# Fiber Type– and Fatty Acid Composition–Dependent Effects of High-Fat Diets on Rat Muscle Triacylglyceride and Fatty Acid Transporter Protein-1 Content

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**Intramuscular triacylglyceride (TAG) is considered an independent marker of insulin resistance in humans. Here, we examined the effect of high-fat diets, based on distinct fatty acid compositions (saturated, monounsaturated or n-6 polyunsaturated), on TAG levels and fatty acid transporter protein (FATP-1) expression in 2 rat muscles that differ in their fiber type, soleus, and gastrocnemius; the relationship to whole body glucose intolerance was also studied. Compared with carbohydrate-fed rats, the groups subjected to any one of the high-fat diets consistently exhibited enhanced body weight gain and adiposity, elevated plasma free fatty acids and TAG in the fed condition, hyperinsulinemia, and glucose intolerance. TAG content was consistently higher in soleus than in gastrocnemius, but was only significantly elevated by the n-6 polyunsaturated-based diet. FATP-1 levels in soleus were double those in gastrocnemius muscle in carbohydrate-fed animals. High-fat diets caused an elevation in FATP-1 protein content in soleus, but a reduction in gastrocnemius. In conclusion, the hyperinsulinemic hyperlipidemic condition upregulates FATP-1 expression in soleus and downregulates that of gastrocnemius. Hypercaloric saturated, monounsaturated, or n-6 polyunsaturated lipid diets cause equivalent whole body insulin resistance in rats, but only an n-6 polyunsaturated acid-based diet triggers intramuscular TAG accumulation.**


OBESITY, ALTHOUGH multifactorial, may be induced by chronic ingestion of high-fat diets and is a prevalent cause of insulin resistance and type 2 diabetes.[1,2] Indeed, accumulation of body fat can be encompassed by reduced whole body glucose consumption and insulin sensitivity.[2] Impairment of skeletal muscle glucose uptake and insulin responsiveness are considered key contributors to this lipid-induced metabolic derangement.[3,4] In humans, muscle insulin insensitivity has been correlated with intramuscular accumulation of triacylglycerides (TAG) with or without obesity.[3,5-10] The underlying rationale of muscle glucose intolerance induction is that TAGs are an intracellular source of consumable fatty acids that compete with glucose.[1,2] Furthermore, fatty acids may act as inhibitory regulators of glucose metabolism either through lipid-derived second messengers that interfere with insulin regulation or through activation of transcription factors, which prime lipid metabolism.[4,11,12]

Skeletal muscle TAG synthesis depends on the availability of circulating esterifiable long chain fatty acids, which are taken up by the muscle cells. Marked differences in lipid metabolism exist between muscles of different fiber type. In fact, red oxidative muscles, such as soleus, exhibit much higher TAG pools[13-15] than do muscles with a high percentage of white glycolytic fibers, such as gastrocnemius. Muscle uptake of fatty acids is considered to be facilitated by a number of specific transporter families, fatty acid transporter proteins (FATP), fatty acid translocase (FAT/CD36), and FABPpm.[16] These 3 genes are expressed to equivalent levels in skeletal muscle of fed rats, at higher amounts in red compared with white muscle.[17] However, their relative contribution to fatty acid uptake under different physiologic situations is not well understood:[17] the only explicit information comes from CD36 knockout mice,[18] which showed about a 50% reduction in the transport of derivatives of pentadecanoic acid into skeletal muscle. Among the large family of FATP,[19] the first isolated member, FATP-1,[20] is mostly expressed in adipose tissue, although it is also present in muscle.[21] While much is known about adipocyte FATP-1 function and expression, it being upregulated by fatty acids through a peroxisome proliferator-activated receptor gamma (PPARgamma) mediated-mechanism and downregulated by insulin,[22] there is little information on its regulation in muscle and its relationship to lipid accumulation. The present research therefore aims to elucidate this latter aspect.

In summary, the effect of dietary fat-induced obesity, based on different fatty acid compositions, on intramuscular TAG and its correlation with insulin resistance has not been studied in detail. Using a rat model, we address this issue and study the effects of hyperlipidemia, brought on by hypercaloric fat diets composed of saturated, monounsaturated, or n-6 polyunsaturated fatty acids and the ensuing hyperinsulinemia on TAG levels in soleus and gastrocnemius muscles. We also report fiber type– and fatty acid type–dependent modulation of intramuscular lipid accumulation and FATP-1 expression.

## MATERIALS AND METHODS

### *Animals, Diets, and Food Intake Control*

Male Wistar rats were from Interfauna (Harlan Ibérica, Barcelona, Spain) and had an average weight of 200 to 225 g. They were placed in standard cages, 2 rats per cage, fitted with special powder feeders and kept at a constant temperature of 23°C with a 12-hour light-dark

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*Submitted September 23, 2003; accepted March 25, 2004.*

*Supported by Grant No. 01/0838 and C03/08 RCMN from the Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo and SAF2003-04223 from the Ministerio de Ciencia y Tecnología, Spain. A.F-M. is the recipient of a fellowship from the Ministerio de Ciencia y Tecnología and A.M.G-F. of a Distinció de la Generalitat de Catalunya per a la Promoció de la Recerca Universitària, Spain.*

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*0026-0495/04/5308-0024$30.00/0*

*doi:10.1016/j.metabol.2004.03.011*

**Table 1. Composition of Diets**

| | Control Diet | High-Fat Diets | | |
|---|---|---|---|---|
| | HC | HSF | HOF | HLF |
| Ingredients (g/100 g of diet) | | | | |
| Protein | 17.5 | 25.4 | 25.4 | 25.4 |
| Sucrose | 2.9 | 8.5 | 8.5 | 8.5 |
| $\alpha$-Starch | 63.3 | 16.9 | 16.9 | 16.9 |
| Lard | 3.3 | 33.9 | - | - |
| High oleic sunflower oil | - | - | 33.9 | - |
| Sunflower oil | - | - | - | 33.9 |
| Fiber (cellulose) | 5.5 | 8.4 | 8.4 | 8.4 |
| Vitamin mixture | 1.0 | 1.5* | 1.5* | 1.5* |
| Mineral mix | 6.0 | 4.7† | 4.7† | 4.7† |
| DL-Methionine | 0.3 | 0.4 | 0.4 | 0.4 |
| Choline bitartrate | 0.2 | 0.3 | 0.3 | 0.3 |
| Energy (kcal/100 g) | 300 | 508 | 508 | 508 |

NOTE. The caloric content and ingredients of diets based on HC or HSF, HOF, and HLF are listed.

*AIN-93-VX vitamin mixture; †AIN-93-M mineral mixture.

cycle and free access to water and food. During the first week of accommodation, rats were fed with a standard high-carbohydrate diet (HC) (A04 Panlab, Barcelona, Spain) and thereafter, groups of 6 to 7 Wistar rats were fed for 4 weeks with various high-fat diets or with the carbohydrate diet (8 animals), as described in Table 1. The high-fat diets were prepared at the Nestlé Research Center (Lausanne, Switzerland) and differed in the fat component, this being: lard-based diet (HSF) (lard: 26% C16:0, 16% C18:0, 45% C18:1, 12% C18:2 and 1% C18:3); high oleic sunflower oil–based diet (HOF) (Trisun 80: 4% C16:0, 4% C18:0, 81% C18:1 and 9% C18:2) or sunflower oil–based diet (HLF) (sunflower oil: 6% C16:0, 5% C18:0, 18% C18:1 and 65% C18:2). Rats and food were weighed every 2 days to calculate food intake and control weight gain. Animal treatment protocols were approved by the CEEA of the University of Barcelona (Barcelona, Spain). Blood metabolites and insulin were measured in ad libitum-fed animals (at day 27 of treatment) or overnight fasted animals (at day 28).

### *Glucose Tolerance Test and Tissue Sampling*

Eighteen hour-fasted animals (day 28 of treatment) were anesthetized with pentobarbital (70 mg/kg of body weight) and a glucose bolus (2 g/kg of body weight) was administered by intraperitoneal (IP) injection. Animals were bled via the tail before glucose administration and, subsequently, 10, 20, 30, 60, 90, and 120 minutes after. At the end of the test (2 hours after glucose injection), gastrocnemius and soleus muscles were excised and immediately frozen in liquid $N_2$ and stored at −80°C. The abdominal cavity was then opened and the epididymal fat pads were removed and weighed before freezing in liquid $N_2$. This protocol was approved by the CEEA of the University of Barcelona (Barcelona, Spain).

### *Western Blot Analysis*

Muscle samples were powdered in a mortar under liquid $N_2$ and thereafter homogenized in 50 vol ice-cold 50 mmol/L Tris-HCl buffer (pH 7.4) with 1 mmol/L EDTA, 100 mmol/L KCl, 300 mmol/L sucrose, 10 mmol/L $\beta$-mercaptoethanol, 1 mmol/L leupeptin, and 1 mmol/L benzamidin before being centrifuged at 10,000 × *g* at 4°C for 15 minutes. The resulting supernatants (100 $\mu$g of protein) were used for standard Western blot analysis. Protein concentration was measured with Bio-Rad protein assay reagent (Bio-Rad, Hercules, CA). FATP-1 antibody was from Santa Cruz (I-20, Santa Cruz, CA). Detection of the primary antibody was accomplished using the Lumi-Light western blotting substrate (Roche, Basel, Switzerland).

### *Measurement of Metabolite and Insulin*

Plasma insulin levels were assayed by enzyme-linked immunosorbent assay (ELISA) (Crystal Chem, Chicago, IL). TAGs and free fatty acids were measured in plasma samples using kits from Sigma Chemicals (St Louis, MO) and Roche. Blood glucose was analyzed with a reflectometer GlucoTouch Lifescan (Johnson & Johnson).

For TAG measurements in muscle, 50 to 100 mg samples of frozen muscles were finely powdered and homogeneized in buffer (100 mmol/L KCl, 20 mmol/L KF, 0.5 mmol/L EDTA, 0.05% Lubrol, pH 7.9). Samples were centrifuged at 10,000 × *g* at 4°C for 15 minutes, and TAG content was assayed in the supernatant using a kit from Sigma Chemicals.

### *Statistical Analysis and Calculations*

All data are presented as means ± SEM. Statistical comparisons were made with Statgraphics plus 2.1. (Manugistics, Rockville, MD) by 1-way analysis of variance (ANOVA) to determine significance at a threshold of $P < .05$. QUICKI, quantitative insulin sensitivity check index, was calculated as QUICKI = 1/[log(Gb) + log (Ib)], where Gb is the fasting plasma glucose (mg/dL), and Ib is the fasting plasma insulin ($\mu$U/mL).

## RESULTS

### *Effect of High-Fat Diets on Body Weight and Visceral Fat Weight*

Rats were fed for 4 weeks with high-fat diets based on saturated fat (HSF), monounsaturated oleic acid (HOF), or n-6 polyunsaturated linoleic acid (HLF) (Table 1). Lipid ingestion enhanced body weight gain over the 4 weeks (120 ±19 g, 97 ± 12 g, and 140 ± 29 g of weight increase for HSF, HOF, and HLF diets, respectively) compared with rats fed a high-carbohydrate diet (HC) (68 ± 14 g of increase). HOF induced a lower increase compared with HLF and HSF (with significance of $P < .02$ and $P < .05$, respectively). Intake of high-fat diets was lower than that of the HC diet, but the energy ingestion per day was still higher: 63 ± 3 kcal in HC, 77 ± 4 kcal in HSF, 75 ± 1 kcal in HOF and 85 ± 5 kcal in HLF. The highest energy intake was observed with the HLF diet, the significance of the differences being: $P < .001$ versus HC, $P < .01$ versus HSF and $P < .001$ versus HOF. Fat feeding consistently enhanced the accumulation of white adipose tissue over carbohydrate feeding, as assessed by the weight of epididymal fat tissue at the end of treatment: 8.8 ± 3.2 g ($P < .002$) in HSF-, 7.9 ± 2.4 g ($P < .001$) in HOF-, and 7.8 ± 3.1 g ($P < .01$) in HLF-fed animals compared with 3.8 ± 1.1 g in those fed with carbohydrates.

### *Circulating Insulin and Metabolite Levels*

Feeding animals with a high-fat diet resulted in a marked increase (between 2-fold and 5-fold) of plasma insulin concentration in both the 18-hour–fasted and fed conditions (Table 2) compared with HC-fed animals. In the fed condition, HSF caused the greatest increase: 2-fold compared with HC. In fasted animals, the major increment in insulinemia (5-fold) over the HC group was observed in the HLF group.

In the fed condition, higher plasma TAG levels were observed in animals subjected to fat diets compared with the HC

**Table 2. Changes in Plasma Metabolites and Insulin After Dietary Treatment**

| | Diets | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | HC | | HSF | | HOF | | HLF | |
| | Fast | Fed | Fast | Fed | Fast | Fed | Fast | Fed |
| Insulin (pg/mL) | 562 ± 73 | 2,265 ± 192 | 1,447 ± 238† | 4,082 ± 279§ | 1,985 ± 249‡ | 3,172 ± 351* | 2,720 ± 570‡ | 3,682 ± 460† |
| Triglyceride (mg/dL) | 52 ± 6 | 104 ± 10 | 64 ± 10 | 153 ± 17* | 45 ± 4 | 146 ± 13* | 47 ± 5 | 145 ± 23* |
| Free fatty acid (mmo/L) | 0.80 ± 0.05 | 0.38 ± 0.02 | 0.90 ± 0.08 | 0.75 ± 0.03† | 0.99 ± 0.03 | 0.76 ± 0.10* | 0.92 ± 0.05 | 0.73 ± 0.05† |
| Glucose (mg/dL) | 78 ± 3 | 109 ± 9 | 94 ± 2† | 99 ± 2 | 89 ± 1* | 112 ± 12 | 82 ± 5 | 116 ± 24 |

NOTE. After 4 weeks of dietary treatment, circulating metabolites and insulin were measured in ad libitum fed animals or overnight fasted animals. Values are means ± SEM. HC (n = 8), HSF (n = 7), HOF (n = 7), and HLF (n = 6). The significance of the differences compared with fasted or fed animals subjected to an HC diet was: *$P < .05$, †$P < .01$, and ‡$P < .001$.

group, whereas in starved animals, no significant differences were detected. Likewise, major differences in circulating free fatty acid concentrations were determined in fed animals, reaching 2-fold higher levels in the 3 fat groups compared with the HC group, whereas in fasted animals, free fatty acid levels were equivalent, irrespective of diet composition.

HSF and HOF groups exhibited elevated fasting glucose compared with the HC group, while the elevation in the HLF group did not achieve statistical significance. Under the fed condition, plasma glucose was comparable in all groups. Similarly, no marked changes occurred in plasma lactate levels, either in fasted or fed animals, as a function of the type of diet (data not shown).

To estimate insulin sensitivity, the quantitative insulin sensitivity check index (QUICKI) was calculated. The QUICKI index is based on fasting plasma glucose and insulin and has proven to be sufficient to accurately assess insulin responsiveness in humans.[23] QUICKI values were as follows: HC 0.324 ± 0.016, HSF 0.279 ± 0.013, HOF 0.270 ± 0.010, and HLF 0.263 ± 0.018. Significance values for the differences compared with HC were $P < .0005$ for HSF or HOF and $P < .0001$ for HLF.

### *Impairment of Glucose Tolerance After Fat Feeding*

All fat diets caused glucose intolerance as assessed by an IP glucose tolerance test (Fig 1). Higher plasma glucose levels were detected at 60, 90, and 120 minutes in fat fed animals compared with the HC group.

### *Effect of High-Fat Diets on Soleus and Gastrocnemius TAG Content*

Soleus muscle TAG content was about 3-fold higher (Fig 2) than that of gastrocnemius, irrespective of the diet composition, in agreement with previous data.[11-13] Even though HSF and HOF diets increased soleus TAG content by 31% and 28%, respectively, compared with HC animals, significance was not achieved and a clear increment of 59% was noted only with HLF. Similarly, TAG content in gastrocnemius was only notably increased (66%) in the HLF group compared with the HC group.

### *FATP-1 Expression*

In carbohydrate-fed animals FATP-1 expression was 2.03 ± 0.22-fold ($P < .02$) higher in soleus than in gastrocnemius. Potential changes in FATP-1 content in skeletal muscle following diet-induced hyperinsulinemia and hyperlipidemia were studied (Fig 3). In soleus muscle of rats fed with either of the fat diets, the amount of FATP-1 protein was significantly higher than in rats fed HC, the upward trend being HLF >HOF >HSF. In contrast, in gastrocnemius muscle, FATP-1 expression was reduced in HSF and HOF lipid-fed animals compared with HC, whereas in HLF animals, the reduction was not significant.

## DISCUSSION

We report that 4-week administration of high-fat diets based on saturated, monounsaturated, or n-6 polyunsaturated fatty acids enhanced body weight gain and adiposity and caused fasting and fed hyperinsulinemia compared with a standard carbohydrate-based diet. Insulin sensitivity was decreased in animals subjected to either lipid diet compared with those fed carbohydrate, as assessed by the QUICKI index, which is based on fasting insulin and glucose levels. Fat diets also impaired glucose tolerance, according to the 2-hour glucose values after the glucose tolerance test, which were higher in lipid-fed than carbohydrate-fed animals. This is consistent with the view that the rapid delivery of dietary fatty acids leads to insulin insen-

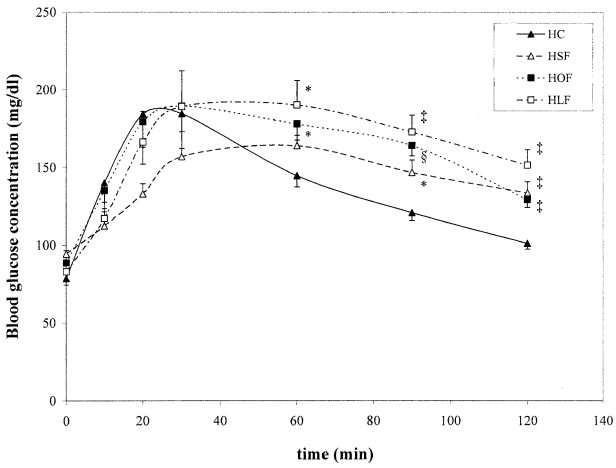


**Fig 1. Lipid diet-induced glucose intolerance. Four weeks after dietary treatment, animals were fasted overnight and injected IP with a glucose isotonic solution (2 g glucose/kg animal weight). Blood glucose was monitored over the next 2 hours. Values are means ± SEM. (▲) HC n = 8, (△) HSF n = 7, (■) HOF n = 7, and (□) HLF n = 6. The significance of the differences compared with the HC animals was: *$P < .05$, ‡$P < .01$, and §$P < .001$. Significance was determined by ANOVA post hoc test.**

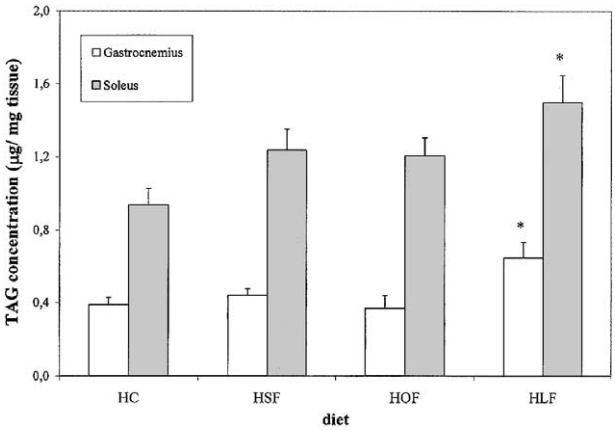


**Fig 2. Influence of high-fat diets on intramuscular accumulation of TAG. Four weeks after dietary treatment, animals were fasted overnight and subsequently subjected to an IP glucose tolerance test. At the end of the test, TAG content was analyzed in extracts from soleus (▩) and gastrocnemius muscles (□). Values are means ±SEM. HC (n = 8), HSF (n = 7), HOF (n = 7), and HLF (n = 6). The significance of the differences compared with the HC-fed group was *$P < .05$. Significance was determined by ANOVA post hoc test.**

sitivity.[24-26] Minor differences were detected among fat diets: saturated fat promoted the greatest elevation in fasting plasma glucose and fed insulin, whereas n-6 polyunsaturated fat led to the highest energy intake, body weight gain, and reduction in QUICKI index.

We provide evidence that the type of dietary fat influences the intramuscular accumulation of TAG. There were comparable marked increases of TAG in soleus and gastrocnemius muscles from animals fed a fat diet rich in n-6 polyunsaturated fatty acids compared with the carbohydrate-rich diet, whereas saturated or monounsaturated fatty acid–rich diets caused minor nonsignificant increases. These changes are similar to those in energy intake and body weight gain, but differ from those in circulating fatty acid or TAGs. However, it should be taken into account that n-6 polyunsaturated fatty acids are the most active ligands of transcription factor PPARgamma, which specifically promotes fatty acid deposition and adipogenesis[11,12] and thus could account for this enhanced response. Results are also consistent with our previous observation that unsaturated fatty acids are preferentially and readily used for TAG synthesis in cultured human muscle cells.[27] Likewise, in a study by Jucker et al,[28] TAG content in a mixture of red and white muscles was found to be elevated in rats fed safflower oil compared with carbohydrate-fed animals, whereas a diet based on fish oil (comprising $\omega$3 fatty acids) lowered TAG levels.

Because cell content of FA transporters has been proposed to limit TAG accumulation,[29] FATP-1 expression was analyzed in both muscle types. FATP-1 protein in soleus was double that found in gastrocnemius in carbohydrate-fed animals, consistent with TAG levels. Previous studies have shown moderately higher expression of fatty acid carrier proteins (FATP-1, FABPpm, and FAT/CD36) and fatty acid transport in red compared with white muscle.[17,21] Here, an elevation in FATP-1 content was observed in soleus from animals fed high-fat diets compared with the HC group, but mostly in those nurtured with n-6 polyunsaturated fatty acids, followed by monounsaturated and saturated fatty acids, respectively. Strikingly, we found that FATP-1 content was downregulated in gastrocnemius muscle from all the high-fat-fed groups compared with HC, the degree of decline being saturated and monounsaturated greater than n-6 polyunsaturated fatty acids. Previous notions about regulation of FATP-1 expression come from studies in adipocytes, where it is downregulated by insulin[30] and upregulated by polyunsaturated fatty acids through activation of PPARgamma.[31] An insulin response element, typical of genes negatively regulated by insulin,[30] and a peroxisome proliferator response element (PPRE) that can be activated by PPARgamma[22] have been consistently identified in the FATP-1 gene regulatory region. Based on these data, we propose that the differential response to high-fat diets of the FATP-1 gene in soleus and gastrocnemius relies on distinct PPARgamma sensitivity. In soleus, predominantly formed by red oxidative fibers, the activation of PPARgamma by fatty acids appears to overcome hyperinsulinemia, whereas in gastrocnemius, which contains a high percentage of white glycolytic fibers, weaker PPARgamma function seems to expose the insulin inhibitory action. In agreement with this hypothesis, linoleic acid, which is the most active PPARgamma ligand,[32] exerted the strongest activator effect on soleus, while it partially recovered FATP-1 expression in gastrocnemius. A potential explanation for a higher sensitivity of oxidative muscles to PPARgamma activation compared with glycolytic ones[4,17,33] is a distinct content of the PPARgamma coactivator, PGC-1, which is much higher in soleus than in gastrocnemius.[33] According to our hypothesis, treatment with the PPARgamma agonist, BRL-49653, promoted a robust induction of FATP-1 gene expression in rat adipose tissue and, to a lesser extent, in muscle in vivo.[31] Moreover, insulin infusion reduced expression of FATP-1 in

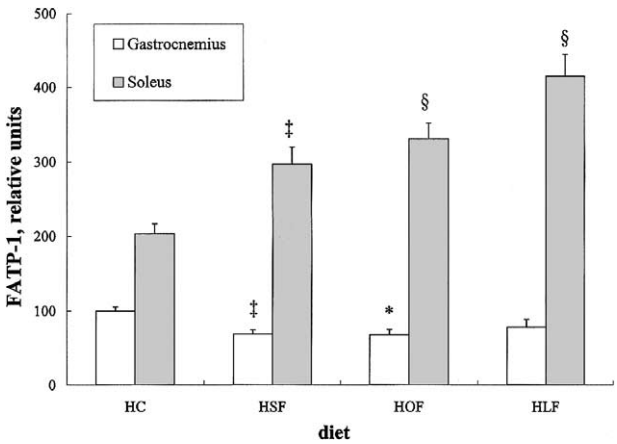


**Fig 3. FATP-1 expression in soleus and gastrocnemius muscles. Four weeks after dietary treatment, animals were fasted overnight and subsequently subjected to an IP glucose tolerance test. At the end of the test, FATP-1 protein content was analyzed by Western blot in extracts from soleus (▩) and gastrocnemius (□) muscles. Values are expressed as a percentage of those in gastrocnemius from the HC group. They are means ±SEM. HC (n = 8), HSF (n = 7), HOF (n = 7), and HLF (n = 6). The significance of the differences compared with the HC group was *$P < .05$, ‡$P < .01$, and §$P < .001$. Significance was determined by ANOVA post hoc test.**

human vastus lateralis muscle in lean women, but not in adipocytes.[34]

Thus, our data indicate that hyperlipidemia-hyperinsulinemia has the opposite effect on FATP-1 expression in soleus and gastrocnemius; and that FATP-1 content does not invariably correlate with TAG levels in skeletal muscle, which argues against its fundamental in vivo limiting role. We may only speculate that either transport of fatty acids is nonlimiting in these conditions or that enhanced expression of other fatty acid transporters, FAT or FABPpm, accounts for such import. On the other hand, we also demonstrate that intramuscular TAG is dissociated from saturated and monounsaturated dietary-induced obesity and insulin resistance.

## ACKNOWLEDGMENT

We thank Alexandra Arias for providing technical assistance. A. F-M was recipient of a fellowship from the Ministerio de Ciencia y Tecnología, Spain.

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