Hyperinsulinemia Is Characterized by Jointly Disturbed Plasma VLDL, LDL, and HDL Levels

A Population-Based Study

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Plasma very low density lipoprotein (VLDL) cholesterol and triglyceride, low density lipoprotein (LDL) cholesterol and triglyceride, high density lipoprotein (HDL) cholesterol, glucose and insulin response (sums of 1- and 2-hour postload oral glucose levels), body mass index (BMI), and blood pressure were determined in a representative sample (n = 542) of the adult Israeli Jewish population. Persons with diabetes or on antihypertensive medications were excluded. Total VLDL and LDL fractions were estimated from their cholesterol and triglyceride subtraction levels that were standardized relative to the mean of the reference group (participants free of glucose intolerance, obesity, and hypertension—the GOH conditions). Hyperinsulinemia and disturbed levels of VLDL and LDL were defined as levels equal to or greater than the 75th percentile and those of HDL, equal to or less than the 25th percentile of their respective reference group distributions. When VLDL was disturbed jointly with LDL and HDL, the mean insulin response adjusted for age, gender, glucose response, BMI, blood pressure, and smoking was high compared to the reference group (166.0 vs. 122.5, p < 0.001). With isolated disturbed VLDL, or disturbed LDL and HDL but normal VLDL, the mean insulin response resembled the reference group. The adjusted risk ratio for this jointly disturbed lipoprotein profile among hyperinsulinemic individuals was 3.4 (95% confidence limits 2.6 to 4.4, p < 0.001) with no further association with the GOH conditions. We conclude that hyperinsulinemia is characterized by an atherogenic lipoprotein profile. (Arteriosclerosis 8:227-236, May/June 1988)
Methods

Participants and Clinical Procedures

The current study investigated a subgroup of the Israel Study of Glucose Intolerance, Obesity, and Hypertension (The Israel GOH Study). Begun in 1969, this is an ongoing, nationwide, longitudinal study of a sample of 5711 individuals born between 1912 and 1941 (Phase I sample drawn from the Israel Central Population Registry). During 1969 to 1972, these individuals were visited at home where measurements of blood pressure, weight, and height and information on regular use of medications were obtained. Glucose tolerance was not examined in Phase I.

Between 1977 and 1982, a representative group of the original sample, 2769 participants (Phase II sample), had their weight, height, and blood pressure recorded and regular medication use verified by inspection of drug receptacles at home. Their blood pressures were measured with a standard mercury sphygmomanometer in the sitting position. Four measurements were obtained, two before and two after the interview. Consequently, they attended regional medical centers where their fasting plasma glucose was determined, and, for those persons not known to be diabetic, an oral glucose tolerance test was given. During 1979 to 1982, 1211 participants (ages 37 to 70 years), who were not known diabetics, were tested for fasting plasma lipoprotein and insulin response at 1 to 2 hours after the oral glucose load. All patients signed an informed consent form, and the study was approved by the hospital ethics committee.

The current study group was part of a representative subsample of 632 individuals from the group of 1211 selected for a dietary interview and for whom there was complete data on glucose tolerance, insulin response, and all lipoproteins. This subsample constituted 11.1% of the original Phase I sample. The recruitment rate was similar to that of the Phase I study. During the interview, these diabetics and nonobese (11.3%) or nonobese (10.7%), and in those in the youngest to the oldest, in both genders (11.4% in men and 10.7% in women), among individuals in Phase I who were obese (11.3%) or nonobese (10.7%), and in those in Phase I who were hypertensive (10.8%) or normotensive (11.2%). This suggests that there was no selection bias related to the GOH conditions.

For the purpose of the current analysis, diabetics and individuals on antihypertensive medications (including diuretics) were excluded, leaving 542 persons, 288 men and 254 women. Diabetics were excluded because we wanted participants in the range in which the degree of insulin resistance increases.11-14 Individuals on antihypertensive medications were excluded because this treatment may lead to a disturbed lipoprotein profile. Alcohol consumption in our group was low (mean 51 g/week, only 2% consuming >50 g/day), and the rate of use of any kind of estrogen by women was only 4.9%. Neither factor is associated with the GOH conditions.

Laboratory Procedures

Analysis and quality control of lipoprotein levels conformed to the Lipid Research Clinics Program. Plasma cholesterol and triglyceride levels (mg/dl) were determined with the Technicon Autoanalyzer II (AA-II) analytical system (Technicon Instruments Corporation, Tarrytown, NY). The total cholesterol measuring procedure adapted to the AA-II was the Liebermann-Burchard reaction. Triglycerides were analyzed fluorometrically after conversion to flurophore. Lipoproteins were separated by ultracentrifugation at a saline density of 1.006 g/ml to yield a supernatant fraction containing VLDL and an infranatant fraction containing both LDL and HDL. Cholesterol and triglycerides were measured in the total plasma and in the 1.006 g/ml supernatant and infranatant fractions. HDL cholesterol was measured in the 1.006 g/ml infranatant fraction after precipitation of the apo B-containing lipoproteins by means of heparin and manganese chloride.

Glucose (mg/dl) was determined by a routine automated Technicon Autoanalyzer II method by using potassium ferriicyanide reduction. Plasma insulin (mU/l) was determined in duplicate by using the Phadebas Radioimmunossay kit (Pharmacia Diagnostics, Piscataway, NJ). The within-assay coefficient of variation was 4% and the between-assay variation was 8%.

Data Analysis

The associations between lipoproteins, GOH conditions, and insulin response were analyzed by using both continuous and categorical forms of the variables. These variables are described below.

GOH Conditions

Relative weight. The continuous form was body mass index \(\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}\). The categorical form was obesity defined as BMI ≥ 25; this was mostly moderate obesity since only 13.5% of the subjects had BMI ≥ 31.

Blood pressure. The continuous form was systolic blood pressure. Diastolic blood pressure was not used because preliminary analysis indicated that systolic blood pressure accounted for all the effect. The categorical form was hypertension defined by at least two of the four measurements (mm Hg) showing either systolic blood pressure > 145 or diastolic blood pressure > 93. This was mostly mild hypertension, since diastolic blood pressure ≥ 100 was found in only 8% of the patients.

Glucose tolerance. The continuous form was the sum of 1- and 2-hour postload plasma glucose levels (sum glucose) representing the area under the glucose response curve, which is the established measure of glucose tolerance.1 The categorical form was glucose tolerance classified according to the National Diabetes Data Group criteria. We defined abnormal glucose tolerance as the combined categories of nondiagnostic and impaired glucose tolerance.

GOH categories. The study group was divided into two categories: 1) the reference group of individuals free of the GOH conditions (nonobese, normotensive persons with normal glucose tolerance), and 2) the GOH group of individuals with one or more of the GOH conditions.

Insulin Response

The continuous form was the sum of the 1- and 2-hour postload levels (sum insulin) as a measure of the area...
under the insulin response curve, which reflects insulin sensitivity. The categorical form was defined relative to the distribution of sum insulin in the reference group. Levels equal to or greater than the 75th percentile of this distribution were termed hyperinsulinemic.

Lipoproteins

Lipoprotein subfractions. The continuous form included the lipoprotein subfractions VLDL cholesterol (VLDL-C), VLDL triglycerides (VLDL-TG), LDL cholesterol (LDL-C), LDL triglycerides (LDL-TG), and HDL cholesterol (HDL-C). The categorical form included disturbed levels of VLDL-C, VLDL-TG, LDL-C, and LDL-TG which were defined as levels equal to or greater than the 75th percentile of their distribution in the reference group. Also included was HDL-C when it was equal to or less than the 25th percentile.

Estimating total VLDL, LDL, and HDL fractions. The lipoprotein measurements most relevant for this study would have been concentrations of the total VLDL, LDL, and HDL fractions. Since these measurements are not feasible in epidemiologic studies, the usual approach has been to use the major lipid components — VLDL-TG, LDL-C, and HDL-C — as measures of these fractions. In principle, however, a combined measure that takes into account VLDL-C, LDL-TG, and HDL-TG should be more precise and afford greater power for detection of the associations of the total fractions with other factors. This is particularly true of VLDL and LDL in which VLDL-C and LDL-TG constitute up to 25% of the lipid mass of the respective particles. To achieve such a combined measure we devised a method by which standardized values of VLDL, LDL, and HDL (S-VLDL, S-LDL, and S-HDL) were calculated for each person. This method, which is outlined below, is based on the following premises: 1) Since VLDL and LDL particles contain both cholesterol and triglycerides, the cholesterol and triglyceride concentrations within each fraction constitute two measurements of the same particles as if expressed in different units. 2) The standardized values (the measurement of each lipoprotein subfraction in terms of its distance from the respective mean concentration in the reference group divided by the respective standard deviation in that group) may be used to convert the cholesterol and triglyceride measurements of each lipoprotein fraction to comparable units. (For an analogous application, see reference 36.) 3) Averaging the standardized concentrations of cholesterol and triglycerides within each fraction yields an estimate of the standardized total lipid content of these fractions. This contention should hold true irrespec-

tive of changes in the cholesterol/triglyceride ratio within a given fraction relative to the mean ratio in the reference group. (Thus, if the ratio changes but the total amount of lipid within the fraction resembles the reference group mean, this implies a reduction in cholesterol content and a proportionate increase in triglyceride content, or vice versa. Consequently, the mean of the standardized values of the lipoprotein subfractions should remain unchanged. By the same token, an increased mean must reflect an overall increase in lipid content.) Moreover, if the ratio of the total lipid content to the nonlipid components is not considerably changed relative to the mean in the reference group, the standardized value will be an estimate of the total fraction and not just its lipid portion. The relative constancy of this ratio was indeed, expected in our study group because of the moderate elevation of blood pressure, moderate degree of glucose intolerance, moderate levels of obesity, and moderate levels of disturbed lipoproteins.

The following formula illustrates the calculation of the standardized VLDL-TG for a specific individual (SVLDLTGi) derived from the actual measured value (VLDLTGi) and the respective reference group mean (VLDLTGr) and standard deviation (σ VLDLTGr):

\[ SVLDLTGi = \frac{VLDLTGi - VLDLTGr}{σ VLDLTGr} \] (1)

The standardized values SVL DLCi, SLDLTi, SL DLCi, and S HDLi were calculated similarly. The respective means and standard deviations in the reference group used for these calculations are presented in Table 1. These are consistent with the data from the Jerusalem Lipid Research Clinic Study when we take into account the fact that our reference group excluded those with the GOH conditions. The standardized values of the total VLDL and LDL fractions in each individual (SVL DLCi, SLD Li) were calculated as the means of SVL DLCi and SVL DTGi and of SL DLCi and SL DTGi, respectively:

\[ SVL DLCi = \frac{SVL DTGi + SVL DLCi}{2} \] (2)

\[ SL DLCi = \frac{S LD LTGi + S LD Li}{2} \] (3)

Because HDL-TG was negligible under the study conditions, S HDLci was assumed to represent the standardized value of the total HDL fraction (SHDLi).

S-VLDL, S-LDL, and S-HDL thus represented the continuous form of the lipoprotein fractions. Their categorical form was defined as the disturbed levels equal to or great-

| Table 1. Parameters of Distributions of Lipoprotein Subfractions and Sum Insulin in the Reference Group |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| VLDL-C | VLDLTG | LDL-C | LDL-TG | HDL-C | Sum insulin |
| Mean | 34.7 | 58.0 | 138.1 | 49.2 | 45.9 | 112.7 |
| SD | 18.0 | 35.3 | 40.9 | 20.0 | 12.2 | 64.3 |
| No. of excluded outliers | 3 | 6 | 3 | 5 | — | — |
| 75th percentile | 40 | 75 | 165 | 60 | 35 | 137.3 |

The reference group included 165 persons.
*Computed after exclusion of outliers, exceeding three standard deviations. †75th percentile (for HDL-C, the 25th percentile) of the distribution, including outliers.
er than the 75th percentile of the respective distribution in the reference group for S-VLDL and S-LDL and equal to or less than the 25th percentile for S-HDL.

Validity of the standardized values as estimates of the lipid content of VLDL and LDL fractions. The contention that the standardized values are better estimates of the total fractions than VLDL-TG and LDL-C is supported by the following: 1) HDL-C was better correlated with S-VLDL than with VLDL-TG \((r = 0.192 \text{ vs. } -0.137)\) and with S-LDL than with LDL-C \((r = 0.222 \text{ vs. } -0.054)\); 2) VLDL-TG was better correlated with S-LDL than with LDL-C \((0.159 \text{ vs. } 0.071)\); and 3) the highest correlation was between S-LDL and S-VLDL \((r = 0.245)\).

Definition of disturbed lipoprotein profiles. Our objective was to evaluate whether hyperinsulinemia was associated with specific combinations of disturbed lipoprotein levels. To this end, we adopted a classification system of lipoprotein profiles analogous to that currently prevailing in the classification of hyperlipidemias. In these definitions, the cut-off point used to categorize disturbed lipoprotein levels is the 95th percentile of the normal population. However, because the shifts in the distributions of lipid levels under the study conditions were expected to be mostly within the ostensibly normal range, we used the 75th, rather than the 95th, percentile of the reference group as the cut-off point for defining disturbed S-LDL and S-VLDL levels, and we added disturbed S-HDL levels (<25th percentile of the reference group) to the characterization of the patterns.

We used these cut-off points to divide the study group into eight mutually exclusive categories representing all possible combinations of disturbed lipoprotein fractions: 1) all three (VLH), 2) S-VLDL and S-LDL (VL), 3) S-VLDL and S-HDL (VH), 4) S-LDL and S-HDL (LH), 5) S-VLDL (V), 6) S-LDL (L), 7) S-HDL (H), and 8) none (N).

Statistical Analysis

Lipoprotein levels were compared: 1) in each of the GOH conditions and in the total GOH group vs. the reference group, 2) in hyperinsulinemic vs. normoinsulinemic individuals within the total study group, in each of the GOH conditions, and in the total GOH group. These analyses were done in two ways: 1) We used the Mantel-Haenszel rate ratios of disturbed lipoproteins with test-based 95% confidence limits. These are presented throughout the text in brackets following the rate ratios. 2) We used Hotelling's \(T^2\) (Biomedical Computer Programs — BMDP, University of California Program 3D, Berkeley, CA) which simultaneously compared the distribution of all lipoproteins as continuous variables.

The equality of the adjusted means of sum insulin in the eight lipoprotein profile categories was tested by an analysis of covariance (BMDP Program 2V), which used log-transformed sum insulin as the dependent variable. The grouping factor was the lipoprotein profile according to the eight categories. The covariates were age, BMI, systolic blood pressure, and sum glucose as continuous variables and gender and smoking as categorical (dummy) variables. The adjusted means of the log-transformed sum insulin for each lipoprotein profile were obtained from this analysis and are presented in their antilogarithmic form.

The analysis was repeated with gender as a grouping factor so that we could enter a gender-lipoprotein profile interaction term.

The independent effect of the GOH conditions, as opposed to the effect of hyperinsulinemia, on the rate of specific lipoprotein profiles was evaluated by logistic regression analysis (BMDP Program LR). This analysis used the rates of specific disturbed lipoprotein profiles as the respective dependent variables and hyperinsulinemia, the GOH conditions, gender, age, and smoking as the categorical, independent variables. To ensure that the effect of hyperinsulinemia was not due to increased BMI in hyperinsulinemic individuals, this analysis was repeated with BMI as a continuous variable.

Because the effects of hyperinsulinemia on the lipoprotein profile were found to be statistically similar in both men and women, only the results for the total group are presented. This simplifies the tables.

Results

Of the 542 individuals comprising the study group, 113 (20.8%) were glucose-intolerant, 270 (49.8%) were obese, 192 (35.4%) were hypertensive, and 252 (46.5%) were hyperinsulinemic. The reference group numbered 165 (30.4%) individuals, and 377 (69.6%) belonged to the GOH group. These rates resembled those in the 960 individuals of the 1211 in the insulin group who, like the current study group, were not diabetics or taking antihypertensive medications (23.9% glucose-intolerant, 51.3% obese, 36.1% hypertensive, 46.4% hyperinsulinemic, and 28.7% in the reference group). This indicates that the current study group was not selective.

All three GOH conditions were significantly associated with increased rates of disturbed levels of all five lipoprotein subfractions and, consequently, of S-VLDL, S-LDL, and S-HDL. This was indicated by the ratios of these rates to the respective rates in the reference group, which were all above 1.0 (1.2 to 1.9, Table 2). There were no significant differences in the rates of disturbed lipoproteins between the seven mutually exclusive GOH categories, representing all possible combinations of GOH conditions (i.e., hypertension alone, obesity alone, abnormal glucose tolerance alone, hypertension with obesity, and so on; data not shown).

Hyperinsulinemia was also significantly associated with increased rates of disturbed levels of all five lipoprotein subfractions and of S-VLDL, S-LDL, and S-HDL. This was demonstrated by the ratios of these rates to the respective rates in the absence of hyperinsulinemia in the total study group, which were all significantly greater than 1.0 (1.4 to 1.9, Table 3). Moreover, the increased burden of disturbed lipoproteins associated with hyperinsulinemia was present to the same extent within the reference group as within each of the seven mutually exclusive categories representing all possible combinations of GOH conditions (data not shown).

In their continuous form, S-VLDL, S-LDL, and S-HDL were also significantly correlated with sum insulin, BMI, sum glucose, and systolic blood pressure (Table 4). Of these univariate correlations, those with sum insulin were the strongest.
Table 2. Ratio of Rates of Disturbed Lipoproteins In Each of the GOH Conditions to Those in the Reference Group

<table>
<thead>
<tr>
<th>Lipoprotein levels</th>
<th>Glucose intolerance</th>
<th>Obesity</th>
<th>Hypertension</th>
<th>Total GOH group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>VLDL-C</td>
<td>VLDL-TG</td>
<td>LDL-C</td>
<td>S-HDL-</td>
</tr>
<tr>
<td>N</td>
<td>S-VLDL</td>
<td>S-LDL</td>
<td></td>
<td>P†</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>113</td>
<td>1.46</td>
<td>1.40</td>
<td>1.25</td>
</tr>
<tr>
<td>Obesity</td>
<td>270</td>
<td>1.19</td>
<td>1.30</td>
<td>1.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>192</td>
<td>1.23</td>
<td>1.31</td>
<td>1.51</td>
</tr>
<tr>
<td>Total GOH group</td>
<td>377</td>
<td>1.18</td>
<td>1.22</td>
<td>1.44</td>
</tr>
</tbody>
</table>

The disturbed levels of S-VLDL, S-LDL, and S-HDL were strongly associated (Table 5). The rate of disturbed levels of each of the three lipoprotein fractions increased almost twofold when one of the two others was disturbed and at least threefold when both of the two other fractions were disturbed. The correlation coefficient of S-VLDL with S-LDL was 0.245; of S-VLDL with S-HDL, -0.192; and of S-LDL with S-HDL, -0.222. All were highly significant (p < 0.001).

In 321 individuals of the total study group (48.3%), none of the lipoprotein fractions was disturbed (profile N). In 31 persons (5.7%), all three fractions were disturbed (profile VH); in 71 persons (13.1%), two fractions were disturbed (profiles VH, VL, and LH); and in 178 persons (32.8%), only a single fraction was disturbed (profiles V, L, and H) (Figure 1). In the VLH group, the most disturbed profile, the mean lipoprotein subtraction levels were moderately disturbed: VLDL-TG, 163 ± 94.2; VLDL-C, 81.2 ± 40.4; LDL-C, 159 ± 50.4; LDL-TG, 104.5 ± 58.1, and HDL-C, 27.2 ± 7.2. The comparative levels in group N were: VLDL-TG, 46.1 ± 20.2; VLDL-C, 28.5 ± 9.9; LDL-C, 130.4 ± 35.2; LDL-TG, 43.1 ± 13.0; and HDL-C, 51.6 ± 9.5.

The lipoprotein profile groups differed significantly in BMI, sum glucose, and systolic blood pressure in the expected direction; thus, the lowest levels were in the N group, there were intermediate levels when one fraction was disturbed, and the highest levels were reached when more than one fraction was disturbed (Table 6). The absolute increase in the means of all three GOH variables in their continuous form, from the least disturbed to the most disturbed profiles, was, however, moderate. The trend within the categories with more than one disturbed fraction with respect to levels of BMI, blood pressure, or glucose response was somewhat inconsistent and showed no significant differences. Gender ratio indicated significantly lower rates of disturbed profiles among women, particularly with respect to HDL alone or in combination. The only exception was the profile of isolated LDL disturbance (L) which included a significant preponderance of women.

Mean sum insulin levels, adjusted for the covariates, gender, age, BMI, sum glucose, systolic blood pressure, and smoking, were significantly higher in the VLH, VH, and VL lipoprotein profile groups relative to group N (167.3, 167.1, and 163.5 vs. 122.5; p < 0.001 for each comparison). In contrast, the mean insulin levels were similar, or only slightly and nonsignificantly higher than group N in the
were not significant, indicating that the association of these gender-lipoprotein profile interaction term on insulin level lipid profiles with insulin response was similar for both men and women.

Figure 1. The means of sum insulin (mU/l) in the eight lipoprotein profile categories, adjusted for BMI, sum glucose, systolic blood pressure, gender, age, and smoking. Asterisks denote lipoprotein profile categories in which the adjusted means differed significantly (* p < 0.001) from category N (with undisturbed levels of all lipoproteins). The numerals inside the bars denote the number of cases.

Table 6. Male/Female Ratio and Means of BMI, Sum Glucose, and Systolic Blood Pressure in Lipoprotein Profile Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>M/F</th>
<th>BMI</th>
<th>Sum glucose</th>
<th>Systolic b.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>31</td>
<td>22/9</td>
<td>25.6±3.4</td>
<td>264.4±60.1</td>
<td>130.3±20.8</td>
</tr>
<tr>
<td>VH</td>
<td>24</td>
<td>21/3</td>
<td>27.6±3.9</td>
<td>276.5±87.5</td>
<td>136.1±19.1</td>
</tr>
<tr>
<td>VL</td>
<td>28</td>
<td>14/14</td>
<td>26.1±3.2</td>
<td>255.4±64.8</td>
<td>135.6±17.6</td>
</tr>
<tr>
<td>LH</td>
<td>19</td>
<td>16/3</td>
<td>26.1±3.0</td>
<td>277.2±85.3</td>
<td>134.8±7.7</td>
</tr>
<tr>
<td>C</td>
<td>59</td>
<td>37/22</td>
<td>26.1±3.2</td>
<td>260.7±53.2</td>
<td>127.0±17.7</td>
</tr>
<tr>
<td>L</td>
<td>73</td>
<td>29/44</td>
<td>25.4±2.9</td>
<td>246.6±63.1</td>
<td>129.0±19.1</td>
</tr>
<tr>
<td>H</td>
<td>46</td>
<td>36/10</td>
<td>25.3±3.5</td>
<td>242.0±66.2</td>
<td>131.0±23.5</td>
</tr>
<tr>
<td>N</td>
<td>262</td>
<td>113/149</td>
<td>25.0±3.6</td>
<td>243.7±59.6</td>
<td>127.2±19.1</td>
</tr>
<tr>
<td>ρ</td>
<td>&lt;0.01</td>
<td>-0.01</td>
<td>0.04</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Distribution of Lipoprotein Profiles by Presence of GOH Conditions and Hyperinsulinaemia

<table>
<thead>
<tr>
<th>Lipoprotein profile</th>
<th>Reference</th>
<th>GOH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoinsulinemic (n = 125)</td>
<td>Hyperinsulinemic (n = 40)</td>
</tr>
<tr>
<td>VLH</td>
<td>2.4</td>
<td>10.0</td>
</tr>
<tr>
<td>VL, VH</td>
<td>5.6</td>
<td>7.5</td>
</tr>
<tr>
<td>LH</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>V, L, H</td>
<td>30.4</td>
<td>37.5</td>
</tr>
<tr>
<td>N</td>
<td>60.8</td>
<td>45.0</td>
</tr>
</tbody>
</table>

LH (137.7), V (137.4), L (130.1), and H (120.2) groups (Figure 1). The independent effects of gender and of the gender-lipoprotein profile interaction term on insulin level were not significant, indicating that the association of these lipid profiles with insulin response was similar for both men and women.

The rate of VLH, VL, and VH lipoprotein profiles was more than doubled in hyperinsulinemic, as compared to normoinsulinemic, individuals in both the reference group (17.5% vs. 8.0%) and the GOH group (23.6% vs. 9.7%) (Table 7). The similarity of the rate of these profiles in normoinsulinemic individuals in the reference and GOH groups is noteworthy, especially in view of the big difference in mean BMI between them, 22.5 vs. 25.8 (p < 0.001). In contrast, the hyperinsulinemic individuals in the reference group had only slightly higher BMI (23.2) than the respective normoinsulinemic individuals, despite significantly higher rates of VLH, VL, and VH lipoprotein profiles. The mean BMI in hyperinsulinemic individuals in the GOH group was 27.2. The rate of the LH profile in the reference group was less than 1%, while in the GOH group there was a similar increase in both normoinsulinemic and hyperinsulinemic individuals (5.5% and 4.2%). No difference in the rates of isolated disturbed fractions (V, L, or H) was observed between hyperinsulinemic and normoinsulinemic individuals nor between the reference or GOH groups.

An analysis of the trends observed in Table 7 by using a logistic regression that accounted for the effects of age, gender, and smoking again indicated that hyperinsulinemia was associated with significantly excessive rates of disturbed levels of VLDL in combination with disturbed LDL or HDL (VLH, VL, VH) (Table 8). Their analysis also indicated that there was no additional effect of GOH conditions on these associations. The prevalence of the combination of disturbed levels of LDL and HDL when VLDL was normal (LH) was significantly higher in the GOH conditions but not in hyperinsulinemia. The prevalence of isolated disturbed levels of the three fractions (V, L, H) was not related to hyperinsulinemia or to the GOH conditions. Apart from these associations, we observed significantly higher rates of disturbed lipoprotein profile in men as compared to women and in individuals over age 60 as compared to those under 60.

Discussion

Lipoprotein abnormalities are present in glucose intolerance,1–7 obesity,2–6,8 and untreated hypertension,9–10 conditions that are ubiquitously associated with each other.17,42–46 The GOH conditions, as well as lipoprotein abnormalities, are all independently associated with hyperinsulinemia.1,2,11–24 The present report demonstrates a significant excess of disturbed lipoprotein levels, namely elevated VLDL and LDL and reduced HDL, associated with the GOH conditions and hyperinsulinemia in a sample of a free-living Caucasian adult population. In particular, this study deals with two issues not previously addressed.8,21–24

First, the strong metabolic linkage between VLDL, LDL, and HDL1,25,26,27 makes it important to evaluate lipoprotein abnormalities in terms of concomitant changes in all three fractions.26 Second, to what extent can lipoprotein abnormalities in the GOH conditions be accounted for by the attendant hyperinsulinemia? This latter question was partly addressed in one study,21 but no previous study has related hyperinsulinemia to combined lipid disturbances.

We found that hyperinsulinemia was characterized by a
joint pattern of elevated VLDL, in combination with elevated LDL and reduced HDL, and that this pattern was unrelated to the GOH conditions once the association with hyperinsulinemia was accounted for. In addition, in a small portion of the GOH group, a joint disturbance of LDL and HDL with normal VLDL was associated with the GOH conditions and not with hyperinsulinemia. Isolated disturbed levels of VLDL, LDL, and HDL were apparently unrelated to hyperinsulinemia or to the GOH conditions and were no more common than was to be expected from the cut-off points used for their definition.

We have attempted to integrate our data with those from kinetic-metabolic and epidemiologic studies, with the aim of identifying factors that underly the disturbed lipoprotein levels in the GOH conditions. Current knowledge suggests that the invariably increased VLDL levels in impaired glucose tolerance, type II diabetes, and obesity are mainly due to increased synthesis. Decreased VLDL clearance plays a significant role only in the presence of severe hypertriglyceridemia, which occurs in only a minority of these cases. The increased VLDL synthesis has been attributed to increased flow of substrates, such as glucose and free fatty acids, to the liver or, alternatively, to hyperinsulinemia or its attendant insulin resistance to which this synthesis is directly proportional. Our data suggest that hyperinsulinemia and insulin resistance are the major factors determining increased VLDL synthesis.

In the case of LDL, not all epidemiologic and case-control studies show increased levels in the GOH conditions. Nevertheless, LDL production increases in obesity and type II diabetes and is positively correlated with insulin response. Except in severe hypertriglyceridemia, LDL formation resembles the normal condition by the similar proportion of LDL derived from VLDL. This implies that, irrespective of the apparently increased direct LDL removal in these conditions, the net LDL production increases in correlation with increased VLDL synthesis and hyperinsulinemia. This is consistent with our finding that elevated LDL levels in the GOH conditions occur primarily in association with VLDL elevation and hyperinsulinemia. Similarly, reduced LDL catabolic rate seems to play a major role only in the small number of severe hypertriglyceridemic cases as in the case of VLDL. In most cases, the fractional catabolic rate is normal and the absolute catabolic rate increases with increased LDL production and hyperinsulinemia. This positive correlation of hyperinsulinemia with LDL catabolism may be caused by the stimulatory effect of insulin on LDL receptor activity. Thus, although LDL production increases, LDL blood levels may remain normal under these conditions as long as normal LDL removal processes are not saturated. It is of interest to note that in normal individuals, the main determinant of LDL levels is production and not catabolic rate.

On the other hand, the pattern of concurrently elevated LDL, reduced HDL, and normal VLDL, which we found to be associated with the GOH conditions but not with hyperinsulinemia, suggests that other factors may determine LDL levels in these conditions. These could be factors that reduce receptor-mediated LDL removal through LDL modifications such as glucosylation; changes in size, cholesterol/triglyceride ratio, and lipoprotein distribution; or, an altered intracellular metabolic state. Another possibility is defective lipoprotein transfer reactions. However, our data indicate that any such factors are less important than the insulin-enhanced processes in the disturbance of LDL levels.

When we consider HDL, there is only one preliminary report of a kinetic study in the GOH conditions, in which the authors show reduced synthesis in type II diabetes. The interrelationships of HDL with VLDL and LDL are far from clear. HDL levels are inversely correlated with VLDL and LDL levels from the normal to the pathologic range. Yet HDL can be derived in vitro from VLDL and LDL and is reportedly inhibited, with concomitantly increased transfer to HDL. However, it is now thought that HDL levels partly reflect plasma lipoprotein lipase activity. The low HDL levels in the GOH conditions may thus be linked to relative (to synthesis) or to absolute low lipoprotein lipase activity, which seem to characterize insulin-resistant states. The process may be further compromised by reduced cellular HDL binding caused by possible competition from increased LDL levels in hyperinsulinemia. Our findings suggest that the low HDL levels in the GOH conditions are linked to hyperinsulinemia and to insulin resistance.

It should be noted that, to date, no parallel kinetic studies of lipoprotein levels in hypertension have been conducted. However, hypertension is an independent state of hyperinsulinemia and insulin resistance and the association of hypertension with the lipoprotein profiles via the hyperinsulinemia in our study was similar to glucose intolerance and obesity. Thus, it is reasonable to assume that the trends for these two conditions will also be true for hypertension.

A point of interest is the similarity of the interrelation-
ships between lipoprotein profile, insulin response, and the GOH conditions in both men and women, despite the lower rate of disturbed profiles in women.

The question of the extent to which conclusions from our data can be extrapolated to other populations should be addressed. Although the population from which our sample is derived is similar to other Caucasian populations in rates of obesity and hypertension, our group is unique in its relatively high rate of glucose intolerance and thus, may not be representative of other populations. However, the basic metabolic relationships between carbohydrate and lipid metabolism are qualitatively similar in practically all populations and all ages.1 2 5 34 42 43 The association of hyperinsulinemia with disturbed lipoprotein levels has also been reported in studies of a variety of populations and a wide range of ages.1 2 5 21-24 31 Thus, we suggest that the above described patterns provide the major pathophysiological basis for the disturbed lipoprotein profile in the GOH conditions in most populations and population strata.

The pattern of disturbed lipoprotein profile, which characterizes hyperinsulinemia, is reminiscent of that of combined familial hyperlipidemia (CFH), which is marked by increased LDL and VLDL.85 90 as well as low HDL (although the latter is not part of its definition).72 73 It is of interest to note that CFH is associated with increased rates of obesity and type II diabetes,88 90 and that extraneous changes, such as diet, may alter the VLDL/LDL ratio in this disorder.75 These manifestations of CFH, as well as the overproduction of VLDL and increased LDL turnover in many cases,85 73 75 suggest that, at least in some cases, CFH may be an expression of hyperinsulinemia and insulin resistance.

Finally, our results agree with a hypothesis of insulin atherogenicity.21 22 23 75 Hyperinsulinemia and insulin resistance underlie all the major pathophysiological risk factors for atherosclerosis: obesity, glucose intolerance, hypertension, increased VLDL and LDL, reduced HDL, and the recently reported low lipoprotein lipase activity.77 All epidemiologic studies have addressed the independent risk associated with each lipid or lipoprotein but they have not considered the combined patterns.85 It is clear from the literature, however, that the main characteristic of the lipoprotein profile that is associated with increased risk for atherosclerosis is a concomitant disturbance in all three fractions.75 Eisenberg92 has suggested on the basis of metabolic studies that, rather than incriminating individual lipoprotein fractions, the overall profile should be considered. When all plasma systems operate efficiently, HDL levels will be high and will be accompanied by normal VLDL and LDL levels, reflecting a basically "healthy" plasma fat transport system that is nonatherogenic. Our data suggest that hyperinsulinemia and insulin resistance play a major role in disturbing this balance.

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