Fatty liver in familial hypobetalipoproteinemia: roles of the *APOB* defects, intra-abdominal adipose tissue, and insulin sensitivity

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Abstract **Fatty liver is frequent in the apolipoprotein B (apoB)-defective genetic form of familial hypobetalipoproteinemia (FHBL), but interindividual variability in liver fat is large. To explain this, we assessed the roles of metabolic factors in 32 affected family members with apoB-defective FHBL and 33 related and unrelated normolipidemic controls matched for age, sex, and indices of adiposity. Two hour, 75 g oral glucose tests, with measurements of plasma glucose and insulin levels, body mass index, and waist-hip ratios were obtained. Abdominal subcutaneous, intraperitoneal (IPAT), and retroperitoneal adipose tissue masses were quantified by MR imaging, and hepatic fat was quantified by MR spectroscopy. Mean ± SD liver fat percentage values of FHBL and controls were 14.8 ± 12.0 and 5.2 ± 5.9, respectively ($P = 0.001$). Means for these measures of obesity and insulin action were similar in the two groups. Important determinants of liver fat percentage were FHBL-affected status, IPAT, and area under the curve (AUC) insulin in both groups, but the strongest predictors were IPAT in FHBL (partial $R^2 = 0.55$, $P < 0.0002$) and AUC insulin in controls (partial $R^2 = 0.59$, $P = 0.0001$). Regression of liver fat percentage on IPAT fat was significantly greater for FHBL than for controls ($P < 0.001$). In summary, because apoB-defective FHBL imparts heightened susceptibility to liver triglyceride accumulation, increasing IPAT and insulin resistance exert greater liver fat-increasing effects in FHBL.—** Tanoli, T., P. Yue, D. Yablonskiy, and G. Schonfeld. **Fatty liver in familial hypobetalipoproteinemia: roles of the *APOB* defects, intra-abdominal adipose tissue, and insulin sensitivity. *J. Lipid Res.* 2004.** 45: **941–947.**

Supplementary key words abdominal adipose tissue • insulin resistance • apolipoprotein B

Nonalcoholic fatty liver [NAFL] is highly prevalent in human populations. It may develop into nonalcoholic steatohepatitis and in some cases into cirrhosis requiring liver transplantation (1–5). The overwhelming majority of NAFL cases are associated with obesity, dyslipidemia, hypertension, insulin resistance, type 2 diabetes mellitus, and atherosclerotic cardiovascular disease (6–9). This constellation defines the metabolic syndrome (10, 11). Several mouse models have been engineered that result in fatty liver: mouse overexpressors of genes specifying enzymes or transcription factors of the fatty acid synthetic pathway (12), knockouts of genes of the hepatic fatty acid oxidation pathways (13), and genes that regulate the development of adipose tissue (14). Some of these mice exhibit aspects of the metabolic syndrome, such as insulin resistance.

In humans, one among many causes of fatty liver is naturally occurring familial hypobetalipoproteinemia (FHBL) (15–22). It is defined by <5th percentile plasma levels of LDL-cholesterol and/or total apolipoprotein B (apoB), segregating in families as an autosomal dominant trait (23, 24). Three genetic subclasses of FHBL have been identified to date: *1*) mutations of the apoB gene (*APOB*) that lead to dysfunctional export of hepatic triglycerides via the VLDL export system and to fatty liver in humans (25–28) and mouse models (29, 30); *2*) FHBL linked to a susceptibility locus on chromosome 3p21 (31, 32); and *3*) FHBL linked to neither of the above (P. Yue, M. R. Averna, and G. Schonfeld, unpublished observations). We have reported that the mean liver triglyceride content in apoB-impaired FHBL subjects (group 1 above) is ~5-fold that of controls (33), but liver fat content in FHBL subjects (as well as in the controls we studied) varies greatly among individuals. In seeking sources of variation, we determined indices of adiposity such as the waist-hip ratio and the body mass index (BMI) and indices of insulin action such as area under the curve (AUC) for glucose and insulin during oral glucose tolerance tests in both FHBL and control subjects. Mean values for these parameters did not differ in the two groups, suggesting that higher levels of liver fat in FHBL subjects were not attributable to more adiposity or insulin resistance in FHBL subjects.

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However, both groups of indices were strongly correlated with liver fat in both FHBL subjects and controls (33). Since that report, we have expanded the number of FHBL subjects and controls and added direct measurements of abdominal adipose tissue by MR imaging. Abdominal fat (34) has been segmented anatomically into subcutaneous (SAT), intraperitoneal (IPAT), and retroperitoneal abdominal adipose tissue (RPAT). The various anatomic sites exhibit quantitatively differing physiological activities, such as basal and stimulated rates of lipid and carbohydrate metabolism (35). We now report on the roles of abdominal adiposity and insulin sensitivity in liver fat contents of subjects with the apoB-defective form of FHBL and matched controls. Lean FHBL subjects and lean controls tended to have similar amounts of liver fat. However, the slope of the regression lines of liver fat on intra-abdominal fat (i.e., IPAT) diverged with increasing amounts of liver fat. The line for FHBL subjects was significantly steeper than the line for controls. This suggests that FHBL subjects are more susceptible to developing fatty livers at any given amount of abdominal adipose tissue than are controls.

MATERIALS AND METHODS

Study subjects, protocols, and routine chemistries

The Washington University Human Studies Committee approved our protocols and informed consent procedures. No subjects were acutely ill or taking any medications known to affect lipid metabolism. Recently, we reported on the liver fat contents of 22 FHBL subjects with a variety of APOB truncation mutations and 16 normolipidemic controls matched for gender, BMI, and age (33). Since then, we have studied an additional 10 FHBL subjects and 17 controls. Thus, the total number of subjects is 32 FHBL subjects and 33 controls. The specific apoB defects of FHBL subjects and the citations to their original descriptions are provided in the legend to **Table 1**. The controls consist of relatives and unrelated volunteers matched for age, gender, and indices of obesity. No upper "normal" limit on the liver fat content of our control group was set because the amount of liver fat was continuously distributed. Thus, the control group included subjects who probably would have been classified as having fatty livers had a cutoff point been applied (a frequently used cutoff point is liver fat = 5%) (36).

Plasma lipids and lipoproteins were quantified on plasma obtained after 12 h of fasting by enzymatic methods (Wako Chemicals, Richmond, VA) after separation of lipoproteins by combined ultracentrifugal and precipitation methods according to Lipid Research Clinic protocols (37). Liver chemistry profiles were within normal limits. ApoB and apoA-I levels were determined by immunonephelometry (38). Oral glucose tolerance tests were performed 12 h after fasting using 75 g of glucose. Plasma glucose and insulin measurements were performed in the Washington University General Clinical Research Center's Core Laboratory using routine methods. For the MR spectroscopy (MRS) study, subjects were instructed not to change their diets and to abstain from ethanol for at least 1 week before the studies. MRS and MRI studies were usually performed after fasting for 10 to 12 h. We have previously shown that diurnal variation of liver fat is small (33).

Quantitation of abdominal fat masses by magnetic resonance imaging

Subjects were scanned using a 1.5 T Siemens Magnetom Vision scanner (Siemens, Erlanger, Germany). Axial MRI scans of the abdomen were obtained using a body coil. Gradient echo sequences were used with a repetition time of 160 ms and an echo time of 2.7 ms. Seventeen contiguous slices of 1.0 cm thickness were obtained from the diaphragmatic surface of the liver in the caudal direction. The duration of acquisition was 19 s. All images were acquired on a 116 × 256 matrix within a 33.8 × 45.0 cm^2 field of view. During image acquisition, subjects were asked to hold their breath in full inspiration. The Analyze 3.1 image-analysis software program (Biomedical Imaging Resource) was used for the quantification of adipose tissue volume. Eight contiguous slices (with the first slice from the top of the right kidney; in deep inspiration, these slices usually correspond to vertebra levels L1, L2, and L3) were used for the quantification of SAT and intra-abdominal adipose tissue (IAAT). IAAT was divided into RPAT and IPAT compartments using anatomical structures as markers, such as pancreas, ascending and descending colon, inferior vena cava, and aorta. Analyze software allows segmentation of the images into various compartments using threshold values and knowledge of anatomy. We used this feature for the segmentation of images into SAT, RPAT, and IPAT. Different threshold values were assigned to each compartment. The total number of pixels in eight slices was calculated for each compartment. The number of pixels was converted to volume. Average volume per slice was calculated. From this average volume, the average mass of adipose tissue (kilograms) per slice was derived [assuming that adipose tissue is composed of 84.67% fat, 12.67% water, and 2.66% proteins and that the density of adipose tissue is 0.9196 kg/l (34, 39)]. Thus, the mass of fat per slice = the average volume of adipose tissue in liters × 0.846 × 0.9196.

Magnetic resonance spectroscopy

As reported above, a 1.5 T Siemens Magneton Vision scanner was used with a body radio frequency (RF) coil as a transmitter and a small flex coil as a receiver. A localized volume MR tech-

TABLE 1. Clinical characteristics of study subjects

Subjects (Male/Female)	Liver Fat	Age	Total TG	VLDL-TG	Total Cholesterol	VLDL-C	LDL-C	HDL-C	apoA-I	apoB
	%	*years*	*mg/dl*							
Control (12/20)	5.2 ± 5.9	41 ± 16	107 ± 71	80 ± 72	175 ± 31	17 ± 13	111 ± 27	47 ± 11	124 ± 23	86 ± 28
FHBL[a] (19/14)	14.8 ± 12.0	44 ± 18	62 ± 50	49 ± 49	104 ± 26	11 ± 12	41 ± 18	52 ± 19	124 ± 32	28 ± 16
P	<0.001	0.45	0.004	0.06	<0.001	0.08	<0.001	0.19	0.24	<0.001

apoA-I, apolipoprotein A-I; C, cholesterol; TG, triglyceride.

[a] Thirty-three familial hypobetalipoproteinemia (FHBL) subjects were from the following families: F39 (apoB-4, n = 11), F37 (apoB-9, n = 3), F50 (apoB-29, n = 2), F40 (apoB-31, n = 1), F41 (apoB-38.9, n = 1), F45 (apoB-52, n = 8), F46 (apoB-54.8, n = 2), F48 (apoB-70.5, n = 1), F49 (apoB-75, n = 1), and F51 (apoB-89, n = 3). Of 32 control subjects, 10 were from F39 and 4 were from F52; the others were from the general population.

nique based on a double-spin echo PRESS sequence (40) without water suppression was used. Accurate voxel localization was achieved using specially designed numerically optimized RF pulses (41). Each individual signal acquisition occurred over 512 ms with a repetition period of 2 s. Ten signal averages were obtained over a 20 s period. Both the anatomical images and the spectroscopic data were obtained while subjects held their breath.

For accurate quantification of low-intensity fat signal in the presence of the strong signal from water (dynamic range problem), a digital low-pass Savitszky-Golay filter with bandwidth of 30 Hz centered at water resonance frequency was applied to model the strong water time domain signal. Bayesian probability theory was used for further data analysis of digitally separated water and fat signals (Bayesian programs were written by Dr. G. Larry Bretthorst). Data were analyzed by modeling the water and fat signals each as an exponentially decaying sinusoid.

Three 2 × 2 × 2 cm voxels were examined in each subject. The coefficient of variation of replicate values of the triplicate determinations for three voxels was 1.5% (n = 31 MRS examinations). Two data sets with spin echo times of 23 and 53 ms were obtained from each voxel and used to evaluate the spin density for fat and water contributions. The MRS liver fat percentage was reported as the spin density of the aliphatic ^{1}H signal divided by the sum of the spin densities of aliphatic plus water ^{1}H signals.

We have reported on the comparability of chemical measurements of liver triglycerides and liver fat measured by MRS (33). The regression of weight percentage liver triglyceride (chemical) on MRS liver fat percentage was $y = 0.807x$ ($R^2 = 0.986$).

Statistical analysis

All statistical analyses were done using SAS (SAS Institute, Cary, NC). Results shown are means ± SD. Pearson correlation coefficients were used as appropriate. Log transformation of liver fat percentage was used because it was not normally distributed. The Chi-square test was used to compare sex differences between FHBL and control groups, and the Kruskal-Wallis test was used to compare age differences. The PROC GLM was used to compare means of groups with α levels of 0.01. Multivariate stepwise regression was used to determine the independent sources of liver fat variation among individuals, with MRS liver fat percentage or log (liver fat percentage) as the dependent variable. The values for liver fat percentage are presented as measured, without adjustments for covariates (e.g., age, BMI, etc.).

RESULTS

Study subjects

Assignment of FHBL-affected status in all subjects is based on genetic analysis of *APOB*. The clinical characteristics of the subjects are given in Table 1. As expected, there were clear-cut differences between affected and unaffected subjects in liver fat percentage and plasma levels of total and LDL-cholesterol and apoB, but other characteristics, such as age, gender distribution, body weight, BMI, and waist-hip ratio were similar. Liver fat percentage was significantly correlated with serum alanine aminotransferase and alanine aminotransferase-aspartate aminotransferase ratio in FHBL subjects ($r = 0.558$ and 0.580, respectively, both $P < 0.001$) and less so in controls ($r = 0.339$, $P = 0.057$ and $r = 0.419$, $P = 0.017$, respectively). Liver fat percentage also tended to increase with age (liver fat vs. age $r = 0.366$, $P = 0.051$ in FHBL subjects and $r = 0.324$, $P = 0.099$ in controls).

SAT, IPAT, and RPAT: correlation with each other and with liver fat percentage

Mean values of SAT, RPAT, and IPAT were comparable to those reported by others (34, 39), and the mean values were similar in the FHBL and control groups (**Table 2**).

RPAT and IPAT were strongly correlated with each other ($r > 0.87$, $P < 0.001$ in both subject groups), but neither was significantly correlated with SAT ($r = 0.2$ and 0.4, $P > 0.2$ and 0.07, respectively, in FHBL subjects and controls). SAT, RPAT, and IPAT were varyingly correlated with BMI, waist-hip ratio, and age (**Table 3**).

Liver fat percentage was significantly correlated with several of the indices of adiposity in both subject groups, but the correlation coefficient was largest with IPAT (**Table 4**). Linear regression lines and equations of liver fat on IPAT are shown in **Fig. 1**. The slope of the line for FHBL subjects is statistically significantly steeper than the line for controls ($P < 0.0001$). The conclusion is not altered if log (liver triglyceride) is used on the ordinate (not shown).

Correlation of liver fat with indices of glucose tolerance and insulin action

Mean fasting glucose and insulin levels, HOMA index, and AUC insulin were similar in the two subject groups (**Table 5**), in agreement with previous results (33). Liver fat percentage was correlated with fasting insulin and the HOMA index in both FHBL and control groups. However, the correlation was strongest between liver fat percentage and insulin AUC (**Table 6**). Correlations between abdominal fat masses and insulin AUC were significant.

Multivariate analysis

Compatible with what we reported previously, the genetic status of *APOB* is the most important factor in pre-

TABLE 2. Indices of adiposity and abdominal fat masses

Subjects	BMI	W/H	SAT	RPAT	IPAT
	kg/m²	*cm/cm*	*kg/slice*		
Control	26.8 ± 4.9	0.84 ± 0.09	0.133 ± 0.056	0.028 ± 0.026	0.049 ± 0.044
FHBL	25.6 ± 3.9	0.86 ± 0.08	0.109 ± 0.044	0.028 ± 0.021	0.049 ± 0.040
P	0.29	0.33	0.11	0.94	0.98

BMI, body mass index; IPAT, intraperitoneal; RPAT, retroperitoneal abdominal adipose tissue; SAT, subcutaneous; W/H, waist-hip ratio. n = 33 and 32 for FHBL and control groups, respectively, for BMI and W/H; n = 24 and 27 for FHBL and control groups, respectively, for SAT, IPAT, and RPAT.

TABLE 3. Correlations between indices of adiposity, abdominal fat masses, and age

Variable	SAT	RPAT	IPAT	Age
BMI				
Control	0.633 (0.0004)	0.749 (0.0001)	0.708 (0.0001)	0.231 (0.2039)
FHBL	0.796 (0.0001)	0.685 (0.0002)	0.664 (0.0004)	0.255 (0.1504)
W/H				
Control	0.407 (0.3049)	0.609 (0.0008)	0.727 (0.0001)	0.051 (0.7829)
FHBL	0.511 (0.0107)	0.699 (0.0001)	0.722 (0.0001)	0.262 (0.1421)
Age				
Control	0.043 (0.8301)	0.429 (0.0254)	0.271 (0.1705)	–
FHBL	0.454 (0.0259)	0.662 (0.0004)	0.582 (0.0028)	–

Values in parentheses are *P* values. n = 24 and 27 for FHBL and control groups, respectively.

dicting liver fat when we consider FHBL and control groups together. Considering the two groups separately, in the FHBL group, liver fat percentage was positively correlated with IPAT (partial $R^2 = 0.547$, $P < 0.0002$), apoB level (partial $R^2 = 0.189$, $P = 0.0028$), and HOMA index (partial $R^2 = 0.0812$), with an overall model R^2 of 0.9355 ($P < 0.0001$). The strongest predictors of log liver fat were IPAT, apoB level, and AUC insulin. In controls, liver fat percentage was related to AUC insulin (partial $R^2 = 0.499$, $P = 0.0005$) and HOMA (partial $R^2 = 0.1264$, $P = 0.0163$), with an overall model R^2 of 0.720. Log liver fat was predicted by AUC insulin, HOMA index, and IPAT. Thus, genetic status, IPAT, and measures of insulin action were important determinants of liver fat in both groups, and apoB concentration was significant in FHBL subjects. IPAT modulated liver fat to a greater extent in FHBL subjects than in controls. Conversely, indices of insulin action were more important modulators of liver fat in controls than in FHBL subjects. SAT was not important in determining liver fat in either group.

DISCUSSION

The associations between obesity and fatty liver and between diabetes and fatty liver are well documented (10). However, few reports have directly examined the quantitative relationship between liver fat and abdominal fat, and the results are not consistent. For example, Doron et al. (42) reported a correlation of liver fat to subcutaneous fat but not to intra-abdominal fat. Seppala-Lindroos et al. (7) reported no significant correlation between liver fat and "visceral fat volume" in normal men, and Tiikkainen et al. (43) reported no correlation between liver fat and abdominal fat in obese women. On the other hand, Nguyen-Duy et al. (44) found visceral and liver fat to be correlated. To our knowledge, no reports exist on simultaneous measurements of liver and abdominal fat in the same subjects with FHBL.

Taking all FHBL subjects reported by us previously (33) and in this article, mean liver fat percentage values measured by MRS were ~3-fold those of controls. We had reported a 5-fold difference previously (33). The smaller multiple is probably attributable to the inclusion of controls with liver fat values ranging up to 29%. As mentioned above, because liver fat percentage is a continuous variable in both groups of subjects, we chose not to apply any arbitrary cutoff points to set a "normal" value. Rather, we present all of the data.

There was great interindividual variability with respect to liver fat in both the FHBL and control groups. The variability was not attributable to the method used to quantify liver fat, because similar values were obtained on repeated determinations of the same pixel, in three different 2 × 2 × 2 cm pixels examined in any given liver, and over time in any given study subject (33), i.e., intraindividual variability was small. Furthermore, we attempted to minimize other sources of variability by requesting that patients not drink alcohol or change their diets before the tests.

Nevertheless, interindividual variability in liver fat contents persisted. To assess some of the potential sources of this variability, we measured indices of insulin action, indices of generalized and abdominal adiposity, and abdominal fat masses directly by MRI. Then, we performed univariate and multivariate statistical analyses. In both FHBL subjects and controls, the correlation between liver fat and indices of adiposity was strongest for IPAT. If abdominal adipose tissue can indeed affect liver fat contents, the mechanisms are not clear, but there are two possibilities: *1*) the flux of fatty acids from adipose to liver would provide more precursors; and *2*) cytokines/hormones (e.g., adipsin, leptin, tumor necrosis factor-α) secreted from adipose could affect the liver (45). There were also significant correlations between indices of insulin action and liver fat, and it is known that chronic exposure of liver to high levels of circulating insulin results in increased hepatic lipogenesis (46, 47).

Considering FHBL and control groups together, the important factors determining liver fat were FHBL-affected

TABLE 4. Correlations between liver fat contents, indices of adiposity, and abdominal fat masses

Subjects	Liver Fat vs. BMI	Liver Fat vs. W/H	Liver Fat vs. SAT	Liver Fat vs. RPAT	Liver Fat vs. IPAT
Control					
r	0.426	0.321	0.275	0.389	0.548
P	0.015	0.078	0.164	0.045	0.003
Sample size	32	31	27	27	27
FHBL					
r	0.571	0.478	0.402	0.579	0.638
P	<0.001	<0.006	0.052	0.003	<0.001
Sample size	32	32	24	24	24

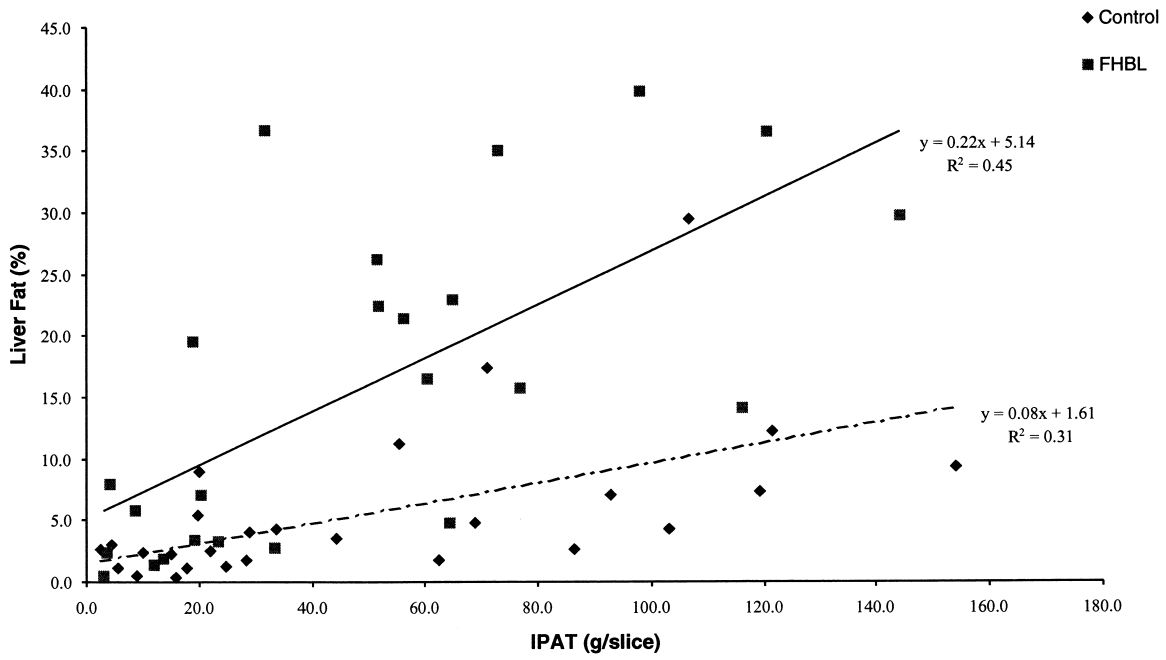

Fig. 1. Regression of liver fat percentage on intraperitoneal adipose tissue (IPAT) in human subjects with apolipoprotein B-defective familial hypobetalipoproteinemia (FHBL) and matched controls. The slopes of the regression lines are significantly different ($P = 0.0001$).

status, IPAT, and AUC insulin. On stepwise regression analysis, IPAT accounted for 55% of the variation in liver fat in FHBL subjects, and apoB accounted for 19% (R^2 for the model was 0.94); HOMA index and AUC glucose each accounted for <10% of the variation. In controls, on the other hand, AUC insulin accounted for 50% of the variation, HOMA index for 13%, and IPAT for only 8% (R^2 for the model was 0.71). Furthermore, the regression line of liver fat on IPAT, although positive in both groups, was significantly steeper in FHBL subjects than in controls. Thus, although intra-abdominal fat was an important determinant of liver fat in both groups, it was more important in FHBL subjects than in controls. Conversely, indices of insulin action were more important in controls. This shows that the apoB mutations alter the metabolic relationships between abdominal fat depots and liver fat.

Why is IPAT a stronger predictor of liver fat percentage in FHBL subjects than in controls? IPAT (and RPAT), by means of some unknown agent, seems to be an important actor in setting the load of hepatic triglycerides available for export in both FHBL subjects and controls. If the hepatic triglyceride-increasing activity of IPAT depends on its size, IPAT of increasing sizes would present similarly increasing loads of precursors or stimulants of triglyceride for hepatic export in FHBL subjects and controls. But the VLDL-exporting system of livers is impaired only in FHBL subjects relative to controls. At lower loads of transportable hepatic triglyceride (i.e., smaller masses of IPAT), even an impaired system may be adequate, and hepatic triglyceride accumulation would be similar in FHBL subjects and controls. But as hepatic triglyceride loads increase (i.e., as IPAT masses increase), the capacity of the impaired VLDL system would become increasingly limiting to export in FHBL subjects. This would lead to selectively greater amounts of triglyceride accumulation in FHBL subjects, as we observed. The accumulation occurred despite the attempts of FHBL livers to compensate by diminishing fatty acid synthesis (48) and secreting more VLDL particles (suggested by the positive relationship of liver fat percentage to plasma apoB levels on multivariate analysis). Livers of controls, with presumably fully functional VLDL systems, responded to increased lipid loads by

TABLE 5. Indices of insulin action in FHBL and control subjects

Subjects	Basal Glucose	Basal Insulin	AUC Glucose	AUC Insulin	HOMA[a]
	mg/dl	*μU/ml*	*mmol/l/h*	*μU/ml/h*	
Control	89 ± 17	9 ± 12	5.27 ± 2.18	91.1 ± 65.6	1.6 ± 1.2
FHBL	95 ± 9	7 ± 5	6.00 ± 3.01	113.5 ± 62.8	1.6 ± 1.3
P	0.29	0.89	0.29	0.19	0.94

AUC, area under the curve.
[a]HOMA was expressed as fasting plasma glucose (mmol/l) × fasting plasma insulin (μU/ml)/22.5.

TABLE 6. Correlations between liver fat content and indices of insulin action

Subjects	Liver Fat vs. Basal Glucose	Liver Fat vs. Basal Insulin	Liver Fat vs. AUC Glucose	Liver Fat vs. AUC Insulin	Liver Fat vs. HOMA
Control					
r	0.285	0.468	0.432	0.531	0.437
P	0.167	0.018	0.017	0.003	0.014
FHBL					
r	0.046	0.256	0.059	0.632	0.529
P	0.805	0.163	0.759	<0.001	0.003

more efficiently exporting hepatic VLDL-triglyceride. Thus, IPAT would appear to be a stronger correlate of liver fat percentage in FHBL subjects, overriding the importance of indices of insulin action, which is more discernible in controls.

Another potential source of interindividual variation may have been the "genetic background" of our study subjects. Some of the correlates of liver fat, such as adiposity (49) and other features of the metabolic syndrome, appear to have genetic components in humans (50–53) and mice (54, 55). The amount of liver fat itself appears to be at least in part genetically determined. In a survey of 10 inbred mouse strains, liver triglyceride contents varied severalfold between the different strains (X. Lin et al., unpublished observations). The identities of the genes contributing to this variation remain to be determined.

In summary, the accumulation of fat in liver of subjects with the apoB-defective form of FHBL is determined by several factors, including the genetic *APOB* defects per se, which render these subjects particularly susceptible to the effects of adiposity and insulin resistance.

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