Apolipoprotein, Low Density Lipoprotein Subfraction, and Insulin Associations with Familial Combined Hyperlipidemia

Study of Utah Patients with Familial Dyslipidemic Hypertension

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Familial dyslipidemic hypertension (FDH) is a syndrome recently described from sibships selected for early familial hypertension and found to have one or more of three fasting lipid abnormalities [high triglycerides, low high density lipoprotein (HDL) cholesterol, high low density lipoprotein (LDL) cholesterol]. In further analyses of these same 131 hypertensive subjects, apolipoprotein A-I and B, fasting plasma insulin (adjusted for body mass index), and detailed anthropometrics were different in two subgroups of FDH. Of 83 FDH patients, 19 met the criteria for familial combined hyperlipidemia (FCHL); 44 did not, but still had high triglyceride and/or low HDL cholesterol levels. When compared to 20 normolipidemic hypertensive patients, the 19 hypertensive patients with FCHL had 196% higher very low density lipoprotein cholesterol ($p=0.0001$), 33% higher apolipoprotein B ($p=0.0002$), smaller LDL particles ($p=0.007$), and 73% higher fasting insulin ($p=0.003$), (HDL) cholesterol. In the other 44 FDH patients without FCHL, only 33% lower HDL ($p=0.0001$), with only 3% lower apolipoprotein A-I levels ($p=0.20$), significantly higher subscapular skinfolds ($p=0.02$), weights ($p=0.002$), body mass index ($p=0.006$), knee widths ($p=0.0007$), and waist circumferences ($p=0.0009$), smaller, denser LDL subfractions ($p=0.001$), and increased apolipoprotein B levels ($p=0.01$) compared to the normolipidemic hypertensive group. Increased fasting insulin levels were similar to the normolipidemic group and significantly lower than the FCHL group after adjustment for body mass index, suggesting a relationship between obesity and fasting insulin levels only in the non-FCHL group.

We conclude that FDH consists of at least two subgroups: 1) FCHL with high apolipoprotein B, small LDL particles, and increased fasting plasma insulin levels, and 2) a less well-defined residual having upper central obesity with low HDL cholesterol and high triglyceride levels. Elevated insulin levels found in both groups, but possibly originating through different physiological mechanisms, may provide the pathophysiological connections between dyslipidemia, obesity, and hypertension. (Arteriosclerosis 9:335–344, May/June 1989)

Abnormal lipids and hypertension are both risk factors for coronary artery disease. Both aggregate in families with proven genetic transmission of certain lipid abnormalities. In an effort to find subsets of hypertensive individuals who may have specific genetic syndromes, we examined 131 individuals from 58 Utah sibships having two or more siblings with the onset of hypertension before age 60. The most striking concordant abnormalities in these sibships were high density lipoprotein (HDL) cholesterol levels below the age- and sex-specific 10th percentile 3.9 times more often than expected, and triglyceride and low density lipoprotein (LDL) cholesterol levels above the 90th percentile 3.0 and 1.9 times, respectively, more often than expected. Hyper tension before age 60 occurring in two or more siblings who also have some lipid abnormality was descriptively referred to as "familial dyslipidemic hypertension" (FDH). It seems to occur in 15% or more of patients with hypertension and in at least one half of patients with early familial hypertension.

In the report, apolipoproteins (apo) A-I and B, low density lipoprotein (LDL) subfractions, fasting plasma insulin levels, and detailed anthropometric measures were analyzed to more fully characterize patients with FDH and to investigate whether FDH might be a mixture of hypertensive patients with two or more dyslipidemic syndromes.

**Methods**

Details of patient selection and hypertension validation have been given previously. The families were selected from a population-based collection of 15 475 "Health...
Family Trees’ filled out by the parents of high school students, which give the family’s reported family history of common cardiovascular and cancer diseases. Of 24569 living individuals with reported hypertension from 8122 sibships with one or more siblings with hypertension, 6129 (25%) were in 2226 sibships reported to have two or more siblings with onset of hypertension before age 60. The hypertensive siblings living within a 50-mile radius of Salt Lake City were contacted by mail and telephone to validate their hypertension and to invite the validated hypertensive siblings to clinic.

A person with hypertension was defined as one who was currently on antihypertensive medication or had previously been on antihypertensive medication and had a blood pressure above 140/90 mm Hg during the visit to the University of Utah Cardiovascular Genetics Clinic. The first 131 subjects in 58 sibships having confirmed early familial hypertension who were evaluated at our clinic between October 1986 and May 1987 were analyzed for this report. Since many Utah families are large, it was required that at least 30% of the sibship had hypertension. The mean total sibship size was 5.9 siblings, ranging from two to ten siblings. Therefore, in sibships of seven or more, there had to be at least three hypertensive siblings.

**Definition of Familial Dyslipidemic Hypertension Syndrome**

FDH is a term used to describe two or more siblings with early familial hypertension (before age 60) who also have one or more of three lipid abnormalities: LDL cholesterol or triglycerides greater than the 90th percentile or HDL cholesterol less than the 10th percentile of the Lipid Research Clinic’s tables. Of 58 sibships with early familial hypertension, sibships where only one of the two or more hypertensive siblings had an abnormal lipid profile were classified in our earlier report as discordant sibships (n=21) and are only included in the bimodality analyses described below. Those that had hypertensive siblings with no abnormal lipid profiles (n=10) were labeled concordant normolipidemic sibships (with early familial hypertension).

The sibships with FDH were subdivided into those with (19 sibships in 8 sibships) and without (44 sibships in 19 sibships) familial combined hyperlipidemia (FCHL), defined as at least one sibling with LDL cholesterol above the 90th percentile and at least one other sibling with triglyceride levels above the 90th percentile. If these criteria were met, then all hypertensive siblings with any lipid abnormality in that sibship were classified as belonging to a familial combined sibship, even if they only had normal HDL levels. Six hypertensive siblings with normal lipids (two in familial combined sibships and four in other FDH sibships) were excluded from the comparisons of the two subsets of FDH since they apparently did not have FDH.

**Clinic and Laboratory Measurements**

Fasting blood samples, obtained between 9:00 A.M. and 9:00 A.M., were analyzed for total cholesterol, HDL cholesterol, triglycerides, very low density lipoprotein (VLDL) cholesterol, and LDL cholesterol. Calculated LDL was used in the analysis for the definition of FDH since the age- and sex-specific percentile Lipid Research Clinic tables were based upon calculated LDL. However, if the triglyceride level was greater than 400 mg/dl, then the measured LDL cholesterol level was used. The means for measured LDL versus calculated LDL cholesterol for patients with triglyceride levels under 400 mg/dl were less than 2 mg/dl apart, with a correlation of 0.91. The difference between calculated and measured LDL was not correlated with triglyceride level.

A fast micromethod for fractionation of plasma lipoproteins and quantification of their cholesterol content was used to assay LDL and VLDL cholesterol. Plasma lipoproteins (200 μl of EDTA plasma) were centrifuged in a Beckman TL-100 table-top ultracentrifuge for 4 hours at 60K rpm at room temperature and then separated into top (VLDL) and bottom (LDL and HDL) fractions by silicic. The measured HDL cholesterol was then subtracted from the cholesterol concentration in the bottom fraction to obtain the LDL cholesterol concentration.

Apo A-I and apo B were assayed by kinetic nephelometry using Beckman reagents. Bands 1 through 7 of the LDL subfractions were identified by gradient gel (2% to 16%) electrophoresis as described by McNamara, et al. with the following modifications: A 10:3 (vol/vol) mixture of EDTA plasma and sucrose/bromphenol blue with 50% sucrose was used; 3.0 μl of buffer cooled to 5°C was added to a Pharmacia GE 2/4 apparatus (Pharmacia, Incorporated, Piscataway, NJ); and 8 to 10 μl of plasma/sucrose sample was added per lane. Sudan black B stain (Beckman Instruments, Incorporated, Brea, CA) was used on the gels. For statistical analysis, the major band was used when multiple bands were present. Insulin was measured by a magnetic solid phase radioimmunoassay kit (Serono Diagnostics, Norwell, MA).

Height (mm) without shoes was measured with a stadiometer. Weight was measured to the nearest 0.5 pounds with an adjustment for clothing. Body mass index was calculated as weight (kg) divided by height (m) squared. Skinfold thicknesses were measured according to standard procedures by using Harpenden calipers and averaging three measurements at each site. Knee and ankle widths were measured with slide calipers, while wrist circumference, waist, and hip girth were measured with a steel tape. Waist girth was measured at the midpoint between the 12th rib and the iliac crest, and hip girth was measured at the maximum circumference over the buttocks.

The lipid values were adjusted for the medication effects of diuretics and beta-blockers with data from other published long-term studies, as described previously. The adjustment factors were all 5% or less, except for the effects of beta-blockers on triglycerides and VLDL cholesterol which were 20%.

**Statistical Methods**

Triglyceride and VLDL cholesterol values were natural log transformed to remove skewness. Two individuals from different sibships with triglyceride levels over 1000 mg/dl (1940 and 2270 mg/dl) were taken out of the sample when analyzing triglycerides and VLDL cholesterol to remove outlier effects on the regression equations and comparisons of the means. Analysis of covariance using
the SAS (SAS Institute, Cary, NC) general linear model procedure was used to adjust the variables for age, sex, and a sex-age interaction term. Since many of the variables are associated with obesity, another model was also fit and adjusted for body mass index. The means of the adjusted variables are reported along with the standard error of the mean.

Maximum likelihood analysis was used to test whether the insulin and apo B distributions could actually be a mixture of two or three distributions. Tests for bimodality and trimodality were done assuming one to three modes normally distributed with either common or separate standard deviations. If assuming separate standard deviations for the distributions did not significantly increase the fit of the model, common standard deviations were used.

Results

About one third of the sibships with FH met lipid criteria for having FCHL. While their mild hypertension was being treated, only three patients were receiving treatment for their more severe dyslipidemia. Table 1 shows the distribution of lipid abnormalities in individuals and in sibships for sibships classified with and without FCHL. About one half of individuals with FCHL had isolated LDL cholesterol (24%) or triglyceride (24%) abnormalities, while 19% had triglyceride and HDL cholesterol abnormalities. In the non-FCHL group, 40% had isolated HDL cholesterol abnormalities, with another 31% having both HDL cholesterol and triglyceride abnormalities. Almost two thirds of the FCHL sibships had HDL cholesterol abnormalities. Fifty-eight percent of the non-FCHL sibships had triglyceride and HDL cholesterol abnormalities, while another 28% had triglyceride and LDL cholesterol abnormalities. Only one sibship appeared to have isolated low HDL cholesterol.

Comparison of FCHL and Non-FCHL Subgroups

Table 2 compares the normal lipid group to the FH group subdivided into those with FCHL and those without FCHL (non-FCHL). The ages and male/female ratios of the three groups are similar. Siblings with FCHL had higher total cholesterol, LDL cholesterol, apo B, triglycerides, HDL cholesterol, and apo A-I than those with non-FCHL. These age- and sex-adjusted differences remained significant for further adjustment for body mass index. The LDL subtraction distributions were not different between the two groups, nor were the ratios of apo B to LDL cholesterol or of apo A-I to HDL cholesterol.

Fasting insulin levels were not significantly higher in the FCHL than the non-FCHL group (p=0.21) until after adjustment for body mass index (p=0.004). Adjusting for body mass index decreased the non-FCHL group mean insulin level to 16.2 mU/l and increased the mean insulin level to 22.1 mU/l in the FCHL group. Fasting plasma glucose levels were not different between the two groups. The non-FCHL group had larger waist circumferences and knee and ankle widths than the FCHL group. After adjusting the triceps skinfold thickness for body mass index, the non-FCHL group had significantly thinner (19.7 mm) triceps skinfolds than did the FCHL group (22.7 mm, p=0.04).

Familial Dyslipidemic Subgroup Compared to Normal Group

The mean LDL subtraction band was higher (smaller LDL) in the two FH subgroups than in the normal group. The differences in the percentages of individuals with major bands 5 or 6 (smaller LDL) versus those with the less dense bands 1 and 2 were even more remarkable (Figure 1). There were 35.0%, 47.9%, and 5.0% of the FCHL, non-FCHL, and normal groups, respectively, that had bands 5 or 6 as the major band compared to 20.0%, 16.7%, and 35.0% of having bands 1 or 2.

The FCHL group was mildly (but not significantly) more obese than the normolipidemic hypertensive group with respect to all of the anthropometric variables. However, the non-FCHL group had significantly greater knee widths (p=0.0007), waist circumferences (p=0.0009), weight (p=0.002), body mass index (p=0.006), and subcapular
Table 2. Age- and Sex-adjusted Study Variable Means of Utah Patients with or without Familial Combined Hyperlipidemia

| Variable                     | FCHL       | Non-FCHL * | Normolipidemic | ρ: FCHL vs. non-FCHL |
|------------------------------|------------|------------|----------------|----------------------|
| Males/females                | 8/11       | 22/22      | 10/10          | 0.56                 |
| Age (years)                  | 47.9±1.9   | 46.6±1.2   | 47.0±1.8       | 0.57                 |
| Total cholesterol (mg/dl)    | 267±6.9†   | 220±4.2    | 202.5±9.1      | 0.0001               |
| LDL cholesterol (mg/dl)      | 166.7±6.7‡ | 141.2±5.8  | 136.2±8.5      | 0.02                 |
| VLDL cholesterol (mg/dl)     | 39.7±1.2   | 29.8±1.1†  | 13.4±1.2       | 0.13                 |
| HDL cholesterol (mg/dl)      | 41.4±2.3   | 33.6±1.5†  | 49.9±2.2       | 0.006                |
| Triglyceride (mg/dl)         | 248.4±1.1† | 184.0±1.1† | 84.2±1.1       | 0.03                 |
| Apolipoprotein B (mg/dl)     | 122.0±5.6§ | 108.6±3.7‖ | 91.4±5.4       | 0.05                 |
| Apolipoprotein A-I (mg/dl)   | 102.9±5.0  | 90.1±3.3   | 97.9±5.0       | 0.04                 |
| LDL subfraction (band 1-7)   | 4.01±0.29‖ | 4.00±0.16‖ | 2.93±0.27      | 0.97                 |
| Fasting insulin (mU/l)       | 20.7±2.0‖  | 17.7±1.3‡  | 12.0±2.0       | 0.21                 |
| Fasting glucose (mg/dl)      | 106.7±7.6  | 102.6±5.0 | 90.2±7.4       | 0.66                 |
| Height (cm)                  | 172.5±1.6  | 172.5±1.1  | 169.5±1.6      | 0.99                 |
| Weight (kg)                  | 85.2±4.0   | 94.1±2.7‖  | 78.7±3.9       | 0.07                 |
| Body mass index (kg/m²)      | 28.5±1.3   | 31.6±0.8‖  | 27.4±1.2       | 0.04                 |
| Triceps skinfold (mm)        | 21.4±1.7   | 21.3±1.1   | 18.7±1.6       | 0.97                 |
| Subscapular skinfold (mm)    | 27.7±2.4   | 29.8±1.5‖  | 23.2±2.2       | 0.47                 |
| Suprailiac skinfold (mm)     | 24.2±3.0   | 26.1±2.0   | 19.5±3.0       | 0.51                 |
| Waist/hip ratio              | 0.90±0.02  | 0.89±0.01  | 0.87±0.01      | 0.52                 |
| Knee width (mm)              | 93.1±1.9   | 99.6±1.3§ | 91.8±1.8       | 0.006                |
| Ankle width (mm)             | 65.9±1.00  | 70.3±0.66  | 66.8±0.97      | 0.0004               |
| Wrist circumference (cm)     | 15.5±0.64  | 17.5±0.41§ | 15.0±0.60      | 0.01                 |

Values are means±SE.

*Familial dyslipidemic hypertension without familial combined hyperlipidemia (FCHL).
†p<0.0001, ‡p<0.05, §p<0.001, ‖p<0.01, FCHL or non-FCHL vs. normolipidemic group.

Skinfolds (p=0.02) than did the normal group. Figure 2 shows the percent increase of the two FCH subgroup means compared to the normal group for plasma insulin and anthropometric variables. Upper central obesity in the non-FCHL group is suggested by subscapular skinfolds 28% above and triceps skinfolds only 14% above the normolipidemic group. The ratio of scapular to triceps skinfold thickness was higher in non-FCHL (1.65) than in either FCHL (1.54, not significant) or normolipidemic (1.36, p=0.03) hypertensives. The FCH subgroups had much higher fasting plasma insulin levels, but not fasting plasma glucose levels, than the normolipidemic group.

Figure 3 shows similar comparisons for lipid and lipoprotein concentrations. The non-FCHL group had high VLDL cholesterol levels, low HDL cholesterol and apo A-I levels, and normal LDL cholesterol levels which (from Figure 1) consisted of smaller LDL particles. The ratios of apo B to LDL cholesterol and apo A-I to HDL cholesterol were significantly higher in the non-FCHL group compared to the normolipidemic group (2.85 vs. 1.99, p=0.002 for apo A-I/HDL-C and 0.80 vs. 0.68, p=0.004 for apo B/LDL-C). The FCHL group had similar apo A-I but reduced HDL cholesterol levels compared to the normolipidemic group, with elevated LDL cholesterol and apo B levels.

Figure 1. Percent of study patients with low density lipoprotein (LDL) subfraction bands 1–2, 3–4, and 5–6 for these hypertensive subgroups: Familial combined hyperlipidemia (FCHL), other lipid abnormalities (Non-FCHL), and normolipidemia. The higher numbered bands represent smaller LDL particles.
Figure 2. Percent difference in mean plasma insulin, body mass index, triceps and subscapular skinfold thicknesses of two subgroups of patients with familial dyslipidemic hypertension (FDH), familial combined hyperlipidemia (FCHL), and nonfamilial combined hyperlipidemia (Non-FCHL) compared to normolipidemic patients with early familial hypertension.

Figure 3. Percent difference in mean lipids and lipoproteins of two subgroups of patients with familial dyslipidemic hypertension (FDH), familial combined hyperlipidemia (FCHL), and nonfamilial combined hyperlipidemia (Non-FCHL) compared to normolipidemic patients with early familial hypertension.

The ratios of apoproteins with lipoprotein cholesterol in FCHL were not significantly different from the normolipidemic group. VLDL cholesterol levels were almost 200% higher than in the normolipidemic group.

**Bimodality Analyses**

Since insulin levels and apo B levels were significantly associated with FCHL, a suggested major gene trait, an analysis for bimodality or trimodality of these two variables was done using all 131 siblings selected only for early familial hypertension. Neither distribution was significantly non-normal after age and sex adjustment; however, both had a few outlier values that seemed higher and separate from the main distribution. Often in these analyses significant multimodality may be found because an upper distribution that contains only these few extreme values is fitted. Therefore, a trimodal model was used to allow these few values to define one mode, while allowing the remaining values to be divided into two modes.

Table 3 shows the adjusted means, standard deviations, and percent of points in each mode for one-, two-, and three-mode models. The \( \chi^2 \) statistic was calculated for each model versus the previous model, that is, model 2 versus model 1 and model 3 versus model 2. Apo B appeared to be bimodal \( (p=0.003) \), with 15% of the sample in the upper distribution. The three-mode model was not significant, but does give an indication where the large lower distribution could be divided after the upper outlying points are included in a high third mode. The means of the two lower distributions are over two standard deviations apart. A common standard deviation for each distribution fit as well as different standard deviations and had fewer parameters to estimate; therefore, this is presented in the table. There were 10 FDH patients with apo B levels above 137 mg/dl (which is the mean of the lower distribution plus two standard deviations). One half of the 10 had FCHL, while two of the non-FCHL patients had LDL abnormalities, but no triglyceride abnormalities. The remaining three patients were from the same sibship that probably had FCHL but had LDL cholesterol levels between the 85th and 89th percentiles and were classified as having non-FCHL.

Insulin was significantly trimodal \( (p=0.003) \); however, there were only four points (3%) in the highest mode. The means of the two lower distributions were 1.9 pooled standard deviations apart with 65% of the insulin values in the upper distribution. The two lower modes were still significantly different \( (p=0.0009) \) when using a bimodal model after deleting the four values in the high distribution.

Both insulin and apo B appear to be bimodal in this sample of early familial hypertensive patients. Although a bivariate analysis of bimodality for insulin and apo B was not done, the linear correlation between the two variables from all 131 patients was not significant \( (r=0.12, p=0.19) \).

**Discussion**

FDH appears clinically as LDL cholesterol, total triglycerides, and HDL cholesterol values in the extreme 10th percentile in hypertensive patients with early (before age 60) familial hypertension. FDH families seem to divide into two subgroups: FCHL with high apo B and very high VLDL cholesterol and insulin; or non-FCHL with low apo A-I, very low HDL cholesterol, and moderately high VLDL cholesterol and plasma insulin. A shift of the LDL distribution toward smaller LDL particles and increased obesity were present in both subgroups of FDH.

Hypertension, obesity, low HDL cholesterol, and high apo B levels have been associated with FCHL. The Lipid Research Clinic study found twice as much hypertension in patients with type II-B or IV lipid abnormalities than controls. Both these types (defined for individuals, not families) have elevated triglycerides and have similarities to the two familial syndromes found in our FDH group. Of the 69 patients in FDH sibships, 46 (67%) had triglyceride or HDL cholesterol abnormalities or both, without LDL cholesterol problems.
Table 3. Bimodality Analysis of Apolipoprotein B and Insulin Levels In Utah Patients with Early Familial Hypertension

| Distribution | First mode | Second mode | Third mode | Significance level* |
|--------------|------------|-------------|------------|---------------------|
| Apolipoprotein B (mg/dl) | | | | |
| Unimodal | 106.5±25.6 | | | |
| Bimodal | 99.2±18.9 | 147.6±18.9 | | 0.003 |
| Trimodal | 90.1±14.0 | 119.8±14.0 | 160.6±14.0 | >0.10 |
| Plasma insulin (mU/L) | | | | |
| Unimodal | 15.6±8.4 | | | |
| Bimodal | 8.5±3.0 | 19.2±7.9 | | 0.0005 |
| Trimodal | 7.9±2.7 | 18.2±6.3 | 40.3±1.5 | 0.003 |

Values are means±SD. Proportions are in parentheses.

*Significance test vs. distribution with one less mean. Equal standard deviations fit better for apolipoprotein B, while unequal standard deviations fit better for plasma insulin.

It was originally suggested that FCHL is caused by a single gene affecting triglyceride levels with secondary effects on cholesterol levels.14 FCHL may be present in over 10% of early coronary heart disease patients.25 We found that 30% (8/27) of our FDH sibships met criteria for having FCHL, while the other 70% seemed to be a group of dyslipidemic hypertensive patients with different characteristics. In our total sample (selected only for early familial hypertension), FCHL was found in almost one sixth of the sibships.

Because the differences in lipid, insulin, and anthropometric variables suggest that FDH patients are a mixture of at least two different subgroups, FCHL probably does not include families with abnormal triglycerides and HDL cholesterol levels in the absence of increased LDL cholesterol, even though low HDL cholesterol was present in five of eight of the FCHL sibships. Data in these families also suggest that some misclassification of FCHL or non-FCHL is unavoidable if only these standard lipid test results and cut-point definitions are used. In several of the FCHL families with three or four affected siblings, failing to screen a single sibling with high LDL cholesterol would leave two or more other siblings with high triglycerides, low HDL, or both that would be classified as non-FCHL without the other sibling. In several families, siblings with lipid values just short of the extreme 10th percentile cut-points probably have FCHL. Three sibships were not classified as having FCHL because one sibling was only one mg/dl below the 90th percentile for either LDL cholesterol or triglyceride level. Considering the inevitable misclassification of some subjects, the magnitude of differences between FCHL and non-FCHL for pertinent variables in Table 2 may be conservative underestimates of real differences.

Higher fasting insulin levels in the FCHL group compared to the normolipidemic group, even after adjustment for body mass index, suggests that the increased insulin in the FCHL group was probably not obesity-related but rather, was associated with higher triglycerides and VLDL cholesterol levels caused by the underlying FCHL defect. However, obesity could compound the abnormal triglyceride and insulin profiles. The insulin increase in the non-FCHL group seemed to be more directly related to obesity and its associated triglyceride increases. Fasting serum glucose levels were similar between the two groups and do not account for the difference in insulin levels. It is important to keep in mind that the "normal group" consisted of patients with normal lipids, but with early familial hypertension. Even though there was no obesity difference between the FCHL and normal groups, both groups tended to be obese with mean body mass index values of 29 and 27 kg/m², respectively. The differences between the two FDH subgroups indicated that those without FCHL had larger body frame size and more obesity but similar fat patterning as the FCHL group.

LDL subtraction distributions showed a similar percentage increase in bands of smaller LDL (suggesting more coronary risk26) in both dyslipidemic subgroups, despite significantly increased LDL cholesterol and apo B concentrations in the FCHL subgroup. The HDL cholesterol and apo A-I concentrations were lower in the non-FCHL group than in the FCHL group with no difference between the two groups for the ratio of apo A-I to HDL cholesterol.

The sibships with FDH, but without FCHL are less clearly defined and may themselves be heterogeneous. Table 1 indicates there may be three subgroups: 1) increased LDL and decreased HDL cholesterol (37%), 2) increased triglycerides and decreased HDL cholesterol (58%), and 3) low HDL cholesterol (5%). These sibships had even lower HDL cholesterol levels than the FCHL group with moderate triglyceride and VLDL cholesterol elevations. The triglycerides were not at the level of familial hypertriglyceridemia and yet were elevated enough to make a diagnosis of a pure familial low HDL abnormal-
itty doubtful (except, perhaps, for one sibling). Even though 40% of the non-FCHL patients had isolated HDL cholesterol abnormalities, all but one non-FCHL sibling had other lipid abnormalities in the other siblings. The associations with body size and skinfold thicknesses indicate that obesity is involved. Body frame measurements (wrist and knee) were increased in the non-FCHL group even after adjustment for body mass index.

Although it is still unclear to what extent diuretic medications affect glucose or insulin levels, differences in the types of medications taken by patients in the FDH and normal hypertensive groups could have contributed to the insulin differences. However, medication usage was similar in the two groups, with 32% taking diuretics only, 43% taking beta-blockers with or without diuretics, and 25% taking other forms of medication in the FDH group compared to 30%, 50% and 20%, respectively, for the normal lipid group. Also, a differential medication effect between subgroups would be expected to influence plasma glucose as well as insulin, which did not appear to be the case. The greater possibility of misclassification due to medication effects was in defining FDH. Even though we adjusted for the reported long-term medication effects on the lipids to define FDH, this "mean" adjustment may not be adequate for individual patients.

**Possible Pathophysiologic Mechanisms**

One study found that 69% of the variance of the LDL subfraction distribution could be explained by plasma triglycerides and HDL cholesterol. In our study, triglycerides and HDL cholesterol explained 51% of the variance. These correlations accounted for the smaller LDL found in both the FCHL and non-FCHL groups, since they had familial lipid patterns of increased triglycerides and low HDL. Apo B has been shown to be higher and apo A-I lower, in patients with the smaller LDL subfractions. Our FCHL group had elevated apo B levels, while the non-FCHL group had increased apo B and somewhat reduced apo A-I levels, in conjunction with small LDL in both groups. Also it has been suggested that small, dense LDL is inherited with a single locus determining the distribution. Therefore, the association of small, dense LDL with familial lipid abnormalities further supports a genetic etiology.

An increased prevalence of diabetes or glucose intolerance in conjunction with increased insulin levels and obesity in the two dyslipidemic groups might be expected. High triglyceride and low HDL cholesterol are also characteristics of noninsulin-dependent diabetes mellitus. However, only four patients in the non-FCHL group had type II diabetes (three on medication, one on dietary therapy), and one other had an elevated fasting serum glucose level (>140 mg/dl) and glycosuria. There was one medicated diabetic and two patients with elevated glucose levels in the FCHL group. We do not have glucose tolerance data on these patients to help identify the presence of a glucose intolerant state, which itself is familial. However, because of the elevated insulin levels in these two groups, many would likely show some glucose intolerance. Despite probable differences in primary etiology, both groups of FDH patients may share some intermediate steps in pathophysiology relating hyperinsulinemia, dyslipidemia, and hypertension to each other.

Many studies, in both diabetic and normal populations, have documented a consistent association between higher fasting insulin levels and increased plasma triglycerides and decreased HDL cholesterol concentrations. In one population, joint alterations in VLDL, LDL, and HDL cholesterol were associated with hyperinsulinemia while isolated VLDL or LDL and HDL cholesterol alterations were not. The increased insulin levels in our FCHL group, with frequent presentation of multiple lipid abnormalities, is consistent with these findings.

The role of insulin with respect to hypertension is still unclear. One study found a univariate association between insulin and blood pressure or hypertension, but not after adjusting for other variables, such as obesity, fat patterning, or plasma glucose concentration. Other studies have found independent associations, associations only in diabetics, or associations only in the obese. Another found higher insulin levels in hypertensive patients who were not obese. These differences may arise from the different characteristics of the population sample used in each study. Hypertension is likely quite heterogeneous, with some types unrelated to insulin and other types, like FDH, in which hyperinsulinemia may well play an important role.

Many normotensive persons have dyslipidemias like those found in this hypertensive population. However, as we have previously shown, there is a strong association between familial hypertension and the lipid abnormalities. What are some likely explanations relating hypertension to dyslipidemia? Is insulin one of the links between the two diseases? Insulin and glucose abnormalities seem to be linked to dyslipidemia and coronary artery disease, both in cross-sectional and prospective follow-up studies. Free fatty acid infusion can result in insulin resistance and there is an elevated insulin response to a glucose load in patients with elevated triglyceride turnover. Incubation of various cell lines with VLDL results in insulin resistance associated with either a decrease in insulin receptors or postbinding resistance. Increased insulin also favors triglyceride production, forming a vicious cycle.

Hypertension in obese and normal weight patients has been related to an insulin-resistant state. The most common explanations for these insulin relations are alterations of sympathetic stimulation and renal sodium reabsorption. One study has shown alterations in intracellular sodium and potassium concentrations associated with glucose intolerance, obesity and hypertension, while others have shown that sodium-potassium exchange and sodium-hydrogen exchange across cell membranes are increased in the presence of insulin. Other transport systems, such as sodium-lithium counter-transport or lithium-potassium co-transport, may also be involved, since they have been shown to be associated with lipids, hypertension, and body mass index.

A possible sequence of events might be that genetic inheritance of a specific lipid abnormality, such as FCHL,
may be associated with insulin resistance, resulting in hyperglycemia, and/or hyperinsulinemia. In the non-FCHL group, obesity-related VLDL cholesterol increases may produce the insulin resistance. These alterations in the glyceric state, along with lipid changes in cell membrane composition, could then have cellular level effects upon the ion transport mechanisms that control blood pressure. There is ample evidence that free fatty acids and lipids can change cellular membrane composition and transport properties,17-18 although a recent study has shown that, after exercising, to produce lipid changes, these changes did not correlate with the changes in the ion transport systems.19

Therefore, even though we have learned many of the details involved in coronary heart disease, hypertension, diabetes, and obesity, we have much work to do before a cohesive understanding of the pathophysiology is obtained. This understanding probably will not come until we can first subdivide large groups of patients into smaller homogeneous subgroups, each with their own characteristics, to prevent dilution or confounding of associations due to different disease etiologies.

Because we found a high prevalence of FCHL in sibships selected only for early familial hypertension, normotensive persons with FCHL should have annual blood pressure screening. Also, all patients found to have early familial hypertension should routinely have total cholesterol, triglycerides, and HDL cholesterol levels determined. Perhaps this recommendation should also be extended to all hypertensive patients regardless of age. If abnormal levels are found, the patient should be strongly advised to encourage all first-degree relatives to have their lipid levels measured.

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Index terms: anthropometrics • apolipoproteins • coronary artery disease • genetics • hyperlipidemia • hypertension • insulin • low density lipoprotein subtractions