Prospective Evaluation of HDL Cholesterol Changes After Diet and Physical Conditioning Programs for Patients with Type II Diabetes Mellitus

ROBERT M. KAPLAN, Ph.D., DAWN K. WILSON, M.A., SHERRY L. HARTWELL, M.S., KATHERINE L. MERINO, B.A., AND JANET P. WALLACE, Ph.D.

High-density lipoprotein (HDL) cholesterol is known to be low in patients with diabetes mellitus. Low HDL levels are correlated with premature cardiovascular mortality in several major epidemiologic studies and many investigators believe increases in HDL cholesterol may reduce the risk of coronary heart disease. We evaluated dietary and exercise interventions in relation to HDL cholesterol in patients with type II diabetes mellitus. Sixty-five volunteers were randomly assigned to one of four experimental conditions: diet, exercise, diet plus exercise, or education control. Three months after entering the program, those exposed to the dietary intervention had significant increases in HDL cholesterol. HDL increases for the other two treatment groups did not differ significantly from the education control.

Although ultracentrifugal and protein fractionation methods were introduced in the late 1940s, it has only been within the last decade that there has been an intense focus on lipoprotein fractions and subfractions. In this paper, we concentrate on high-density lipoprotein cholesterol (HDL).

Although the mechanism is unknown, substantial epidemiologic evidence demonstrates the inverse association between HDL cholesterol and coronary heart disease (CHD). Epidemiologic evidence also indicates that individuals with non-insulin-dependent diabetes mellitus (NIDDM, or type II diabetes) are at increased risk for cardiovascular disease. Several epidemiologic studies show that low HDL concentrations are predictive of CHD in nondiabetic individuals. Barrett-Connor and colleagues recently reported that individuals with NIDDM in a community sample had significantly lower HDL than their nondiabetic neighbors.

Although the evidence is not definitive, there is reason to believe that increasing HDL may provide some protective benefit against CHD. This may be particularly important for diabetic individuals who have low HDL and are known to be at increased risk for CHD. The current study evaluates behavioral interventions that may result in increased HDL.

Nearly all of the patients participating in the study were obese. There is substantial correlational evidence for an inverse association between HDL and obesity. Although weight loss appears to cause increases in HDL cholesterol, some studies have produced contradictory evidence: for example, Thompson and colleagues found significant reductions in HDL cholesterol among women who had achieved significant weight reduction. To date, there have been very few prospective studies of HDL changes in NIDDM subjects. Since NIDDM individuals have a distinct lipid profile, such investigations are of great interest.

The evidence relating changes in HDL to physical activity has been even less consistent. Some studies demonstrate a correlation between HDL cholesterol and degree of physical activity, while others show no acute changes in HDL as a result of exercise.

The present study is a prospective, randomized experimental trial comparing diet, exercise, diet plus exercise, and an education control group. Safeguards were taken to avoid some problems that characterize earlier research: for instance, many studies evaluate behavioral changes in self-selected groups of patients; we assigned patients to treatments in a nonbiased way to avoid the effects of self-selection. Another difficulty is that compliance with life-style changes tends to be poor. To avoid this problem, intensive behavior modification interventions were used with weekly supervision.

SUBJECTS AND METHODS

Subjects. Sixty-five adults (28 men and 37 women) with a diagnosis of NIDDM participated in the study. Subjects were either referred to the study by their physicians or recruited through newspaper and radio advertisements. To be admitted
to the study, the patient had to have fasting plasma glucose >140 mg/dl or have a confirmed diagnosis of NIDDM from the referring physician. All patients had confirmed hyperglycemia beginning in adulthood and all were overweight (mean quetelet = 4.40, SD = 0.86). Twenty-four patients (37%) were managed on diet alone, 24 (37%) were managed on oral agents, and 17 (26%) were taking insulin. All potential participants attended recruiting meetings at which one of four programs was offered according to a randomly predetermined schedule. Before entering the program, each patient signed a written, informed consent form and presented a second referral questionnaire completed by their own physician. Seventy-eight persons volunteered and were assigned to groups. Among these, 68 completed all aspects of the screening. Five subjects dropped out or did not report for the 3-mo evaluation, leaving 63 for analysis. Chi-square tests did not detect significant differences in sex distribution or current therapy between the original volunteers and those used in the analysis. In addition, t-tests demonstrated that the original volunteers were comparable with those completing the 3-mo evaluation in age, weight, cholesterol subfractions (HDL, LDL), and triglycerides.

Each patient was then tested at the Exercise Physiology laboratory by the adult fitness program at San Diego State University. Thirty milliliters of venous blood was drawn, a resting and an exercise EKG were performed, and the patient was weighed in a hydrostatic tank, using a correction for residual volume of air in the lungs. Skinfold measures were also obtained from 10 sites. The blood sample was used to determine glycosylated hemoglobin (Isolab Quik-Sep Kit QS-9100 method, Akron, Ohio) and a screening chemical chemistry panel was obtained from the San Diego Institute of Pathology. All blood samples were obtained in the morning after a 12-h fast.

Fasting plasma glucose was measured by a hexokinase method and lipoproteins were measured through the standardized Lipid Research Center (LRC) laboratory at the University of California, San Diego. The LRC method separates plasma into lipoprotein fractions by a combination of ultracentrifugation and precipitation with heparin and manganese chloride. Using these methods it is possible to obtain a direct estimate of HDL cholesterol and indirect estimates of LDL and VLDL cholesterol levels.

Groups. Each volunteer participated in 10 weekly sessions. One-quarter of the volunteers participated in a diet behavior modification group. Over the course of 10 wk, the participants learned behavioral principles for controlled eating and weight loss. They were also taught techniques involving cognitive modification, positive reinforcement, coping with stress, dealing with environmental determinants of eating in restaurants, and prevention of relapse. The second and ninth sessions were specifically devoted to prescription of a diet with 50% complex carbohydrate, 30% protein, and 20% fat. Adherence to this diet was stressed throughout the remaining eight sessions. Dietary information was presented by a registered dietitian and the behavior modification program was administered by a graduate student in psychology. Each weekly session lasted 2 h. In addition, the patients received homework assignments and were asked to keep extensive records throughout the 10-wk period.

The exercise intervention also lasted 10 wk. Participants were enrolled in the adult fitness program at San Diego State University. Each participant was given an individual exercise prescription based on laboratory test results. Exercise sessions were supervised by physical education graduate students. Participants were taught stretching exercises and foot care to prevent injury and exercise pacing to monitor progression. In conjunction with the program, 10 behavior modification sessions were conducted by a graduate student in psychology. The purpose of these sessions was to improve adherence to exercise. The behavior modification strategy was similar in all respects to that designed to improve adherence in the diet group. The first session focused on goal setting and self-monitoring. Other sessions dealt with individual exercise prescriptions, planning, barriers to exercise, cognitive modification, reinforcers, choice of routes, behavioral contracts, and maintaining exercise routines during vacations. During eight of the 10 sessions, the participants stretched for 30 min and gradually increased walking to 40–60 min at 60–70% of their maximal work capacity. Subjects kept weekly diaries to record exercise.

The third group received a combination of diet and exercise programs. To control contact time with staff, the third group was enrolled in the dietary intervention for 5 wk and then participated in the exercise program for the remaining 5 wk. Each of these programs was an abbreviated version of the entire diet or exercise program.

The choice of a control condition is very important in research of this type. One of the major problems is that only motivated individuals volunteer to participate. In addition, substantial attention is given to those in the other conditions. Thus, it was important to find a control condition in which patients receive an equal amount of attention and are equally motivated to stay with the program. For this purpose we used an education control group. Several studies have failed to demonstrate that information about diabetes self-care has a substantial impact on metabolic control or other variables. It appears that information alone is not enough to motivate patients to make lifestyle changes. Behavior modification programs seem to have been successful because they provide specific instruction for the implementation of these new behaviors. Thus, we offered a traditional diabetes education lecture series as a control condition. Members of this control group attended weekly lectures by diabetes specialists including an endocrinologist, podiatrist, opthalmologist, psychologist, registered dietitian, an official of the American Diabetes Association, a representative from a company that manufactures home glucose-monitoring equipment, a psychophysiologist, and an exercise physiologist. Each lecture presented recent facts about diabetes care but did not provide specific individualized instruction for making lifestyle changes.

Twelve weeks after entering the program, each patient was invited to the laboratory to be weighed and measured and a blood sample was obtained for lipoprotein analysis.
TABLE 1
Comparison of groups before treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Mean</th>
<th>F(1/72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>yr</td>
<td>54</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose after 12-h fast</td>
<td>mg/dl</td>
<td>187</td>
<td>2.13</td>
<td>NS</td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>%</td>
<td>8.67</td>
<td>0.72</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>mg/dl</td>
<td>199.6</td>
<td>0.86</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>mg/dl</td>
<td>44</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>mg/dl</td>
<td>126</td>
<td>0.42</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dl</td>
<td>184</td>
<td>0.98</td>
<td>NS</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>bpm</td>
<td>73</td>
<td>1.04</td>
<td>NS</td>
</tr>
<tr>
<td>Obesity index*</td>
<td>wt/ht² × 100</td>
<td>4.41</td>
<td>0.65</td>
<td>NS</td>
</tr>
<tr>
<td>Weight</td>
<td>lb</td>
<td>195</td>
<td>0.59</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>mm/Hg</td>
<td>85</td>
<td>0.76</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>mm/Hg</td>
<td>132</td>
<td>1.27</td>
<td>NS</td>
</tr>
<tr>
<td>VO₂, maximum</td>
<td>ml/min/kg</td>
<td>22.51</td>
<td>1.72</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Obesity index is calculated using pounds and inches.

RESULTS

There is no evidence that there were significant differences between the groups before the interventions. (Table 1 summarizes pretreatment comparisons.) Across 13 variables there were no statistically significant differences between groups. Chi-square tests demonstrated no differences between the groups in the proportions taking insulin, oral agents, or no medication. In addition, the groups were evenly matched by sex. (The number of men and women in each group is given in Table 2.)

Figure 1 presents the comparison between groups for weight loss. The diet group lost more weight than the other three groups and this difference was statistically significant. The analysis was performed as a 2 × 2 analysis of variance. The factors in the ANOVA were diet (given or not given) and exercise (prescribed or not prescribed). The dependent variable was weight at the follow-up and initial weight was used as a covariate. There was a main effect for diet (F[1/60] = 10.86, P < 0.05) and a significant interaction between diet and exercise (F[1/60] = 4.02, P < 0.05). The interaction suggests that patients not exercising lost more weight when they were in the diet condition than the non-exercising, nondiet group. However, patients in diet plus exercise or exercise-only groups did not lose as much weight as the diet-only group.

Figure 2 shows the changes in HDL cholesterol. This was also analyzed by 2 × 2 ANOVA with initial HDL removed as a covariate. Those in the diet group experienced a significant increase in HDL cholesterol while those in the control group experienced a slight decrease. This was reflected in a significant main effect of diet (F[1/60] = 10.86, P < 0.01)

TABLE 2
Pre- and posttreatment lipid values by group

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Women</th>
<th>Men</th>
<th>M</th>
<th>SEM</th>
<th>M</th>
<th>SEM</th>
<th>M</th>
<th>SEM</th>
<th>M</th>
<th>SEM</th>
<th>M</th>
<th>SEM</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-C</td>
<td></td>
<td>HDL-C</td>
<td></td>
<td>LDL-C</td>
<td></td>
<td>Triglycerides</td>
<td></td>
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<td>Triglycerides</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet and exercise</td>
<td>9</td>
<td>7</td>
<td>197</td>
<td>11.4</td>
<td>44</td>
<td>4.0</td>
<td>130</td>
<td>11.6</td>
<td>209</td>
<td>33.5</td>
<td>200</td>
<td>10.0</td>
<td>45</td>
</tr>
<tr>
<td>Diet</td>
<td>9</td>
<td>7</td>
<td>208</td>
<td>15.8</td>
<td>43</td>
<td>2.5</td>
<td>137</td>
<td>13.0</td>
<td>195</td>
<td>22.4</td>
<td>193</td>
<td>13.7</td>
<td>48</td>
</tr>
<tr>
<td>Exercise</td>
<td>10</td>
<td>8</td>
<td>202</td>
<td>15.8</td>
<td>44</td>
<td>2.8</td>
<td>127</td>
<td>8.2</td>
<td>164</td>
<td>15.3</td>
<td>206</td>
<td>9.8</td>
<td>45</td>
</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>6</td>
<td>188</td>
<td>11.9</td>
<td>46</td>
<td>2.8</td>
<td>120</td>
<td>9.1</td>
<td>186</td>
<td>27.8</td>
<td>189</td>
<td>9.4</td>
<td>42</td>
</tr>
</tbody>
</table>

All values are given in mg/dl;
T-C, total cholesterol;
HDL-C, high-density lipoprotein cholesterol;
LDL-C, low-density lipoprotein cholesterol;
M, mean;
SEM, standard error of the mean.
and a significant interaction between diet and exercise (F [1/60] = 9.32, P < 0.01). Duncan multiple-range tests showed that all three treated groups experienced greater increases in HDL than the control group. Those in the diet-only group also experienced greater increases than the exercise and diet plus exercise groups (P < 0.05).

The results for LDL cholesterol were similar to those for HDL. (Means for LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides are summarized in Table 2.) Analysis of variance demonstrated significant differences between groups for changes in LDL (F [3/60] = 3.17, P < 0.05). Duncan's new multiple-range tests showed that the diet group experienced significant decreases in LDL in comparison with the other groups (14 mg/dl). However, these results should be interpreted cautiously because the diet group had higher LDL values at the initial visit (although the differences were not statistically significant). Differences in changes in triglycerides were nonsignificant. There were no interactions between HDL changes and medical regimen. In other words, the results were not significantly different for patients taking insulin, oral hypoglycemic medication, or no medication. There was a significant negative correlation between changes in LDL and changes in triglycerides (r = -0.52, P < 0.01). Decreases in LDL were correlated with increases in triglycerides.

As expected, women had higher levels of HDL cholesterol than men (t = 2.79, df = 63, P < 0.01). However, the only difference between men and women for changes in HDL was in the diet plus exercise group. Men in this group experienced a slight decline in HDL (2.5 mg/dl), while women experienced an increase (3.88 mg/dl). However, this difference was only marginally significant (t = 1.78, df = 15, P < 0.10).

Six months after the initiation of the program, a second optional exercise EKG was performed. Fifty-one patients volunteered for this test. Chi-square tests showed that those taking the second EKG were not different from the original sample by sex and treatment group distribution. A three-way factorial analysis of variance (diet × exercise × sex) revealed only one significant effect before treatment (F [1/44] = 10.28, P < 0.01). Men exhibited greater oxygen consumption than women (27.87 versus 20.25 ml/min/kg) but within sex groups all treatment conditions were comparable. After 6 mo (3 mo after the completion of the treatments) there was a significant two-way interaction between diet and exercise (F [1/44] = 4.30, P < 0.05) and a significant three-way interaction between diet, exercise, and sex (F [1/44] = 11.68, P < 0.01). Further analysis revealed that the exercise group improved physical conditioning more than the other groups, but that this effect characterized men but not women.

A variety of analyses failed to demonstrate the effect of the interventions on diabetes control as measured by glycosylated hemoglobins. However, these effects may not be expected to appear until some time after the weight loss has been achieved.

**DISCUSSION**

Data from the present study show that a dietary behavior modification condition produces short-term changes in weight, HDL, and possibly LDL for patients with NIDDM. Patients participating in an exercise, diet plus exercise, or education control group did not experience the same change in weight and lipids.

The results of this study are consistent with several previous reports showing that weight loss is accompanied by increases in HDL. In particular, Olefsky et al. successfully demonstrated that caloric restriction resulted in increases in HDL cholesterol in both normal and hyperlipoproteinemic patients. The design of our study does not allow us to separate the effects of dietary characteristics (i.e., high-complex car-
HDL CHOLESTEROL CHANGES AFTER DIET AND PHYSICAL CONDITIONING/R. M. KAPLAN AND ASSOCIATES

bohydate) from the effects of weight loss. It is of some interest that in India HDL cholesterol has been found to be higher in undernourished diabetic adults in comparison with well-nourished diabetic adults.24

The results for the exercise interventions are difficult to interpret. There was a significant physical conditioning effect for men but not women in the exercise group. Although some investigators have shown increases in HDL concentrations after a physical conditioning program,18-20 others have failed to find these effects.21 Furthermore, the change in HDL concentrations may be dependent on the intensity and duration of the exercise conditioning sessions.25,26

It is important to note, however, that the exercise program in the present study began very slowly and at a low intensity (60-70%). Since the population was sedentary and high in body fat, the exercise progression was done slowly to avoid injury and drop-out. A continuous aerobic stimulus was not maintained until the last part of the intervention. In addition, the exercise stimulus was not introduced to the diet and exercise group until the last 5 wk of the intervention. Failure to obtain a conditioning effect for women may have resulted from the failure to progress to a sufficient level of exercise intensity. However, studies by Frey and Doerr27 and Wynne and Frey28 found that 10-wk programs improved cardiovascular fitness without affecting HDL concentrations. Two recent papers report failures to increase HDL or improve metabolic control among NIDDM patients assigned to exercise at a variety of intensities. One of these studies maintained patients at a constant weight29 while the other achieved significant weight loss.30

In contrast, Lopez and colleagues19 found increases in HDL after physical conditioning. The HDL increases were delayed, however, and occurred only after several weeks of training. We are continuing to follow this group of patients at 6-mo intervals and hope to report long-term effects on HDL in future papers.

Finally, it is important to comment on subfractions of HDL. HDL cholesterol is carried by two subfractions of HDL: HDL2 and more dense HDL3. New evidence suggests that only the HDL2 subfraction may be inversely associated with CHD. The HDL1 subfraction is considered unrelated to heart disease.31 Exercise may increase HDL2 but promotes slight decreases in HDL3. Thus, net benefits of exercise may be masked when only total HDL is studied.32 The effects of dietary changes on HDL2 are not well characterized in the literature. Future investigations may focus on HDL subfractions.

ACKNOWLEDGMENT: This work was supported by Grants RO1 AM 27901 and KO4 00809 from the National Institutes of Health, NIADDK.

REFERENCES


From the Center for Behavioral Medicine, San Diego State University, San Diego, California 92182.

Address reprint requests to Robert M. Kaplan, Ph.D., at the above address.


