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SHORT-TERM ADMINISTRATION OF ISOTRETINOIN ELEVATES PLASMA TRIGLYCERIDE CONCENTRATIONS WITHOUT AFFECTING INSULIN SENSITIVITY IN HEALTHY HUMANS

THESE

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Une courte administration d'acide 13-cis rétinoïque chez l'homme en bonne santé augmente les taux plasmatiques de triglycérides sans influencer la sensibilité à l'insuline

Les mécanismes responsables de la résistance à l'insuline associée à l'hypertriglycéridémie chez l'homme sont mal connus. Il a été proposé que l'hypertriglycéridémie n'engendrait une résistance à l'insuline que lorsqu'elle est associée à une augmentation du transfert de lipides dans le muscle. Selon cette hypothèse, une hypertriglycéridémie secondaire à la diminution de l'élimination de particules riches en triglycérides ne devrait pas engendrer de résistance à l'insuline.

Afin de vérifier cette hypothèse, nous avons étudié la sensibilité à l'insuline (au niveau du corps entier et du tissu adipeux) chez 15 sujets volontaires masculins avant et après 5 jours d'un traitement par l'acide 13-cis rétinoïque (1 mg/kg/j), un dérivé de la vitamine A qui diminue l'élimination des particules riches en triglycérides. Au cours d'un clamp hyperinsulinémique euglycémique à 3 paliers, nous avons mesuré le métabolisme global du glucose dépendant de l'insuline (6,6 $^2H_2$ glucose), l'oxydation du glucose (calorimétrie indirecte), la lipolyse ($^2H_5$ glycérol) et la lipolyse du tissu adipeux sous-cutané (microdialyse). L'acide 13-cis rétinoïque a augmenté le taux plasmatique de triglycérides de 0.97 ± 0.15 à 1.30 ± 0.22 mmol/l ($p < 0.02$) mais n'a pas eu d'effet sur le métabolisme global du glucose et la lipolyse.

Ces observations sont compatibles avec une diminution de l'élimination des particules riches en triglycérides induite par l'acide 13-cis rétinoïque. L'inhibition de la production endogène du glucose et la diminution du glycérol sous-cutané induites par l'insuline n'ont pas été affectées par l'administration d'acide 13-cis rétinoïque.

Nous concluons que la diminution de l'élimination des particules riches en triglycérides induite par 5 jours d'acide 13-cis rétinoïque n'a pas d'influence sur les mécanismes antilipolytiques ou sur le métabolisme du glucose dépendant de l'insuline. Ces résultats soutiennent le concept que la résistance à l'insuline associée à l'hypertriglycéridémie se développe principalement quand la production de triglycérides est augmentée.

Short-Term Administration of Isotretinoin Elevates Plasma Triglyceride Concentrations Without Affecting Insulin Sensitivity in Healthy Humans

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The mechanism underlying hypertriglyceridemia-associated insulin resistance in humans remains poorly understood. It has been proposed that hypertriglyceridemia only produces insulin resistance when associated with an increased lipid delivery to muscle. Accordingly, hypertriglyceridemia secondary to a decreased clearance of triglyceride-rich particles should not cause insulin resistance. To verify this hypothesis, we assessed whole body and adipose tissue insulin sensitivity in 15 healthy male volunteers before and after a 5-day administration of isotretinoin (1 mg/kg/d), a vitamin A derivative that decreases the clearance of triglyceride-rich particles. Whole body insulin-mediated glucose disposal (6,6 $^2H_2$glucose), glucose oxidation (indirect calorimetry), lipolysis ($^2H_5$ glycerol), and subcutaneous adipose lipolysis (microdialysis) were evaluated during a 3-step hyperinsulinemic euglycemic clamp. Isotretinoin increased plasma triglyceride from 0.97 ± 0.15 to 1.30 ± 0.22 mmol/L ($P < .02$), but did not change whole body insulin-mediated glucose disposal and lipolysis. These observations are consistent with an isotretinoin-induced inhibition of very-low-density lipoprotein (VLDL)-triglyceride clearance. The suppression of endogenous glucose production and the reduction in subcutaneous adipose glycerol concentrations by insulin remained equally unaffected after isotretinoin administration. We conclude that the impaired clearance of triglyceride-rich particles secondary to a 5-day isotretinoin administration does not impair insulin-mediated antilipolysis or glucose disposal. The data support the concept that hypertriglyceridemia-associated insulin resistance develops primarily when triglyceride production is increased.

HYPERTRIGLYCERIDEMIA is often associated with insulin resistance.[1,2] The nature of this relationship in humans remains unclear. Several observations made in animals suggest that an increase in very-low-density lipoprotein (VLDL) assembly and secretion by the liver may lead to an increase in free fatty acid (FFA) delivery to the extrahepatic tissues, which may induce insulin resistance.[3] High-fructose diet increases VLDL production, raises plasma triglycerides concentration, and induces insulin resistance in rodents.[4-6] Furthermore, recent studies have shown that overexpression of muscle and/or liver lipoprotein lipase in rodents causes tissue-specific insulin resistance.[7,8] In addition, we recently reported that the inhibitory effects of lipids on whole body glucose utilization were increased in athletes during exercise and hyperinsulinemia, suggesting that endurance training increases muscle lipid uptake during contraction while reducing glucose transport and oxidation.[9] These observations indicate that tissue-specific uptake of lipids is of importance in the development of insulin resistance.

In contrast, hypertriglyceridemia secondary to reduced utilization of triglyceride-rich lipoproteins appears to be associated with unchanged or increased whole body insulin sensitivity. Overexpression of apolipoprotein (apo)C-III, which inhibits lipoprotein lipase, reduces the clearance of triglyceride-rich particles and does not change or increases insulin action in mice.[10] More recently, it was observed that hypertriglyceridemia can be induced by overexpressing human apoC-I in mice,[11,12] presumably through a decrease in the hepatic clearance of VLDL. These animals were shown to have increased whole body insulin sensitivity. Altogether these observations suggest that increased delivery of VLDL-triglycerides or uptake of VLDL-associated lipids by peripheral tissues may be an important factor in the regulation of tissue insulin sensitivity. Hyperinsulinemia secondary to insulin resistance may subsequently further elevate plasma triglyceride concentrations by increasing FFA reesterification and VLDL secretion,[2] thus generating a vicious cycle.

Isotretinoin, a vitamin A derivative used in the treatment of acne, elevates plasma triglyceride levels in approximately 1 of 5 subjects.[13-15] A reduction in the clearance of VLDL particles has been identified as the most likely mechanism underlying this adverse effect. It appears secondary to an increase in the content of apoC-III in VLDL, which interferes with lipoprotein lipase-mediated intravascular lipolysis.[16] Alternatively, an increase in VLDL production was postulated and may result from a stimulation of the re-esterification of FFA in the liver or from a stimulation of hepatic de novo lipogenesis.[17] Here, we performed a detailed assessment of the effects of a short-term administration of isotretinoin on lipid metabolism and insulin sensitivity in healthy humans. Our results corroborate that isotretinoin elevates plasma triglyceride concentrations through a reduction of triglyceride clearance. Moreover, they indicate that isotretinoin does not impair insulin sensitivity, a finding consistent with the hypothesis that hypertriglyceridemia primarily induces insulin resistance when associated with increased lipid delivery to insulin-sensitive tissues.

MATERIALS AND METHODS

Subjects

A total of 15 male healthy volunteers were enrolled in this study. Each volunteer had previously been treated with isotretinoin on average 5 years earlier (range, 3 to 10). Seven of them had increased their plasma triglyceride concentration by more than 1 mmol/L during this

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Table 1. Characteristics of Study Participants

Subject No.	Age (yr)	Weight (kg)	Height (m)	BMI (kg/m^2)	Waist/Hip Ratio	% Fat	Δ Triglyceride After First Treatment (mmol/L)	Δ Triglyceride During This Study (mmol/L)
1	38	59	1.75	19.3	0.8	21.5	0.06	0.5
2	23	72	1.84	21.3	0.6	20.1	0.1	−0.01
3	20	73	1.83	21.8	0.8	16.4	−0.08	0.24
4	39	84	1.73	28.1	0.9	30.6	−0.06	0.38
5	22	87	1.86	25.1	0.8	14.7	0.1	0.19
6	26	68	1.72	23	0.8	16.4	0.08	0.58
7	29	71	1.80	21.9	0.8	20.1	0.0	−0.18
8	30	74	1.78	23.4	0.8	21.5	−0.18	0.45
9	29	81	1.81	24.7	0.8	26.2	3.09	1.57
10	24	99.5	1.7	34.4	0.9	29.4	1.09	1.06
11	33	86	1.88	24.3	0.9	21.5	1.49	0.19
12	23	75	1.77	23.9	0.9	24	1.22	−0.05
13	25	77	1.69	26.9	0.9	29.4	1.36	−0.01
14	23	93	1.85	27	0.9	27.6	1.4	0.14
15	40	73	1.83	21.8	0.9	23	2.65	−0.18

treatment and the remaining 8 had had unchanged levels. All volunteers were in good physical condition, had no personal history of diabetes, alcoholism, renal, or hepatic insufficiency, and had normal liver function tests and plasma triglyceride concentrations. Their characteristics are shown in Table 1. Mean age was 28.3 ± (SEM) 1.7 years (range, 20 to 40), body mass index (BMI) 24.5 ± 0.9 kg/m^2 (range, 19 to 34), percentage body fat (determined using skinfold thickness measurement[18]) 22.8% ± 1.3% (range, 15% to 30%), fat-free mass 60.1 ± 1.8 kg (range, 46 to 74), and waist-to-hip ratio 0.83 ± 0.02 (range, 0.6 to 0.9). The Ethical Committee of the Lausanne University Medical School approved the experimental protocol, and every subject provided an informed written consent.

General Procedure

Experiments began in the morning after an overnight fast. Volunteers were requested not to consume caffeine or alcohol containing drinks at least 24 hours before the study; furthermore, they were asked not to get involved in any strenuous physical activity during the 2 days preceding the study.

Each volunteer took part to the same protocol twice, once before and once after isotretinoin had been taken for 5 days at a dose of 1 mg/kg/d. Compliance was ascertained by assessment of mucocutaneous side effects. Upon arrival in the metabolic laboratory, volunteers had one indwelling venous cannula inserted into a vein of their right wrist. The right hand was subsequently placed into a thermostabilized box heated at 56°C to achieve partial arterialization of venous blood. Blood samples were periodically collected through this catheter. A second indwelling cannula was inserted into an antecubital vein of the contralateral arm for infusion of glucose and glycerol tracers, insulin, and glucose. In addition, 2 microdialysis probes (20,000-d cut-off, 3-cm membrane length; CMA/Microdialysis, Stockholm, Sweden) were inserted percutaneously into the abdominal subcutaneous adipose tissue, one on each side of the navel, after administration of light intradermal anesthesia (xylocaine 1%, 0.1 to 0.2 mL). The probes were connected to a microinjection pump and continuously perfused, one with a sterile Ringer solution and the other with a sterile Ringer solution supplemented with epinephrine at a concentration of 1 μmol/L. Effluent dialysate was collected as 15 to 30-minute fractions. Respiratory exchanges were continuously monitored using a ventilated hood.

A primed continuous infusion of 6,6-$^2H_2$ glucose and $^2H_5$ glycerol was started at 7:30 AM. Two hours after the infusion was initiated, a hyperinsulinemic euglycemic clamp was started. Three levels of insulin (0.6, 1.2, and 2.4 pmol/kg/min) were perfused. Each level lasted 75 minutes. The exogenous glucose was labeled with 1.25% 6,6-$^2H_2$ glucose to avoid dilution of the tracer by the glucose infusion. Blood samples were collected at 5-minute intervals for monitoring of plasma glucose concentrations and at 15 or 30-minute intervals for measurements of plasma hormones, substrate concentrations, and 6,6-$^2H_2$ glucose and $^2H_5$-glycerol enrichment.

Analysis

Plasma glucose concentration was determined using a Beckman Glucose Analyzer 2 (Beckman Instruments, Brea, CA). Plasma insulin concentration was determined by radioimmunoassay (kit from Linco, St Charles, MO). Plasma triglyceride concentration was determined by an enzymatic and colorimetric method (BioMérieux, Marcy-l'Etoile, France). Plasma FFA concentration was determined by an enzymatic and colorimetric method (kit Wako, Neuss, Germany). Isotopic enrichment of glucose[19-22] and glycerol[23] was determined by gas chromatography-mass spectrometry (GC 5890/ MS5971, Hewlett-Packard, Palo Alto, CA). VLDL particles were separated from plasma by preparative ultracentrifugation (45,000 rpm, 4°C, for 17 hours). Total VLDL-lipids were extracted by a modification of Folch's method.[24] The triglycerides fraction of VLDL-lipids was isolated by solid-phase extraction on aminopropyl silica columns. Fatty acid methyl esters were obtained from transmethylation of VLDL-triglycerides and the ratio of palmitate to linoleate was determined by gas chromatography–mass spectrometry. Glycerol concentration in dialysate was determined by an enzymatic method using a CMA microdialysis analyzer (CMA, Stockholm, Sweden).

Calculation

Glucose and glycerol appearance and disappearance were calculated from plasma 6,6 $^2H_2$ glucose and $^2H_5$-glycerol isotopic enrichments, respectively, using Steele's equations.[19,25] To further evaluate the relationship between triglyceride and insulin sensitivity, the change in fasting plasma triglyceride concentrations induced by isotretinoin was calculated as fasting triglyceride$_{(isotretinoin)}$ − fasting triglyceride$_{(no\ isotretinoin)}$. Similarly, the changes in insulin sensitivity was calculated as glucose rate of disappearance [GRd]$_{(isotretinoin)}$ − GRd$_{(no\ isotretinoin)}$ at the 2 highest insulin infusion rates. A correlation between these 2 parameters was then sought.

Table 2. Fasting Hormones and Substrate Concentrations Before and After Isotretinoin Administration

	Before Treatment (day 1)	After Treatment (day 6)
Triglycerides (mmol/L)	0.97 ± 0.15	1.30 ± 0.22*
VLDL-triglyceride (mmol/L)	0.60 ± 0.13	0.77 ± 0.14
Free fatty acids (mmol/L)	0.47 ± 0.03	0.49 ± 0.04
Plasma glucose (mmol/L)	5.6 ± 0.1	5.6 ± 0.1
Plasma insulin (pmol/L)	59 ± 6	60 ± 6

*$P < .02$ *v* day 1.

Statistics

Results are given as the mean ± SEM. Means were compared using analysis of variance (ANOVA) for repeated measurements and paired Student's *t* test. Simple regression analysis was used to search for a correlation between changes in plasma triglycerides and changes in insulin-mediated glucose disposal.

RESULTS

The effects of isotretinoin administration on basal substrate and hormone concentrations are shown in Tables 1 and 2. A 5-day isotretinoin treatment significantly increased fasting plasma triglyceride values (Table 1). The changes in plasma triglyceride levels observed 3 to 10 years earlier, when the subjects had received isotretinoin as a treatment for acne, are also shown for comparison. There was no correlation between the changes in plasma triglycerides observed in this study and those observed 3 to 10 years previously.

Lipid Metabolism

A 5-day administration of isotretinoin increased total plasma triglyceride and VLDL-triglyceride on average by 33% ($P <$ .02) and 37%, respectively (Fig 1). The ratio of palmitic to linoleic acid in VLDL-triglyceride was the same before (2.1 ± 0.4) and after (2.2 ± 0.5) isotretinoin administration. Total cholesterol (4.3 ± 0.3 *v* 4.5 ± 0.3 mmol/L) and high-density lipoprotein (HDL)-cholesterol (1.0 ± 0.1 *v* 0.9 ± 0.1 mmol/L) remained unchanged. Fasting plasma FFA were identical after isotretinoin and in control experiments and were suppressed to the same extent at each step of euglycemic insulinemia (Fig 2). Similarly, fasting glycerol turnover and its suppression by insulin were not affected by isotretinoin administration (Table 3). Adipose interstitial glycerol concentrations were identical in the basal state irrespective of stimulation by epinephrine. Furthermore, suppression of adipose interstitial glycerol by insulin, both without and with epinephrine, was identical before and after isotretinoin (Fig 3). Lipid oxidation was progressively suppressed by graded doses of insulin, but this effect was not affected by isotretinoin (Table 3).

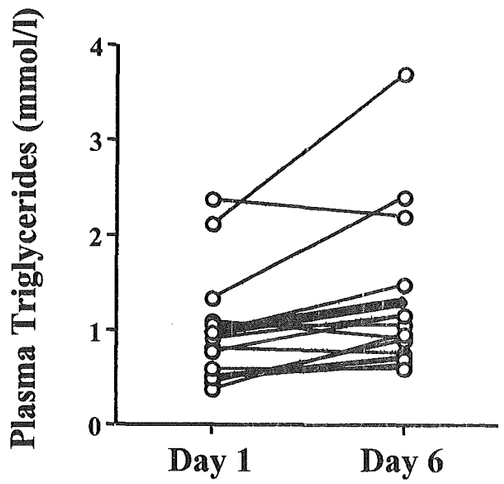

Fig 1. Total plasma triglyceride concentration before and after a 5-day treatment with isotretinoin. The thick line represents the average values of the 15 volunteers.

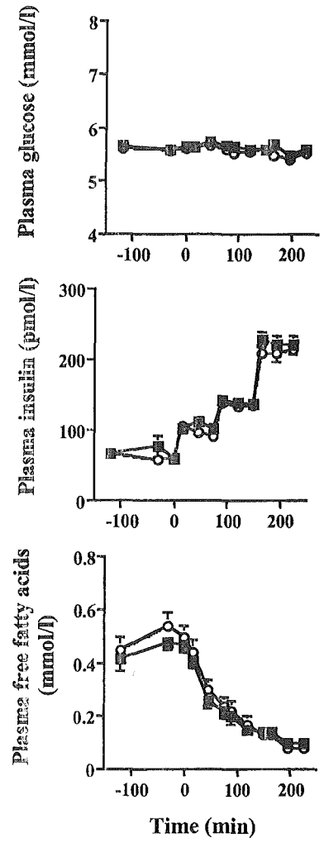

Fig 2. Plasma glucose, insulin, and FFA concentrations during a 3-step hyperinsulinemic clamp before (○) and after (■) a 5-day treatment with isotretinoin.

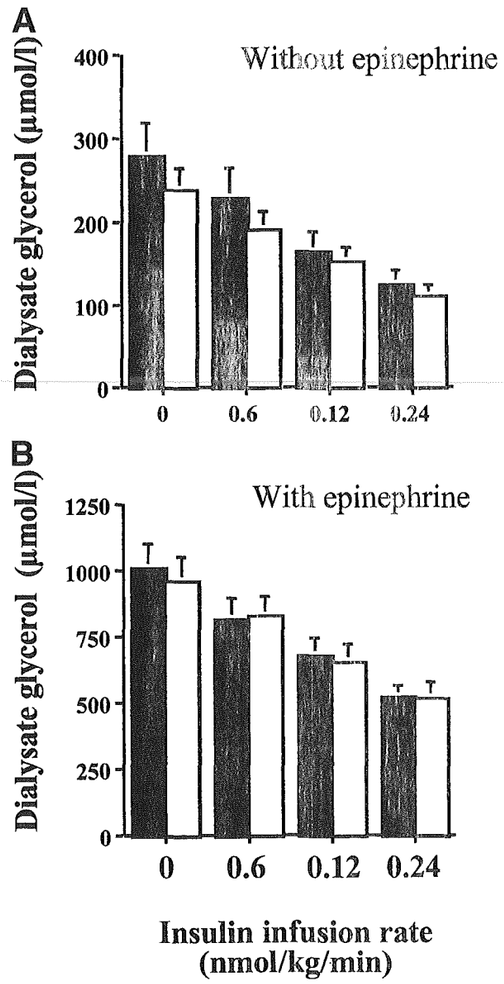

Fig 3. Concentration in the dialysate collected from subcutaneous periombilical adipose tissue in fasting conditions (0) and during insulin infusion at 0.6, 1.2, and 2.4 nmol/kg/min. (A) Probes were infused with plain Ringer solution; (B) probes were infused with Ringer containing 10^{-6} mol/L epinephrine to stimulate lipolysis. Black bars represent volunteers before, and open bars after a 5-day treatment with isotretinoin.

Glucose Metabolism

Glucose production, utilization, and oxidation in basal and insulin-stimulated conditions are shown in Table 4. Before isotretinoin administration, all of these parameters of glucose metabolism were stimulated in a dose-dependent fashion by insulin. However, there was no difference between the test performed at baseline and after a 5-day isotretinoin administration. Endogenous glucose production was inhibited at each step of hyperinsulinemia. Here again, isotretinoin administration did not alter the suppressive effect of insulin.

Relationship Between Changes in Fasting Plasma Triglyceride and Insulin Sensitivity

Figure 4 shows a plot of changes in insulin sensitivity (evaluated as GRd during infusion of 1.2 and 2.4 pmol insulin/min *v* changes in fasting plasma triglyceride concentrations). There was no correlation between these 2 variables.

DISCUSSION

A 5-day administration of isotretinoin at a dose of 1 mg/kg/d produced an average of 33% increase in fasting triglyceride concentration, and an average of 37% increase in basal VLDL-triglyceride concentration in these healthy male volunteers. Hypertriglyceridemia can develop as the result of either an increase in hepatic triglyceride synthesis and secretion, or a decreased clearance of triglycerides from the circulation. Several reports in the literature indicate that isotretinoin reduces the clearance of VLDL-triglyceride in animals.[26-28] Various mechanisms have been shown to be possibly involved in this process. In humans, it has been reported that isotretinoin increases the level of VLDL apoCIII[16] and hence inhibits lipoprotein lipase. In rats, isotretinoin has also been observed to decrease lipoprotein lipase activity at a post-transcriptional level.[28]

In contrast, the effects of isotretinoin on hepatic triglyceride synthesis have not been documented in humans. Stimulation by isotretinoin of triglyceride secretion would imply either an increased hepatic fatty acid re-esterification or a stimulation of hepatic de novo lipogenesis. Our results indicate that neither of these processes was acutely stimulated after isotretinoin. First, isotretinoin did not increase basal plasma FFA concentration or whole body glycerol turnover, nor basal subcutaneous adipose tissue glycerol concentration. In order to assess adipose tissue lipolysis more sensitively, we also measured epinephrine-stimulated lipolysis in subcutaneous adipose tissue. This was equally unaffected by isotretinoin. Furthermore, suppression of plasma FFA, interstitial adipose tissue glycerol (with or without

Table 3. Lipid Metabolism Before and After Isotretinoin Administration

	Before Isotretinoin (day 1)				After Isotretinoin (day 6)			
		Insulin Infusion (pmol/kg/min)				Insulin Infusion (pmol/kg/min)		
	Fasting	0.6	1.2	2.4	Fasting	0.6	1.2	2.4
Glycerol turnover (µmol/kg/min)	2.74 ± 0.91	1.56 ± 0.15	1.53 ± 0.20	1.18 ± 0.18	2.49 ± 0.19	1.64 ± 0.12	1.46 ± 0.13	1.25 ± 0.11
Net lipid oxidation (mg/kg/min)	0.9 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	1.0 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.5 ± 0.1

Table 4. Glucose Metabolism Before and After Isotretinoin Administration

	Before Isotretinoin (day 1)				After Isotretinoin (day 6)			
		Insulin infusion (pmol/kg/min)				Insulin Infusion (pmol/kg/min)		
	Fasting	0.6	1.2	2.4	Fasting	0.6	1.2	2.4
Total glucose disposal (µmol/kg/min)	11.8 ± 0.6	12.8 ± 0.6	14.1 ± 0.6	20.5 ± g 0.7	12.2 ± 0.5	12.4 ± 0.4	14.4 ± 0.7	21.4 ± 0.7
Endogenous glucose production (µmol/kg/min)	11.8 ± 0.6	7.3 ± 1.0	4.6 ± 0.8	1.4 ± 0.5	12.2 ± 0.5	8.4 ± 0.7	4.5 ± 0.7	1.7 ± 0.6
Net glucose oxidation (µmol/kg/min)	12.9 ± 0.8	12.9 ± 0.5	16.3 ± 0.8	16.7 ± 1.0	12.6 ± 1.0	13.4 ± 0.9	14.1 ± 0.9	17.0 ± 1.1

stimulation by epinephrine), and whole body glycerol turnover by graded doses of insulin were not modified by isotretinoin. This strongly argues against an enhanced adipose tissue lipolysis. In addition, whole body lipid oxidation and its suppression by a graded dose of insulin were not altered by isotretinoin. This observation speaks against the hypothesis that isotretinoin increased hepatic FFA re-esterification since it would imply an alteration of the ratio of lipolysis to fat oxidation. It remains possible that isotretinoin altered hepatic lipid oxidation specifically, but that this effect was not detected by whole body

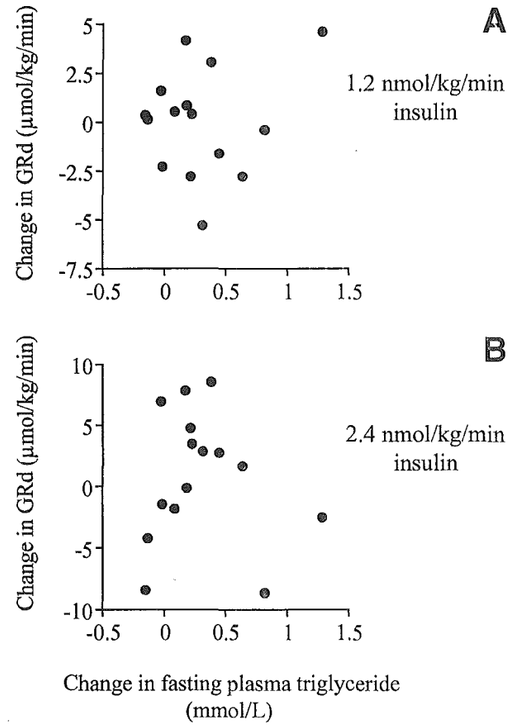

Fig 4. Changes in insulin sensitivity [GRd measured during infusion of 1.2 (A) and 2.4 (B) nmol/min insulin] plotted *v* changes in fasting plasma triglyceride concentrations induced by isotretinoin. There was no significant correlation between these 2 variables.

indirect calorimetry. Second, an increased hepatic de novo lipogenesis would result in an increased ratio of palmitic acid to linoleic acid, an essential fatty acid, in VLDL-triglyceride.[29] Isotretinoin, however, did not alter the ratio of palmitate to linoleate. In view of these considerations, our observations support the hypothesis that isotretinoin inhibited VLDL-triglyceride clearance. It remains possible that a stimulation of VLDL-triglyceride secretion occurred as a result of changes in intrahepatic triglyceride sorting, even in the absence of any changes in de novo lipogenesis and fatty acid re-esterification. Further studies, with a detailed evaluation of VLDL-triglyceride kinetics, will be required to unambiguously evaluate the mechanisms responsible for isotretinoin-induced hypertriglyceridemia.

Approximately 1 f 5 patients treated with isotretinoin develops a significant hypertriglyceridemia.[13-15] We therefore selected 2 subgroups of patients previously treated with isotretinoin; at this first occasion, patients of one group had had marked hypertriglyceridemia whereas the other had not shown changes in plasma triglyceride concentration (data shown in Table 1). We had expected that the same pattern of response to isotretinoin would be repeated in the present study and would allow us to clearly sort out the effects of isotretinoin per se of those related to hypertriglyceridemia. Contrary to our expectation, there was no correlation between the increase in plasma triglyceride after the first exposure and those observed in this study (data shown in Table 1). The reason for this remains unclear, but it is likely that some environmental factors changed over the 3- to 10-year period that separated the 2 exposures and accounted for this discrepant response. Further studies will be required to identify such factors. The increase in plasma triglyceride concentration was also much smaller in the present study than after the first exposure, possibly due to the shorter time of exposure to isotretinoin. It therefore remains possible that a larger increase in plasma triglyceride concentration may have been required to reduce insulin sensitivity.

The present study allowed us to sensitively assess the effect of isotretinoin on whole body and regional insulin sensitivity. It included hyperinsulinemic clamp studies at 3 levels of insulinemia. During the first step, low insulin concentrations were attained and provided insight into the effects of insulin in inhibiting adipose tissue lipolysis. The second and third steps involved higher insulin concentrations exerting graded effects to inhibit hepatic glucose production and stimulate skeletal muscle glucose utilization. Similarly, suppression of endogenous glucose production or of adipose tissue lipolysis (indi-

rectly assessed from subcutaneous adipose tissue glycerol) was identical with or without isotretinoin. Similarly, insulin-mediated whole body glucose utilization and oxidation were not affected by isotretinoin administration. Since one or several of these parameters are invariably altered in insulin-resistant states,[30] our observation strongly argues against isotretinoin-induced insulin resistance, at least after a 5-day treatment.

We considered the hypothesis that the magnitude of hypertriglyceridemia (a 0.3-mmol/L increment on average) induced by isotretinoin was too small to significantly affect insulin sensitivity. This hypothesis, however, appears unlikely since a large compilation of data obtained in healthy Europeans showed a significantly lower insulin sensitivity in individuals with similarly mild degrees of hypertriglyceridemia.[31] This observation has recently been confirmed by Moro et al who showed in a large cohort of subjects that there is an association between plasma triglyceride and insulin sensitivity even at plasma triglyceride levels in the normal range.[32] Furthermore, there was absolutely no changes in insulin-mediated glucose utilisation even in the few individuals who showed substantial increases in plasma triglyceride concentrations in response to isotretinoin.

We also considered the hypothesis that duration of hypertriglyceridemia in the present study was too short to alter insulin sensitivity. However, a recent study reported only a modest 7% decrease in insulin-mediated glucose disposal in patients treated for 5 months with this agent.[33] In a previous report, we observed features consistent with insulin resistance in patients who had developed isotretinoin-induced hypertriglyceridemia 5 years previously, as well as in their first-degree relatives.[34] This suggests that interaction between genetic factors and isotretinoin may lead to the development of insulin resistance. The genes involved in the pathogenesis of insulin resistance in this condition and their role in triglyceride metabolism remain to be determined.

Isotretinoin-induced hypertriglyceridemia, therefore, differs from familial combined hyperlipidemia or hypertriglyceridemia secondary to high-fructose diets, which are both associated with insulin resistance.[1,2,6] This novel observation allows more in-depth focus on the mechanisms linking hypertriglyceridemia and insulin resistance in these latter conditions. An increased secretion of triglyceride-rich particles may lead to both hypertriglyceridemia and insulin resistance, the latter by increasing the amount of fat delivered to insulin-sensitive tissue. Alternatively, insulin resistance in extrahepatic tissue may be the primary event, and secondarily may lead to hypertriglyceridemia by increasing adipose tissue lipolysis and hepatic fatty acid re-esterification.

In conclusion, the present study emphasizes recent observations[11,12] that elevated triglyceride concentrations may occur without insulin resistance. These observations are consistent with the hypothesis that an increased hepatic triglyceride secretion, together with an increased delivery of triglyceride to skeletal muscle or other organs and tissues involved in metabolic control, are required to induce insulin resistance.

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