Fronzo RA, Tobin JD, Andres R: Glucose clamp technique. A method for quantifying insulin secretion and resistance. Am J Physiol 273:E214-E223, 1979
11. Turk D, Alzaid A, Dinneen S, et al: The effects of non-insulin-dependent diabetes mellitus on the kinetics of onset of insulin action in hepatic and extrahepatic tissues. J Clin Invest 95:755-762, 1995
12. Biolo G, Toigo G, Ciocchi B, et al: Slower activation of insulin action in hypertension associated with obesity. J Hypertens 16:1783-1788, 1998
13. Björntorp P: Body fat distribution, insulin resistance, and metabolic diseases. Nutrition 13:795-803, 1997
14. Heath EM, Adams TD, Matthews Daines M, et al: Bioelectric impedance and hydrostatic weighing with and without head submersion in persons who are morbid obese. J Am Diet Assoc 98:869-875, 1998
15. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057, 1979
16. Bogardous C, Lillioja S, Nyomba BL, et al: Distribution of in vivo insulin action in Pima Indians as mixture of three normal distributions. Diabetes 38:1423-1432, 1989
17. Molarius A, Seidell JC, Sans S, et al: Waist and hip circumferences, and waist-hip ratio in 19 populations of the WHO MONICA Project. Int J Obes Relat Metab Disord 23:116-125, 1999
18. Prager R, Wallace P, Olefsky JM: Hyperinsulinemia does not compensate for peripheral insulin resistance in obesity. Diabetes 36: 327-334, 1987
19. Jensen MD, Haymond MW, Rizza RA, et al: Influence of body fat distribution on free fatty acid metabolism in obesity. J Clin Invest 83:1168-1173, 1989
20. Martin ML, Jensen MD: Effects of body fat distribution on regional lipolysis in obesity. J Clin Invest 88:609-613, 1991
21. Svedberg JG, Stromblad G, Wirth A, et al: Fatty acids in the portal vein of the rat regulate hepatic insulin clearance. J Clin Invest 88:2054-2058, 1991
22. Ferrannini EE, Barrett J, Bevilacqua S, et al: Effect of fatty acids on glucose production and utilization in man. J Clin Invest 72:1737-1747, 1983
23. Boden G, Chen X, Ruiz J, et al: Mechanisms of fatty acid-induced inhibition of glucose uptake. J Clin Invest 93:2438-2446, 1994
24. Bulow J, Madsen J, Astrup A, et al: Vasoconstrictive effect of high FFA/albumin ratios in adipose tissue in vivo. Acta Physiol Scand 125:661-667, 1985
25. Stepniakowski KT, Goodfriend TL, Egan BM: Fatty acids enhance vascular alpha-adrenergic sensitivity. Hypertension 25:774-778, 1995
26. Davda RK, Ullian ME, Stepniakowski KT, et al: Oleic acid inhibits endothelial cell nitric oxide synthase by a PKC-independent mechanism. Hypertension 26:764-770, 1995
27. Chowdhury B, Lantz H, Sjostrom L: Computed tomography-determined body composition in relation to cardiovascular risk factors in Indian and matched Swedish males. Metabolism 45:634-644, 1996
28. Lillioja S, Young AA, Culter CL, et al: Skeletal muscle capillary density and fiber type are possible determinants of in vivo insulin resistance in man. J Clin Invest 80:415-424, 1987
29. Reaven GM, Lithell H, Landsberg L: Hypertension and associated metabolic abnormalities. The role of insulin resistance and the sympathoadrenal system. N Engl J Med 334:374-381, 1996
30. De Fronzo RA: The effect of insulin on renal sodium metabolism: A review with clinical implications. Diabetologia 21:165-171, 1981
31. Rizzoni D, Porteri E, Castellano M, et al: Endothelial dysfunction in hypertension is independent from the etiology and from vascular structure. Hypertension 31:335-341, 1998