Serum Lipoproteins Improve After Successful Pharmacologic Antidepressant Treatment: A Randomized Open-Label Prospective Trial

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Objective: Despite reports of lower plasma cholesterol in depressed patients, major depressive disorder has been shown to increase cardiovascular risk. Our objective was to study the composition of lipoproteins in depressed patients and controls and to examine the effects of pharmacologic treatment and treatment response on lipoprotein composition.

Method: Lipoprotein composition was analyzed in 65 adult inpatients at a university psychiatric hospital in Germany with *DSM-IV* major depressive disorder and 33 healthy controls (recruited via newspaper and radio ads) matched for age and sex. After the cross-sectional study phase, the patients were randomized in an open-label prospective trial to treatment with either mirtazapine or venlafaxine. Lipoproteins were reanalyzed after 4 weeks of treatment. Main outcome measures were total cholesterol, the low-density lipoprotein (LDL) to high-density lipoprotein (HDL) cholesterol ratio, and the LDL triglycerides to apolipoprotein B ratio. Secondary outcome measures were total triglycerides, HDL and LDL cholesterol levels, and apolipoproteins A1 and B levels. Comparisons were made between the 2 drug groups and between remitters and nonremitters as measured by the 21-item Hamilton Depression Rating Scale. The study was conducted from April 2003 through December 2007.

Results: Total cholesterol at baseline was lower in patients than in controls (mean ± SD = 4.99 ± 0.98 mmol/L vs 5.63 ± 1.01 mmol/L; $P = .003$), with significantly lower HDL cholesterol ($P < .001$) and LDL cholesterol ($P = .03$) in patients. However, the ratio of LDL triglycerides to apolipoprotein B, an index of size and atherogenic potential of LDL particles, was higher in depressed subjects (mean ± SD = 0.46 ± 0.14 mmol/g vs 0.38 ± 0.09 mmol/g; $P = .002$). Irrespective of treatment allocation, we found significant improvement of cardiovascular risk parameters in remitters but found deterioration in nonresponders. The LDL cholesterol mean change from baseline (remitters vs partial responders vs nonresponders) was −0.06 mmol/L versus +0.39 mmol/L versus +0.56 mmol/L ($P = .014$); the mean change in LDL/HDL cholesterol ratio was −0.50 versus +0.14 versus +0.80 ($P = .002$); and the mean change in the LDL triglycerides per apolipoprotein B ratio was −0.01 versus −0.01 versus +0.08 ($P = .045$). No drug-specific changes in lipid concentrations during treatment were observed except for total cholesterol (venlafaxine group mean = −0.02 mmol/L and mirtazapine group mean = +0.37 mmol/L; $P = .033$).

Conclusions: In depressed patients, lipoprotein structure is changed toward LDL particles with a higher atherogenic potential. Remission from depression is associated with an improvement of the LDL/HDL cholesterol ratio, shifting lipoproteins toward a less atherogenic composition. Our findings should be confirmed in a larger study, as they have relevance for both researchers and clinicians.

Trial Registration: German Clinical Trial Registry Identifier: DRKS00000008

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In patients suffering from depression, plasma cholesterol has been found to be lower than in individuals without affective disorders. This link between low cholesterol and depression has been established in both prospective[1] and cross-sectional[2–5] studies. Since hypercholesterolemia is recognized as one of the most important risk factors for cardiovascular disease,[6] lower cholesterol levels should result in attenuation of cardiovascular risk in depressed patients. In contrast, major depression has been demonstrated to increase cardiovascular mortality, mainly due to coronary artery disease, in both patients with and patients without preexisting heart disease[7–11] (for a review, see reference 12).

So far, it is not known if pharmacologic antidepressant treatment improves the excess cardiovascular risk. On the other hand, total cholesterol has been shown to increase during treatment with various antidepressants.[4,13,14]

Although various factors unrelated to plasma lipid metabolism have been suggested to explain the association of depression with cardiovascular risk,[15] we hypothesized that composition and architecture of lipoproteins may be altered in depression and, consequently, an untoward lipoprotein architecture may contribute to the excess risk, even in the face of apparently beneficial low total cholesterol concentrations.

It is well known that differentiation of cholesterol-containing plasma lipoproteins provides more accurate risk estimates: separating high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol fractions and calculating LDL/HDL cholesterol or apolipoprotein B/apolipoprotein A1 ratios.[16] Even more superior risk prediction is yielded by differentiation of LDL particle size: "small, dense" LDL particles, resulting from packing of LDL particles

with higher amounts of triglycerides, have a higher propensity to be oxidized, to be trapped in the subendothelial space, and, subsequently, to form the seed of an atherosclerotic plaque.[17]

We have previously shown that depression is associated with insulin resistance,[18] that insulin resistance is linked to a preponderance of small, dense LDL particles, as expressed by an increased triglyceride per apolipoprotein B ratio,[19] and that successful antidepressant treatment improves insulin sensitivity.[20,21] Consequently, we hypothesized that the apparently beneficial effect of low total cholesterol in depressed patients may be obviated by a preponderance of triglyceride-rich, small, dense LDL particles and that pharmacologic treatment of depression may improve the composition of lipoproteins despite leading to an increase of total cholesterol.

In the present article, we report cross-sectional and prospective data. In the cross-sectional part, lipoprotein composition in patients with major depression was compared to healthy controls. In the prospective part of the trial, we studied lipoprotein compositions in depressed patients who underwent a 28-day course of pharmacologic antidepressant treatment with mirtazapine or venlafaxine. We chose these frequently used antidepressant drugs because they differ with respect to their propensity to induce short-term weight gain.[22] We analyzed changes in lipoprotein composition, depending on response to antidepressant treatment.

METHOD

The study was conducted with inpatients at a university psychiatric hospital in Germany. Healthy controls were recruited via ads in local newspapers and radio stations. The study was preapproved by the institutional ethics committee, and subjects gave written informed consent prior to study inclusion. This trial was registered at the German Clinical Trial Registry (registration information is available at http://www.drks.de/DRKS00000008) and was conducted from April 2003 through December 2007.

We screened consecutive patients admitted for *DSM-IV* major depressive disorder who scored at least 18 points on the 21-item Hamilton Depression Rating Scale (HDRS-21).[23] Exclusion criteria were substance-related disorders and lifetime diagnosis of schizophrenia or bipolar disorder. In addition, patients were not included if they used lipid-lowering or antidiabetic medication or were dieting.

From healthy volunteers, who responded to newspaper and radio ads, we selected 33 subjects who could be matched to participating patients with respect to age and sex. Significant psychiatric or somatic diseases were excluded by a detailed history, psychiatric interview, and physical examination. Healthy volunteers underwent the same study procedures as patients at baseline and served as controls for the cross-sectional analysis.

Intervention

After a 1-week washout period without psychotropic medication, patients were randomized to treatment with either mirtazapine (final dosage [mean ± SD]: 52.4 ± 36.8 mg/d) or venlafaxine (final dosage: 183.7 ± 59.7 mg/d) in flexible dosages for 4 weeks. Medication was given according to the randomization procedure but was open-label. Throughout the study period, neither group was allowed any other psychotropic medication except lorazepam and zolpidem. After the washout period and again after 28 days of antidepressant treatment, blood was drawn from an antecubital vein for analysis of parameters of lipid metabolism at 8:30 AM. Each sample was immediately centrifuged and stored at –20°C until measurement.

Outcome Measures

In the cross-sectional analysis, we compared total cholesterol, the LDL to HDL cholesterol ratio, and the LDL triglycerides to apolipoprotein B ratio between depressed patients and healthy controls.

In the prospective trial, we compared (1) patients who were randomized to venlafaxine with those randomized to mirtazapine and (2) patients who did not respond or achieved only partial response on either treatment to those patients who achieved complete remission. Main outcome measures, again, were total cholesterol, the LDL to HDL cholesterol ratio, and the LDL triglycerides to apolipoprotein B ratio. Treatment remission was assumed when the final HDRS-21 score was < 8. Treatment response was assumed with a reduction of the initial score on the HDRS-21 scale of 50%, or at least 10 points.

Secondary outcome parameters were total triglycerides, HDL and LDL cholesterol levels, and apolipoproteins A1 and B levels.

Laboratory Analyses

Chylomicrons and very-low-density lipoprotein (VLDL) cholesterol were separated from LDL and HDL cholesterol by a single centrifugation step over a time period of 18 hours at 100,000*g* in a 50.4 Ti rotor with a Beckman L-50 ultracentrifuge (Beckman Coulter, Munich, Germany). After removal of the VLDL supernatant, the LDL fraction was precipitated with a phosphotungsten acid/magnesium chloride reagent before measurement of HDL composition. The compositions of the VLDL fractions, HDL fractions, and the infranatant were determined by measurement of cholesterol, triglycerides, unesterified polyester, and apolipoproteins on an automated Hitachi 911 analyzer (Roche Diagnostics, Mannheim, Germany). The LDL composition was calculated from the bottom fractions. Total apolipoproteins A1, B, C3, and E were analyzed by immunoturbidimetric assays using goat antihuman polyclonal antisera (Greiner Bio-One, Bad Homburg, Germany). We used the CHOD-PAP method for measurement of cholesterol (CHOL kit; Roche Diagnostics, Mannheim, Germany), the GPO-PAP method for triglycerides and free glycerol (triglyceride GPO-PAP kit; Roche Diagnostics, Mannheim, Germany), the COD-PAP method for free cholesterol (free cholesterol C kit; WAK-Chemie, Bad Homburg, Germany), and the ACS-ACOD method for measurement of free fatty acids (NEFA-C kit; WAK-Chemie, Bad Homburg, Germany).

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Statistical Analysis

All data are expressed as means ± SD. For cross-sectional analyses between patients and healthy controls, the Student *t* test for unpaired samples was used. Gender distribution was compared using the Fisher exact test. For analysis of prospective data, analysis of variance for repeated measurements with post hoc *t* tests was performed. Age and gender were used as covariates in order to standardize for these possible confounders. Gender distribution was assessed using the Fisher exact test or—when more than 2 groups were analyzed—the χ^2 test. Age of patients in different groups was compared using the Student *t* test or—when more than 2 groups were analyzed—1-way analysis of variance. Statistical significance was accepted at $P \leq .05$.

RESULTS

Of 105 screened patients, 92 fulfilled the inclusion criteria, consented to be included in the study, and were randomized to either mirtazapine (n = 46) or venlafaxine (n = 46). Thirteen patients dropped out because of adverse events, insufficient effect of study drugs, withdrawal of consent, or early discharge from the hospital because of rapid remission. Sixty-five patients completed all phases of the study and had complete baseline lipid data (see Consolidated Standards of Reporting Trials [CONSORT] flow diagram [Figure 1]); 61 patients had complete baseline and follow-up data to be analyzed for this study. There were no significant differences between initially included patients and completers with respect to age, gender, baseline body weight, or total cholesterol. However, completers were initially slightly, but significantly, more depressed than noncompleters (HDRS-21 score: 22.7 ± 4.3 vs 20.3 ± 6.2, respectively).

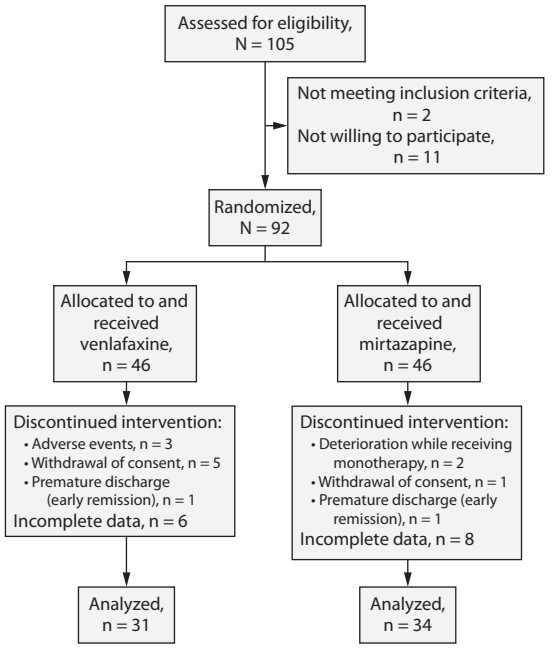
Baseline Data: Depressed Patients Versus Healthy Controls

Total cholesterol was significantly lower in patients compared to healthy controls (Table 1). This result was due to both significantly lower HDL cholesterol and significantly lower LDL cholesterol. The finding of lower HDL cholesterol in depressed patients was supported by significantly lower apolipoprotein A1, the major constituent of HDL cholesterol particles. Consequently, there was a trend, although not significant, toward a higher ratio of LDL to HDL cholesterol in patients than in controls. The amount of LDL triglycerides per apolipoprotein B was markedly and significantly higher in patients compared to controls, pointing to an adverse LDL cholesterol composition in depressed patients.

Changes During Antidepressant Treatment: Mirtazapine Versus Venlafaxine

The course of body weight differed significantly between groups: after 4 weeks of treatment, body weight slightly decreased in patients treated with venlafaxine, while body weight increased with mirtazapine treatment (Table 2). Lipoprotein levels were analyzed after adjustment for age and gender. There were significant differences (analysis of variance: interaction of treatment group by time) for total cholesterol and total triglycerides: with mirtazapine treatment, total cholesterol and triglycerides increased, while, with venlafaxine treatment, cholesterol remained stable and triglycerides decreased (Table 2). However, there were no significant group differences in cholesterol-containing lipoproteins: HDL cholesterol improved slightly, irrespective of treatment allocation, in remitters and responders ($P < .001$); LDL cholesterol, LDL to HDL cholesterol ratio, and LDL triglycerides per apolipoprotein B showed no marked changes in either group.

Figure 1. CONSORT Flow Diagram of Depressed Patients' Disposition Through the Study



Abbreviation: CONSORT = Consolidated Standards of Reporting Trials.

Changes During Antidepressant Treatment: Remitters Versus Nonremitters

During antidepressant treatment, 30 patients achieved complete remission (venlafaxine, 14; mirtazapine, 16) and 22 achieved partial response (venlafaxine, 12; mirtazapine, 10), while 9 did not respond (venlafaxine, 2; mirtazapine, 7). As gender and age distribution of remitters, responders, and nonresponders appeared uneven (although not significant in χ^2 testing or 1-way analysis of variance), we performed subsequent testing with adjustment for gender and age (Table 3). Levels of LDL cholesterol remained unchanged in patients who achieved complete remission of depressive symptoms, while LDL cholesterol increased significantly in patients who achieved only partial response or no response (Table 3). There was a trend in the same direction for total cholesterol, while HDL cholesterol showed an inverse trend, resulting in a significant difference in the LDL to HDL cholesterol ratio, which markedly improved in remitters, changed in an adverse direction in nonresponders, and remained unchanged in partial responders who did not achieve remission criteria.

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Table 1. Gender, Body Mass Index, Age, and Lipid Parameters of Depressed Patients Prior to Treatment Compared to Healthy Controls[a]

Variable	Depressed Patients Prior to Treatment (N = 65)	Healthy Controls (N = 33)	*P* Value[b,c]
Gender, female/male, n/n (% female)	42/23 (64.6)	23/10 (69.7)	.91
Body mass index, mean ± SD	25.5 ± 5.6	24.5 ± 3.6	.35
Age, mean ± SD, y	50.1 ± 1.7	49.8 ± 14.8	.73
Total cholesterol, mean ± SD, mmol/L	4.99 ± 0.98	5.63 ± 1.01	**.003**
Total triglycerides, mean ± SD, mmol/L	1.43 ± 0.68	1.18 ± 0.45	.06
LDL cholesterol, mean ± SD, mmol/L	3.28 ± 0.99	3.72 ± 1.00	**.03**
HDL cholesterol, mean ± SD, mmol/L	1.05 ± 0.26	1.39 ± 0.35	**<.001**
LDL/HDL cholesterol ratio, mean ± SD	3.36 ± 1.32	2.92 ± 1.31	.12
Apolipoprotein A1, mean ± SD, g/L	1.72 ± 0.35	2.00 ± 0.42	**<.001**
Apolipoprotein B, mean ± SD, g/L	1.02 ± 0.23	1.08 ± 0.30	.25
Apolipoprotein A1/B ratio, mean ± SD	0.62 ± 0.18	0.57 ± 0.22	.14
LDL triglycerides per apolipoprotein B, mean ± SD, mmol/g	0.46 ± 0.14	0.38 ± 0.09	**.002**

[a]Cholesterol and triglycerides data are given in SI units. To convert to mg/dL, multiply triglycerides values × 87.7 and cholesterol values × 38.7. For triglycerides, 200 mg/dL corresponds to 2.30 mmol/L; for cholesterol, 200 mg/dL corresponds to 5.20 mmol/L.
[b]Gender was tested with a χ^2 test; all others were tested with *t* tests.
[c]Boldface type indicates significance at $P \leq .05$.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 2. Lipid Parameters in Patients Treated With Venlafaxine Versus Mirtazapine[a]

Variable	Venlafaxine (n = 28)	Mirtazapine (n = 27)	Statistic[b]	*P* Value[c]
Gender, female/male, n/n	22/6	15/12	*F* = 0.60	.062
Age, mean ± SD, y	49.4 ± 15.6	50.9 ± 16.6	*t* = −0.25	.98
Body weight, kg				
Baseline, mean ± SD	70.9 ± 15.6	73.6 ± 19.1		
Day 28, mean ± SD	70.2 ± 14.5	75.2 ± 18.6		
Mean change	−0.7	+1.6	*F* = 16.70	**<.001**
Total cholesterol, mmol/L				
Baseline, mean ± SD	5.01 ± 1.09	5.07 ± 0.87		
Day 28, mean ± SD	4.99 ± 1.10	5.44 ± 1.07		
Mean change	−0.02	+0.37	*F* = 4.73	**.033**
LDL cholesterol, mmol/L				
Baseline, mean ± SD	3.25 ± 1.04	3.35 ± 0.79		
Day 28, mean ± SD	3.40 ± 1.06	3.61 ± 1.10		
Mean change	+0.15	+0.26	*F* = 0.42	.52
HDL cholesterol, mmol/L				
Baseline, mean ± SD	1.09 ± 0.27	1.02 ± 0.26		
Day 28, mean ± SD	1.22 ± 0.36	1.10 ± 0.33		
Mean change	+0.13	+0.18	*F* = 0.83	.36
LDL/HDL cholesterol ratio				
Baseline, mean ± SD	3.24 ± 1.33	3.58 ± 1.35		
Day 28, mean ± SD	3.08 ± 1.32	3.60 ± 1.31		
Mean change	−0.16	+0.02	*F* = 0.52	.47
Apolipoprotein B/A1 ratio				
Baseline, mean ± SD	0.57 ± 0.17	0.66 ± 0.20		
Day 28, mean ± SD	0.56 ± 0.17	0.65 + 0.21		
Mean change	−0.01	−0.01	*F* = 0.10	.76
LDL triglycerides per apolipoprotein B, mmol/g				
Baseline, mean ± SD	0.46 ± 0.12	0.44 ± 0.12		
Day 28, mean ± SD	0.44 ± 0.11	0.46 ± 0.12		
Mean change	−0.02	+0.02	*F* = 0.27	.60
Total triglycerides, mmol/L				
Baseline, mean ± SD	1.46 ± 0.55	1.43 ± 0.80		
Day 28, mean ± SD	1.22 ± 0.42	1.60 ± 0.69		
Mean change	−0.24	+0.17	*F* = 8.46	**.005**

[a]Three cases in the venlafaxine group and 7 in the mirtazapine group had to be excluded because of incomplete data at follow-up.
[b]Statistical evaluation: for gender, Fisher exact test was used; for age, *t* test was used; for all others, analysis of variance repeated-measures interaction time by group was used, with adjustment for age and gender.
[c]Boldface type indicates significance at $P \leq .05$.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Changes in the apolipoprotein B to A1 ratio paralleled those of the LDL to HDL cholesterol ratio. In addition, we observed a slight further increase in the LDL triglycerides to apolipoprotein A1 ratio in nonresponders only. This ratio remained virtually unchanged in remitters and partial responders.

All these changes were independent of medication. Similar changes were found, at least as trends, when mirtazapine-treated and venlafaxine-treated patients were analyzed separately (data not shown).

In linear regression analysis, the reduction in the HDRS-21 score correlated with the reductions in the LDL to HDL cholesterol ratio ($r = 0.377$; $P = .004$) and the LDL triglycerides to apolipoprotein B ratio ($r = 0.273$; $P = .04$).

DISCUSSION

In summary, the present study confirmed previous results of lower total and lower LDL cholesterol in depressed patients compared to healthy controls. However, the protective HDL cholesterol concentrations were lower as well. Moreover, LDL particles contained more triglycerides in depressed patients. This finding, which has not been reported previously, points to a preponderance of small, dense LDL particles, which are more easily trapped in the subendothelial space, are easily oxidized, and, thus, may give rise to the inflammatory process of atherosclerosis. Therefore, the apparent advantage of lower LDL cholesterol seems to be obviated by an untoward lipoprotein architecture in depressed patients.

In the intervention part of the study, medication assignment appeared to have limited influence on serum lipid concentrations. Even though the trajectories of body weight differed between antidepressant drug groups, among the lipid parameters only total cholesterol and total triglycerides behaved significantly differently. The HDL concentrations improved in remitters and in responders to treatment in both groups. There were no medication-associated differences in total cholesterol level, HDL cholesterol level, the LDL to HDL cholesterol ratio, or the LDL triglycerides per apolipoprotein B. However, we found a significant and clinically meaningful influence of remission of depressive symptoms on lipid composition: remission or partial response was associated with more favorable courses in LDL cholesterol, the LDL/HDL cholesterol ratio, the apolipoprotein A1/apolipoprotein B ratio, and LDL triglycerides per apolipoprotein B.

To the best of our knowledge, the composition of LDL particles has not been studied

Table 3. Lipid Parameters in Remitters Compared to Responders (with incomplete remission) and Nonresponders to Pharmacologic Antidepressant Treatment[a]

Variable	Remitters (N = 30)	Responders (N = 22)	Nonresponders (N = 9)	Statistic[b]	*P* Value[c]
Gender, female/male, n/n	18/12	17/5	5/4	$\chi^2 = 2.14$	.18
Age, mean ± SD, y	52.0 ± 14.2	54.1 ± 18.2	43.0 ± 14.4	$F = 1.63$	.21
Body weight, kg					
Baseline, mean ± SD	75.1 ± 16.9	66.0 ± 15.7	84.6 ± 19.5		
Day 28, mean ± SD	75.7 ± 16.0	66.3 ± 15.3	84.0 ± 21.1	$F = 0.85$	.43
Total cholesterol, mmol/L					
Baseline, mean ± SD	5.13 ± 0.89	5.00 ± 0.91	4.82 ± 1.38		
Day 28, mean ± SD	5.13 ± 0.95	5.30 ± 0.91	5.39 ± 1.96		
Mean change	±0	+0.30	+0.57	$F = 2.26$	.11
LDL cholesterol, mmol/L					
Baseline, mean ± SD	3.44 ± 0.73	3.26 ± 0.87	3.00 ± 1.45		
Day 28, mean ± SD	3.38 ± 1.00	3.65 ± 0.79	3.56 ± 1.86		
Mean change	−0.06	+0.39	+0.56	$F = 4.62$	**.014**
HDL cholesterol, mmol/L					
Baseline, mean ± SD	1.00 ± 0.27	1.14 ± 0.27	1.04 ± 0.26		
Day 28, mean ± SD	1.14 ± 0.32	1.23 ± 0.35	1.04 ± 0.39		
Mean change	+0.14	+0.06	±0	$F = 1.62$	.21
LDL/HDL cholesterol ratio					
Baseline, mean ± SD	3.81 ± 1.43	3.06 ± 1.17	3.10 ± 1.26		
Day 28, mean ± SD	3.31 ± 1.37	3.20 ± 1.12	3.90 ± 1.74		
Mean change	−0.50	+0.14	+0.80	$F = 6.83$	**.002**
Apolipoprotein B/A1 ratio					
Baseline, mean ± SD	0.66 ± 0.20	0.57 ± 0.16	0.63 ± 0.18		
Day 28, mean ± SD	0.60 ± 0.18	0.58 ± 0.16	0.71 ± 0.28		
Mean change	−0.06	+0.01	+0.08	$F = 4.98$	**.010**
LDL triglycerides per apolipoprotein B, mmol/g					
Baseline, mean ± SD	0.48 ± 0.11	0.44 ± 0.12	0.34 ± 0.10		
Day 28, mean ± SD	0.47 ± 0.13	0.43 ± 0.11	0.42 ± 0.10		
Mean change	−0.01	−0.01	+0.08	$F = 3.31$	**.045**
Total triglycerides, mmol/L					
Baseline, mean ± SD	1.52 ± 0.76	1.25 ± 0.56	1.67 ± 0.68		
Day 28, mean ± SD	1.52 ± 0.66	1.21 ± 0.49	1.64 ± 0.64		
Mean change	±0	−0.04	−0.03	$F = 0.53$	.94

[a]Four cases had to be excluded from analysis because of incomplete data in the course of follow-up.
[b]Statistical evaluation: for gender, the χ^2 test was used; for age, a 1-way analysis of variance was used; for all others, analysis of variance repeated-measures interaction time by group was used, with adjustment for age and gender.
[c]Boldface type indicates significance at $P \leq .05$.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

previously in depressed patients. Previous studies have addressed the concentrations of total cholesterol or the concentrations of HDL and LDL cholesterol with somewhat differing results. Some studies[2–4,24] found significantly lower cholesterol in depressed patients, whereas others[25–27] found no significant difference; one group[28] found no difference in total cholesterol but found lower HDL cholesterol. One group[5] found gender-specific differences, while other groups[13,29] found lower cholesterol in suicidal depressive patients only. Even though these results are heterogeneous, there appears to be consensus that cholesterol is either comparable or lower in depressive patients. In addition, lower cholesterol tends to be associated with more severe depression or suicidality. Our data showing a significant association of depression with lower cholesterol are in line with this trend in the literature.

As the concentration of LDL and HDL cholesterol is more closely linked to cardiovascular risk, some studies[4,24,27,30] investigated cholesterol subfractions, with even more conflicting results, particularly for HDL; for example, HDL cholesterol was lower in patients than in healthy controls in 3 studies,[24,27,30] while it was higher in only 1 study.[4] This heterogeneity may well result from changes in nutritional status in the course of depression. In cross-sectional studies, differences in antidepressant pretreatment also may account for conflicting results. Our study sought to minimize this problem by measuring lipid concentrations after a medication washout phase. We found lower HDL cholesterol in depressed patients, thus counteracting the apparently favorable effects of lower total cholesterol on cardiovascular risk.

Another way to predict cardiovascular risk is to measure LDL particle size. The LDL particles with a high load of triglycerides are packed more densely and are smaller than LDL particles with a lower triglyceride load. As a consequence, they are more prone to be trapped in the subendothelial space, where they are easily oxidized and trigger the inflammatory process of atherosclerosis.[17,31,32] Triglyceride-rich, small, dense LDL particles have been shown to be very sensitive indicators of insulin resistance, even in healthy, normolipemic young adults.[19] To the best of our knowledge, LDL size and composition have not been studied previously in depressed patients. Our finding of small, dense LDL particles in major depressive disorder shows that lower cholesterol concentrations do not necessarily have a protective effect since cholesterol is transported in more atherogenic lipoproteins.

During treatment, total cholesterol increased. The triglyceride load of LDL particles did not change. However, HDL cholesterol increased significantly, resulting in a significantly improved LDL to HDL cholesterol ratio. This effect was limited to subjects who achieved at least partial response of depressive symptoms. In addition, changes in the ratio of triglycerides to apolipoprotein B differed significantly according to response: in nonresponders, this ratio was increased even more, signifying increasing cardiovascular risk, while, in responders or remitters, the ratio was virtually unchanged or was slightly improved.

Few previously published studies have investigated changes in lipoproteins during antidepressant treatment. One study,[33] in which patients received various antidepressant drugs according to clinical judgment, did not find changes in cholesterol during treatment. Another study[14] in both bipolar patients and patients with major depressive disorder reported an increase in cholesterol with treatment of depressive episodes, while cholesterol decreased with treatment of mania. The levels of HDL and LDL cholesterol were not reported in either study. An increase in total cholesterol was reported in a Kuwaiti study.[4] Thus, our finding of slightly increasing cholesterol with treatment is in line with 2 of 3 previous studies. In contrast to our results, in the study by Olusi and Fido,[4] HDL cholesterol did not

change significantly, while LDL increased. These differences may be due to treatment with tricyclic antidepressants in their study, while in our study patients received either mirtazapine or venlafaxine. We have previously reported[34] that lipoproteins, particularly triglyceride-rich lipoproteins, are less favorably affected by the tricyclic antidepressant amitriptyline compared to paroxetine.

One important novel finding of our study is that remission plays a critical role. We see favorable changes in the LDL to HDL cholesterol ratio in remitters only—not in nonremitters. To our knowledge, no previous studies are available that report LDL and HDL in remitters and nonremitters.

The mechanism of lipoprotein change was not the scope of the present study. However, we have previously reported considerable improvement of insulin sensitivity in responders to pharmacologic antidepressant treatment.[20,21] As HDL cholesterol is closely correlated with insulin sensitivity, this correlation may be 1 factor that contributes to the improved LDL to HDL cholesterol ratio. Further explanations include cortisol effects on insulin sensitivity[35] or increased physical activity and changing food preferences with remitting depression.

The main limitation of our study is sample size. Subtle differences between venlafaxine and mirtazapine may have been missed due to lack of power. Therefore, our results need confirmation in a larger study. Further, effects on cholesterol may be more pronounced if higher doses are taken for a longer interval. For venlafaxine, the US package insert[36] mentions the risk of clinically relevant increases of cholesterol if venlafaxine is taken for 3 months rather than 4 weeks, as in our study. As an additional limitation, these subjects were recruited from patients of a referral center and represent a selected patient population. Accordingly, control subjects were selected from volunteers to carefully match our study patients. As a consequence, the study population may not represent the general population in all aspects, in contrast to a population-based study.

If our findings are confirmed, they are of relevance for both researchers and clinicians. For researchers, our observation of small, dense LDL particles may further the understanding of the paradox of low cholesterol and high cardiovascular risk in depression. For clinicians, our finding of improved LDL to HDL cholesterol ratio in patients responding to modern antidepressant drugs may be reassuring and helpful when potential risks and benefits of pharmacologic treatment are explained to concerned patients.

Drug names: lorazepam (Ativan and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others), zolpidem (Ambien, Edluar, and others).

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