Seven-Year Changes in Body Fat and Visceral Adipose Tissue in Women

Associations with indexes of plasma glucose-insulin homeostasis

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OBJECTIVE — To study the associations between changes in body fatness, visceral adipose tissue (AT), and indexes of plasma glucose-insulin homeostasis over a 7-year follow-up period.

RESEARCH DESIGN AND METHODS — A sample of 30 nondiabetic women aged 35.2 ± 5.6 (SD) years at baseline was studied.

RESULTS — Changes in visceral AT and in subcutaneous AT (measured by computed tomography) as well as changes in body fat mass (obtained by hydrostatic weighing) were significantly related to changes in fasting plasma insulin levels and in plasma insulin area measured after a 75-g oral glucose load ($0.47 \leq r \leq 0.62$; $P < 0.01$). Changes in visceral AT but not in body fat mass or in subcutaneous AT area were significantly associated with changes in plasma glucose area ($r = 0.37$; $P < 0.05$). When two subgroups of women with similar mean increases in body fat mass but with either small or large increases in visceral AT were compared, the subgroup with the largest gain in visceral AT showed the greatest deterioration in indexes of plasma glucose-insulin homeostasis. On the other hand, when two subgroups with similar mean increases in visceral AT but with different changes in body fat mass were compared, both subgroups showed similar changes in plasma glucose and insulin concentrations.

CONCLUSIONS — Results of this 7-year follow-up study in women suggest that changes in indexes of plasma glucose-insulin homeostasis are significantly associated with changes in visceral AT, even after control for changes in body fat mass.

Cross-sectional studies have shown that abdominal obesity, especially when characterized by a preferential accumulation of visceral adipose tissue (AT), is associated with alterations in indexes of plasma glucose-insulin homeostasis in women (1–5). So far, only one prospective study in Japanese-American men (6) has demonstrated that an excess in visceral AT accumulation was associated with the subsequent development of type II diabetes over a follow-up period of 30 months. Oppert et al. (7) also reported a deterioration of plasma glucose-insulin homeostasis after a 100-day overfeeding study, which led to significant increases in body fat mass and visceral AT. On the other hand, intervention studies have shown that weight loss was associated with improved glucose tolerance and decreased insulin concentrations (8–11). In this regard, Fujioka et al. (12) have demonstrated in women that a decrease in visceral AT accumulation obtained after 8 weeks on a low-calorie diet was accompanied by reductions in plasma glucose and insulin levels. Leenen et al. (13) have also demonstrated that visceral fat loss obtained by dieting was associated with an improved plasma lipid-lipoprotein profile in both men and women.

Age and menopausal status are known correlates of visceral AT accumulation. It has been shown that a preferential visceral AT deposition is found with increased age (14,15) and with the occurrence of menopause (14,16). Concomitantly, glucose tolerance also tends to deteriorate with age (17–19), and when premenopausal and postmenopausal women are compared, an altered plasma glucose-insulin homeostasis is usually found in the latter group (19–21).

Obviously, additional factors such as a positive family history of diabetes also influence glucose tolerance and insulin action. In this regard, it has been reported that the prevalence of type II diabetes was increased in first-degree relatives of type II diabetic subjects (22).

The aim of the present study was to investigate the potential relationship of changes in body fatness and in visceral AT accumulation to variation in indexes of plasma glucose-insulin homeostasis observed over a 7-year follow-up period in a sample of women who were all initially premenopausal.

RESEARCH DESIGN AND METHODS

Subjects

Women who volunteered for this study are from a sample of premenopausal women recruited through the media who were first tested in 1986–1987 and who agreed to be retested in 1994. Women were initially recruited to examine, in a cross-sectional design, the potential associations between AT distribution measured by computed tomography (CT) and some metabolic variables predictive of cardiovascular disease risk. Cross-sectional results on this cohort have been previously reported (2,23,24). Thirty-five

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AT, adipose tissue; CT, computed tomography; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

of them were retested in 1994. These women covered a wide range of BMI values (from 19.9 to 42.0 kg/m^2 at baseline). Among these subjects, eight women reached menopause during the 7-year follow-up period. Three women reached natural menopause, four had a hysterectomy, and the information was missing for one woman. The duration of menopause was variable, going from 2 months to 6.5 years. Before being retested, all women were subjected to a medical examination. Four women used medication (lipid-lowering [n = 1], antihypertensive [n = 2], or hormonal supplementation [n = 1]), and they were kept in the study. One woman had a jejuno-ileal bypass surgery after the 1987 testing and was thus excluded. After the administration of the oral glucose tolerance test (OGTT) (as described below), it was found, according to the criteria of the National Diabetes Data Group (25), that two women had developed type II diabetes during the 7-year follow-up period, and they were excluded from the study sample. Furthermore, three women had developed impaired glucose tolerance (25), but they were kept in the study. Two women had missing values for abdominal AT areas measured by CT as well as for waist and hip circumferences in 1987 and were excluded from the analyses. The final sample on which the present paper is based included 30 women. In this group, nine women had a family history of diabetes, which was considered positive when subjects reported that at least one full sibling or parent had diabetes. For the first 6 months of the follow-up period, 17 women were involved in an exercise training program (26). These 17 women were compared with those (n = 13) who did not participate in the exercise training program, and it was found that neither changes in body fat mass, visceral AT area, nor plasma glucose and insulin areas were statistically different among the two subgroups. All women signed an informed consent document before being retested, and the present protocol was approved by the Medical Ethics Committee of Laval University.

Anthropometry and body composition

Body weight, height, and waist and hip circumferences were measured following the procedures recommended at the Airlie Conference (27). Waist girth was measured at the narrowest part of the torso while the subject was standing, while the hip circumference was measured at the level of the greatest gluteal protuberance. Waist and hip circumferences were recorded to the nearest millimeter and the waist-to-hip ratio (WHR) was then calculated.

The mean of six measurements with the hydrostatic weighing technique was used to determine body density (28). Pulmonary residual volume was measured before immersion in the hydrostatic tank, using the helium dilution method of Meneely and Kaltreider (29). Percent body fat was derived from body density using the equation of Siri (30), and body fat mass was calculated. Three women did not complete the hydrostatic weighing test and therefore, for analyses involving body fat mass, the sample size reached 27.

CT

Visceral AT accumulation was assessed by CT, which was performed on a Siemens Somatom DRH scanner (Erlangen, Germany) as previously described (31). Briefly, subjects were examined in the supine position with both arms stretched above the head. The CT scan was performed at the abdominal level between L4 and L5 vertebrae using a radiograph of the skeleton as a reference to establish the position of the scan to the nearest millimeter. Total abdominal AT area was calculated by delineating the surface with a graph pen and then computing the AT surface using an attenuation range of −190 to −30 Hounsfield units (32,33). Abdominal visceral AT area was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The abdominal subcutaneous AT area was calculated by subtracting the amount of abdominal visceral AT from the total abdominal AT area.

OGTT

A 75-g OGTT was performed in the morning after an overnight fast. Blood samples were collected in EDTA-containing tubes (Miles Pharmaceuticals, Rexdale, Ontario, Canada) through a venous catheter from an antecubital vein at

Table 1—*Characteristics of the sample of 30 women at baseline and at follow-up*

Variables	Baseline	Follow-up	Changes (95% CI)
Age (years)	35.2 ± 5.6	42.4 ± 5.6	7.2 ± 0.3‡ (7.1–7.3)
BMI (kg/m^2)	31.1 ± 6.5	31.4 ± 7.4	1.2 ± 3.9 (−0.2–2.6)
Body fat mass (kg)	32.8 ± 13.5	34.2 ± 16.1	1.9 ± 9.4 (−1.6–5.4)
Waist girth (cm)	87.8 ± 14.8	91.9 ± 16.2	4.1 ± 9.2* (0.8–7.4)
WHR	0.80 ± 0.04	0.82 ± 0.06	0.02 ± 0.04* (0.01–0.03)
Abdominal AT areas			
Total (cm^2)	539.0 ± 243.7	578.6 ± 263.6	39.6 ± 135.2 (−8.8–88.0)
Visceral (cm^2)	98.2 ± 46.1	130.3 ± 64.4	32.1 ± 49.2† (14.5–49.7)
Subcutaneous (cm^2)	440.8 ± 202.9	448.4 ± 209.9	7.5 ± 91.1 (−25.1–40.1)
OGTT			
Fasting glucose (mmol/l)	5.0 ± 0.4	5.1 ± 0.4	0.2 ± 0.3† (0.1–0.3)
Fasting insulin (pmol/l)	74.0 ± 47.7	78.6 ± 43.2	4.6 ± 41.3 (−10.2–19.4)
2-h glucose (mmol/l)	6.1 ± 1.3	6.9 ± 1.3	0.7 ± 1.7* (0.1–1.3)
Glucose area (mmol · l^{-1} · min^{-1}) × 10^{-3}	1.14 ± 0.20	1.26 ± 0.20	0.11 ± 0.21† (0.03–0.19)
Insulin area (pmol · l^{-1} · min^{-1}) × 10^{-3}	75.0 ± 46.3	84.3 ± 40.9	9.3 ± 48.3 (−8.0–26.6)

Data are means ± SD; *Significant change, $P < 0.05$; †$P < 0.01$; ‡$P < 0.0001$. For body fat mass, n = 27.

Table 2—*Pearson correlation coefficients for the relationships between changes in morphological variables and changes in plasma glucose and insulin levels over the 7-year follow-up period in the sample of 30 women*

	7-year changes in				
	Fat mass	Visceral AT	Subcutaneous AT	Waist girth	WHR
7-year changes in					
Fasting glucose	0.34	0.28	0.25	0.22	0.03
Fasting insulin	0.47*	0.61*	0.51*	0.39†	−0.01
2-h glucose	0.09	0.22	0.14	0.10	−0.07
Glucose area	0.19	0.37†	0.29	0.29	0.08
Insulin area‡	0.47*	0.54*	0.62*	0.60*	0.35

*$P < 0.01$. †$P < 0.05$; ‡Spearman correlation coefficients were used. For fat mass, $n = 27$.

−15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min for the determination of plasma glucose and insulin concentrations. Plasma glucose was measured enzymatically (34), whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation (35). The total glucose and insulin areas under the curve during the OGTT were determined with the trapezoid method. In premenopausal women, measurements were performed while the subjects were in the early follicular phase, between the 5th and 12th day of their menstrual cycle.

Studies on subgroups

Within the total sample, subgroups were formed according to changes in body fat mass and in visceral AT area. First, two subgroups of women ($n = 8$ in each subgroup) with similar mean increases in body fat mass but with either small or large increases in visceral AT were formed. Second, two subgroups were formed ($n = 8$ in each subgroup), this time with similar mean increases in visceral AT but with either small or large changes in body fat mass. These two pairing analyses were independent from each other; therefore, some women could be used for both analyses. We also made sure that the number of women who went through menopause during the 7-year follow-up period or presented a positive family history of diabetes was similar among the subgroups compared.

Statistical analyses

Paired Student's t tests were performed to test the significance of changes in variables measured over the 7-year follow-up period within the total sample as well as within each subgroup studied. Unpaired Student's t tests were used to compare subgroups. Pearson correlation coefficients were used to examine associations among changes observed for variables studied over the 7-year period. For variables not normally distributed, Spearman correlations were performed. Stepwise multiple regression analyses were also performed to determine independent predictors of changes in metabolic variables. The first model included changes in visceral AT and changes in body fat mass as the independent variables. In the second model, changes in visceral AT and changes in abdominal subcutaneous AT were tested as independent variables. All analyses were performed on the SAS statistical package (SAS Institute, Cary, NC).

RESULTS — Table 1 shows that mean changes in BMI, body fat mass, and total and subcutaneous abdominal AT areas measured by CT were not significantly different from zero, whereas waist girth and WHR ($P < 0.05$) as well as visceral AT area ($P < 0.01$) significantly increased over the 7-year follow-up (Table 1). Table 1 also shows that significant increases in plasma glucose concentrations in the fasting state ($P < 0.01$) and at 120 min after the glucose load ($P < 0.05$) as well as in plasma glucose area ($P < 0.01$) were found. Plasma insulin levels, measured either in the fasting state or after the glucose load, were not significantly altered over the 7-year period (Table 1).

Correlation coefficients were computed to study the potential relationships between changes in morphological variables and changes in indexes of plasma glucose-insulin homeostasis. Table 2 shows that changes in visceral AT, abdominal subcutaneous AT, waist girth, and body fat mass were significantly associated with changes in fasting plasma insulin levels and in the area under the curve of insulin concentrations during the OGTT ($0.39 \leq r \leq 0.62$; $0.05 > P < 0.01$). Changes in plasma glucose area were also significantly related to changes in visceral AT area ($r = 0.37$; $P < 0.05$). Changes in morphological variables and in indexes of plasma glucose-insulin homeostasis remained unaltered by the removal of the four women taking medication. Furthermore, the exclusion of these women did not alter the magnitude of the correlations between changes in morphological and metabolic variables (results not shown). Figure 1 shows that relationships between changes in visceral AT and changes in fasting insulin levels or in plasma glucose area were linear throughout the observed ranges. All other significant associations presented in Table 2 were also found to be linear (results not shown).

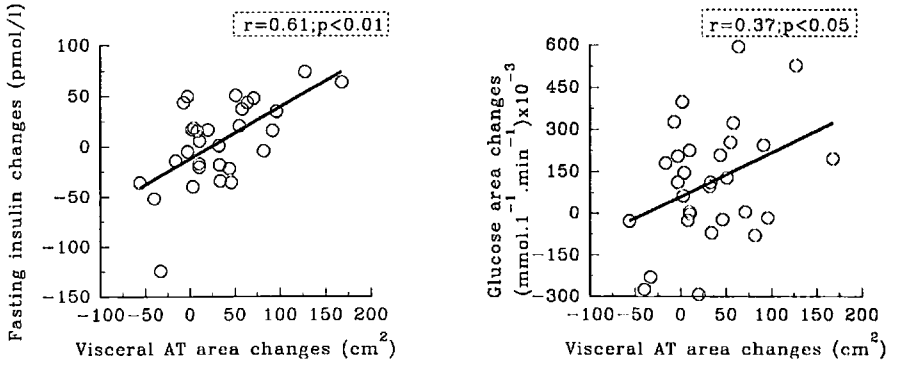

Figure 1—*Relationships between 7-year changes in visceral adipose tissue area versus changes in fasting plasma insulin levels and in plasma glucose area in the sample of 30 women.*

Table 3—*Pearson correlation coefficients for the relationships between baseline morphological variables and changes in plasma glucose and insulin levels over the 7-year follow-up period in the sample of 30 women*

	Baseline morphological variables				
	Fat mass	Visceral AT	Subcutaneous AT	Waist girth	WHR
7-year changes in					
Fasting glucose	−0.23	−0.28	−0.23	−0.31	−0.36*
Fasting insulin	−0.20	−0.30	−0.22	−0.24	−0.19
2-h glucose	0.16	0.10	0.14	0.10	−0.04
Glucose area	0.04	−0.03	−0.06	0.10	−0.04
Insulin area†	−0.02	−0.03	−0.26	−0.10	−0.24

*$P < 0.05$. †Spearman correlation coefficients were used. For fat mass, $n = 27$.

Table 3 indicates that no significant associations were found between baseline values of morphological variables and 7-year changes in plasma glucose and insulin levels, except for WHR measured at baseline, which was negatively and significantly related to changes in fasting glucose levels ($r = -0.36$; $P < 0.05$).

When women who became postmenopausal were removed from the study sample, changes in body fat mass, visceral AT, and waist girth remained significant correlates of changes in fasting insulin and in plasma insulin area, whereas variations in plasma glucose area were no longer significantly related to changes in visceral AT. Changes in waist girth, WHR, and visceral AT area remained significant when only premenopausal women were considered. However, the mean change in plasma glucose area was of lower magnitude (0.07 compared with 0.11 [mmol · l^{-1} · min^{-1}] × 10^{-3} in the total sample) when postmenopausal women were excluded, and the change was no longer statistically significant ($P = 0.12$) (results not shown).

To further discriminate the importance of changes in body fat mass versus changes in visceral AT on plasma glucose-insulin homeostasis, we have paired, on a group basis, women with similar body fat mass increases but with either small or large increases in visceral AT. Subgroup characteristics are presented in Table 4. Figure 2 shows plasma glucose and insulin levels during the OGTT in the two subgroups. No difference in glucose and insulin levels measured in 1987 were found between the two subgroups. However, women with large increases in visceral AT showed significant increases in plasma glucose levels in the fasting state and at 15, 45, and 60 min after the glucose load. Trends for a significant increase in glucose levels at 30 min ($P = 0.07$) and in plasma glucose area ($P = 0.08$) were also observed. Fasting insulin levels were increased at follow-up compared with baseline ($P = 0.06$) in women showing large gains in visceral AT. In comparison, women with small gains in visceral AT did not show any significant increase in either plasma glucose or insulin levels. On the other hand, we have also paired, on a group basis, women with similar changes in visceral AT but with either small or large gains in body fat mass. Table 5 shows that the subgroup referred to as low body fat mass gainers actually presented a mean decrease in body fat mass. It can be noted in Table 5 that the difference between the two subgroups for changes in subcutaneous AT area did not reach statistical significance ($P = 0.20$). No differences in plasma glucose and insulin levels measured at baseline were found between the two groups. Figure 3 shows that women with large gains in body fat mass showed significant increases in plasma glucose levels in the fasting state and at 15 min after glucose ingestion. No changes in plasma insulin concentrations were observed among this subgroup. Women with small gains in body fat mass also showed some significant changes in plasma glucose levels during the follow-up (fasting, 15, 90, and 120 min), and their plasma glucose area was also significantly increased. A significant increase in plasma insulin levels at 15 min was also observed among small gainers of body fat mass. Comparison of these two subgroups of women (low versus high body fat mass gainers) revealed that there was no difference in 7-year changes in plasma glucose or insulin levels between the two groups (results not shown). Women were also paired to form two subgroups displaying a significant difference in abdominal subcutaneous AT changes (low or high subcutaneous AT gains) but no difference in visceral AT changes, and results were similar to those

Table 4—*Characteristics of the two subgroups of women with similar increases in body fat mass over the 7-year follow-up period but with either small or large gains in visceral adipose tissue*

	Low visceral AT gain		High visceral AT gain	
Variables	Baseline	Changes	Baseline	Changes
Age (years)	33.0 ± 4.6	7.3 ± 0.3	37.1 ± 6.3	7.2 ± 0.4
Body fat mass (kg)	34.4 ± 15.9	1.6 ± 8.0	30.5 ± 13.2	1.3 ± 7.6
Subcutaneous AT area (cm^2)	494.6 ± 232.5	−14.4 ± 57.2	375.3 ± 191.8	6.6 ± 92.5
Visceral AT area (cm^2)	99.9 ± 49.9	3.8 ± 39.1	84.6 ± 30.5	50.6 ± 44.3*
Family history of diabetes	2/8		3/8	
Menopausal at follow-up	2/8		3/8	

Data are means ± SD. *Significant difference between the two subgroups, $P = 0.04$. In each subgroup, $n = 8$.

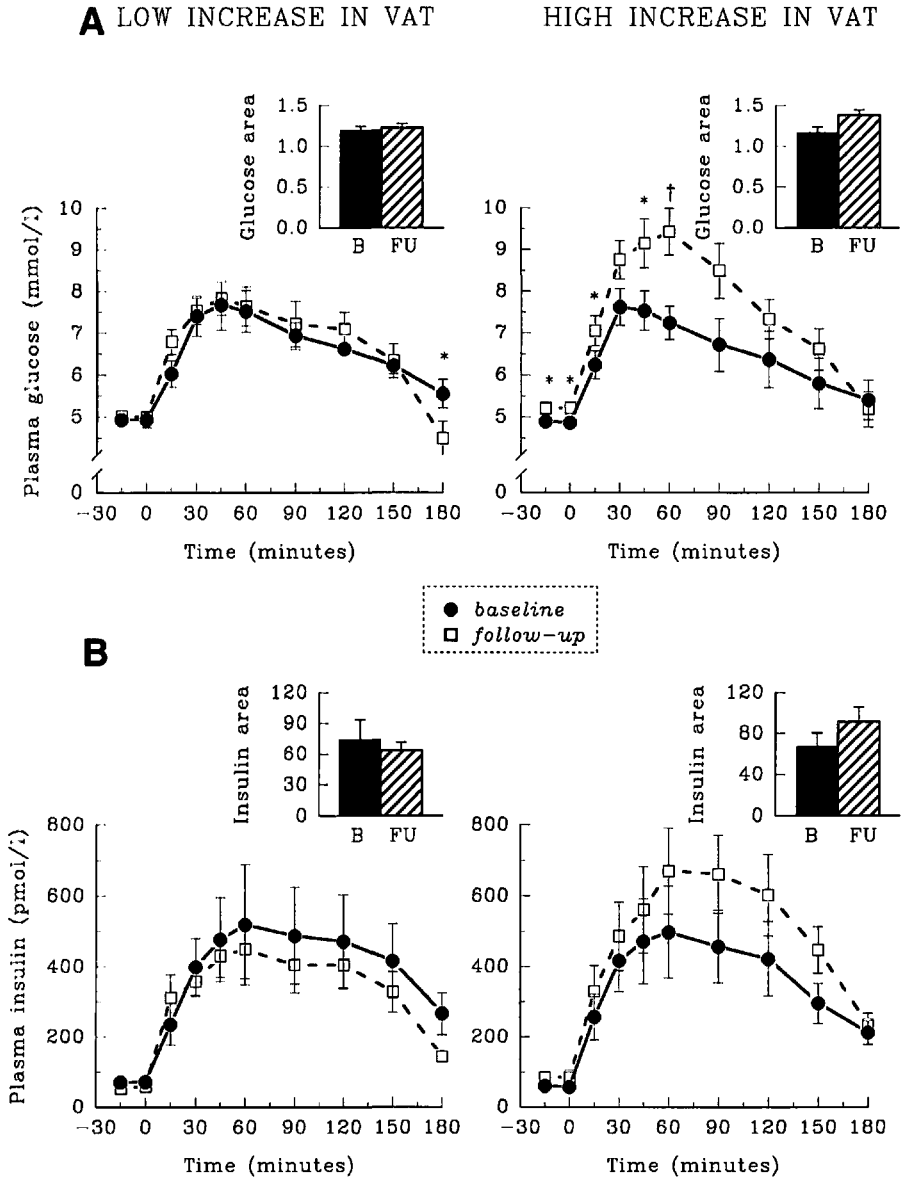

Figure 2—*Plasma glucose (A) and insulin (B) concentrations in the fasting state and during the OGTT in two subgroups of eight women showing similar increases in body fat mass but with small versus large gains in visceral adipose tissue area over the 7-year follow-up period. Bar charts show plasma glucose (mmol · l^{-1} · min^{-1}) × 10^{-3} and insulin areas (pmol · l^{-1} · min^{-1}) × 10^{-3}. B, baseline; FU, follow-up; VAT, visceral adipose tissue. Significant changes between baseline and follow-up: *P < 0.05, †P < 0.01.*

obtained when low and high body fat mass gainers were compared (not shown).

Finally, results of stepwise multiple regression analyses are presented in Table 6. When changes in body fat mass and changes in visceral AT were introduced in the model as independent variables, it was found that the change in visceral AT was the only significant predictor of changes in metabolic variables studied (changes in plasma glucose area, fasting insulin levels, and insulin area). When changes in subcutaneous and in visceral AT areas were studied as independent variables, it was found that visceral AT change was the only independent predictor of changes in plasma glucose area and in fasting insulin levels. On the other hand, the change in abdominal subcutaneous AT was an independent predictor of changes in plasma insulin area whereas visceral AT changes did not significantly improve the explained variance of this model.

CONCLUSIONS— Overall, women gained visceral AT during this 7-year follow-up study. This result is concordant with the notion that visceral AT deposition generally increases with age (14,15). In accordance with previous results (17–19), glucose tolerance, assessed by plasma glucose area in the present study, also generally deteriorated over the years. Our results also showed that changes in both body fat mass, abdominal subcutaneous AT, and in visceral AT were significantly associated with changes in plasma insulin levels (either fasting or after the glucose load). However, only changes in visceral AT were significantly correlated with changes in the area under the curve of plasma glucose concentrations. This finding suggests that it is the specific enlargement of the visceral fat depot, rather

Table 5—*Characteristics of the two subgroups of women with similar increases in visceral AT over the 7-year follow-up period but with either small or large gains in body fat mass*

	Low body fat mass gain		High body fat mass gain	
Variables	Baseline	Changes	Baseline	Changes
Age (years)	35.5 ± 7.1	7.3 ± 0.2	34.7 ± 6.2	7.2 ± 0.4
Body fat mass (kg)	33.3 ± 16.1	−2.7 ± 9.0	34.9 ± 13.8	5.5 ± 7.1*
Subcutaneous AT area (cm^2)	434.3 ± 217.3	−33.2 ± 92.6	499.0 ± 217.9	25.1 ± 84.0
Visceral AT area (cm^2)	106.1 ± 60.1	22.2 ± 45.4	97.4 ± 50.2	26.5 ± 40.4
Family history of diabetes	3/8		2/8	
Menopausal at follow-up	2/8		3/8	

Data are means ± SD. *Significant difference between the two subgroups, $P = 0.07$. In each subgroup, $n = 8$.

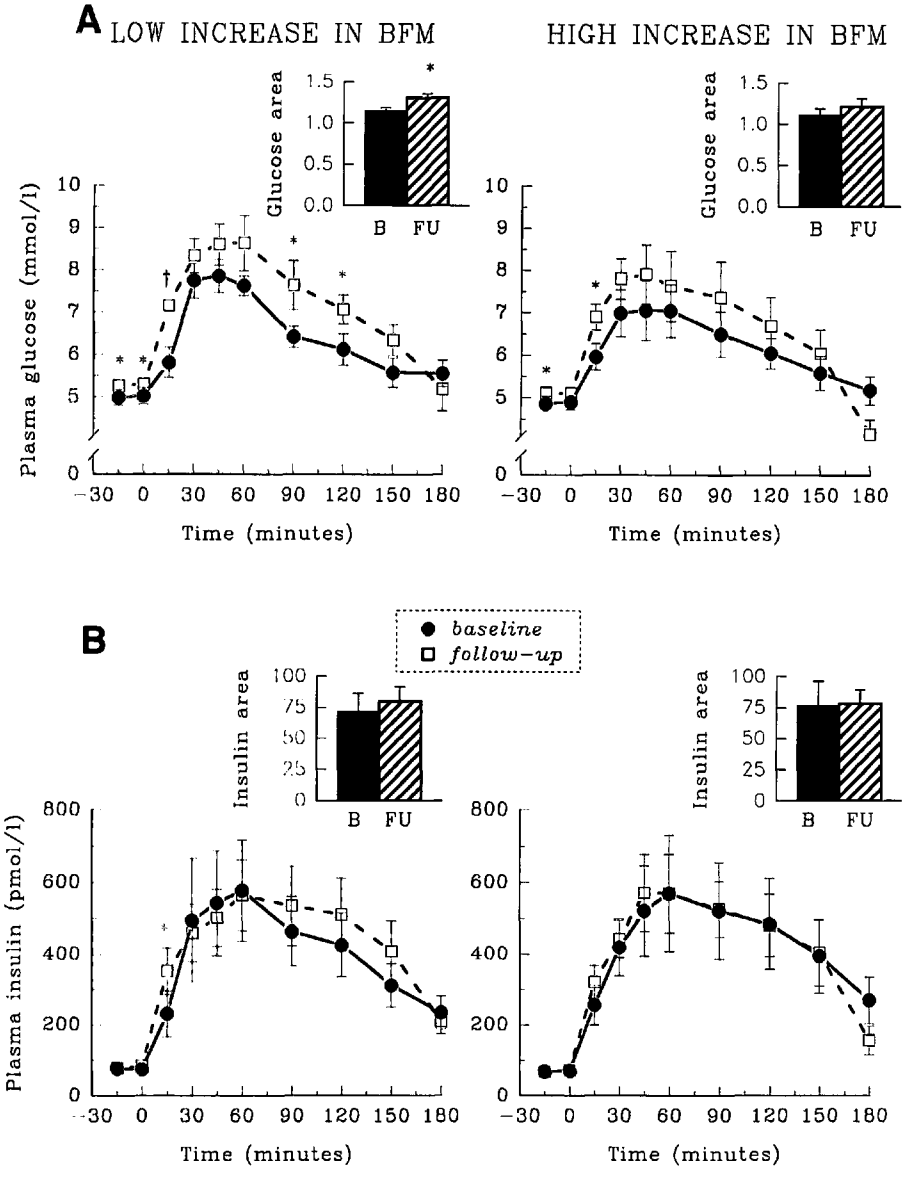

Figure 3—*Plasma glucose (A) and insulin (B) concentrations in the fasting state and during the OGTT in two subgroups of eight women showing similar increases in visceral adipose tissue area but with small versus large gains in body fat mass over the 7-year follow-up period. Bar charts show plasma glucose (mmol · l^{-1} · min^{-1}) × 10^{-3} and insulin areas (pmol · l^{-1} · min^{-1}) × 10^{-3}. B, baseline; FU, follow-up; BFM, body fat mass. Significant changes between baseline and follow-up: *P < 0.05, †P < 0.01.*

than the absolute gain in body fat, that increases the risk of developing glucose intolerance in this group of women. Our results also indicate that the relationships between changes in visceral AT area and changes in indexes of plasma glucose-insulin homeostasis were linear throughout the observed ranges. These results suggest that women who have lost visceral AT were as likely to improve their plasma glucose-insulin homeostasis as women who gained visceral AT were to deteriorate their metabolic profile.

Changes in waist girth were significantly associated with changes in plasma insulin levels in the fasting state and after the glucose load, a finding that further supports the notion that waist girth is a useful correlate of the metabolic risk, as previously suggested in cross-sectional analyses where waist girth was found to be associated with plasma glucose and insulin levels as well as with plasma lipid-lipoprotein concentrations (36). Changes in WHR, however, did not appear to adequately reflect the variation found in plasma glucose-insulin homeostasis in this sample of women.

Another finding that deserves some discussion in the present study is the lack of prospective association between baseline values of morphological variables and subsequent changes in plasma glucose and insulin levels. This suggests that women with high initial levels of body fat and visceral AT were not more susceptible to show a subsequent deterioration in plasma glucose-insulin homeostasis and that it was the variation rather than the initial levels of body fat mass and visceral AT that predicted changes in plasma glucose-insulin homeostasis. These results are quite important from a clinical point of view since they emphasize the importance of intervention strategies aiming at reducing body fat mass and visceral AT levels to obtain improvement in plasma glucose-insulin homeostasis.

One of the objectives of the present study was to discriminate between the effect of changes in body fatness and changes in visceral AT on the variation in plasma glucose-insulin homeostasis noted over the 7-year follow-up period. Our results indicate that the subsample of women with the largest increase in visceral AT showed significant deterioration in their indexes of plasma glucose-insulin homeostasis. Women with small gains in visceral AT, although having increases in body fat mass and in subcutaneous AT areas similar to those with large visceral AT gains, did not show, however, significant alterations in their plasma glucose and insulin levels. These results suggest that the specific deposition of visceral AT explained to a larger extent the variation in indexes of plasma glucose-insulin homeostasis than the absolute or subcutaneous accumulation of body fat. To further explore this possibility, additional analyses were performed in which women with similar increases in visceral AT but with either small or large increases in body fat mass or in abdominal subcutaneous AT were compared. The two subgroups showed about similar changes in plasma glucose levels, whereas plasma insulin levels essentially did not change during the 7-year follow-up period in the two subgroups. This suggests that as long as the visceral AT deposition is controlled, the concomitant variation of body fat mass or subcutaneous AT should have trivial effects on plasma glucose-insulin homeostasis. Menopause status and family history of diabetes are not

Table 6—*Stepwise multiple regression analyses for the prediction of changes in plasma glucose area, fasting plasma insulin levels, and plasma insulin area in the sample of 30 women*

	Variance explained		
	7-year changes in:		
	Plasma glucose area	Fasting plasma insulin	Plasma insulin area
Variables entered			
Model 1			
Visceral AT area (%)	18.0*	35.8‡	37.8‡
Body fat mass (%)	8.1	0.3	0.0
Model 2			
Visceral AT area (%)	13.6*	37.4†	1.6
Subcutaneous AT area (%)	0.2	0.0	34.4‡

*For model 1, $n = 27$. †Independent predictor, $P < 0.05$; ‡$P < 0.001$.

likely to have influenced the results reported herein since we made sure to have a similar number of postmenopausal women and women displaying a positive family history of diabetes in each subgroup analyzed.

Results from stepwise multiple regression analyses confirmed those obtained by pairing analyses, as the change in visceral AT was found to be an independent predictor of changes in plasma glucose-insulin homeostasis whereas the change in body fat mass did not significantly improve the explained variance for any of the metabolic variables studied. When subcutaneous AT area changes were entered into the model instead of body fat mass, results obtained were somewhat different. In fact, changes in abdominal subcutaneous AT were found to be a better predictor of changes in plasma insulin area than were visceral AT changes.

Results of the present study are concordant with previous cross-sectional observations, which have used the WHR to distinguish between upper body obesity and lower body obesity. Kissebah et al. (37) and Evans et al. (38) have demonstrated that upper body obesity was associated with a deterioration in glucose tolerance and hyperinsulinemia. We have also previously demonstrated that when obese women matched for the percentage of body fat but having either low or high levels of visceral AT assessed by CT were compared, significant alterations in plasma glucose and insulin levels were found in obese patients with high levels of visceral AT compared with those with low levels of visceral AT (2). It has therefore been suggested that the effect of upper body obesity on plasma glucose-insulin homeostasis was independent from and additive to the effect of obesity per se. More specifically, some studies have reported that upper body obesity was associated with a decreased hepatic clearance of insulin whereas obesity per se was rather related to an increased insulin secretion (2,39,40). These previous observations are concordant with our findings, which underlined the potential independent contribution of subcutaneous AT changes in the prediction of changes in plasma insulin area. In the present study, changes in plasma insulin area probably reflected to a large extent the adaptation of insulin secretion. Unfortunately, plasma C-peptide levels, which would have provided a more precise estimation of insulin secretion, were not measured in this study. At this point, it should be pointed out, however, that results obtained from stepwise multiple regression models should be interpreted with caution since visceral AT changes displayed a high level of collinearity with changes in both body fat and subcutaneous AT area.

Overall, the exclusion from the study sample of women who went through menopause during the 7-year follow-up period did not substantially affect the outcome of the analyses with the exception of the association between changes in visceral AT and changes in plasma glucose area, which was no longer significant when only premenopausal women were considered. The interaction between menopause status and visceral AT accumulation on glucose tolerance is an issue that will clearly need more attention because our study was not designed to specifically examine the effect of menopause on plasma glucose-insulin homeostasis. Our group of women who went through menopause during the follow-up was rather small ($n = 8$) and heterogeneous with regard to the duration of menopause. Furthermore, some women reached natural menopause whereas other had a hysterectomy. Considering these limitations, it was difficult to draw specific conclusions on this subgroup of women, and further studies on larger and more homogeneous samples of postmenopausal women are clearly warranted.

In summary, results of the present study have shown that changes in body fat mass and in visceral AT observed over a 7-year follow-up period were significantly and positively associated with changes in most indexes of plasma glucose-insulin homeostasis. When subgroups of women with similar changes in body fat mass and in abdominal subcutaneous AT but with either small or large gains in visceral AT were compared, it was found that the latter subgroup showed a significant deterioration in plasma glucose-insulin homeostasis whereas women with small gains in visceral AT showed no deterioration in their metabolic profile.

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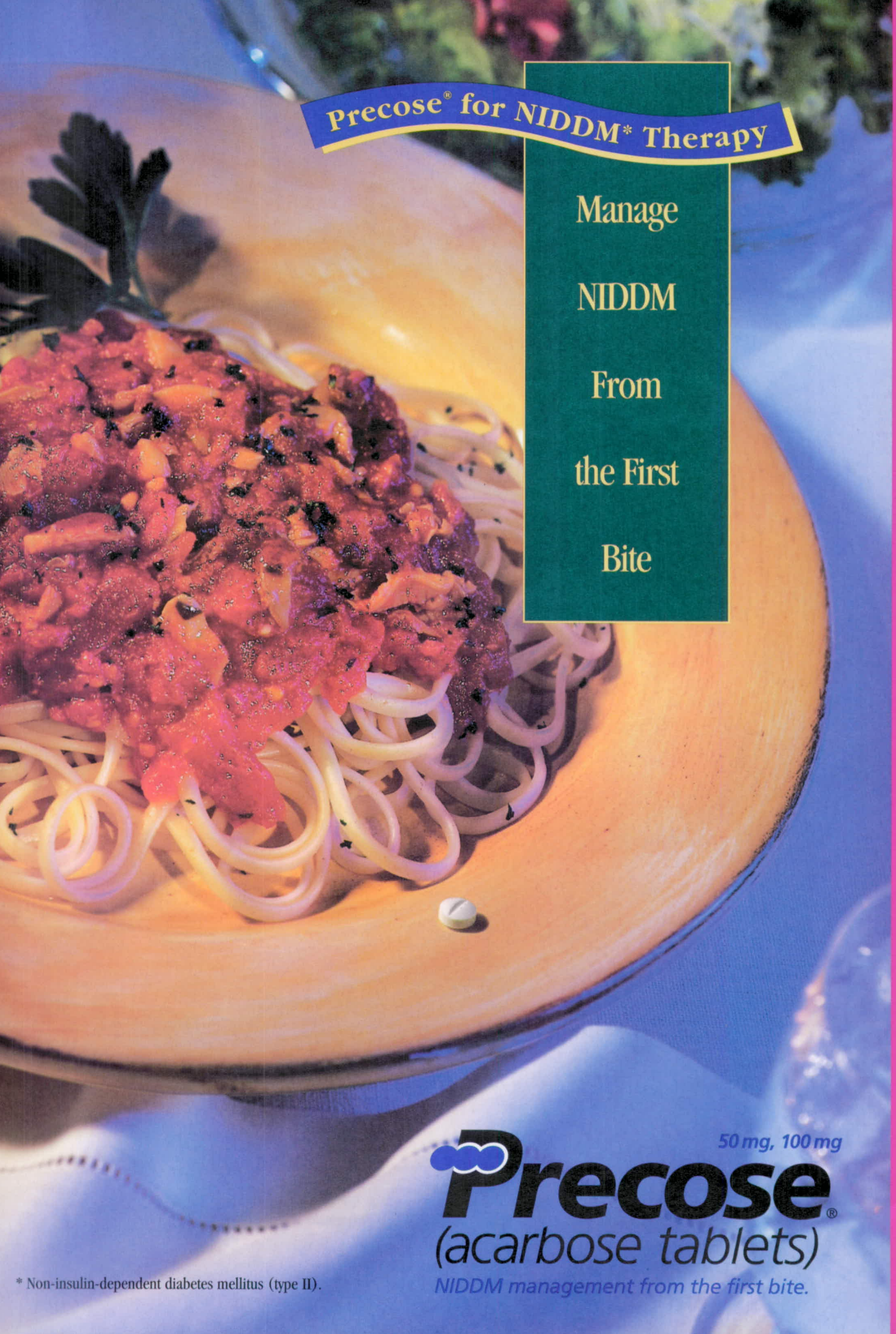

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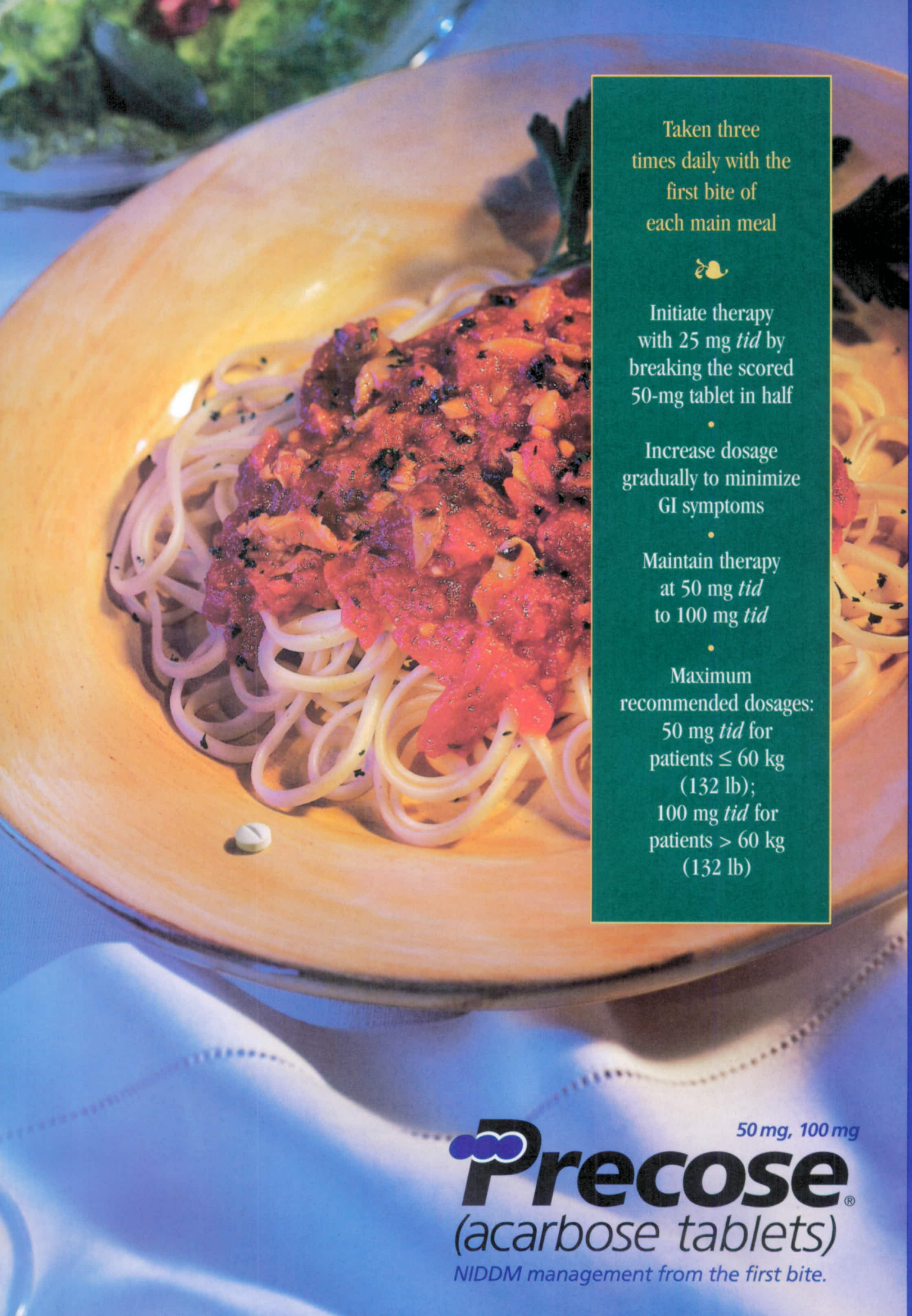

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INDICATIONS AND USAGE

PRECOSE®, as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed on diet alone. PRECOSE® may also be used in combination with a sulfonylurea when diet plus either PRECOSE® or a sulfonylurea do not result in adequate glycemic control. The effect of PRECOSE® to enhance glycemic control is additive to that of sulfonylureas when used in combination, presumably because its mechanism of action is different.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of PRECOSE® should be considered. The use of PRECOSE® must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

CONTRAINDICATIONS

PRECOSE® is contraindicated in patients with known hypersensitivity to the drug and in patients with diabetic ketoacidosis or cirrhosis. PRECOSE® is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, PRECOSE® is contraindicated in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine.

PRECAUTIONS

General

Hypoglycemia: Because of its mechanism of action, PRECOSE® when administered alone should not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea. Oral glucose (dextrose), whose absorption is not inhibited by PRECOSE®, should be used instead of sucrose (cane sugar) in the treatment of mild to moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by PRECOSE®, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Elevated Serum Transaminase Levels: In clinical trials, at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with PRECOSE® was the same as with placebo. In long-term studies (up to 12 months, and including PRECOSE® doses up to 300 mg t.i.d.) conducted in the United States, treatment-emergent elevations of serum transaminases (AST and/or ALT) occurred in 15% of PRECOSE®-treated patients as compared to 7% of placebo-treated patients. These serum transaminase elevations appear to be dose related. At doses greater than 100 mg t.i.d., the incidence of serum transaminase elevations greater than three times the upper limit of normal was two to three times higher in the PRECOSE® group than in the placebo group. These elevations were asymptomatic, reversible, more common in females, and, in general, were not associated with other evidence of liver dysfunction.

In international post-marketing experience with PRECOSE® in over 500,000 patients, 19 cases of serum transaminase elevations > 500 IU/L (12 of which were associated with jaundice) have been reported. Fifteen of these 19 cases received treatment with 100 mg t.i.d. or greater and 13 of 16 patients for whom weight was reported weighed < 60 kg. In the 18 cases where follow-up was recorded, hepatic abnormalities improved or resolved upon discontinuation of PRECOSE®.

Loss of Control of Blood Glucose: When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Information for Patients: Patients should be told to take PRECOSE® orally three times a day at the start (with the first bite) of each main meal. It is important that patients continue to adhere to dietary instructions, a regular exercise program, and regular testing of urine and/or blood glucose.

PRECOSE® itself does not cause hypoglycemia even when administered to patients in the fasted state. Sulfonylurea drugs and insulin, however, can lower blood sugar levels enough to cause symptoms or sometimes life-threatening hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea or insulin will cause a further lowering of blood sugar, it may increase the hypoglycemic potential of these agents. The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be well understood by patients and responsible family members. Because PRECOSE® prevents the breakdown of table sugar, patients should have a readily available source of glucose (dextrose, D-glucose) to treat symptoms of low blood sugar when taking PRECOSE® in combination with a sulfonylurea or insulin.

If side effects occur with PRECOSE®, they usually develop during the first few weeks of therapy. They are most commonly mild-to-moderate gastrointestinal effects, such as flatulence, diarrhea, or abdominal discomfort and generally diminish in frequency and intensity with time.

Laboratory Tests: Therapeutic response to PRECOSE® should be monitored by periodic blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

PRECOSE®, particularly at doses in excess of 50 mg t.i.d., may give rise to elevations of serum transaminases and, in rare instances, hyperbilirubinemia. It is recommended that serum transaminase levels be checked every 3 months during the first year of treatment with PRECOSE® and periodically thereafter. If elevated transaminases are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist.

Renal Impairment: Plasma concentrations of PRECOSE® in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with PRECOSE® is not recommended.

Drug Interactions: Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel-blocking drugs, and isoniazid. When such drugs are administered to a patient receiving PRECOSE®, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from patients receiving PRECOSE® in combination with sulfonylureas or insulin, patients should be observed closely for any evidence of hypoglycemia.

Intestinal adsorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., amylase, pancreatin) may reduce the effect of PRECOSE® and should not be taken concomitantly.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Nine chronic toxicity/carcinogenicity studies were conducted in three animal species (rat, hamster, dog) including two rat strains (Sprague-Dawley and Wistar).

In the first rat study, Sprague-Dawley rats received acarbose in feed at high doses (up to approximately 500 mg/kg body weight) for 104 weeks. Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors. This study was repeated with a similar outcome. Further studies were performed to separate direct carcinogenic effects of acarbose from indirect effects resulting from the carbohydrate malnutrition induced by the large doses of acarbose employed in the studies. In one study using Sprague-Dawley rats, acarbose was mixed with feed but carbohydrate deprivation was prevented by the addition of glucose to the diet. In a 26-month study of Sprague-Dawley rats, acarbose was administered by daily postprandial gavage so as to avoid the pharmacologic effects of the drug. In both of these studies, the increased incidence of renal tumors found in the original studies did not occur. Acarbose was also given in food and by postprandial gavage in two separate studies in Wistar rats. No increased incidence of renal tumors was found in either of these Wistar rat studies. In two feeding studies of hamsters, with and without glucose supplementation, there was also no evidence of carcinogenicity.

Acarbose showed no mutagenic activity when tested in six *in vitro* and three *in vivo* assays.

Fertility studies conducted in rats after oral administration produced no untoward effect on fertility or on the overall capability to reproduce.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. The safety of PRECOSE® in pregnant women has not been established. Reproduction studies have been performed in rats at doses up to 480 mg/kg (corresponding to 9 times the exposure in humans, based on drug blood levels) and have revealed no evidence of impaired fertility or harm to the fetus due to acarbose. In rabbits, reduced maternal body weight gain, probably the result of the pharmacodynamic activity of high doses of acarbose in the intestines, may have been responsible for a slight increase in the number of embryonic losses. However, rabbits given 160 mg/kg acarbose (corresponding to 10 times the dose in man, based on body surface area) showed no evidence of embryotoxicity and there was no evidence of teratogenicity at a dose 32 times the dose in man (based on body surface area). There are, however, no adequate and well-controlled studies of PRECOSE® in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers: A small amount of radioactivity has been found in the milk of lactating rats after administration of radiolabeled acarbose. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, PRECOSE® should not be administered to a nursing woman.

Pediatric Use: Safety and effectiveness of PRECOSE® in pediatric patients have not been established.

ADVERSE REACTIONS

Digestive Tract: Gastrointestinal symptoms are the most common reactions to PRECOSE®. In U.S. placebo-controlled trials, the incidences of abdominal pain, diarrhea, and flatulence were 21%, 33%, and 77% respectively in 1075 patients treated with PRECOSE® 50-300 mg t.i.d., whereas the corresponding incidences were 9%, 12%, and 32% in 818 placebo-treated patients. Abdominal pain and diarrhea tended to return to pretreatment levels over time, and the frequency and intensity of flatulence tended to abate with time. The increased gastrointestinal tract symptoms in patients treated with PRECOSE® is a manifestation of the mechanism of action of PRECOSE® and is related to the presence of undigested carbohydrate in the lower GI tract. Rarely, these gastrointestinal events may be severe and might be confused with paralytic ileus.

Elevated Serum Transaminase Levels: See PRECAUTIONS.

Other Abnormal Laboratory Findings: Small reductions in hematocrit occurred more often in PRECOSE®-treated patients than in placebo-treated patients but were not associated with reductions in hemoglobin. Low serum calcium and low plasma vitamin B_6 levels were associated with PRECOSE® therapy but were thought to be either spurious or of no clinical significance.

Caution: Federal law prohibits dispensing without a prescription.

PZ500036BS 4/96 Bay g 5421 PRECOSE®/5202/0/8/USA-1
 6160 Printed in U.S.A.

References

1. Precose® (acarbose tablets) Package Insert.
2. Coniff RF, Shapiro JA, Robbins D, et al. Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM. *Diabetes Care.* 1995;18(6):817-824.
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4. American Diabetes Association. Implications of the Diabetes Control and Complications Trial. *Diabetes Care.* 1993;16(11):1517-1520.
5. Hanefeld M. Acarbose efficacy review. *Practical Diabetes Suppl.* 1993;10(6):S21-S27.

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What is Carbohydrate Counting and Why Teach It?

Carbohydrate Counting is a new diabetes meal planning approach found to be effective during the Diabetes Control and Complications Trial (DCCT). Studies have proven that carbohydrate(CHO) intake is the main factor affecting blood glucose, and that although they vary in *nutritive* value, all carbohydrates have nearly equal impact on blood sugar. Therefore, emphasis is placed on the total amount of CHO consumed, rather than the type.

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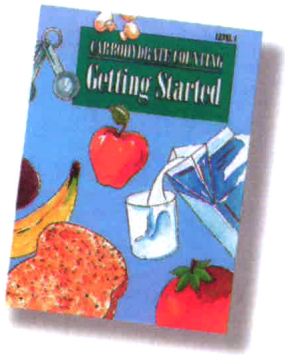
Getting Started (Level 1):



Introduces the concepts of carbohydrate counting. Patients will learn which foods contain carbohydrates and how to consume consistent amounts on a daily basis. Intended for all diabetes patients (IDDM, NIDDM, or GDM). #CCCL1

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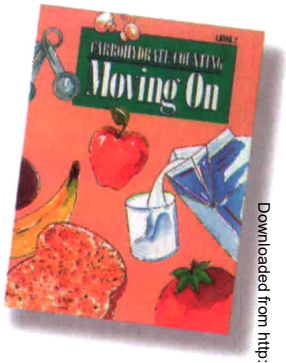

Patients learn to identify and interpret patterns in their blood glucose levels based on their food intake, medication, and physical activity (known as pattern management). Intended for any patient who has mastered the basics of carbohydrate counting. #CCCL2

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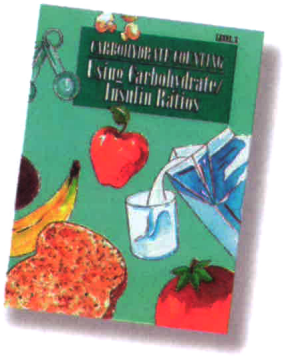

Building on the skills taught in levels 1 and 2, it teaches patients to adjust insulin for changes in food or physical activity using a ratio of carbohydrate intake to insulin dosage. Intended for patients on intensive insulin management (multiple daily injections or insulin pump) who have mastered insulin adjustment and supplementation. #CCCL3

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