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GENE-DIET INTERACTIONS IN LIPOPROTEIN METABOLISM

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I. Introduction

The study of genetic variations affecting lipoprotein metabolism has added to our understanding of genetic contributions to atherosclerosis. Although genetics plays an important role in CAD [1], single gene defects affecting lipoprotein metabolism which cause early CAD account for only a small percentage (5%) of coronary disease in the population [2, 3]. These include Type III hyperlipoproteinemia (apolipoprotein E mutation), familial defective apoB-100 (elevated apoB), and familial hypercholesterolemia (elevated LDL) [4]. These disorders are more important for elucidating mechanisms for lipoprotein metabolism and CAD rather than for public health intervention. However, genetic defects affecting proteins do relate to the variability of lipoprotein concentrations in the general population [5] and alter the lipoprotein transport pathways for fat and cholesterol metabolism [6, 7]. Diet also affects the levels of lipoproteins [8, 9], yet it has become apparent that the wide variation of lipid and lipoprotein values of individuals on the "average American diet"[10-20] is strongly influenced by genetic differences. For the population at large, current preventive efforts for improving lipoprotein profiles are aimed at reducing total fat intake (particularly saturated fat) and cholesterol and increasing the carbohydrate content of the diet. Yet on average, these efforts decrease total cholesterol levels 10-15% with initial reductions in dietary fat [21].

Hypo- or hyper-responsiveness to dietary cholesterol and saturated fat have been difficult to document because of intraindividual variability in the range of dietary modification employed [22]. Yet, individual metabolic characteristics in cholesterol metabolism do contribute to the regulation of total cholesterol levels. Some of these known mechanisms underlying
differences in dietary responsiveness have been reviewed by Grundy and Denke [9] and include factors associated with the production, transport, and secretion of lipoproteins. Individual genetic susceptibility to diet-induced changes in lipid and lipoprotein levels have also recently been considered. A threshold for cholesterol absorption and metabolism forms the evidence for genetic as well as environmental factors that are involved in cholesterol metabolism.

Following is a brief summary of the genetic lipoprotein disorders that account for both premature CAD in families and lipoprotein heterogeneity in the general population. Accompanying the description of each lipoprotein disorder is a summary of the current evidence in humans for genetic-mediated responsiveness to dietary fat and cholesterol.

II. LDL Receptor in Cholesterol Homeostasis. The LDL-cholesterol level in the blood is controlled, in part, by LDL receptors located in cell membranes [23]. These LDL receptors recognize and bind to two protein-components of lipoproteins, apoB-100 and apoE [24].

At least thirty-four different mutations in the LDL-receptor gene have been identified [25]. A genetic mutation that affects the gene which encodes the receptor (occurring in 1/500 persons) impairs LDL receptor function and may result in elevated blood LDL levels [familial hypercholesterolemia (FH)] and increased risk of CAD [23]. However, FH patients show marked interindividual variation in clinical symptoms [26], indicating that factors other than this genetic mutation must influence the pathogenesis of CAD [27, 28]. One possible mechanism for this observed variation may be the existence of a second LDL receptor-related protein (LRP) which functions as a receptor for apoE-enriched lipoproteins [29], and which has been shown to prevent the accumulation of atherogenic chylomicron remnants and beta
VLDL [30, 31] in patients with homozygous FH (possessing two defective alleles) [32]. Normolipidemic FH heterozygotes (possessing one defective allele) have higher than usual fractional catabolic rates for LDL and low input of LDL apoB [33], which may explain normal concentrations of LDL-C. Also, the possible existence of a suppressor gene, which when inherited with the mutant LDL receptor gene, may explain the observation of normal LDL-cholesterol levels in FH heterozygotes [34]. Other candidate genes currently under investigation for LDL lowering in FH include apoC-III, hepatic lipase, and HMG-CoA reductase (controls sterol synthesis) [25]. Other factors thought to influence genetic expression of the LDL receptor defect include variation at the gene loci for apoB, Lp(a), and apoE as discussed below.

Genetic variation at the LDL-receptor gene locus has also been associated with differing plasma lipid levels in the normal population [35-37], explaining 9.6% of the population variance in LDL-C levels [37].

A. Plasma Cholesterol Level and Dietary Fat and Cholesterol Responsiveness. The relationship between changes in nutrient intake and changes in blood cholesterol is shown to be strongly influenced by the initial concentration of total cholesterol [38]. Figure 1 [38] shows that the usefulness of serum cholesterol as a marker of change in dietary fat intake in women depends, in part, on the distribution of cholesterol values in the population studied. The difference between predicted and observed change in serum cholesterol is greatest at the extremes of the cholesterol distribution. Thus, variation in study results of dietary influences on lipoprotein levels may be a result of the choice of study subjects.

Recent studies [39-42] have suggested that there may be a correlation between an individual's sensitivity to changes in dietary saturated fat intake and sensitivity to dietary cholesterol. From these studies it appears that
dietary sensitivity might be defined more precisely if individuals are first identified as responsive or unresponsive to dietary fat manipulation as well as normo- or hypercholesterolemic (Tables 1,2) [40]. The cholesterolemic response to dietary change is consistently individually determined and suggests fundamental differences in cholesterol metabolism. For instance, responsiveness or unresponsiveness to dietary cholesterol in humans is shown to be stable for at least 6 years [43]. This phenomenon may be important for studying genetically determined hypercholesterolemia for the majority of the population without single gene defects such as FH.

Miettinen and Kesaniemi [44] suggest that cholesterol absorption efficiency and absorbed dietary cholesterol regulate cholesterol synthesis and elimination in normal populations and are important determinants of within-population variation in the levels of total, LDL, and HDL cholesterol. In normal subjects, efficient intestinal cholesterol absorption down-regulates LDL-receptor mediated catabolism of LDL and enhances LDL synthesis [45]. The percentage decrease in LDL receptor activity correlates inversely with the percentage increase in LDL cholesterol; implying that high levels of dietary cholesterol down-regulate the LDL receptor. These changes in LDL reflect changes in the degree of saturation of the receptor-dependent component of LDL degradation [46]. In FH patients, however, cholesterol absorption and synthesis are inversely related and no association is observed between the efficiency of cholesterol absorption and total cholesterol levels [47] due to defective LDL-ApoB receptor.

McNamara et al. [48] conducted 75 studies in 50 normolipidemic men to examine the effects of dietary fat and cholesterol on lipid and lipoprotein levels, cholesterol absorption, and sterol synthesis. The range of intakes of dietary cholesterol tested were 159-905 mg/day and variations in
polyunsaturated to saturated fat ratio (P:S) were 0.20-2.37 within a diet supplying 35% of calories from fat. The results indicate that the change in dietary cholesterol has a marginal influence on lipid levels; while changes in dietary fat quality have a small but consistent effect on plasma cholesterol levels. About 20% of the subjects exhibited a decrease in total cholesterol on a high P:S diet, regardless of cholesterol intake. The lack of a significant dietary cholesterol effect on total cholesterol levels in most subjects was attributed to a reduction in the absorption of exogenous cholesterol and the feedback suppression of endogenous cholesterol synthesis. The results also demonstrate that the degree of saturation of dietary fat has no effect on the feedback response to dietary cholesterol. Additionally, the response to dietary fat and cholesterol were highly individualized; the thirty-one percent of the subjects who lacked feedback control of endogenous cholesterol synthesis may benefit from dietary modification.

It has been well documented that hepatic LDL receptors regulate cholesterol synthesis in the liver in accordance with the influx of dietary cholesterol, yet it has not been clear if there is also an effect on intestinal cholesterol synthesis. Current available data, however, do support a role of dietary cholesterol in the regulation of cholesterol synthesis in the intestine (reviewed by Field [49]). Cholesterol synthesis (and/or esterification) in the intestine is shown to be regulated by the cholesterol requirements of the cell [49]. For instance, during influx of cholesterol and certain fats into the intestine, cholesterol synthesis decreases and esterification increases. Dietary fats are known to alter membrane fatty acid composition and promote lipoprotein secretion and cholesterol absorption. The exact mechanisms for regulation of cholesterol synthesis in the intestine, however, are unknown.
Other investigators have demonstrated metabolic compensation for changes in dietary fat and cholesterol [50, 51]. Craig et al. [50] demonstrated in vitro that the supply of lipid is a determinant of apolipoprotein synthesis and secretion by the liver, and that cholesterol may be of particular importance in the initiation of apolipoprotein synthesis. For example, cholesterol alone stimulates synthesis and secretion of Apos E and A-I as well as HDL formation. Fatty acids and cholesterol are both necessary, however, for the cell to synthesize apoB-containing lipoproteins. Additionally, Patsch et al. [51] demonstrated that dietary cholesterol increases the size of HDL, possibly reflecting an increase in reverse cholesterol transport.

III. Apolipoprotein B. Genetic variation of the principal ligand (recognition site) for the LDL receptor, apoB, is shown to predict atherosclerosis [52], and may contribute to serum cholesterol regulation in FH [53]. ApoB is also essential for the synthesis and secretion of chylomicrons and VLDL, in addition to serving as the ligand for the interaction of LDL with the LDL receptor [24, 54]. ApoB exists in two major forms: apoB-100 derived from the liver, and apoB-48 from the intestine [55]. Genetic disorders affecting apoB include: familial combined hyperlipoproteinemia and familial defective apoB-100.

Familial combined hyperlipidemia (elevated cholesterol and triglycerides) is another condition in which increased CAD risk may be related to distribution of IDL [30, 31, 56] and LDL [57] subclasses, although its association with mutations in the apoB gene is still under question [58]. These patients have relatively more VLDL, LDL-III, and IDL than do unaffected controls [57]. In contrast, patients with familial hypertriglyceridemia (FHTG) have elevated VLDL, due to genetically low VLDL triglyceride removal, but normal or low LDL levels [59]. Again, the
basic genetic defects have not been identified in either of these two disorders, although recent findings have identified associations of DNA variation at the apoB gene locus with VLDL levels and CAD [60], and an association between FCHL and variation within the apolipoprotein AI-CIII-AIV gene cluster [61].

Elevated serum apoB levels in familial defective apoB-100 are associated with elevated LDL levels and an increased risk of premature atherosclerosis [62, 63]. This altered protein, with only 32% of normal LDL-receptor binding activity, occurs at a frequency of about 1/500 in populations in the United States [64] where elevated LDL levels are common. Familial defective apoB-100 is apparently not, however, a major contributor to high LDL cholesterol levels in Finland, another population characterized by both elevated LDL levels and a high incidence of CAD [65]. Thus, elevated LDL in different populations may, in part, be due to different genetic defects.

Hyperapobetalipoproteinemia (hyperapoB) is also a familial lipoprotein disorder characterized by an increase in small dense LDL particles, and a delayed clearance of post-prandial triglycerides and free fatty acids. To date, defects in the apoB gene do not appear to explain the hyperapoB phenotype. The activity of three proteins involved in triglyceride acylation and cholesterol esterification are being investigated in relation to the pathophysiology of hyperapoB [66].

Recent data suggests that variation in the apoB gene also influences the metabolism of LDL in the normal population, and that the variation in LDL metabolism differs by ethnic background [67]. For example, variation in the apoB gene in subjects from the United Kingdom and Finland was shown to affect the rate of LDL catabolism, which is not observed in subjects from Italy and Spain. The major observed effect of apoB variation in a South African
population is on the rate of LDL synthesis. These findings may help to explain different population responses to dietary manipulation.

A. Hypertriglyceridemia and Diet Responsiveness.
Hypertriglyceridemic patients treated with fish oil [n-3 fatty acids (FA)] show consistent reductions in total and VLDL-triglyceride levels [68] caused primarily by an inhibition of VLDL-triglyceride synthesis [69]. However, LDL response during n-3 FA supplementation is much more variable [70] and seems to vary depending on differences in LDL and VLDL composition and metabolic behavior [71-73]. For example in FH treated with n-3 FA, LDL is decreased [74] while LDL is increased in FHTG (Figure 2)[71], FCHL, mild hypercholesterolemia [75], and in patients with non-insulin dependent diabetes mellitus. This variability in response may be a result of the range of dose administered, but is most likely due to the heterogeneity of lipoprotein disturbances [72]. For instance, FHTG is characterized by an overproduction of VLDL triglyceride relative to LDL apoB and cholesterol levels [76]. FCHL, on the other hand, is associated with increased LDL apoB in the presence of small, dense LDL subclasses [57].

Hypertriglyceridemic patients treated with high carbohydrate diets (60% energy) show consistent increases in plasma glucose, insulin, and triglyceride concentrations and reductions in HDL cholesterol levels [77]. Although high carbohydrate-low fat diets have been universally recommended to reduce CAD risk [21], these metabolic events in hypertriglyceridemic patients in response to carbohydrate feeding have been associated with enhanced risk of CAD [78]. These results point to the importance of learning more about the interaction of metabolic lipoprotein abnormalities with dietary intervention before uniform dietary recommendations are made.
B. Apolipoprotein B and Diet Responsiveness. Lipoprotein responses to an oral fat test were studied in hypertriglyceridemic patients with and without hyperapobetalipoproteinemia (HyperapoB) and in normal triglyceridemic controls with and without HyperapoB [79]. After the fat load, elevations in triglyceride and decreases in HDL2 cholesterol levels were greater for all patients with HyperapoB. This study suggests that the measurement of LDL apoB may lead to the recognition of metabolic relationships previously unrecognized and provide a clue to interactions of diet with VLDL chylomicron and HDL2 metabolism.

Genetic variation at the apoB gene locus was found to explain 6.3% of the phenotypic variance in apoA-I change in response to a low-fat diet (24.1% fat) [80]. One common apoB allele (M+) was associated with a reduction in apoA-I levels, whereas a less common apoB allele (M-) was associated with an increase in apoA-I levels in response to change in dietary fat intake.

IV. Apolipoprotein E. The role of genetic variation at the apoE locus in determining the interindividual variation in lipid and lipoprotein levels in populations is well documented [81-83] and also seems to be involved in influencing the genetic risk of atherosclerosis [84]. ApoE is a protein constituent of chylomicrons, chylomicron remnants, VLDL, IDL, and HDL. Its major physiologic role is to mediate the interaction of these lipoproteins with the LDL receptor and the chylomicron remnant receptor [85]. The three major allelic forms of apoE (apo E2, E3, and E4) create three homozygous phenotypes (apo E2/2, E3/3, and E4/4) and three heterozygous phenotypes (apo E3/2, E4/3, and E4/2). ApoE3 is the most common form of apoE and apo E4 and E2 are variants. Sing and Davignon [86] have reported that as much as 16% of the genetic variation of LDL cholesterol levels may be associated with these allelic differences in the apoE gene which have been shown to
effect LDL-apoB variability [87]. The average effects of the apoE alleles on apoB levels, however, vary in different populations [88].

The apoE4 allele predisposes to lower triglyceride and apoE concentrations, higher LDL cholesterol, and elevated LDL apoB [81, 82, 89-93] and occurs at a higher frequency in FH patients [94] and in patients with CAD [91, 95]. The apoE4 phenotype effect, however, is shown to be independent of LDL receptor status, although the magnitude of the effect is greatest in FH [96]. U.S. blacks [97] and Finns, [98, 99] with high rates of CAD, have relatively lower frequencies of the apoE3 allele and higher frequencies of apoE4 than U.S. whites. Patients with Type V hyperlipoproteinemia (elevated chylomicrons and VLDL) also have a high apoE4 gene frequency which is 2.6-fold higher than the Finnish population [100].

The apoE2 allele is defective as a ligand for the receptor mediated clearance of chylomicron remnants, VLDL and IDL. Homozygote (apoE2/2) hypolipidemia population frequencies are about 1% and heterozygotes (apo E4/2 and E3/2) about 14%. Individuals who inherit the apoE2/2 genotype have reduced levels of plasma cholesterol due in part to impaired LDL formation. Approximately 5% of patients with apoE2/2 have an accumulation of chylomicron remnants and IDL and increased frequency of atherosclerotic cardiovascular disease (type III hyperlipoproteinemia). This disorder may be due to interaction of apoE2 with other genetic or environmental factors that act to increase plasma triglyceride levels. This clinical syndrome is similar to familial apoE deficiency [101].

The majority of people with the apoE2/2 phenotype, however, are normolipidemic and do not show atherosclerosis susceptibility. Thus, expression of type III hyperlipoproteinemia requires the interaction of a
known apolipoprotein genotype with additional genetic or environmental factors [102]. One such focus of gene-gene interactions on cholesterol levels is the interaction between genetic variation at the LDL receptor locus and the apoE allele [35, 103]. Environmental factors that could alter the composition of lipoproteins and modulate the binding of apoE with the LDL receptor, thus interfering with hepatic lipoprotein clearance, include age, gender, diet, and hormonal status [103] (see below).

The occurrence of dominant and recessive forms of apoE2/2 may also explain the variability of binding that occurs [103]. A recessive mode of inheritance caused by one apoE2 variant shows reduced expression of FD (no type III hyperlipoproteinemia), while a dominant mode of inheritance with increased expression of FD (as type III hyperlipoproteinemia) occurs in the case of another apoE2 mutant [103].

Individuals who are heterozygous for the apoE2 phenotype (apoE4/2, or apoE3/2) generally show a milder increase in chylomicrons and IDL, low LDL cholesterol, and no increased risk for CAD, unless an individual inherits the aforementioned apoE2 mutant which predisposes to FD [104]. Additionally, the combination of endogenous hypertriglyceridemia and apoE3/2 phenotype is associated with increased VLDL-C levels [96]. Two other genetic apoE variants (apoE1 and apoE5) have also been described [105-107] which lead to FD, again with variable expression of type III hyperlipoproteinemia.

A. Apolipoprotein E and Diet Responsiveness. Most of the studies conducted on genetic-diet interactions and lipoprotein response have evaluated the influence of apoE isoforms as a genetic determinant of lipoprotein levels. The lipoprotein response to diet-induced weight gain is shown to be related to apoE isoform. Gueguen [108] demonstrated in 158
families in France that in conjunction with longitudinal weight gain, individuals with an apoE4 allele show a larger increase in triglyceride and beta lipoprotein levels compared with individuals with no apoE4 allele. It is also shown cross-sectionally, that obese subjects with apoE2 and/or apoE4 also have a higher frequency of hyperlipoproteinemia than non-obese or than obese subjects with the apoE3 phenotype [109]. However, in a different analysis of 63 premenopausal women, Pouliot et al. [110] demonstrated that the associations of body fatness and plasma lipoproteins usually seen cross-sectionally in the population are mainly accounted for by the high frequency of the apoE3 allele, as these associations are altered in the presence of apoE2 and E4 isoforms (Tables 3-5)[110]. Thus, the interaction between the apoE locus and weight gain on change in lipoprotein levels needs further clarification.

Cobb et al. [111] analyzed the association of apoE polymorphism, gender, and dietary fat composition on plasma lipid levels in 67 subjects fed both a "Western Diet" and a "Therapeutic Diet." Dietary polyunsaturated to saturated fatty acid ratio (P:S) was a stronger predictor of lipid concentrations than apoE phenotype, gender, or the latter two combined, although all these factors independently influenced lipoprotein levels. However, in combination with a "Therapeutic Diet," apoE polymorphism has a stronger influence on lipid levels than gender. Finally, an apoE4 isoform was associated with an increase in LDL cholesterol following both the low and high P:S diets.

Tikkanen et al. [112] also demonstrated that apoE isoform-related differences and LDL cholesterol were due to differential responses to dietary lipids. Lipid response to high- and low-fat diets according to apoE phenotypes was analyzed in 110 individuals (56 men and 54 women). The changes in
total cholesterol concentrations were significantly influenced by the apoE phenotypes during exchange from high- to low-fat diet, the magnitude of which again appeared to be greater in subjects with the apoE4 phenotype (Table 6) [112]. Interestingly, it was noted that the correlation between cholesterol levels and apoE phenotype was not significant on the low-fat diet suggesting that the metabolic influence of the apoE phenotype may be dependent on the quantity of fat in the diet. The lack of correlation of apoE phenotype to total serum cholesterol levels has also been demonstrated in human umbilical cord blood where the newborn state provides a model to analyze the influence of the apoE polymorphism on lipoproteins independent of intestinal nutrition in the relatively constant in utero environment [113].

In 230 male subjects with hypercholesterolemia of the Helsinki Heart Study [114], apolipoprotein E polymorphism also influenced the serum cholesterol response to dietary intervention. Subjects with the E4 allele exhibited a greater reduction in serum total cholesterol and LDL-cholesterol than those without the E4 allele, while the changes in HDL-C and triglycerides were not influenced by E4 status. Both baseline serum total cholesterol and E4 phenotype independently predicted the reduction in cholesterol level. However, in contrast with other studies [44, 46] which suggest that the E4 allele is associated with a greater sensitivity to dietary manipulations, there were no differences in baseline levels of total cholesterol and LDL-cholesterol in subjects with and without the E4 allele.

In a recent study [80], Xu et al. also demonstrated that on a basal high fat diet (38.9% fat) the major effect of genotype on lipid traits was due to variation at the apoE gene locus, explaining 14.6% of the phenotypic variance in LDL-C levels and 12.7% of the variance in total cholesterol levels.
However, when 107 individuals switched to a low fat diet (24.1% fat) these effects of variation at the apoE gene locus on the phenotypic variation of LDL and total cholesterol levels disappeared.

Savolainen et al. [115] also showed that the absolute and percentage lipid changes on low- and high-fat diets were equal in 44 subjects (22 men and 22 women) with the common apoE phenotype E3/3 and in those homozygous and heterozygous for the E4 allele (E4/4 and E4/3). Significant gender differences were noted, however; the men responded to dietary change with greater changes in total cholesterol and LDL-C levels than women.

The significance of the association between a particular apoE allele and total cholesterol level in different populations may especially depend on the amount of fat consumed. For example, Finns who have a high frequency of the apoE4 allele, along with high fat diets, have high cholesterol levels, and high rates of CAD [98]. U.S. blacks with similar CAD risk factors as U.S. whites have some of the highest rates of CAD; they also have a high frequency of apoE4 allele compared to U.S. whites [97]. In contrast, Nigerian blacks, with the highest observed frequencies of apoE4 allele among world populations, have the lowest mean cholesterol level reported among studies of the cholesterol/apoE relationship [116]. Nigerians consume a diet that is lower in animal fat than that of U.S. blacks, and in addition, have marked variation in the alleles observed at the genetic loci of apoA-IV, C-II, and H compared to Caucasians [117]. Although the average effect of the apoE4 allele is to increase the cholesterol level in populations, the magnitude of this effect may be modulated by diet or other genetic-environmental interactions.

The mechanisms by which different isoforms of apoE regulate cholesterol concentrations have been explored [82, 118, 119]. Genetically,
intestinal cholesterol absorption efficiency has been related to apoE phenotype in both normal and FH subjects [120, 121], which may contribute to the variation in total cholesterol concentration. Subjects with the E2 allele absorb less cholesterol and those with the E4 allele absorb more cholesterol than individuals with the E3 allele (Figure 3) [120]. Apo E3 and E4 have a different lipoprotein particle distribution (lower density lipoproteins are relatively enriched with apoE4 and high density lipoproteins relatively depleted of apoE4 as compared to apoE3) which may account for the elevated total and LDL cholesterol levels seen in carriers of the E4 allele [119].

Hepatic lipoprotein clearance has also been related to apoE phenotype. Triglyceride-rich particles containing apoE2 are removed more slowly by the liver and apoE4 particles are removed more efficiently than the apoE3-containing particles, an observation not confounded by age, gender, or baseline diet (Figure 4) [118]. This rate of clearance of dietary fat among the apoE phenotypes is related to LDL receptor regulation and could therefore account for the allelic effect on LDL cholesterol levels in the population [118].

Despite the well established effect of different apoE phenotypes on total and LDL cholesterol levels in normal populations, the apoE polymorphism does not contribute to the variation in these levels in FH patients cross-sectionally or when treated with a low-fat diet, and may be masked by the deficiency of the LDL receptor in FH.

V. Defective HDL Metabolism. Defective HDL production (familial hypoalphalipoproteinemia), due to an inability to synthesize its major apolipoprotein, apoA-I, leads to premature CAD [122]. This homozygous apoA-I deficiency has a frequency of < 1/1,000,000 in the population [123]. Eleven variants in the apoA-I gene have been characterized [124]. For
instance, low HDL mass and HDL$_2$ subtraction due to a structural mutation in the apoA-I gene occurs in the disorders apoA-I Milano [125], apoA-I Giessen, A-I Marburg, and A-I Munster2 [126] in which subjects have a partial LCAT deficiency [126-128](see below).

Heterozygotes for gene mutations of the apo A-I, C-III, and -A-IV gene complex (disrupting apoA-I, C-III expression) have HDL levels 62% of normal [129] and also have a higher risk of CAD [130]. Variations in the apoA-IV gene have been shown to account for 11% of the total variability in HDL-cholesterol levels in studies from Austria [131]. In general, however, apoA-IV genetic variability contributes minimally to normal variation in lipids, lipoproteins, and apolipoproteins in the population [132]. Although these particular defects are rare (reviewed by Schaefer [133]), it is still not certain how common other types of apoA-I defects might be present in the general population. However, the apoA-I:apoB ratio has been shown to be the most consistent discriminator of CAD severity [62, 124, 134-137].

Plasma HDL can be separated into two subpopulations of apoA-I containing particles: those that contain apoA-II and those that do not. The proportion of apoA-I with apoA-II to apoA-I without apoA-II in CAD patients is comparable to that in healthy normolipidemics [138]. However, the particle size distribution of these two HDL subpopulations in CAD patients tend to differ significantly from those in healthy normolipidemics. A preponderance of small HDL particles is associated with CAD in a study of 17 patients with CAD and 27 normolipidemic controls [138]. Earlier studies have suggested, however, that both small and large HDL particles are inversely correlated with CAD risk [139, 140].

These human traits in ApoA-I variability phenotypically resemble a newly described Ath-1 gene in the mouse which forms the genetic basis for
the differences in atherosclerotic lesion formation and HDL cholesterol levels among different strains [141]. The *Ath-I* gene appears to act by altering the catabolism of HDL in response to a high-fat diet, resulting in low HDL levels in susceptible mice strains.

**A. Apolipoprotein A and C Polymorphism in Relation to Diet Responsiveness.** In experiments by Schonfeld *et al.* [14], levels of apoA-I and B in subjects respond to variations in dietary cholesterol or \( \frac{P}{S} \) ratio, whereas levels of apo A-II, C-II, C-III or E do not. ApoA-I levels are highest in cholesterol-enriched diets. Zanni [18] also demonstrated an increase in apoA-I levels in test diets highest in saturated fat and cholesterol. In these studies, apoB levels varied consistently with changes in LDL-cholesterol concentrations.

The mechanism by which apoA-I regulates lipoprotein concentration has been explored. Within normal subjects, upon changing from a high to low intake of saturated fat and cholesterol, HDL-C and apoA-I levels decrease and are correlated with a decrease in apoA-I synthetic rate. In contrast, the differences in HDL concentrations between subjects on a high fat diet correlate with apoA-I fractional catabolic rate (FCR) defined as the rate at which labeled apoA-I disappears from plasma [142] (Figure 5) [142]. Differences in hepatic lipase levels between subjects appear to account for a large share of this intersubject variability in apoA-I FCR. This finding suggests that the intrasubject diet-induced decreases in HDL may not be metabolically equivalent to low HDL levels between people on a standard diet. Brinton *et al.* [143] further hypothesized that lipase activity and plasma triglycerides affect HDL composition which modulates FCR, in turn regulating intersubject HDL-C levels.
Others have explored the relationship of interindividual differences in lipoprotein response to diet as a function of apoC-II levels. In normolipidemic subjects, the fasting level of apoC-II is not associated with clearance of triglyceride after a fat load [144]. ApoC-II seems to be mainly involved in cholesterol metabolism through its association with HDL rather than VLDL.

VI. LDL Subclass Patterns. In most healthy people, the major LDL subclass is either LDL-I or LDL-II, while the smaller, denser LDL subclasses, LDL-III and LDL-IV, are present in very small amounts [145]. These LDL subclass patterns follow a dominant mode of inheritance [146] and are related to risk of myocardial infarction [147]. A recently identified genetic trait, termed atherogenic lipoprotein phenotype (alp) found to be present in up to 40% of the population, predisposes to production of small, dense LDL subspecies III and IV, and is associated with increased levels of triglycerides and reduced levels of HDL [148]. This phenotype, however, is not fully expressed until after age 20 in men and after menopause in women [146], which suggests that other genetic or environmental factors may interact to influence expression of alp. Alp may, however, be a marker for one or more genes which influence lipoprotein profiles that predispose an individual to increased risk of atherosclerosis.

A. Hyperinsulinemia. High fasting plasma insulin (hyperinsulinemia), an indicator of CAD [149], is another metabolic feature associated with an atherogenic lipoprotein profile (high triglycerides and low HDL-C). Hyperinsulinemia may reflect insulin resistance and be the cause or result of a constellation of associated metabolic factors, such as a high body mass index and/or abdominal adipose tissue (a high waist to hip girth ratio), hypertension, high triglycerides and LDL-III, or reduced HDL-C levels [150].
The possibility that the fatty acid composition of plasma and membrane lipids has a role in insulin resistance was investigated by Salomaa et al. [151]. In a cross-sectional study, increased intake of dietary saturated fats and subsequent higher proportion of saturated fatty acids in serum and membrane lipids was higher in subjects with impaired glucose tolerance and NIDDM than controls. The possible enhanced lipolytic activity of abdominal adipose tissue may lead to higher plasma free fatty acids which in turn decrease both hepatic removal of insulin and insulin-stimulated glucose uptake by peripheral tissues [152]. Obesity has also been associated with increased activity of HTGL and decreased activity of LPL which in turn may also contribute to increases in triglycerides and reductions in HDL cholesterol levels. Hypertriglyceridemic subjects with normal glucose tolerance often have peripheral insulin resistance, but hepatic insulin sensitivity is preserved [153].

Individuals with the \( \text{alp} \) phenotype (predominance of LDL-III subclass) have a similar clinical profile as patients with hyperinsulinemia, namely, higher fasting triglycerides and lower HDL-C [154]. These lipid and lipoprotein associations with hyperinsulinemia have also been shown in a cross-sectional epidemiological study of 542 persons, independent of glucose intolerance, obesity, and hypertension [155].

B. LDL Heterogeneity and Diet Responsiveness. Small, dense LDL subclasses may be a genetic marker, tied to a gene whose expression affects lipoprotein response to dietary fat and carbohydrate. A low fat-high carbohydrate diet has been shown to induce expression of the \( \text{alp} \) trait in those who do not express it on a high-fat diet (Dreon et al. unpublished observations, 1991). Additionally, reduction of fat intake and substitution of carbohydrate in diets of individuals with the \( \text{alp} \) phenotype results in
aggravation of some of their metabolic abnormalities, namely increases in triglyceride and reductions in HDL cholesterol (Table 7; Dreon et al., unpublished observations). These responses are not observed in individuals who have more of the large, less dense LDL subclasses I and II.

It is known that, in general, consumption of a high carbohydrate diet is associated with increases in plasma triglycerides and decreases in HDL-C [156, 157], which parallels the diet response seen in subjects with the alp trait. Many other studies have also demonstrated relationships between LDL particle size and triglyceride metabolism [158-160]. Additionally, studies of post-prandial lipidemia in normal individuals have suggested that HDL-C is also influenced by triglyceride metabolism through lipolytic enzymes [51]. For example, a possible mechanism for this response was observed in a diet study of thirteen normal male and female subjects where changes in plasma triglycerides and HDL-C seen with low fat-high carbohydrate feeding were associated with reductions in the activity of LPL [161]. Reductions in LPL activity may be the consequence of an increased insulin secretion associated with a high carbohydrate diet [161]. A decline in LPL activity with a low fat-high carbohydrate diet was also observed in subjects with alp (Campos et al., unpublished observations, 1991), which suggests that expression of the alp trait may be linked to reductions in LPL activity which accompanies dietary change.

The influence on insulin sensitivity of a high carbohydrate (55% carbohydrate, 20% fat) versus a high fat (31% carbohydrate, 50% fat) diet was tested in a group of eight normal subjects (three males and five females) [162]. Fasting blood glucose and serum insulin concentrations were unchanged on the two diets, as was the mean whole body glucose uptake (assessed by glucose clamps). A high carbohydrate diet did not enhance
insulin sensitivity yet affected lipoprotein metabolism significantly by reducing LDL-C and HDL-C, and increasing triglycerides. However, in patients with insulin resistance [157, 163, 164], the hyperinsulinemia is accentuated when dietary carbohydrate is increased by 16% of total calories (from 40-56%) and dietary fat is decreased [163].

Although substitution of carbohydrate for saturated fat in the diet is the proposed remedy for high LDL-C levels, there is an associated negative influence resulting in reduced HDL-C and increased triglyceride levels. Substitution of monounsaturated fat for saturated fat has been reported to have a more favorable effect on lipoprotein risk profiles than exchanging carbohydrate for saturated fat, as the former increases the ratio of apoA-I to apoB and HDL to LDL [165, 166].

Recently, others have reported that substitution of dietary protein for carbohydrate significantly lowers plasma total cholesterol, LDL-C, and triglycerides while increasing HDL-C in hypercholesterolemic subjects which may enhance cardiovascular risk reduction obtained by restriction of dietary fat and cholesterol [167].

VII. Conclusion

As evidenced by this review, little is known regarding genetic-diet interactions and plasma lipoproteins. Relatively few genes and their phenotypic expression in response to diet have as yet been examined. Examples of other factors that need to be studied in lipoprotein transport pathways for fat and cholesterol metabolism include the role of lipoprotein and triglyceride lipases, cholesterol ester transfer protein, and polymorphisms in apolipoproteins. Additionally, the genes that control responsiveness to diet need to be identified. As more genetic information about lipoprotein
traits becomes available, it can play a role in more accurately assigning risk to those individuals who do or do not respond to diet therapy.

Successful dietary intervention for lipoprotein modification may in the future be based on identifying genetic markers whose effects we are attempting to modify. We now need to focus our attention on gene identification when looking at lipoprotein responses to diet, as an extension of the studies in diet and lipoproteins performed over the past several decades. The studies of the future will need to involve larger numbers of people. They will also need to include family units to identify the gene(s) and demonstrate genetic heterogeneity. Future research may lead to the development of diets that are tailored to an individual’s need. Appropriate prescriptions can then be made with primary focus on prevention. Diet therapy for the high risk individual in preventive medicine may be different than the conventional public health approach to dietary modification. The optimal dietary strategy that will improve lipoprotein levels and reduce heart disease risk may not be the same for each type of genetic variant.
REFERENCES


58. Rauh, G.; Schuster, H.; Muller, B.; Schewe, S.; Keller, C.; Wolfram, G.; Zollner, N.: Genetic evidence from 7 families that the apolipoprotein
B gene is not involved in familial combined hyperlipidemia.  

59. Sane, T.; Nikkila, E.A.: Very low density lipoprotein triglyceride  
metabolism in relatives of hypertriglyceridemia probands. Evidence  
for genetic control of triglyceride removal. Arteriosclerosis 8: 217-226  
(1988).

60. Paulweber, B.; Friedl, W.; Krempler, F.; Humphries, S.E.; Sandhofer, F.:  
Association of DNA polymorphism at the apolipoprotein B gene locus  
with coronary heart disease and serum very low density lipoprotein  

61. Wojciechowski, A.P.; Farrall, M.; Cullen, P.; Wilson, T.; Bayliss, J.D.;  
Farren, B.; Griffin, B.A.; Caslake, M.J.; Packard, C.J.; Shepherd, J.;  
Thakker, R.; Scott, J.: Familial combined hyperlipidaemia linked to  
the apolipoprotein AI-CIII-AIV gene cluster on chromosome 11q23-q24.  

62. Brunzell, J.D.; Sniderman, A.D.; Albers, J.J.; Kwiterovich, P.O., Jr.:  
Apoproteins B and A-I and coronary heart disease in humans.  

63. Ladias, J.; Kwiterovich, P.J.; Smith, H.H.; Miller, M.; Bachorik, P.S.;  
Forte, T.; Lusis, A.J.; Antonarakis, S.E.: Apolipoprotein B-100 Hopkins  
(arginine4019->tryptophan). A new apolipoprotein B-100 variant in a


92. Eichner, J.E.; Kuller, L.H.; Ferrell, R.E.; Meilahn, E.N.; Kamboh, M.I.: Phenotypic effects of apolipoprotein structural variation on lipid profiles. III. Contribution of apolipoprotein E phenotype to prediction of total cholesterol, apolipoprotein B, and low density lipoprotein


137. Pan, Q.X.; Liu, P.; Wang, S.C.; Pan, J.T.; Sun, B.Y.; Wu, X.Y.; Saltups, A.: The study of serum apoprotein levels as indicators for the severity of


143. Brinton, E.A.; Eisenberg, S.; Breslow, J.L.: Increased apo A-I and apo A-II fractional catabolic rate in patients with low high density lipoprotein-


149. Rönnemaa, T.; Laakso, M.; Pyörälä, K.; Kallio, V.; Puukka, P.: High fasting plasma insulin is an indicator of coronary heart disease in non-
insulin-dependent diabetic patients and nondiabetic subjects.


Relationship between post-heparin plasma lipases, triglycerides and
high density lipoproteins in normal subjects. Horm Metab Res 22: 289-

162. Borkman, M.; Campbell, L.V.; Chisholm, D.J.; Storlien, L.H.:
Comparison of the effects on insulin sensitivity of high carbohydrate
and high fat diets in normal subjects. J. Clin. Endocrinol. Metab. 72:

diet on carbohydrate metabolism in patients with hypertension.
Hypertension 11: 244-248 (1988).

164. Reiser, S.; Powell, A.S.; Scholfield, D.J.; Panda, P.; Fields, M.; Canary,
J.J.: Day-long glucose, insulin, and fructose responses of
hyperinsulinemic and nonhyperinsulinemic men adapted to diets
containing either fructose or high-amylose cornstarch. Am. J. Clin.

165. Mensink, R.P.; deGroot, M.J.M.; van den Broeke, L.T.; Severijnen-
Nobles, A.P.; Demacker, P.N.M.; Katan, M.B.: Effects of monosaturated
fatty acids v complex carbohydrates on serum lipoproteins and
apoproteins in healthy men and women. Metabolism 38: 172-178
(1989).

TABLE 1.  Effect of Dietary Fat Supplementation (5 g Saturated Fat) in Diet-Sensitive and Diet-Insensitive Hypercholesterolemic and Normocholesterolemic Subjects.


Reference Number: [40]

<table>
<thead>
<tr>
<th>Hypercholesterolemic group</th>
<th>Diet-sensitive (n=23)</th>
<th>Diet-insensitive (n=22)</th>
<th>Normocholesterolemic group (n=11)</th>
<th>Combined (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cholesterol</td>
<td>0.32±0.41</td>
<td>0.13±0.34</td>
<td>0.03±0.31</td>
<td>0.19±0.38*</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.20±0.40</td>
<td>0.06±0.31</td>
<td>-0.02±0.28</td>
<td>0.10±0.35†</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.12±0.15</td>
<td>0.09±0.18</td>
<td>0.01±0.14</td>
<td>0.08±0.17‡</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>0.01±0.13</td>
<td>-0.02±0.12</td>
<td>0.05±0.03</td>
<td>0.00±0.13</td>
</tr>
<tr>
<td>Plasma triglyceride</td>
<td>-0.02±0.34</td>
<td>-0.05±0.32</td>
<td>0±0.45</td>
<td>-0.03±0.35</td>
</tr>
</tbody>
</table>

Values of changes in concentration are mmol/l±SD.
Comparisons with baseline values: *p<0.001, †p<0.01, ‡p<0.05.

LDL = low density lipoprotein
HDL = high density lipoprotein
VLDL = very low density lipoprotein
TABLE 2. Effect of Dietary Cholesterol Supplementation (700 mg) in Diet-Sensitive and Diet-Insensitive Hypercholesterolemic and Normocholesterolemic

Reference Number: [40]

<table>
<thead>
<tr>
<th>Hypercholesterolemic group</th>
<th>Diet-sensitive (n=23)</th>
<th>Diet-insensitive (n=22)</th>
<th>Normocholesterolemic group (n=11)</th>
<th>Combined (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cholesterol</td>
<td>0.36±0.37</td>
<td>0.19±0.47†</td>
<td>0.06±0.47</td>
<td>0.23±0.44*</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.30±0.36</td>
<td>0.15±0.46†</td>
<td>0.02±0.40</td>
<td>0.19±0.41*</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.09±0.14</td>
<td>0.07±0.15</td>
<td>0.05±0.13</td>
<td>0.07±0.14*</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>−0.04±0.10</td>
<td>−0.03±0.12</td>
<td>−0.01±0.12</td>
<td>−0.03±0.11</td>
</tr>
<tr>
<td>Plasma triglyceride</td>
<td>−0.07±0.26</td>
<td>−0.10±0.29</td>
<td>0.02±0.31</td>
<td>−0.07±0.28</td>
</tr>
</tbody>
</table>

The values of changes in concentration are mmol/l±SD.
*p<0.001, comparisons with control values. †p=0.06, diet-sensitive versus diet-insensitive.

LDL = low density lipoprotein
HDL = high density lipoprotein
VLDL = very low density lipoprotein


Reference Number: [110]

<table>
<thead>
<tr>
<th>Variable</th>
<th>ApoE Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E2</td>
</tr>
<tr>
<td>N</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.6 ± 4.8</td>
</tr>
<tr>
<td>% Body fat</td>
<td>40.4 ± 8.2</td>
</tr>
<tr>
<td>Body mass index</td>
<td>30.9 ± 7.0</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.80 ± 0.4</td>
</tr>
<tr>
<td>VLDL-C (mmol/l)</td>
<td>0.45 ± 0.30</td>
</tr>
<tr>
<td>VLDL-TG (mmol/l)</td>
<td>0.98 ± 0.67</td>
</tr>
<tr>
<td>VLDL-apoB (g/l)</td>
<td>0.12 ± 0.15</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.39 ± 0.81</td>
</tr>
<tr>
<td>LDL-TG (mmol/l)</td>
<td>0.28 ± 0.12</td>
</tr>
<tr>
<td>LDL-apoB (g/l)</td>
<td>0.75 ± 0.22</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.22 ± 0.29</td>
</tr>
<tr>
<td>HDL-TG (mmol/l)</td>
<td>0.22 ± 0.09</td>
</tr>
<tr>
<td>HDL-apoA-I (g/l)</td>
<td>1.15 ± 0.21</td>
</tr>
</tbody>
</table>

E2, Subjects homozygous or heterozygous for the E2 isoform; E3, subjects homozygous for the E3 isoform; E4, subjects homozygous or heterozygous for the E4 isoform; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; C, cholesterol; TG, triglycerides; apo, apolipoprotein.
TABLE 4. Associations\textsuperscript{a} Between Body Fatness Variables and Plasma Very Low Density Lipoprotein (VLDL) Components in Apolipoprotein E Phenotype Groups.


\textit{Reference Number:} [110]

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{ApoE Group} & \textbf{Lipoprotein Components} & \textbf{Fat Mass} & \textbf{WHR} & \textbf{Abdominal Fat} \\
\hline
E2 & VLDL-C & 0.57\textsuperscript{**} & 0.58\textsuperscript{**} & 0.59\textsuperscript{**} & 0.64\textsuperscript{**} \\
 & VLDL-TG & 0.59\textsuperscript{**} & 0.59\textsuperscript{**} & 0.62\textsuperscript{**} & 0.65\textsuperscript{***} \\
 & VLDL-apoB & 0.42\textsuperscript{*} & 0.38 & 0.38 & 0.38 \\
E3 & VLDL-C & 0.46\textsuperscript{*} & 0.54\textsuperscript{**} & 0.50\textsuperscript{**} & 0.56\textsuperscript{**} \\
 & VLDL-TG & 0.53\textsuperscript{*} & 0.44\textsuperscript{*} & 0.58\textsuperscript{**} & 0.61\textsuperscript{***} \\
 & VLDL-apoB & 0.74\textsuperscript{***} & 0.58\textsuperscript{**} & 0.80\textsuperscript{***} & 0.75\textsuperscript{***} \\
E4 & VLDL-C & 0.10 & 0.13 & 0.32 & 0.11 \\
 & VLDL-TG & 0.43 & 0.28 & 0.53\textsuperscript{*} & 0.33 \\
 & VLDL-apoB & -0.07 & -0.17 & 0.08 & -0.05 \\
\hline
\end{tabular}
\end{table}

\textit{WHR} = \text{waist:hip circumference ratio}

For other abbreviations, refer to Table 3.

\textit{*p} = < 0.05; \textit{**p} = < 0.01; \textit{***p} = < 0.001

\textit{a}All values are log 10.
TABLE 5. Associations Between Body Fatness Variables and Plasma Low Density Lipoprotein (LDL) Components in Apolipoprotein E Phenotype Groups.


Reference Number: [110]

For other abbreviations, refer to Tables 3 and 4.

*p = < 0.05; **p = < 0.01; ***p < 0.001

<table>
<thead>
<tr>
<th>ApoE Group</th>
<th>Lipoprotein Components</th>
<th>Fat Mass</th>
<th>WHR</th>
<th>Total</th>
<th>Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>LDL-C</td>
<td>0.09</td>
<td>0.27</td>
<td>0.05</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>LDL-TG</td>
<td>0.57***</td>
<td>0.34</td>
<td>0.54*</td>
<td>0.54*</td>
</tr>
<tr>
<td></td>
<td>LDL-apoB</td>
<td>0.08</td>
<td>0.38</td>
<td>0.07</td>
<td>0.29</td>
</tr>
<tr>
<td>E3</td>
<td>LDL-C</td>
<td>0.56**</td>
<td>0.46*</td>
<td>0.57**</td>
<td>0.55**</td>
</tr>
<tr>
<td></td>
<td>LDL-TG</td>
<td>0.66***</td>
<td>0.51*</td>
<td>0.69***</td>
<td>0.68***</td>
</tr>
<tr>
<td></td>
<td>LDL-apoB</td>
<td>0.43*</td>
<td>0.43*</td>
<td>0.45*</td>
<td>0.47*</td>
</tr>
<tr>
<td>E4</td>
<td>LDL-C</td>
<td>0.16</td>
<td>0.15</td>
<td>0.44</td>
<td>0.51*</td>
</tr>
<tr>
<td></td>
<td>LDL-TG</td>
<td>0.16</td>
<td>0.23</td>
<td>0.45</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>LDL-apoB</td>
<td>0.29</td>
<td>0.34</td>
<td>0.58*</td>
<td>0.50*</td>
</tr>
</tbody>
</table>
TABLE 6. Changes in Total Plasma Cholesterol and Low Density Lipoprotein Cholesterol During Dietary Study. Source: [112]


Reference Number: [110]

<table>
<thead>
<tr>
<th>Changes</th>
<th>Plasma lipid</th>
<th>E4/E4 (n=8)</th>
<th>E4/E3, E3/E3, or E3/E2 (n=102)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease during intervention</td>
<td>Cholesterol</td>
<td>-1.84</td>
<td>-1.13</td>
<td>0.0097</td>
</tr>
<tr>
<td></td>
<td>LDL chol</td>
<td>-1.51</td>
<td>-0.91</td>
<td>0.0164</td>
</tr>
<tr>
<td>Increase during switchback</td>
<td>Cholesterol</td>
<td>1.52</td>
<td>0.92</td>
<td>0.0141</td>
</tr>
<tr>
<td></td>
<td>LDL chol</td>
<td>1.17</td>
<td>0.68</td>
<td>0.0221</td>
</tr>
</tbody>
</table>

The values are given in mmol/l. LDL, low density lipoprotein.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Pattern A (N=32)</th>
<th>Pattern B (N=9)</th>
<th>mg/dL Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Diet</td>
<td>Low Fat Diet</td>
<td>Baseline Diet</td>
<td>Low Fat Diet</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>175 ± 43</td>
<td>177 ± 37</td>
<td>180 ± 43</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>91 ± 44</td>
<td>80 ± 27</td>
<td>128 ± 45</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>48 ± 7.0</td>
<td>47 ± 9.6</td>
<td>43 ± 12</td>
</tr>
<tr>
<td>LDL Sf 0 - 7 mass</td>
<td>146 ± 59</td>
<td>152 ± 62</td>
<td>182 ± 54</td>
</tr>
<tr>
<td>LDL Sf 7 - 12 mass</td>
<td>114 ± 41</td>
<td>115 ± 43</td>
<td>83 ± 32</td>
</tr>
<tr>
<td>IDL Sf 12 - 20 mass</td>
<td>19 ± 17</td>
<td>22 ± 15</td>
<td>31 ± 23</td>
</tr>
<tr>
<td>VLDL Sf 20 - 400 mass</td>
<td>55 ± 51</td>
<td>46 ± 37</td>
<td>95 ± 49</td>
</tr>
<tr>
<td>HDL3 F1.20 0 - 3.5 mass</td>
<td>191 ± 29</td>
<td>184 ± 34</td>
<td>183 ± 47</td>
</tr>
<tr>
<td>HDL2 F1.20 3.5 - 9 mass</td>
<td>52 ± 28</td>
<td>52 ± 35</td>
<td>34 ± 40</td>
</tr>
</tbody>
</table>

Changes with diet significant: *p < 0.05; **p < 0.01.

† Change in pattern B subjects significantly different from change in pattern A subjects at p < 0.01.
FIGURE 1. Difference Between Predicted (Keys formula) and Observed Changes in Serum Cholesterol, by Baseline Serum Cholesterol and Time After Randomization


Reference Number: [38]
FIGURE 2. Percent Change From Before to After Fish Oil in Lipoprotein Chemical Composition.


Reference Number: [71]
FIGURE 3. Cholesterol Absorption (left), Bile Acid Synthesis (left middle), Cholesterol Synthesis (right middle), and Serum Lathosterol (right) in the Subjects With Various ApoE Phenotypes. The Values Are Expressed as Mean ± SEM of 4 (E2/2, E2/3, E2/4), 22 (E3/3), and 13 (E4/4, E4/3) Subjects. *, Different From the Subjects E2/2, E2/3, and E2/4; + Different From the Subject E3/3; (P < 0.05 or less; Analysis of Variance; F Values of 3/39 for Cholesterol Absorption and 3.17 for Serum Lathosterol).


Reference Number: [120]
FIGURE 4. RP Peak Heights (in micrograms per liter) of Total Plasma, Chylomicron, and Nonchylomicron Fractions During the Vitamin A-Fat Loading Test in Individual Subjects With Different Apo E Phenotypes.


Reference Number: [118]
FIGURE 5. Relationships Between Levels of HDL-C (mg/dl) and Apo A-I, TR (mg/kg per d), and FCR (pools/d). Results are Plotted as Change vs. Change (Low-Fat Diet Value - High-Fat Diet Value) and as Within-Diet Results for High and Low Fat Intake.


Reference Number: [142]
Figure 1

Difference Between Predicted and Observed Change in Serum Cholesterol (mMol/L)

Serum Cholesterol (mMol/L)
Figure 3

Low density lipoprotein cholesterol mmol/l
Figure 4
Between Diets
Change vs. Change

Within Diets

High Fat

Low Fat

Figure 5