WORLD HEALTH ORGANIZATION MEMORANDUM

Classification of Hyperlipidemias and Hyperlipoproteinemias

MANY STUDIES OF atherosclerosis have indicated hyperlipidemia as a predisposing factor to vascular disease. The relationship holds even for mild degrees of hyperlipidemia, a fact that underlines the importance of this category of disorders. Both primary and secondary hyperlipidemias represent such a variety of abnormalities that an internationally acceptable provisional classification is highly desirable in order to facilitate communication between scientists with different backgrounds.

The present memorandum presents such a classification; it briefly describes the criteria for diagnosis of the main types of hyperlipidemia as well as the methods of their determination. Because lipoproteins offer more information than analysis of plasma lipids (most of the plasma lipids being bound to various proteins), the classification is based on lipoprotein analyses by electrophoresis and ultracentrifugation. Simpler methods, however, such as the observation of plasma and measurements of cholesterol and triglycerides, are used to the fullest possible extent in determining the lipoprotein patterns.

The plasma lipids circulate in lipoproteins; each of the four main lipoprotein families, chylomicrons, pre-β (VLDL), β (LDL), and α (HDL) contains cholesterol, triglycerides, and phospholipids; and the metabolism of the four lipoprotein families is different. These facts provide keys to the classification of hyperlipidemias, because they indicate that (1) hyperlipoproteinemia very seldom occurs without hyperlipidemia and, consequently, hyperlipidemia may be used to detect hyperlipoproteinemia; (2) a classification based on lipoproteins offers more information than one based on lipids alone; (3) a classification should distinguish between disorders in the metabolism of lipoproteins as well as lipids.

The proposed classification described here includes, step by step, the use of lipid analyses, lipoprotein analyses, and other clinical and biologic data. It provides an approach to the etiologic and to the pathogenic classification by which the former will ultimately be replaced. The classification for genetic purposes is based on the assumption that the patient has been on a standard diet prior to the analyses.

Hyperlipidemia

Cholesterol (Chol) and triglyceride (TG) analyses are the simplest means for detecting hyperlipoproteinemia. They also provide some information about the type of hyperlipoproteinemia because the proportion of these lipids varies from one lipoprotein family to another.

Knowledge of the concentrations of cholesterol and triglycerides permits the distinction of three general types of hyperlipidemia that roughly correspond to certain types of hyperlipoproteinemias:

(1) High cholesterol concentrations and normal triglyceride concentrations—this group, sometimes called "pure hypercholesterolemia," usually corresponds to hyper-β-lipoproteinemia.

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(2) High triglyceride and normal cholesterol concentrations—this group usually corresponds to either "pure hyperchylomicronemia" or hyperpre-β-lipoproteinemia.

(3) High cholesterol and high triglyceride concentrations—all of the major types of hyperlipoproteinemia, except "pure" hyper-β-lipoproteinemia, may occur in this group.

The heterogeneity of the third group particularly emphasizes the need for a classification based on lipoproteins.

It is possible to refine a little the classifications of hyperlipidemias by adding a total phospholipid (PL) measurement and also by calculating the following ratios: Chol/TG and Chol/PL.

The ratio Chol/TG indicates whether the predominant elevation is in cholesterol or in triglyceride. The ratio Chol/PL often indicates elevation of HDL (α-lipoproteins) when it falls under 0.5. These refinements are not necessary to detect hyperlipidemia but do offer some assistance in classification if lipoproteins are not determined.

Hyperlipoproteinemia

Hyperlipidemia can usually be resolved into one of the abnormal lipoprotein patterns summarized in table 1. For the sake of simplicity, these patterns or types can be numbered according to the system of Fredrickson and his colleagues. These patterns are not to be equated with single diseases and each may have multiple causes. Most, but not all, hyperlipidemia is represented by the six patterns described. The methods of diagnosis described are arranged in the order of practicality. Some tests are diagnostic (definitive) of a given type; others are not.

Table 1

Major Abnormal Lipoprotein Patterns and Their Type Numbers*

Type	Chylomicrons	LDL (β-lp)	VLDL (pre-β-lp)	Floating β-lipoproteins†
I	+			
IIa		+		
IIb		+	+	
III				+
IV			+	
V	+		+	

*+ indicates which lipoprotein "family" (families) occurs in concentration above "normal" in the different abnormal patterns.

†Also known as "broad β-lipoproteins."

Type I—Hyperchylomicronemia

Criteria

(1) Chylomicrons present.

(2) VLDL (pre-β-lipoproteins) normal or only slightly increased.

Methods of Diagnosis

(1) Standing plasma contains a "cream" layer over a clear infranatant layer (diagnostic test).

(2) Plasma cholesterol usually increased; plasma triglyceride increased; Chol/TG less than 0.2; a ratio of less than 0.1 occurs only in type I.

(3) Electrophoresis—a heavy chylomicron band is present and is distinct from any lipoproteins trailing from the pre-β region; sometimes α- (HDL) and β- (LDL) lipoprotein bands are not visible; a pre-β (VLDL) band may be absent or it may appear with diminished, normal, or slightly increased intensity and with trailing into the massive chylomicron band (usually diagnostic).

(4) Ultracentrifugation—chylomicrons, markedly increased; VLDL, usually increased (separation from chylomicrons incomplete); LDL markedly decreased; HDL markedly decreased.

Comment. It must be noted that, in type I, chylomicrons may sometimes be accompanied by an apparent modest increase in VLDL (pre-β). This is partly due to the difficulty of separating these two lipoprotein families. The amount of excess VLDL, however, is always far less than the overwhelming amount of chylomicrons.

Recommended Tests for Diagnosis

(1) Examination of standing plasma.

(2) Electrophoresis.

Type II—Hyper-β-lipoproteinemia

Criterion

Abnormal increase in LDL (β) concentration.

Note. For some purposes it may be convenient to distinguish between two subtypes of this pattern. These are referred to here as IIa and IIb. In both, the criterion for type II, an increase in LDL (β), is present, but in one (IIb) an increase in VLDL (pre-β) is also present. Recognition of IIb is important because it may require treatment additional to that required for "pure" hypercholesterolemia. Both patterns may occur in the same kindreds affected with familial hyper-β-lipoproteinemia; it is mainly for this reason that they must at present be considered under the main rubric of type II.

Type IIa

Criteria

(1) Increase in LDL (β).

(2) Normal VLDL (pre-β) concentrations.

Methods of Diagnosis

(1) Standing plasma clear (very helpful; not always diagnostic).

(2) Plasma cholesterol usually increased; plasma triglycerides normal; Chol/TG always > 1.5.

(3) Electrophoresis—an intensely stained β-lipoprotein band is present; a pre-β band is either not present or, if present, is of normal intensity. Chylomicrons are not visible; α-lipoproteins are usually normal (diagnostic only if accompanied by estimation of LDL concentration).

(4) Ultracentrifugation—LDL (S_f 0–20) is increased. VLDL (S_f 20–400) is normal, HDL is usually normal, and chylomicrons are not increased (diagnostic).

Type IIb

Criteria

(1) Increase in LDL (β).

(2) Increase in VLDL (pre-β).

Methods of Diagnosis

(1) Standing plasma either clear or faintly turbid throughout, without a chylomicron ("cream") layer on the top (not diagnostic).

(2) Plasma cholesterol usually increased; plasma triglyceride always increased; Chol/TG is variable (not diagnostic).

(3) Electrophoresis—β-lipoprotein band is intensely stained; pre-β band is increased in intensity. Chylomicrons are not visible; α-lipoproteins are usually normal (diagnostic only if accompanied by estimations of LDL and VLDL concentrations).

(4) Ultracentrifugation—LDL (S_f 0–20) is increased; VLDL (S_f 20–400) is increased; chylomicrons are not increased; HDL is usually normal (diagnostic).

Comment. Definite determination of type II depends upon the establishment of an abnormal increase in LDL (β) concentrations. This is most precisely obtained by analytical or preparative ultracentrifugation. It may also be estimated from the cholesterol, triglyceride, and HDL-cholesterol concentrations, as described above.

LDL can also be measured by immunochemical analysis of the 1.006 infranatant fractions using anti-LDL sera. (Such antisera also react with VLDL and therefore do not permit accurate LDL determinations on whole plasma.)

The type IIa pattern can usually be ascertained by the cholesterol and triglyceride analyses alone, especially when the Chol/TG ratio is > 2. The exceptions are those patients who may have abnormally increased LDL concentrations in the presence of a normal plasma cholesterol concentration.

The type IIb pattern is difficult to ascertain from plasma lipids alone.

Recommended Tests

(1) Chol plus TG plus electrophoresis, when Chol/TG > 2.

(2) Chol plus TG plus HDL (cholesterol measurements after precipitation) for calculation of LDL (applicable only when type III is excluded and TG < 400). If estimated LDL is increased, assignment of subtypes is: IIa when TG is normal; IIb when TG is increased.

(3) Ultracentrifugal analyses.

Type III—"Floating β" or "Broad β" Pattern

Criterion

Presence of VLDL having abnormally high cholesterol content and abnormal electrophoretic mobility ("floating-β"; "β-VLDL").

Methods of Diagnosis

(1) Standing plasma usually turbid, frequently with a faint chylomicron "cream" layer (helpful but not diagnostic).

(2) Plasma cholesterol nearly always increased; plasma triglycerides nearly always increased; Chol/TG frequently about 1, but may vary from 0.3 to >2.0.

(3) Electrophoresis—on paper, agarose, or cellulose acetate, there is usually a "broad β" band extending from the β position into the pre-β position. This occurs in about two thirds of plasma containing "floating β." A distinct pre-β band is sometimes present and may be increased in intensity: α-lipoproteins usually appear normal. A faint chylomicron band is often present even during periods of very low fat intake (helpful but not diagnostic). On polyacrylamide gel electrophoresis (PGE) a broadened pre-β (VLDL) band is present, and no lipoproteins are seen in the usual position occupied by β-lipoproteins (LDL) on this medium. The concomitant presence of β-migrating lipoproteins on paper, agarose, or cellulose acetate and their absence on polyacrylamide gel is a presumptive test for the type III anomaly and is about 95% accurate. (The combination electrophoretic test is considered diagnostic.)

On starch-block electrophoresis of isolated VLDL, two bands are obtained, one in the usual α_2 position (sometimes called "α_2-VLDL") and one in an abnormal β position ("β-VLDL") (diagnostic).

Paper, agarose, cellulose acetate, or starch electrophoresis of the supernatant fraction of plasma after ultracentrifugation at its unadjusted salt density of 1.006 reveals β-migrating lipoproteins. Normally only pre-β migrating lipoproteins are present in the lipoprotein fraction of density <1.006. (The demonstration of "floating β" is at present the definitive standard against which other diagnostic tests must be compared.)

(4) Ultracentrifugation—in the analytical ultracentrifuge the normally predominating LDL subclass of density 1.010–1.063 (S_f 0–12) is greatly decreased and the LDL subclass of density 1.006–1.019 (S_f 12–20) is disproportionately increased. The VLDL subclass (S_f 100–400) is also increased. Chylomicrons may be increased. This inversion of the usual concentrations of LDL and VLDL usually provides a characteristic pattern in type III; however, it is possible to have similar changes in total S_f 0–20 and S_f 20–400 subclasses in other types (very helpful but not always diagnostic).

The combination of preparative ultracentrifugation and electrophoresis described above may be augmented by a measurement of cholesterol and triglycerides in the VLDL (density <1.006) ultracentrifuge fraction (the latter may possibly be substituted for the former). Normally, the Chol/TG ratio in VLDL is 0.2 or less. Significantly higher ratios (>0.4) are indicative of type III (probably diagnostic).

Comment. The type III anomaly indicates the presence of abnormal VLDL or, more precisely, of abnormal LDL in the VLDL fraction of plasma lipoproteins. It may be suspected from a Chol/TG ratio of 1, especially when repeated analyses show marked lability of both Chol and TG concentrations, and a "broad β" band appears on conventional electrophoresis. This combination may permit a presumptive diagnosis; however, the diagnosis should never be made alone from conventional electrophoresis on a single medium.

The definitive test is the demonstration of "floating β," but an analysis of equivalent value may prove to be the measurement of cholesterol and triglyceride in VLDL; combining electrophoresis on PGE and one other medium permits a presumptive diagnosis. A simpler, accurate diagnostic test is still desired.

Recommended Tests

When the plasma Chol/TG ratio is close to 1 and a "broad β" band is suspected on electrophoresis:

(1) Plasma lipoprotein patterns obtained on polyacrylamide gel and on either paper, agarose, or cellulose acetate should be compared. Absence of β-migrating lipoproteins on PGE and their presence on the other systems permits a presumptive diagnosis.

(2) When possible, confirmation of "floating β" (or VLDL having a high Chol/TG ratio) should be made after preparative ultracentrifugation.

Type IV—Hyperpre-β-lipoproteinemia

Criteria

(1) Increased VLDL (pre-β).
(2) No increase in LDL (β).
(3) Chylomicrons absent.

Methods of Diagnosis

(1) Standing plasma clear or turbid throughout with no overlying chylomicron layer (helpful but not diagnostic).

(2) Plasma cholesterol normal or increased; plasma triglycerides increased; plasma Chol/TG, variable (very helpful, sometimes diagnostic).

(3) Electrophoresis—increased intensity of pre-β-lipoprotein band; β band normal or decreased; α band may be normal, often decreased; chylomicrons not visible. There may be trailing of lipoproteins from the pre-β region to the origin (helpful, but not diagnostic without some quantification; see Comments, below).

All of the isolated VLDL on starch-block electrophoresis has the usual α_2 mobility (α_2-VLDL). There is no β-VLDL, or "floating β," and VLDL has usual Chol/TG ratio of 0.2 or less.

(4) Ultracentrifugation—VLDL (S_f 20–400) is increased; LDL (S_f 0–20) is normal or decreased; HDL is normal or decreased; and chylomicrons are not increased (diagnostic).

Comments. If the plasma cholesterol is definitely normal, triglycerides are clearly increased, and there are no chylomicrons visible on standing plasma, then the determination of type IV is fairly certain. The accuracy of assignment is enhanced if electrophoresis reveals a distinct pre-β band and a distinct and diminished β band. Plasma TG is always used to assess pre-β concentrations with electrophoresis, and it is always elevated in type IV. Conversely, an apparent increase in pre-β lipoproteins on electrophoresis will *not* be accompanied by an increase in plasma TG if most of the pre-β represents "sinking pre-β" (see above). This is a normal phenomenon and its frequent occurrence emphasizes the need for TG concentrations to monitor electrophoresis. One should look for signs of the "type III anomaly"; it is not necessary to exclude the anomaly by specific tests in most instances of type IV.

Recommended Tests

(1) For most samples, Chol plus TG plus observation of plasma plus electrophoresis permits a diagnosis.

(2) Estimate LDL and exclude type III in doubtful cases.

(3) The ultracentrifuge can be very helpful in certain cases.

Type V—Hyperpre-β-lipoproteinemia and Chylomicronemia

Criteria

(1) VLDL increased.
(2) Chylomicrons present.

Methods of Diagnosis

(1) Standing plasma–chylomicron ("cream") layer overlying a turbid infranatant layer (diagnostic, if type III anomaly is excluded).

(2) Plasma cholesterol increased; plasma triglyceride increased; plasma Chol/TG usually >0.15 and <0.6 (helpful but not diagnostic).

(3) Electrophoresis—pre-β band is increased and frequently trails to origin where a distinct accentuation indicates concomitant presence of chylomicrons: β- and α-lipoprotein bands are usually decreased, often markedly so. There is no "floating β" (can be diagnostic, if trailing pre-β does not obscure a chylomicron band).

(4) Ultracentrifugation—chylomicrons and VLDL (S_f 20–400) increased. LDL, particularly subclass S_f 0–12, and HDL are usually decreased (diagnostic).

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