Effect of bezafibrate on postprandial lipidemia in non-insulin-dependent diabetic (NIDDM) patients. V Durlach [1], N Attia [2], D Roche [3], JL Paul [4], F Landron [5], A Girard-Globa [2] *([1] Clinique médicale U62 CHU de Reims, 51092 Reims; [2] Groupe Lipoprotéines, faculté de médecine Xavier-Bichat, 75018 Paris; [3] Laboratoire de biochimie, hôpital Laënnec, 75015 Paris; [4] Laboratoire de biochimie, hôpital Broussais, 78014 Paris; [5] Lipha Santé, Division Oberval, 69008 Lyon, France)*

Alterations of the postprandial (pp) triglyceride (TG) response might play an important role in the development of atherosclerosis-thrombosis in non-insulin-dependent diabetic (NIDDM) patients. The aim of our study was to evaluate the effects on ten male NIDDM patients of a 5 week bezafibrate (BZ) treatment (400 mg/day) on lipid tolerance, 8 h following a standardized test meal (1 100 kcal, 80% lipids, 100 000 IU vitamin A). The patients were obese (BMI 30.3 ± 2.7 kg/m^2), under fair glycemic control (Hb A1c 7.6 ± 1.6%), had moderately elevated fasting TG 2.6 ± 1.1 mmol/L and normal LDL cholesterol (2.6 ± 1 mmol/L).

As expected, BZ reduced fasting TG ($P < 0.01$) but had no effect on total cholesterol (TC) levels. Fasting glycemia was improved from 11.9 ± 3.3 to 9.7 ± 3.4 mmol/L ($P < 0.04$). PP responses were calculated as the incremental area under the curve (AUC). Chylomicron TG were reduced by 40% ($P < 0.01$) in agreement with a retinyl palmitate lowering in this fraction. Free fatty acids (FFA) were reduced by over 50% ($P < 0.05$). Very low density lipoprotein (VLDL)-TG were not reduced; however, pp VLDL particles were larger after treatment, enriched with TG but not with cholesteryl esters (CE). These results might provide further support that BZ acts by activating lipolysis but also suggest that it might improve the uptake of FFA. The TG-rich VLDL produced pp can be lipolyzed rapidly without giving rise to LDL. The decrease in FFA is an interesting metabolic feature and may play a role in the improvement of fasting glycemia.

The hypolipidemic effect of fenofibrate cannot originate from the enhanced carnitine concentration in the rat liver. P Clouet, C Legendre, M Tsoko, F Beauseigneur, J Gresti, J Boichot, J Demarquoy, J Bézard *(Nutrition cellulaire et métabolique, EA DRED 564, université de Bourgogne, BP 138, 21001 Dijon cedex, France)*

Carnitine is essential to long-chain fatty acid degradation in mitochondria, because only carnitine derivatives can be transported across the inner membrane. The enhanced carnitine concentration (x 3.5) in the liver of fenofibrate-treated rats [Henninger et al (1987) *Biochem Pharmacol* 36, 3231] has been assumed to be a factor allowing long-chain fatty acids to be directed preferentially to β-oxidation. One way to verify this

	Control	*Fenofibrate*	*Feno/BBH inhibitor*
Lipid parameters in fed state (in g/L of serum)			
Triacylglycerols	2.06 ± 0.25^a	1.69 ± 0.17^b	1.41 ± 0.15^c
Total cholesterol	0.82 ± 0.06^a	0.49 ± 0.04^b	0.37 ± 0.02^c
Total ketone bodies in fasted state (mg/100 of blood)	18.72 ± 2.35^a	14.01 ± 1.93^b	11.89 ± 1.86^c

Results are means ± SEM ($n = 5$). The values in a row with different superscript letters (a,b,c) are significantly different at $P < 0.05$ (Anova and Fisher's test comparisons).

point was to use a γ-butyrobetaine hydroxylase (BBH) inhibitor in order to reduce, in fenofibrate-treated rats, carnitine concentration to the level of that in controls. By using this product, carnitine concentration was found to be 2.5 times decreased both in normal [Tsoko et al (1995) *Biochem Pharmacol* 49, 1403] and fenofibrate-treated rats, as shown in the present study.

Male Wistar rats (300 g) were treated for 10 days with fenofibrate (100 mg/kg/day) in association or not with 3-(2,2,2-trimethylhydrazinium) propionate (300 mg/kg/day), the BBH inhibitor. The products were added to food. Blood was collected from the retroorbital sinus in fed state for lipid parameters and from the dorsal aorta after 16 h fasting for total ketone body determinations.

The results in the table clearly show that the hypolipidemic effect of fenofibrate was still manifest when liver carnitine concentration was strongly depressed by the BBH inhibitor. In addition, blood ketone bodies, whose concentration usually correlates with liver fatty acid oxidation, were lower when the rats had received both fenofibrate and BBH inhibitor. Consequently, the hypolipidemic effect achieved under these conditions did not seem to be related to enhanced mitochondrial fatty acid oxidation, which requires carnitine. On the whole, the data suggested that an increased carnitine-independent oxidative pathway was responsible for the hypolipidemic effect of fenofibrate. Peroxisomes could be involved, since peroxisomal β-oxidation does not require carnitine and because this activity was found previously to be five times higher after fenofibrate treatment [Henninger et al (1987) *Biochem Pharmacol* 36, 3231]

Effect of fish oil (*Maxepa* R) on sciatic nerve Na/K ATPase activity in diabetic rats. A Gerbi [1], D Raccah [1], T Coste [1], O Barbey [2], JM Maixent [2], P Vague [1] *([1] Laboratoire de diabétologie; [2] Laboratoire de recherche cardiologique, faculté de médecine, Marseille, France)*

Neuropathy is a degenerative complication of diabetes. It is characterized by a decrease in nerve conduction velocity related to an alteration in Na/K ATPase, a membrane-included enzyme with several isoforms.

The decrease of its enzymatic activity could be due to the hyperglycemia-induced disturbance in the membrane lipid pattern. The aim of this study was to restore Na/K ATPase activity and isoforms by modifying the membrane phospholipid composition through nutritional intervention.

We studied the effect of fish oil supplementation (*Maxepa* R), rich in omega three polyunsaturated fatty acids, 0.5 g/kg/day, by forcible feeding, for 8 weeks, in streptozotocin-induced diabetic rats (60 mg/kg). Na/K ATPase activity and ouabain affinity of the different isoforms were determined in sciatic nerve axonal membranes of three groups of rats ($n = 18$): a nondiabetic control group (CO), a diabetic control group (DO) supplemented with olive oil (without omega 3) and a diabetic group supplemented with fish oil (DM).

The results showed that Na/K ATPase activity was partly but significantly restored in sciatic nerve of diabetic rats supplemented with fish oil (DM): 3.56 ± 0.16 µmol Pi.mg $prot^{-1}.h^{-1}$, compared to nondiabetic controls (CO): 4.8 ± 0.7 ($P < 0.05$ vs DM) and diabetic controls (DO): 2.18 ± 0.1 ($P < 0.05$ vs DM). The ouabain affinity study showed that the three isoforms of Na/K ATPase (alpha 1, alpha 2 and alpha 3) were represented in the axonal membranes. Diabetes induced a decrease in alpha 3 activity, which was restored with fish oil.

In conclusion, our results suggested a favorable effect of fish oil supplementation on sciatic nerve Na/K ATPase activity in diabetes, related to a modification of the membrane lipid pattern and this could lead to a nutritional treatment for diabetic neuropathy.