Intake of a Diet High in *Trans* Monounsaturated Fatty Acids or Saturated Fatty Acids

Effects on postprandial insulinemia and glycemia in obese patients with NIDDM

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OBJECTIVE — High intake of *trans* fatty acids and saturated fatty acids (SFAs) is known to increase the risk of coronary heart disease. We studied the effects of diets enriched in various fatty acids on postprandial insulinemia and fasting serum levels of lipids and lipoproteins in obese patients with NIDDM.

RESEARCH DESIGN AND METHODS — Sixteen obese NIDDM patients were studied in a free-living outpatient regimen. After a run-in period, the patients received three different isocaloric diets for 6 weeks using a randomized crossover design. The patients were instructed to keep the energy intake from carbohydrate and protein constant at 50 and 20 E% (percent of energy intake), respectively, on all three diets. The fat composition of the diets differed: saturated fat (SAT) diet (20 E% SFAs, 5 E% polyunsaturated fatty acids [PUFAs], and 5 E% monounsaturated fatty acids [MUFAs]) versus *cis* monounsaturated fatty acid (CMUFA) diet (20 E% *cis*-MUFAs, 5 E% PUFAs, and 5 E% SFAs) versus *trans* monounsaturated fatty acid (TMUFA) diet (20 E% *trans*-MUFAs, 5 E% PUFAs, and 5 E% SFAs). Fasting serum levels of lipids and lipoproteins were measured at baseline and in the fasting state before meal tolerance tests at the end of each study period. Insulin secretion was assessed from incremental serum insulin and C-peptide responses during the meal tests.

RESULTS — BMI, waist-to-hip ratio, and glycemic control remained stable throughout the study. After meal stimulation, postprandial glycemic responses were similar on all diets; however, serum insulin and C-peptide responses were greater following the TMUFA and SAT diets than following the baseline or CMUFA diets ($P < 0.05$). No statistical difference was found in fasting levels of serum lipids (total cholesterol, triglyceride, phospholipid, and nonesterified fatty acids) or lipoproteins of HDL cholesterol, VLDL cholesterol, LDL cholesterol, and apolipoprotein B between diets.

CONCLUSIONS — In the presence of unchanged glycemia, both dietary *trans* fatty acids and SFAs induce an increase in postprandial insulinemia in obese patients with NIDDM.

In the majority of naturally occurring unsaturated fatty acids, the double bonds are in the *cis* configuration. However, many foods also contain *trans* unsaturated fatty acids in which the carbon moieties on the two sides of the double bond point in opposite directions, which leads to a straightening of the molecule structure. Natural sources of *trans* fatty acids are mainly milk, butter, and beef fat, which contain about 5% *trans* fatty acids. Much larger amounts of *trans* fatty acids can be found in manufactured products such as margarine, shortenings comprised of fat, and fats used for frying, which are produced by partial hydrogenation of vegetable or marine oils. Recently there has been concern that a relatively high intake of *trans* fatty acid isomers might adversely affect health (1–11). During an 8-year follow-up study of 85,095 American nurses, it was demonstrated that foods that are major dietary sources of *trans* fatty acids were each significantly associated with higher risks of coronary heart disease (4). Furthermore, some, but not all, short-term studies in healthy subjects have shown induction of an atherogenic fasting serum lipid profile, with significant rises in fasting serum LDL cholesterol and reductions in serum HDL cholesterol levels, with *trans* isomers (5–11).

NIDDM patients have a three- to fivefold higher risk of atherosclerotic manifestations than matched background populations (12–14). A series of known risk factors may be operative, including fasting hyperinsulinemia (-proinsulinemia), insulin resistance, hyperglycemia, dyslipidemia with increased serum levels of triglycerides, and reduced serum levels of HDL-cholesterol and hypertension.

Diet therapy, with an emphasis on weight control, is considered the major intervention to control the metabolic imbalance and attempt to reduce the risk of accelerated atherosclerosis. The dietary treatment of NIDDM patients remains a controversial issue. Most national diet recommendations for NIDDM patients prescribe a relatively high-starch and low-fat diet, although the recommendations have been modified recently with respect to the fat content of the diet (15–17). Several recent studies have reported, however, that adherence to high-carbohydrate diets may cause aggravation of dyslipidemia (18–21). Results from other studies have suggested that diets with a higher total amount of fat and a relatively high content of monounsaturated fatty acids have no adverse effects on serum lipids in

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CMUFA, *cis* monounsaturated fatty acid; E%, percent of energy intake; MUFA, monounsaturated fatty acid; NEFA, nonesterified fatty acid; PUFA, polyunsaturated fatty acid; SAT diet, saturated fat diet; SFA, saturated fatty acid; TMUFA, *trans* monounsaturated fatty acid.

Table 1—*Clinical characteristics of the seven female and nine male NIDDM subjects*

	Baseline diet	SAT diet	CMUFA diet	TMUFA diet
Body weight (kg)	98 ± 3	96 ± 3	96 ± 3	96 ± 3
BMI (kg/m^2)	33.5 ± 1.2	32.5 ± 1.2	32.8 ± 1.1	32.7 ± 1.1
Waist-to-hip ratio	1.04 ± 0.01	1.04 ± 0.01	1.03 ± 0.01	1.04 ± 0.01
HbA_{1c} (%)	7.7 ± 0.4	7.8 ± 0.5	7.7 ± 0.5	7.9 ± 0.5
Serum creatinine (μmol/l)	79 ± 4	79 ± 4	82 ± 5	85 ± 5

Data are means ± SE. All comparisons were nonsignificant.

Table 2—*Results of dietary recording in 16 NIDDM subjects calculated from dietary recordings for 1 week during the baseline period*

Daily calorie intake (MJ/day)	8.4 ± 0.8
Fat (E%)	33 ± 2
SFAs	15 ± 3
PUFAs	8 ± 1
MUFAs	10 ± 2
Carbohydrates (E%)	44 ± 4
Complex	31 ± 3
Simple	13 ± 2
Protein (E%)	18 ± 2
P/S ratio	0.5 ± 0.1
Cholesterol (mg/day)	355 ± 15
Total dietary fiber (g/day)	29 ± 3
Alcohol (E%)	5 ± 1

Data are means ± SE. E%, percent energy intake per day. P/S, polyunsaturated/saturated.

NIDDM patients (19,22–24). To address the question of whether changes in the composition and configuration of dietary fatty acids affect postprandial insulinemia and glycemia as well as fasting lipidemia, and thereby the risk of atherosclerosis in NIDDM patients, we studied the effects of three isocaloric diet regimens, each given for 6 weeks, in a randomized crossover design. The diets were similar in protein and carbohydrate content but different in fat content, containing high *trans* monounsaturated fatty acids (TMUFAs), high *cis* monounsaturated fatty acids (CMUFAs), or high saturated fatty acids (SFAs; SAT diet). All fat-modified diets were compared with a baseline diet.

RESEARCH DESIGN AND METHODS

Subjects

Sixteen obese non–insulin-treated NIDDM patients (seven postmenopausal women and nine men; age 55 ± 3 years [mean ± SE]) were studied at the outpatient clinic of Steno Diabetes Center. The protocol was approved by the local ethical committee, and each patient gave informed consent. The patients were selected and matched according to the following criteria: fasting serum triglyceride <5.0 mmol/l, HbA_{1c} <9.0% (normal range 4.1–6.4%); BMI 25–35 kg/m^2; waist-to-hip ratio: male >1.0, female >0.8; fasting serum C-peptide >0.35 nmol/l; plasma creatinine: male <130 μmol/l, female <110 μmol/l; albuminuria <30 mg/24 h; and stable values of HbA_{1c} (±0.5%) and body weight (±1.5 kg) for the 4 months before entry into the protocol. Patient characteristics at the time of entry into the study are given in Table 1. All patients had known diabetes mellitus for less than 4 years; none had a history of ketosis or insulin or oral antidiabetic drug therapy. No patient had thyroid, kidney, liver, or cardiovascular disease, except for hypertension in six patients, who were normotensive with antihypertensive treatment (the pharmacological antihypertensive treatment was kept unchanged throughout the study period). All patients had normoalbuminuria (22 ± 3 mg/24 h). No patient was taking any hypolipidemic and antidiabetic drugs or hormones known to affect lipid or glucose metabolism. Prior to the study, all patients performed a 1-week dietary recording, which was followed up with a dietary interview by the dietary clinician (baseline diet; Table 2).

Diets

The patients were instructed in the outpatient clinic to consume a diet based on the recommendations of the Diabetes and Nutritional Study Group of the European Association for the Study of Diabetes (15). In fact, their diet contained 44% of total energy (E%) as carbohydrates, 33 E% fat, 18 E% protein, and 3 E% alcohol, as calculated from the dietary tables contained in the Dankost computer program (Table 2; 25). Based on the dietary recordings, the energy intake required to maintain body weight for each patient in the study period was calculated. In all three diets, the relative content of carbohydrates, fat, and protein was kept constant at 50, 30, and 20 E%, respectively. The carbohydrates consisted of 80 E% complex and 20 E% simple carbohydrates. The SAT diet provided 20 E% of total energy intake as saturated, 5 E% as polyunsaturated, and 5 E% as monounsaturated fatty acids, through ingestion of lean meat, butter, whole milk, cheese, and coconut products. The CMUFA diet provided 20 E% of total energy intake as *cis* monounsaturated, 5 E% as saturated, and 5 E% from polyunsaturated fatty acids through ingestion of lean meat, skimmed milk, olive oil, olives, hazel nuts, avocado, walnuts, pistachio nuts, cashews, almonds, low-fat cheese, and a series of very-low-fat meat (e.g., fillings, cold cuts, sausages) from Danish Crown. The TMUFA diet provided 20 E% of total energy intake as *trans* monounsaturated, 5 E% as saturated, and 5 E% as polyunsaturated fatty acids through ingestion of skimmed milk, lean meat, margarine, cheese, and very-low-fat meat from Danish Crown. Intake of bread, pasta, potatoes, rice, fruits, and vegetables was similar in all diets. Correspondingly, cholesterol intake was calculated to 177, 167, and 117 mg/day, and total dietary fiber intake to 46, 55, and 53 g/day, for the SAT, CMUFA, and TMUFA diets, respectively. The patients were instructed and supervised weekly by three trained dietitians. To facilitate compliance, participants and their families were given the olive oils, margarines, nuts, almonds, avocados, and very-low-fat meat products corresponding to each phase of the ongoing diet period for free.

Experimental design

All patients were recruited from the Steno Diabetes Center outpatient clinic. Patients were instructed to maintain their actual physical activity at a constant level. The patients received three different diets, each for 6 weeks, using a randomized crossover design with no washout period. Based on the results from previous studies, alterations in glycemia, insulinemia, and lipidemia were assumed to occur within the first 3 weeks after crossover (5,18,26). The diets were isocaloric to avoid false influence of changes in body weight on serum levels of lipids, lipoproteins, and glycemic control.

Procedures

Before initiation of the study, a 4-h standard

Table 3—*Composition of test meals corresponding to the preceding diet period*

	Baseline diet	SAT diet	CMUFA diet	TMUFA diet
Fat (E%)	30	30	30	30
SFAs	15	20	5	5
PUFAs	5	5	5	5
TUFAs	7	2.5	0	20
CMUFAs	7	2.5	20	0
Carbohydrates (E%)	50	50	50	50
Complex	32	32	32	32
Simple	18	18	18	18
Protein (E%)	20	20	20	20

E%, percent energy intake per day.

meal test (baseline) was performed containing 50 E% as carbohydrates, 30 E% as fat, and 20 E% as protein (Table 3). The baseline test meal was composed of bread, butter, skimmed milk, apple juice, and cheese. After each diet period, a new isocaloric mixed-meal test was performed, where the test meal had the prescribed composition and consisted of the ingredients of the diet eaten in the corresponding period as described above for the SAT, CMUFA, and TMUFA diets, respectively (Table 3). At baseline and after each study period, venous blood samples were drawn after a 12-h overnight fast for analysis of serum total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglyceride, phospholipids, apolipoprotein B, and plasma nonesterified fatty acids (NEFAs). During mixed-meal tests, blood samples were drawn from an antecubital vein at 0, 15, 30 ,45, 60, 75, 90, 120, 140, 180, 210, and 240 min for estimation of plasma glucose, serum insulin, and C-peptide values.

Biochemical analyses

Plasma glucose levels were assayed by a glucose oxidase method. Blood samples for insulin and C-peptide assays were immediately centrifuged at 4°C and stored at −20°C until analysis. Serum insulin was assayed by polyclonal enzyme-linked immunosorbent assay (intra- and interassay CV 0.06 and 0.07, respectively; detection limit: 5.0 pmol/l) (27). In this assay, there is no cross-reactivity with proinsulin or proinsulin conversion intermediates. Serum C-peptide was immunoassayed after removal of proinsulin by polyethylene glycol precipitation using antiserum M1230 (intra- and interassay CV 0.05 and 0.07, respectively; detection limit: 0.06 nmol/l) (28,29). HbA_{1c} was analyzed as previously described (normal range 4.1–6.4%) (30). VLDL cholesterol was isolated by ultracentrifugation prior to analysis. Serum levels of HDL cholesterol were measured after heparin-manganese precipitation of apolipoprotein B, and total cholesterol, VLDL cholesterol, triglyceride, and phospholipid were determined enzymatically using commercial kits from Boehringer Mannheim. LDL cholesterol was calculated as serum total cholesterol minus VLDL and HDL cholesterol. Serum apolipoprotein B was determined immunochemically by immunodiffusion using a commercial radioimmunoassay kit from Pharmacia. NEFAs in plasma were determined by the method of Itaya and Michio (31).

Statistical methods

To compare the baseline periods and the three study periods, and to assess the effect of the order in which the patients received the diets, repeated-measures analysis of variance was performed. The Mann-Whitney rank sum test was used in the analysis of unpaired data, and the Wilcoxon rank sum test was used in the analysis of paired data. All results in the text and tables are presented as means ± SE. The level of significance was set to $P < 0.05$.

RESULTS — HbA_{1c}, waist-to-hip ratio, BMI, body weight, fasting plasma glucose, and serum creatinine remained stable throughout the study period (Tables 1 and 4). Blood pressure measured before meal testing remained unchanged throughout the study period.

Insulin secretion (Figure 1)

No effect of diet order was observed on fasting or postprandial responses of plasma glucose, serum insulin, or C-peptide. Fasting hyperinsulinemia was present in all patients. After mixed-meal stimulation, the postprandial glycemic responses were similar between diets, irrespective of the previous diet regimen. However, to obtain the same postprandial glycemic response, postprandial incremental serum insulin response was 77% higher after the SAT diet than after the CMUFA diet ($P < 0.05$) and 40% higher than after the baseline diet ($P < 0.05$) (Table 4). Further, the postprandial serum insulin response was 59% higher after the TMUFA diet than after the CMUFA diet ($P < 0.05$) and 26% higher than after the baseline diet ($P < 0.05$). Although postprandial incremental serum insulin response was 22% lower after CMUFA diet than at baseline, this difference did not attain statistical significance. The same pattern was evident when evaluating β-cell function from the serum C-peptide measurements; following the SAT

Table 4—*Fasting levels and postprandial responses of serum insulin, C-peptide (incremental area under curve), and plasma glucose (total area under curve) to the four mixed-meal tests*

	Baseline diet	SAT diet	CMUFA diet	TMUFA diet
Fasting serum insulin (pmol/l)	99 ± 13	113 ± 23	99 ± 18	102 ± 13
Serum insulin (nmol/l per 240 min)	13.8 ± 3.2*†	19.5 ± 3.9*‡	10.9 ± 1.6‡§	17.4 ± 3.5†§
Fasting serum C-peptide (pmol/l)	792 ± 91	862 ± 82	784 ± 122	780 ± 77
Serum C-peptide (nmol/l per 240 min)	59 ± 10*†	78 ± 11*‡	55 ± 10‡§	70 ± 13†§
Fasting plasma glucose (mmol/l)	9.0 ± 0.8	8.9 ± 0.9	8.1 ± 1.1	8.7 ± 1.1
Plasma glucose (mmol/l per 240 min)	2,688 ± 228	2,653 ± 273	2,635 ± 328	2,713 ± 322

Data are means ± SE. *†‡§, $P < 0.05$ between marked results; other results nonsignificant.

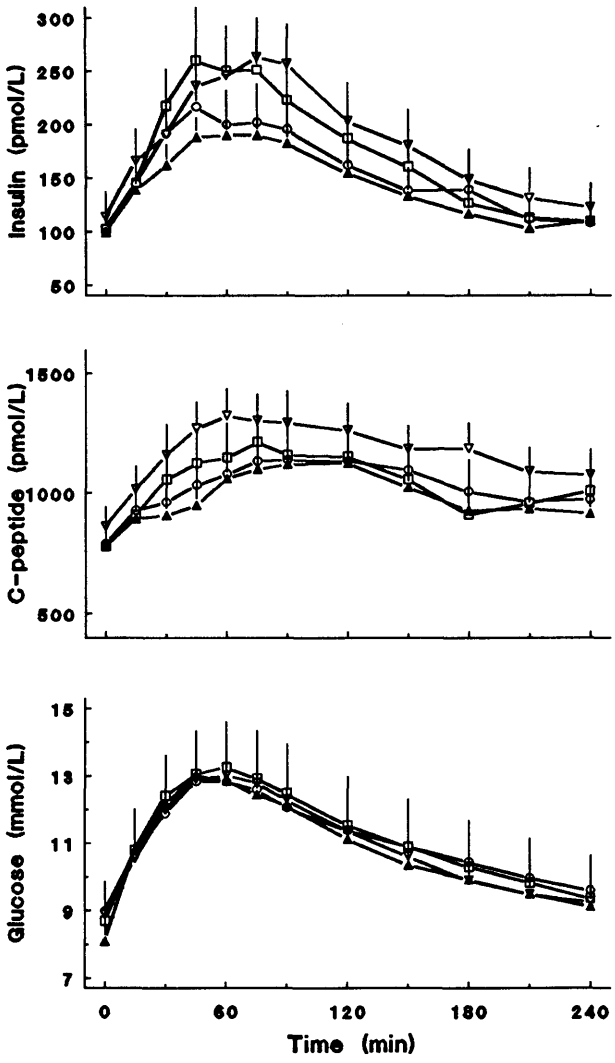

Figure 1—*Responses of serum insulin and C-peptide and plasma glucose to the four mixed-meal tests with compositional changes in fat contents in 16 NIDDM patients after a baseline diet period and three intervention diet periods. Baseline diet (○), SAT diet (▽), CMUFA diet (▲), and TMUFA diet (□). Data are means ± SE.*

diet, the postprandial serum C-peptide response was 42% and 32% higher than after the CMUFA and baseline diets, respectively ($P < 0.05$). Likewise, following the TMUFA diet, the postprandial serum C-peptide response was 27% and 19% higher than after the CMUFA or baseline diets, respectively ($P < 0.05$) (Table 4). No significant difference was found between the CMUFA diet and baseline diet.

Serum lipids and lipoproteins

The order in which the patients received the diets for a 6-week period did not affect the levels of fasting serum lipids and lipoproteins. The changes in these chemical quantities in the entire group of participants are given in Table 5. Serum levels of total cholesterol, VLDL cholesterol, and triglycerides as well as total cholesterol/HDL cholesterol ratios increased, but only slightly after all three diet periods ($P > 0.05$), whereas serum concentrations of LDL cholesterol and phospholipids and the LDL/HDL cholesterol ratios tended to decrease after the CMUFA diet ($P > 0.05$). Serum levels of HDL cholesterol, apolipoprotein B, and NEFAs remained unchanged throughout the study.

Because serum lipid and lipoprotein concentrations may differ between sexes, the results were also considered separately for women and men. Fasting serum concentrations of total cholesterol, HDL cholesterol, LDL cholesterol, LDL/HDL cholesterol, phospholipid, apolipoprotein B, and NEFAs were slightly higher, and serum levels of VLDL cholesterol, triglyceride, and cholesterol/HDL cholesterol ratio were slightly lower in women than in men at baseline ($P > 0.05$). Calculating the 95% CI, none of the fasting levels of serum lipids or lipoproteins showed any significant changes after each diet period between sexes (data not shown).

CONCLUSIONS — In the present study, the effect of diet on postprandial insulin secretion and fasting serum levels of lipids and lipoproteins were studied in normotriglyceridemic obese NIDDM patients following compositional changes in the content of fat, whether CMUFAs, TMUFAs, or SFAs. The ratio in energy intake between the macronutrients of carbohydrates, fat, and protein was kept constant. Indexes of body weight and composition and HbA_{1c} remained unchanged throughout the 18-week study, and postprandial glycemic responses were similar on each test meal. On the SAT or TMUFA diets, postprandial insulin secretion increased, whereas on the CMUFA diet, postprandial insulin secretion remained unchanged. From the present study design, it is, however, impossible to differentiate precisely between a long-term effect of the different diets on postprandial insulinemia and an acute effect of the diets following the test meal, or even a combination of effects. It is unlikely that the postprandial hyperinsulinemia was caused by a reduced hepatic clearance of insulin, since both the SAT and the TMUFA diets were accompanied by a hypersecretion of C-peptide. One important observation was that, although chronic fasting hyperglycemia was seen, postprandial glycemia remained unaltered, indicating that the β-cells were able to adapt to the TMUFA and SAT diets by an augmented insulin secretion.

It is possible that the postprandial hyperinsulinemia induced by the TMUFA and SAT diets in the presence of unchanged glycemia was caused by an increased insulin resistance in the peripheral tissues. This hypothesis is supported by recent findings that insulin resistance is positively correlated with both the ratio of ω-6 polyunsaturated fatty acids (PUFAs) to SFAs in serum phospholipids and decreased concentrations of PUFAs in phospholipids of skeletal muscle membranes (32,33). Furthermore, it has been demonstrated that a diet high in SFAs is an independent risk factor in healthy subjects for both fasting and post-

Table 5—*Fasting serum levels of lipids and lipoproteins at baseline and after three test diets with different composition of dietary fat in the seven female and nine male NIDDM participants*

	Baseline diet	SAT diet	CMUFA diet	TMUFA diet
Serum total cholesterol (mmol/l)	5.8 ± 0.3	6.3 ± 0.3	6.0 ± 0.2	6.0 ± 0.3
Serum HDL cholesterol (mmol/l)	1.22 ± 0.12	1.12 ± 0.09	1.12 ± 0.07	1.10 ± 0.08
Serum VLDL cholesterol (mmol/l)	0.97 ± 0.09	1.20 ± 0.15	1.03 ± 0.19	1.06 ± 0.13
Serum LDL cholesterol (mmol/l)	3.66 ± 0.27	3.68 ± 0.28	3.48 ± 0.26	3.58 ± 0.27
LDL/HDL cholesterol	3.34 ± 0.37	3.45 ± 0.28	3.36 ± 0.32	3.56 ± 0.36
Total cholesterol/HDL cholesterol	5.62 ± 0.47	5.91 ± 0.42	6.05 ± 0.60	6.08 ± 0.60
Serum triglycerides (mmol/l)	2.19 ± 0.27	2.55 ± 0.39	2.51 ± 0.44	2.65 ± 0.43
Serum phospholipid (mmol/l)	3.81 ± 0.11	3.71 ± 0.12	3.46 ± 0.12	3.62 ± 0.13
Plasma NEFAs (mmol/l)	0.74 ± 0.06	0.73 ± 0.06	0.70 ± 0.04	0.80 ± 0.11
Serum apolipoprotein B (g/l)	1.29 ± 0.05	1.28 ± 0.05	1.27 ± 0.04	1.28 ± 0.06

Data are means ± SE. All comparisons were nonsignificant.

prandial hyperinsulinemia compatible with an effect on insulin resistance (34). Thus a reduction in intake of dietary SFAs from 20 to 5 E% reduced fasting serum insulin concentrations by 26% and postprandial serum insulin concentrations by 32% (34). In the present study, a comparable increase in postprandial hyperinsulinemia was seen in NIDDM subjects following intake of diets enriched in saturated or *trans* fatty acids. Although the SFA content in the SAT diet was only 5% higher than in the baseline test meal, intake of the SAT diet was associated with a higher postprandial hyperinsulinemia. The monounsaturated fatty acid (MUFA) contribution was, however, higher in the baseline test meal, and may have contributed to the differences in the level of insulinemia. Furthermore, an effect of the diet ingested during the run-in period cannot be ruled out entirely. In contrast, the CMUFA diet had no deleterious effect on postprandial insulin secretion. Our results support recent data in mild cases of NIDDM, where a high-carbohydrate, low-fat diet did not improve glycemic control or peripheral insulin sensitivity (20,21), whereas, on a predominantly CMUFA diet, peripheral insulin sensitivity improved and postprandial plasma glucose and serum insulin levels decreased in some (22,23,35) but not all NIDDM patients (19).

A second objective of our study was to study whether partial replacement of SAT with CMUFAs or TMUFAs had any impact on fasting levels of lipids and lipoproteins. The length of our study should have been sufficient to test this hypothesis, when compared with the outcome of previous studies (5,18–24,26,35–37), and the subject compliance in our study, as evaluated from dietary interviews, was acceptable. We were, however, unable to demonstrate any significant effect of the diet changes on the fasting profile of lipids and lipoproteins, which in part could be due to lack of statistical power.

Increased levels of fasting serum LDL cholesterol are a major risk factor for coronary heart disease in the general population and in diabetes patients. The fasting serum LDL cholesterol levels in the present study were, however, within the borderline range for both sexes (38,39). The tendency of fasting serum LDL cholesterol concentration to decrease after the CMUFA diet has also been observed in normal subjects (5). Comparable with reports on major changes in macronutrient composition, fasting serum NEFAs and triglyceride concentrations were not affected by the changes in the fat composition alone (23,35). The fasting serum apolipoprotein B level and cholesterol/apolipoprotein B ratio were higher in our patients compared with previous findings, and were unaffected by the dietary regime (40).

A number of reports of the effect of *trans* fatty acids on fasting serum total cholesterol concentration in normal subjects have shown either no effect or an increase in fasting serum total cholesterol that is less than the effect of SFAs (5,8–11,41). Evidence is accumulating that *trans* fatty acids lower fasting serum HDL cholesterol and increase fasting serum LDL cholesterol almost similar to SFAs, and may be as unfavorable as these in terms of increased risk of atherosclerosis (5,41). Although the content of *trans* fatty acids in the present study was high, the lack of adverse effects in terms of higher fasting serum total cholesterol, lower HDL cholesterol, or increased LDL cholesterol was not obvious, but could be due to the limited number of subjects and therefore lack of statistical power. What could also be of importance in relation to the postprandial hyperinsulinemia is the postprandial serum lipids and lipoproteins, which previously has been shown to increase inappropriately in NIDDM (43,44). In this respect, Stinson et al. (45) recently demonstrated that postprandial hyperinsulinemia obtained following consumption of a carbohydrate-rich meal in obese NIDDM subjects promoted cholesterol synthesis.

To summarize, in obese NIDDM patients, partial replacement in the diet of SFAs with either CMUFAS or TMUFAs for 6 weeks was not associated with significant changes in fasting serum lipids and lipoprotein levels. The postprandial glucose tolerance was unaffected by dietary manipulations. However, diets enriched in either SFAs or TMUFAs were both accompanied by a postprandial hyperinsulinemia. Additional metabolic studies in NIDDM patients are needed to assess the effect of dietary compositional changes in the diet, especially dietary fat, on serum lipids and lipoproteins and insulin action (46).

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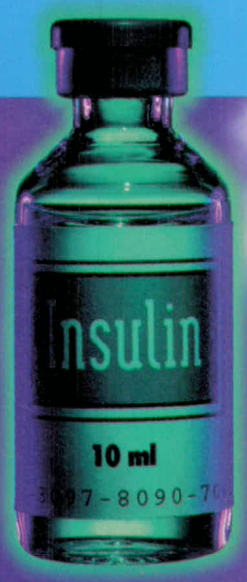

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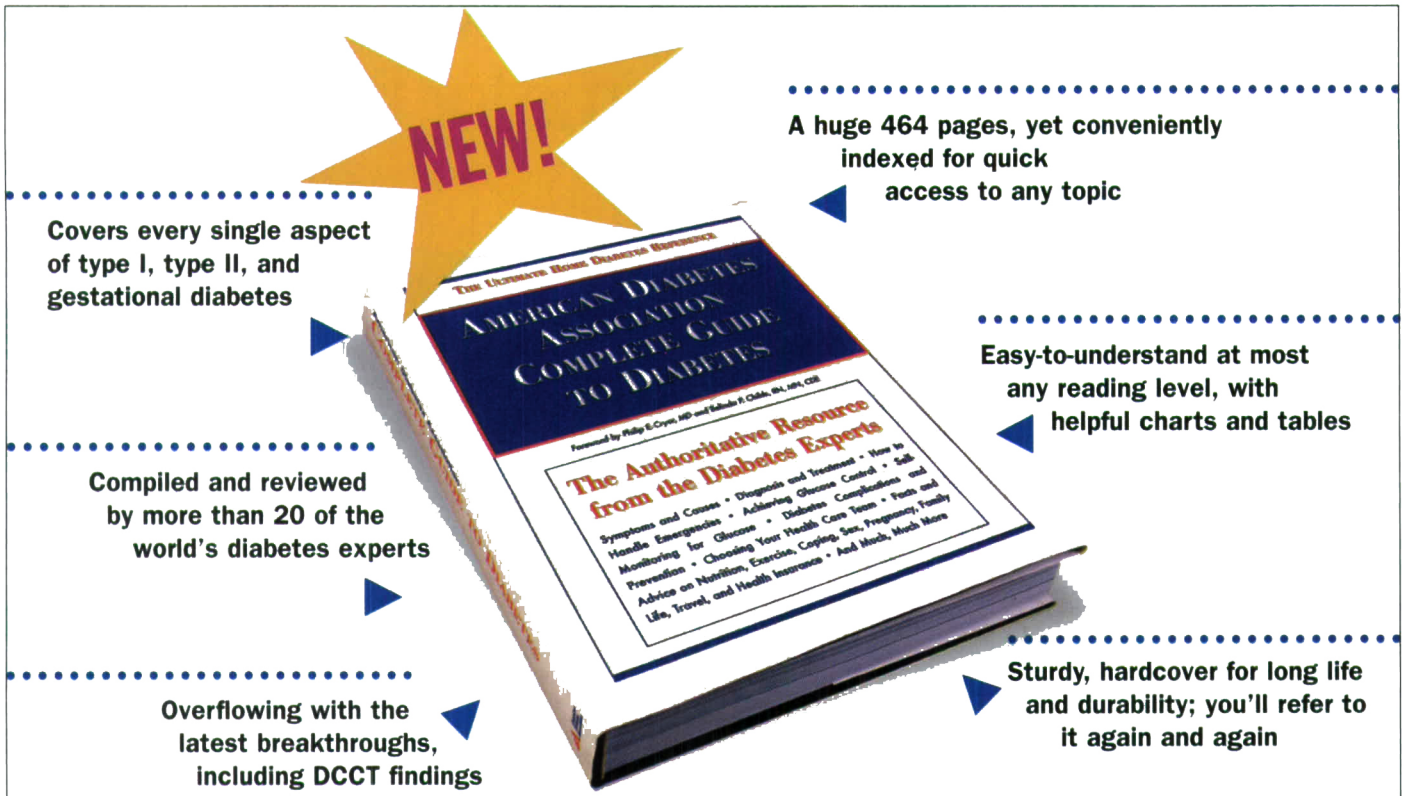

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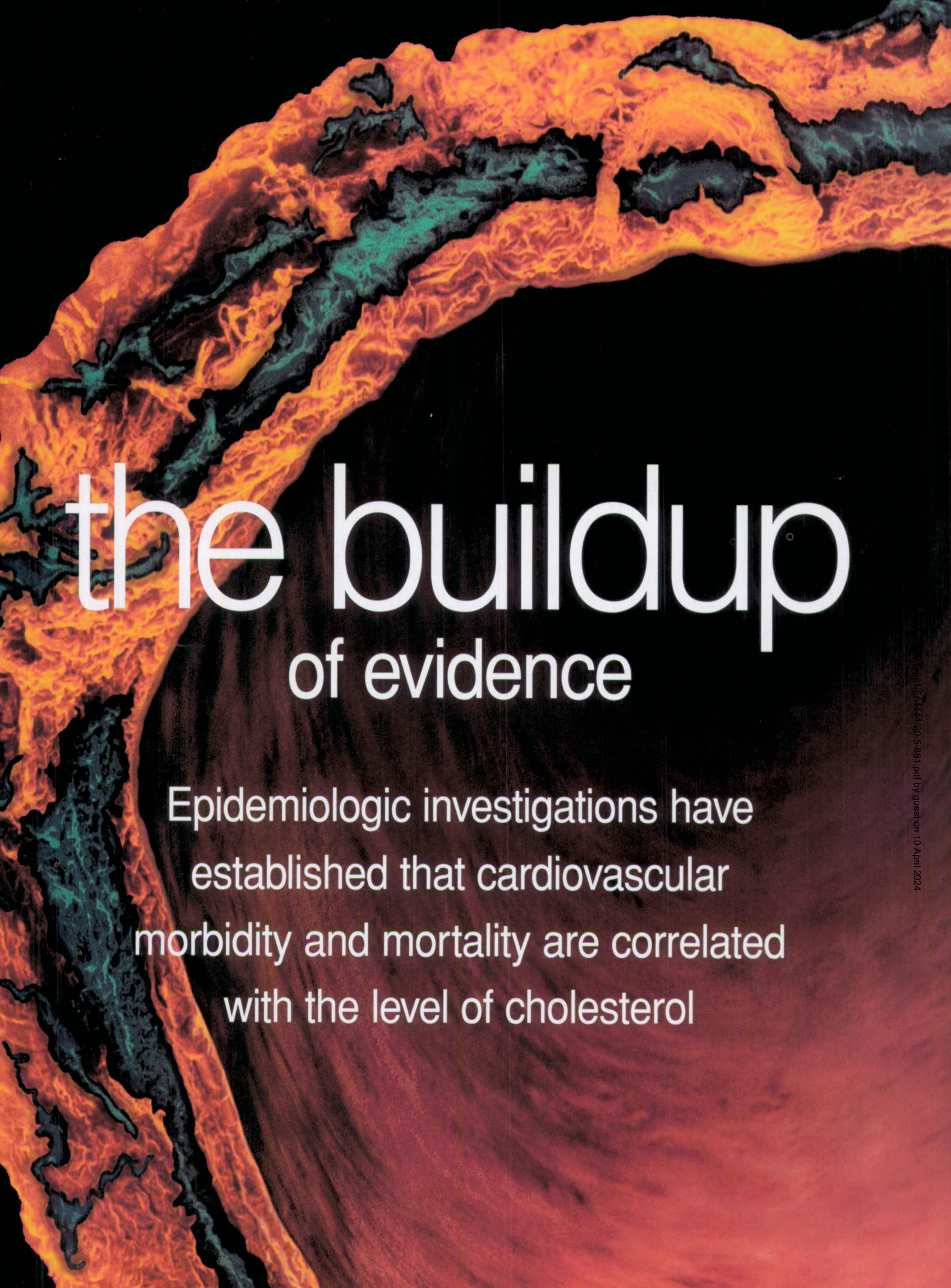

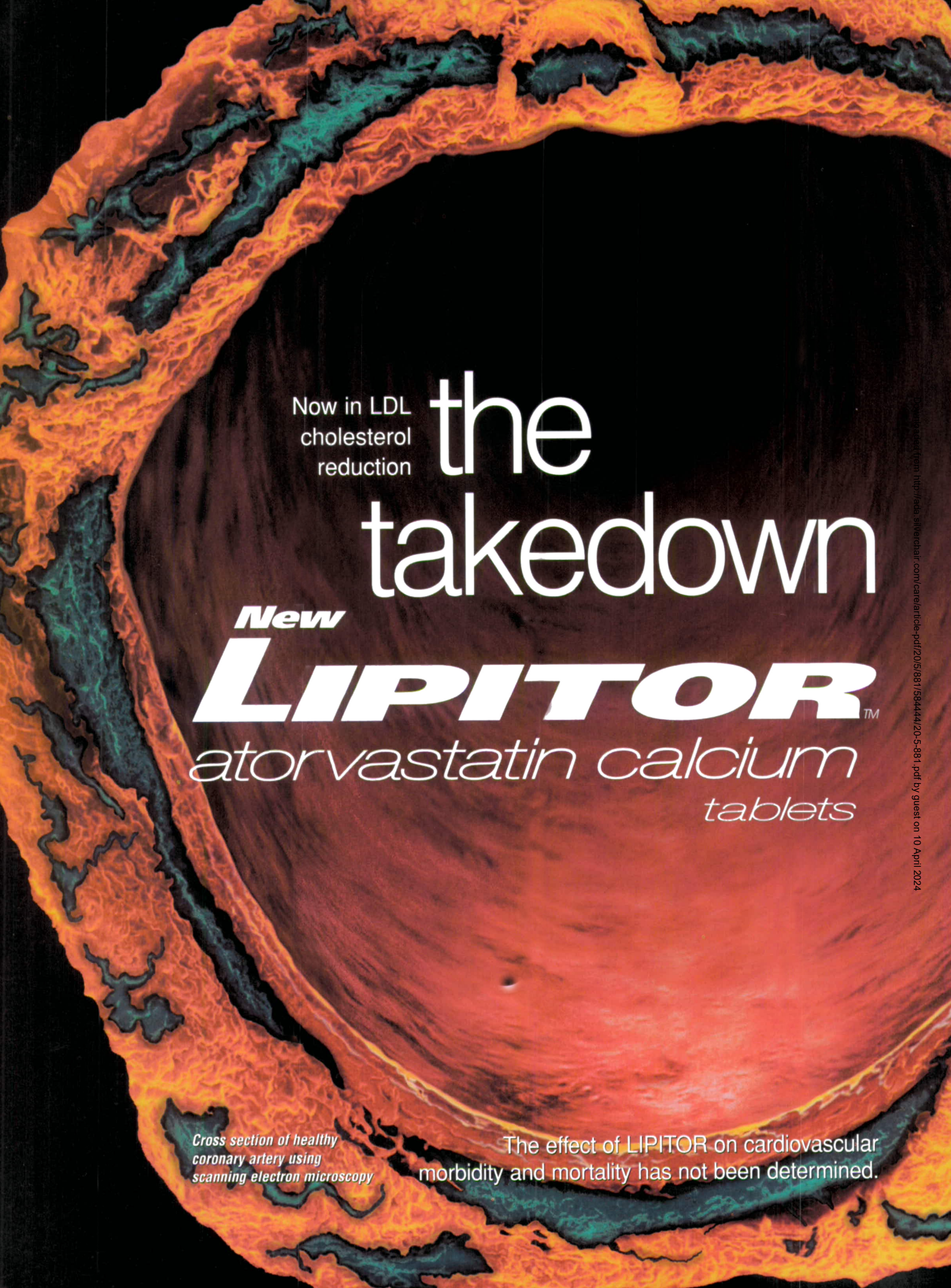

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In clinical trials, the most common adverse events were constipation, flatulence, dyspepsia, and abdominal pain.

As with any statin, it is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter.

LIPITOR is contraindicated in patients with hypersensitivity to any component of this medication; in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women during pregnancy and in nursing mothers.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of creatine phosphokinase (CPK). Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

*The impact on clinical outcomes of the differences in lipid-altering effects between these treatments is not known. This statement does not compare the effects of LIPITOR 10 mg and higher doses of simvastatin, pravastatin, and lovastatin.

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References: 1. Bracs P, Best J, Dart T, et al. A one-year study comparing atorvastatin and simvastatin in patients with hypercholesterolemia. Presented at the 66th Congress of the European Atherosclerosis Society; July 13-17, 1996; Florence, Italy. Abstract. **2.** Egros F, Langan J, Bertolini S, et al. A one-year study comparing atorvastatin and pravastatin in patients with hypercholesterolemia. Presented at the 66th Congress of the European Atherosclerosis Society; July 13-17, 1996; Florence, Italy. Abstract. **3.** Bakker-Arkema R, Fayyad R, Davidson M, et al. One-year study comparing the safety and efficacy of atorvastatin to that of lovastatin. Presented at the 66th Congress of the European Atherosclerosis Society; July 13-17, 1996; Florence, Italy. Abstract.

Lipitor™ (Atorvastatin Calcium) Tablets

Brief Summary of Prescribing Information

CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication. **Pregnancy and Lactation:** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: Liver Dysfunction — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle — Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

PRECAUTIONS: General — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle). ***Antacid:*** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. ***Antipyrine:*** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. ***Colestipol:*** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. ***Cimetidine:*** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. ***Digoxin:*** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. ***Erythromycin:*** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle). ***Oral Contraceptives:*** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. ***Warfarin:*** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. ***Other Concomitant Therapy:*** In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy: Pregnancy Category X — See CONTRAINDICATIONS.** Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers:** Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Treatment experience in a pediatric population is limited to doses of Lipitor up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age. **Geriatric Use:** Treatment experience in adults age ≥70 years with doses of Lipitor up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of Lipitor in this population were similar to those of patients <70 years of age.

ADVERSE REACTIONS: Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences:** Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment:

Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

The following adverse events were reported, regardless of causality assessment, in <2% of patients treated with atorvastatin in clinical trials.

Body as a Whole: Face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. ***Digestive System:*** Gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. ***Respiratory System:*** Pneumonia, dyspnea, asthma, epistaxis. ***Nervous System:*** Paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia. ***Musculoskeletal System:*** Leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. ***Skin and Appendages:*** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. ***Urogenital System:*** Urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. ***Cardiovascular System:*** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia. ***Metabolic and Nutritional Disorders:*** Hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. ***Hemic and Lymphatic System:*** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

OVERDOSAGE: There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Caution – Federal law prohibits dispensing without prescription.

Consult package insert before prescribing Lipitor™ (Atorvastatin Calcium) Tablets.

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