M E D I C A L G R A N D R O U N D S

Parkland Memorial Hospital

December 22, 1977

PLASMA LIPID ABNORMALITIES ASSOCIATED WITH DIABETES MELLITUS

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Introduction

The association of hyperlipidemia with either glucose intolerance or diabetes mellitus would appear to be greater than one would anticipate by chance alone. It is difficult to estimate the magnitude of this association with any degree of precision for several reasons. First, both hyperlipidemia and diabetes mellitus (or glucose intolerance) are somewhat arbitrarily defined and different investigators have used different criteria in the analysis of their data. Second, both hyperlipidemia and diabetes mellitus are influenced at the very least by age, sex, diet, and body weight and these factors are often not adequately represented in the control or comparison groups. Third, diabetes mellitus and hyperlipidemia each represent at least several different disorders which cannot be sorted out adequately at this time (1,2,3). Fourth, the degree of diabetic control in a patient will influence plasma lipid levels and population studies tend to mix together diabetics who are in varying degrees of metabolic control. Thus, any estimate of the prevalence of hyperlipidemia in patients with diabetes mellitus will clearly be imprecise. The major conclusions of several studies are summarized in Table 1 (4-12). In general, most studies indicate that diabetics, as a group, tend to have higher plasma triglyceride levels than "control" subjects and that this abnormality is exaggerated in patients in "poor" diabetic control. The hypertriglyceridemia may partly be explained by obesity since diabetic patients, expecially those with the adult form of the disease, tend to be more overweight than control subjects.

Recently, attention has been focussed on High Density Lipoprotein (HDL) levels in diabetic patients to determine if low HDL levels might help to explain the greater degree of atherosclerosis observed in the diabetic state. Clinical interest in HDL cholesterol derives from the repeated observation that the plasma level of this lipoprotein is inversely correlated with the risk of

Table I Relationship of Hyperlipidemia to Diabetes Mellitus in Nine Representative Studies

Reference	Subjects	Number	Conclusions about Hyperlipidemia in Diabetes
4.	Treated JDM	270	24% of the patients were hyperlipidemic by Fredrickson's Criteria.
5.	Treated JDM	51	Plasma lipids not different from those in control group.
6.	Untreated JDM	135	64% had elevated total lipids (>750 mg/dl) and 43% had hypercholesterolemia (>240 mg/dl). 77% were judged to have abnormal lipoprotein patterns (largely ↑ VLDL). All patients re-examined after treatment became normal.
7.	Treated JDM	40	55% were hyperlipidemic relative to control group with 20% having hypercholesterolemia, 13% hypertriglyceridemia and 23% with both hypercholesterolemia and hypertriglyceridemia. Diabetics had lower HDL and higher LDL levels than the control group.
8.	Treated AODM	98	37.5% were hyperlipidemic (cholesterol >300 mg/dl and/or triglyceride >150 mg/dl).
9.	Diabetic Ketoacidosis Insulin-treated DM Noninsulin-treated DM	? ? ?	91% had hypertriglyceridemia (>90th percentile of control). 20% had hypertriglyceridemia (>90th percentile of control). 35% had hypertriglyceridemia (>90th percentile of control).
10.	Untreated AODM	64	No difference from control.
11.	Untreated AODM Treated AODM	40 79	Plasma TG significantly different from control. Plasma TG significantly different from control.
12.	Mostly treated AODM Mostly treated AODM	107 men 143 women	LDL, HDL and plasma TG not significantly different from control HDL significantly lower and plasma TG significantly higher than control. LDL no different from control.

Abbreviations: JDM - Juvenile Diabetes Mellitus
AODM - Adult-onset Diabetes Mellitus
TG - Triglyceride
VLDL - Very Low Density Lipoprotein
LDL - Low Density Lipoprotein
HDL - High Density Lipoprotein

developing coronary heart disease (13,14). Studies of HDL levels in diabetics are largely preliminary and inconclusive (15-19) but data from the Framingham Study (12) indicates that only in female diabetics is the HDL cholesterol level lower than in control patients (Table 2).

Table 2. Mean Level of Certain Characteristics in Diabetics and Nondiabetics: Framingham Study, Examination 11

Characteristic	Diabetes	No Diabetes	
Men			
High-density lipoprotein cholesterol, *mg/dl*	43.9 (1.28)*	46.0 (0.46)	NS†‡
Low-density lipoprotein cholesterol, *mg/dl*	135.2 (3.72)	142.4 (1.28)	NS
Triglycerides, *mg/dl*	137.9 (8.00)	135.0 (3.48)	NS
Systolic blood pressure, *mm Hg*	148.4 (2.26)	139.1 (0.71)	§
Relative weight, %	125.7 (1.59)	121.5 (0.56)	‖
Number	107	847	
Women			
High-density lipoprotein cholesterol, *mg/dl*	53.5 (1.44)	57.8 (0.44)	**
Low-density lipoprotein cholesterol, *mg/dl*	157.4 (3.29)	154.5 (1.11)	NS
Triglycerides, *mg/dl*	141.3 (6.73)	113.1 (1.67)	§
Systolic blood pressure, *mm Hg*	150.1 (2.08)	138.8 (0.62)	§
Relative weight, %	129.0 (1.97)	120.6 (0.56)	§
Number	143	1215	

* Parenthetical entries refer to standard error of the mean.
† Tests for difference between means for diabetics and nondiabetics are indicated in this column.
‡ NS (not significant) = $P > 0.05$.
§ $P < 0.001$.
‖ $P < 0.05$.
** $P < 0.01$.

It should be recognized that the difference between the mean values of the two groups is numerically quite small.

The interpretation of the plasma HDL levels in diabetic patients is subject to the same shortcomings mentioned earlier with regard to the association of hyperlipidemia and diabetes mellitus.

Outline of Normal Fuel Transport

Before discussing the hyperlipidemic states encountered in diabetes mellitus, a brief and simplified review of the relevant pathways linking insulin,

carbohydrate and lipid metabolism will be presented. See references 20-30 for excellent reviews of specific topics. Glucagon and amino acid metabolism will not be discussed but references 31-35 should be consulted for details.

It is most convenient to consider the metabolic events that occur in the fed and in the fasted or post-absorptive state.

1. Fed State: Following ingestion of a meal, the dietary fat (largely triglyceride) is digested and the digestion products are absorbed by intestinal epithelial cells (Fig. 1).

Fig. 1

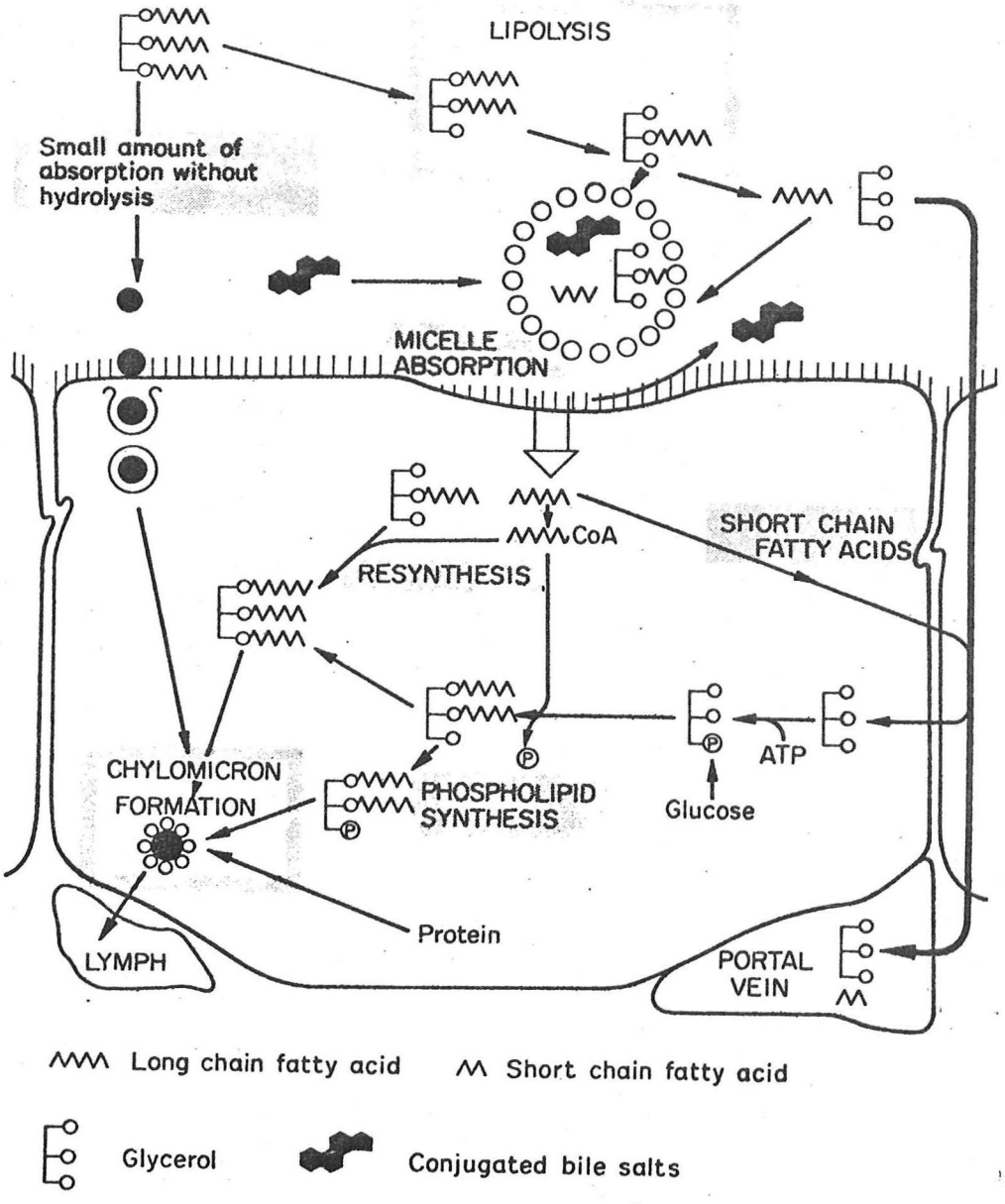


Fig. 3.15 Schematic diagram of digestion and absorption of fat.

Table 3

Characteristics of Plasma Lipoproteins (26,27)

Classification				
Electrophoresis (paper	Origin	pre-β	β	α
Hydrated Density	Chylomicrons	VLDL	LDL	HDL
Composition				
Protein (% by wt)	0.5 - 2.0%	12%	25%	50%
Lipid (% by wt)	98 - 99.5%	88%	75%	50%
Major Lipid	Triglyceride	Triglyceride	Cholesterol	Cholesterol≅ Phospholipid
Origin	Intestine	Liver and Intestine	Metabolic end-product of VLDL.	Liver and Intestine
Function	Transport exogenous (dietary) triglyceride.	Transport endogenous triglyceride.	Transport cholesterol and phospholipid to extra-hepatic cells.	? Transport cholesterol from peripheral cells to liver.

VLDL = Very Low Density Lipoprotein (d<1.006)

LDL = Low Density Lipoprotein (d 1.006-1.063) LDL_1 = d 1.006-1.019, LDL_2 = d 1.019-1.063.

HDL = High Density Lipoprotein (d 1.063-1.215)

In these cells the triglyceride is resynthesized and packaged into triglyceride-rich lipoproteins called chylomicrons (Table 3, Figures 1 and 2). The chylomicrons are secreted into the lacteals and eventually enter the plasma space via the thoracic duct. After entering the plasma, the chylomicrons are rapidly catabolized by an enzyme called lipoprotein lipase (LPL). This enzyme is located in many capillary beds but skeletal muscle and adipose tissue take up most of the chylomicron triglyceride and the remnant chylomicrons return to the liver for complete degradation.

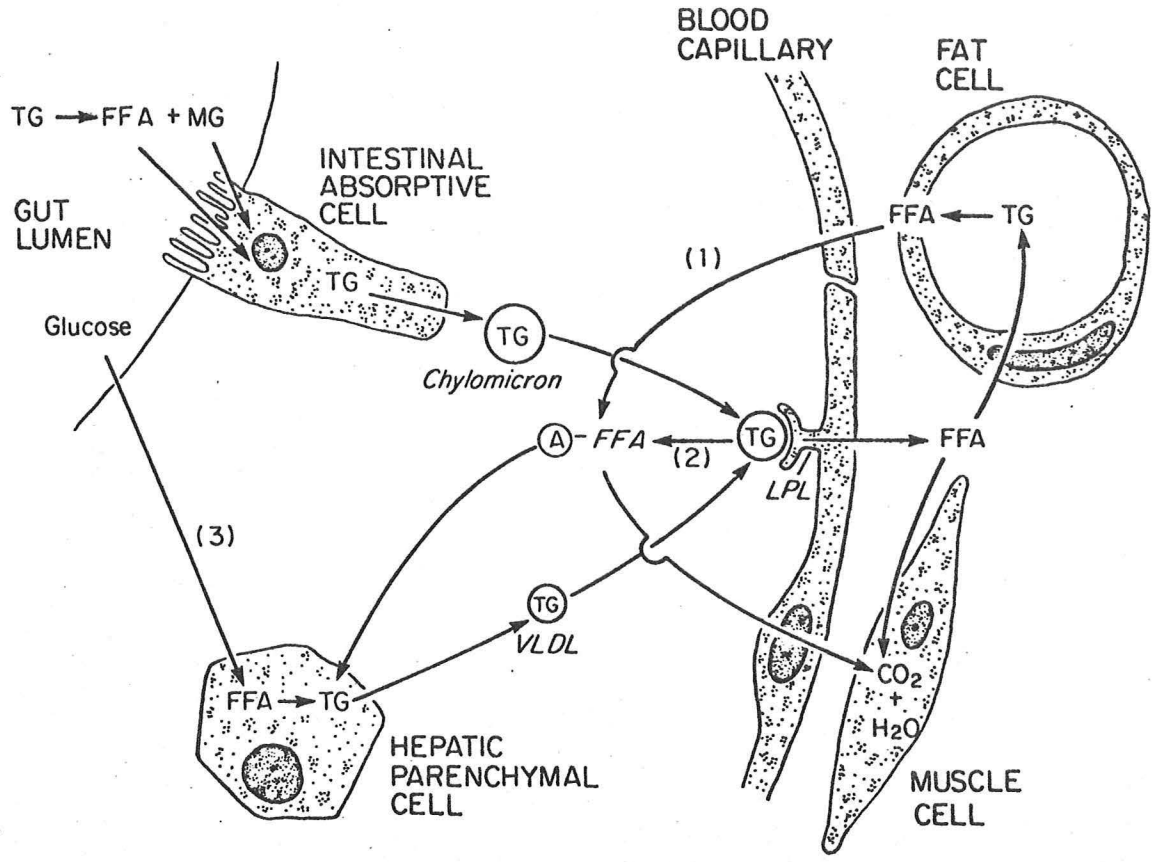


Fig. 2. Sources and fate of plasma triglycerides. Triglycerides (TG) in chylomicrons are derived primarily from absorbed fatty acids (FFA) and monoglycerides (MG), whereas VLDL triglycerides are formed in liver from fatty acids that are derived from the following sources: (1) stored fat

in adipose tissue; (2) hydrolysis of lipoprotein-triglycerides by lipoprotein lipase (LPL) on capillary endothelial cells; and (3) dietary carbohydrates converted to fatty acids in the liver. Fatty acids derived from the first two sources are transported in the blood bound to albumin (A). Fatty acids derived from triglycerides taken up by the liver in remnant lipoproteins also contribute to hepatic triglyceride synthesis (not shown). Whereas the rate of transport of triglycerides in chylomicrons is a direct function of dietary fat intake, transport of triglycerides in VLDL is an "overflow" pathway used to the extent that fatty acids are not needed by the liver for oxidative metabolism or synthesis of biliary lipids. Note that diversion of energy-rich substrates, such as FFA, to muscle can limit their availability for hepatic triglyceride synthesis (from ref. 58).

The Fasted State: The fasted state, also referred to as the post-absorptive state, is defined as the period following an overnight fast and preceding the ingestion of the breakfast meal.

The adipocyte stores fuel as triglyceride for use during the fasted state (or for other energy-demanding situations) and it therefore possesses a second lipase, termed hormone-sensitive lipase (HSL), which is located intracellularly and which is responsible for the hydrolysis of stored triglyceride. The free fatty acids (FFA, or sometimes NEFA for non-esterified fatty acids) liberated from this reaction leave the adipocyte and bind to albumin for transport through the plasma space (Fig. 2). The plasma FFA may be taken up by a variety of tissues but most are utilized by the heart, skeletal muscle and liver. Depending upon the metabolic state of the organism, the FFA arriving in the liver may be incorporated into triglyceride and phospholipid, oxidized to CO_2 and water or converted into ketone bodies (37-39). The triglyceride formed by the incoming FFA may be secreted by the liver in the form of Very Low Density Lipoprotein (VLDL) (Table 3) which also transports triglyceride to extra-hepatic tissues such as adipose tissue and muscle. This lipoprotein is also catabolized by LPL but the end-product is LDL which then serves to transport cholesterol to extra-hepatic tissues (1).

Insulin plays a key role in regulating the changes that occur between the fed and the fasted state and the activities of both TGL and HSL are regulated in opposite directions by changes in the plasma insulin level.

Table 4

Influence of Insulin on Adipose Lipid Balance

Plasma Insulin	LPL	HSL	Lipogenesis	Lipolysis
↑	↑	↓	↑	↓
↓	↓	↑	↓	↑

Thus, in the fed state, when the fuel supply is adequate and insulin levels are elevated, triglyceride is deposited in adipose tissue but in the fasting state, lipolysis occurs because insulin levels are low and hormone-sensitive lipase becomes activated (see figure 3 for outline).

Additional agents have been shown to activate lipolysis in vitro and these are listed in Table 5.

Table 5

Factors Influencing Lipolysis In Vitro (40)

Rapid Stimulation

Epinephrine	Secretin
Norepinephrine	α Melanocyte Stimulating Hormone
ACTH	β Melanocyte Stimulating Hormone
Glucagon	Arginine Vasopressin

Slow Stimulation

Growth Hormone	Cortisone

Suppression

Insulin	PGE_1

Fig.3.

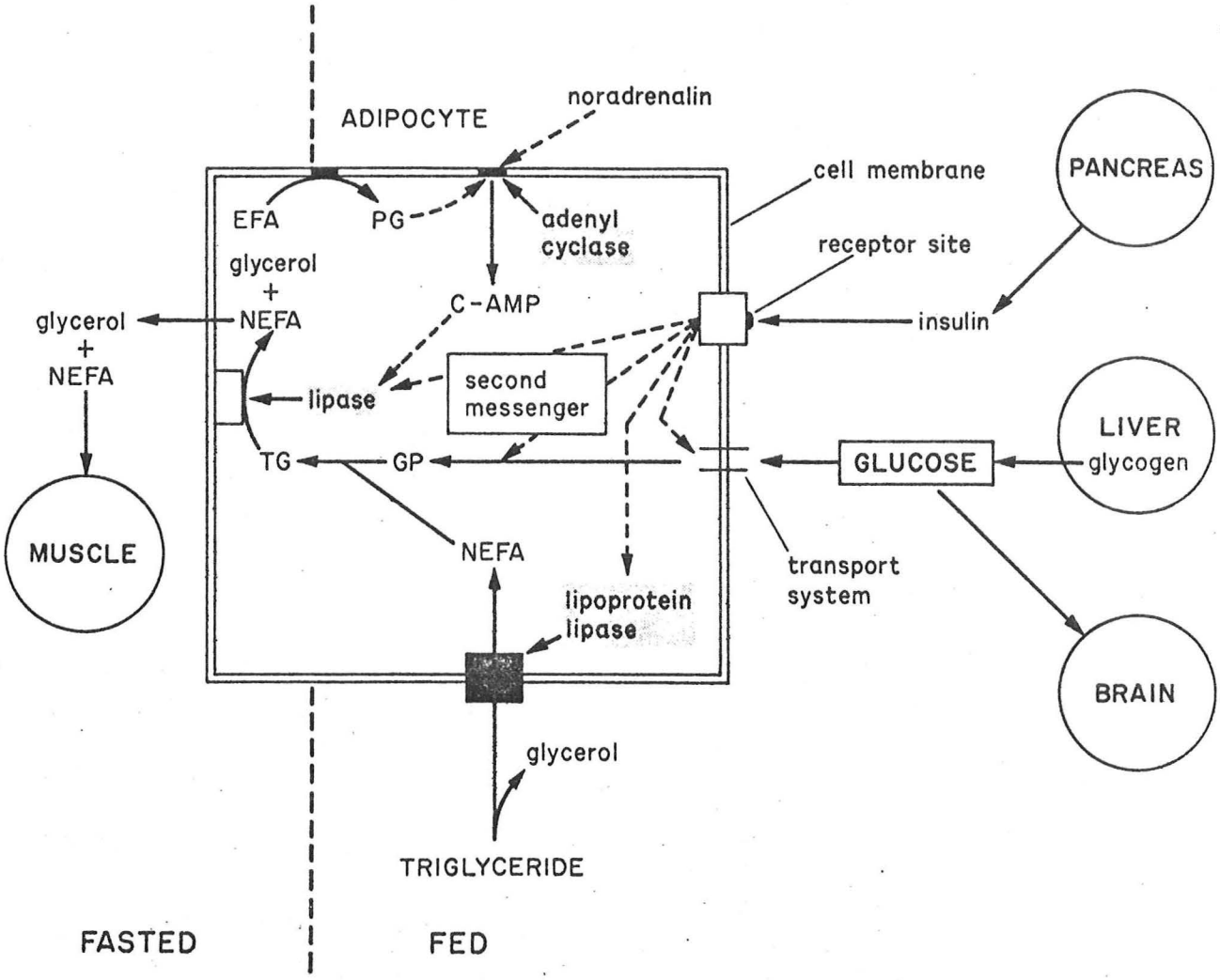


Fig. 7.3 How the flow of substrates into and out of the fat cell is controlled.

From ref. 36.

Additional factors that are known to influence lipoprotein lipase activity in adipose tissue are listed in Table 6.

Table 6

Factors Influencing Adipose Tissue LPL Activity

Increased Activity:	Insulin Fed State
Decreased Activity:	Fasting Diabetes Mellitus Myxedema Uremia

Insulin clearly plays a central role in the regulation of lipogenesis and lipolysis. It probably augments lipid accumulation in adipose tissue by at least three mechanisms:

1) Promotes glucose uptake and conversion to lipid.
2) Promotes uptake of dietary or liver-derived triglyceride by activating LPL.
3) Decreases the rate of lipolysis and FFA release from adipose tissue by hormone-sensitive lipase.

In view of the important role insulin plays in lipid metabolism, it is not surprising that the hyperlipidemic states in diabetic subjects differ depending upon whether insulin deficiency or insulin resistance is present.

The Hyperlipidemic Syndromes of Diabetes Mellitus (20,22,41-46).

Although the distinctions are somewhat arbitrary, there are five hyperlipidemic syndromes encountered in patients with diabetes mellitus and these are listed in Table 7.

Table 7

Hyperlipidemia and Diabetes Mellitus

1. Diabetic Ketoacidosis
2. Poorly controlled diabetes mellitus without acidosis - "Diabetic Lipemia"
3. Glucose intolerance or mild diabetes mellitus, hypertriglyceridemia and obesity.
4. Lipoatrophic Diabetes Mellitus
5. Hyperlipidemia, Chronic Pancreatitis and Resultant Diabetes Mellitus.

A discussion of these syndromes is given below.

1. Diabetic Ketoacidosis with Hyperlipidemia

Case #1. An 8 year old female was previously well until 10 weeks PTA when progressive fatigue was noted. Three weeks PTA the onset of polyuria, polydipsia, and polyphagia were noted along with a seven pound weight loss. One day PTA she developed symptoms of an upper respiratory infection. Laboratory results on the day of admission were as follows:

Urinalysis - 4+ glucose
4+ ketones

Serum - markedly lactescent

Sodium	103 mEq/L
Potassium	2.5 mEq/L
Total CO_2	5 mM/L
Glucose	227 mg/100 ml
Triglyceride	16,800 mg/dl
Cholesterol	1,240 mg/dl
Chylomicrons	4+

Hospital Course: The blood sugar was controlled and the ketonemia cleared within 48 hours after the start of insulin therapy. Plasma lipids remained mildly elevated at 10 days after admission. After eight weeks, the cholesterol was normal but the serum triglyceride remained mildly elevated. Plasma cholesterol and triglyceride levels were normal in the father, mother, two brothers, and one sister.

This patient represents a fairly typical example of diabetic ketoacidosis with hyperlipidemia although the hypertriglyceridemia is not usually this severe. In addition to the above findings, hepatomegaly due to fatty infiltration may occur. Lipemia retinalis is frequently noted but eruptive xanthomatosis is unusual. A few cases of pancreatitis have occurred presumably due to the severe hyperlipidemia. In this setting, measurement of the serum amylase levels by the starch-iodine method may be unsuitable and alternate methods should be employed (56). Also note that the lipemia falsely lowers the serum electrolyte concentrations (57).

It is difficult to know how frequently this situation is encountered in diabetic ketoacidosis. Nikkila reported, without presenting the data, that 91% of patients with diabetic ketoacidosis admitted to the University Hospital of Helsinki had plasma triglyceride levels that were "more or less increased" (above the 90th percentile for a control population) (9). Some years ago, a retrospective study of patient records at Parkland Memorial Hospital indicated that approximately 7% of the patients with DKA had visible lipemia (D. W. Foster, personal communication). This is almost certainly an underestimate of the frequency of this condition.

Actually, this topic was of more intense clinical interest before the days of insulin therapy. A very good report describing the effects of DKA on serum lipoproteins appeared in 1954 (47) and the work of previous investigators dating back to 1916 is briefly summarized therein. The earlier reports largely agreed that "diabetic acidosis was generally characterized by chemical lipemia consisting principally of neutral fat, by hypercholesterolemia, and by a variable degree of lactescence of the separated serum. Tuller et al. (47) reported several findings in their 18 cases that are useful to remember:

1) VLDL (S_f 21-100 and S_f 100-400) was consistently increased (they did not mention chylomicrons).

2) LDL_1 (S_f 12-20) and LDL_2 (S_f 0-11) were also increased but to a lesser degree.

3) Insulin treatment promptly lowered VLDL but the LDL levels often increased.

4) The hyperlipidemia could not be accounted for solely on the basis of dehydration.

5) When patients recovered sufficiently to begin oral feedings, the VLDL fraction rose slightly.

6) The lipoprotein levels did not return to normal in all patients.

7) The lipid disturbance associated with diabetic acidosis is variable among individuals but each patient with diabetic acidosis had some degree of hyperlipoproteinemia.

The final point (No. 7) agrees closely with the findings of Nikkila (9) that most of the patients with DKA had some degree of hyperlipidemia. The variability in the plasma lipids is not too surprising since the amount and types of foods and liquids ingested by the patients and the time of ingestion relative to the first blood tests are often unknown and the severity of the diabetic acidosis also varies from case to case. Furthermore, the cause of the ketoacidosis will vary from patient to patient as will the degree of adiposity. Thus, the conditions for the baseline lipid tests are extremely heterogeneous.

The pathophysiological changes leading to hyperlipidemia in this setting are fairly well understood and differ somewhat depending upon the duration of insulin deficiency. Havel and co-workers studied dogs with catheters placed in the portal vein, hepatic vein, and femoral arteries to determine hepatic metabolism of FFA in both normal and diabetic dogs (49,50). Absolute insulin deficiency induced by the injection of anti-insulin serum produced a rapid increase in fat mobilization and in secretion of VLDL-triglyceride and ketone bodies from the liver. After the insulin deficiency was sustained for one or

more days, the hepatic VLDL-triglyceride secretion rate diminished but since the animals remained lipemic, it was concluded that a defect in catabolism was also operative to retard the clearance of VLDL from the plasma. This catabolic defect relates to the drop in adipose tissue lipoprotein lipase activity following insulin withdrawal (64,65) and this topic will be covered in the section on diabetic lipemia. Thus, the defects leading to hyperlipidemia in the patient with diabetic ketoacidosis are summarized in Table 8.

Table 8

Abnormalities in Triglyceride Metabolism in Diabetic Ketoacidosis

Duration of Insulin Deficiency	Hepatic TG Production	Plasma TG Clearance	Plasma Lipids
early	↑↑	↔ or ↓	↑
late	↓	↓↓	↑↑

A spectrum of hepatic Triglyceride production rates were recently observed in human subjects who were in diabetic ketoacidosis for variable lengths of time and these results tend to uphold the formulation given above (51). The decrease in VLDL secretion *late* is thought to be related to a drop in hepatic protein synthesis secondary to the insulin deficiency.

Strictly speaking, since the FFA are coming only from the adipose tissue, this formulation should lead to the production of only VLDL (endogenous hyperlipemia) but chylomicrons also accumulate in such patients. There are several reasons for the hyperchylomicronemia. First, adipose tissue LPL serves to clear

both VLDL and chylomicrons from the plasma and its activity rapidly drops in insulin deficiency. If the patient ingests any fat, the chylomicrons produced in the intestine will accumulate due to an impaired catabolic rate secondary to the reduced adipose tissue LPL activity. Second, during periods when VLDL secretion is accelerated, the particles are sometimes larger, more triglyceride-rich and more chylomicron-like in physical characteristics (53). Thus, the liver may produce VLDL with chylomicron-like physical properties early after the insulin deficiency occurs. Third, recent evidence indicates that the high levels of FFA seen in DKA may actually be taken up by intestinal mucosal cells and packaged into chylomicrons (54). Thus, the hyperlipemia of DKA is often "mixed" due to an accumulation of both VLDL and chylomicrons. The lipoprotein pattern is type 5 and the plasma is uniformly turbid and may contain a variable cream layer after it has been refrigerated at 4°C for 18 hours. Lipid abnormalities in patients with hyperosmolar non-ketotic coma with hyperglycemia have not been reported but one might predict that these patients would not develop marked hyperlipidemia because the small amounts of insulin present appear adequate to suppress lipolysis. One might expect, therefore, that hepatic VLDL triglyceride production will probably not increase as it does in acute insulin deficiency because the drive of increased plasma FFA levels is not as marked (55).

Treatment of diabetic ketoacidosis by standard techniques will certainly lessen and often reverse the hyperlipidemia. The clearing of visible lipemia can be monitored simply by inspection of the plasma during the course of treatment. At some time period within 2-3 months after the acute episode of DKA but at a time when the diabetes is under adequate control, a fasting plasma sample should be obtained for inspection and for the measurement of cholesterol and triglyceride. If these lipid values remain outside the desirable range, specific therapy of the hyperlipidemia should be considered.

2. Poorly controlled diabetes mellitus without ketoacidosis - "Diabetic Lipemia".

Case #2: 51 year old, white female.

1970 - Onset of polyuria and polyphagia led to a diagnosis of diabetes which was treated with Orinase and a diabetic diet. Wt: 205 lbs.

5/71 - Chol. 480 mg/dl, TG 1,040 mg/dl. Medication was 20 units of NPH insulin daily.

7/71 - Chol. 190 mg/dl, TG 45 mg/dl. Insulin had been increased to 35 U/day.

Lost to follow-up and treated self with the Atkins Diet which lowered her weight to 175 lbs. She discontinued all diabetic medication.

12/73 - Her weight increased to 190 and glycosuria returned. Insulin was re-started.

1/74 - Blood sugars = 200-275 mg%; NPH insulin 20 U/day. Chol. 395 mg/dl, TG 585 mg/dl.

Treatment was begun elsewhere with cholestyramine. In addition, Premarin was prescribed. She did not follow her diet.

3/74 - Patient noted eruptive xanthomas. FBS 350 mg/dl. Fasting lipids x2
Chol. 1,300 mg/dl, TG 9,600 mg/dl.
Chol. 2,500 mg/dl, TG 7,600 mg/dl.

3/13/74 - First seen at Southwestern. FBS 325 mg/dl Chol. 1,200 mg/dl
TG 4,450 mg/dl

Eruptive xanthomas were noted over the upper arms, upper back and shoulders, thighs, and buttocks. Lipemia retinalis was evident. Hepatomegaly was present. The patient complained of troubling but not severe upper abdominal pain.

Premarin and cholestyramine were discontinued and Atromid-S was prescribed. A 1200 calorie ADA diet was recommended and insulin therapy was increased.

4/16/74 - Follow-up: Eruptive xanthomas had subsided and abdominal pain was much improved. Wt: 187 lbs. Hepatomegaly was no longer present. FBS 200 mg/dl, Chol. 279 mg/dl, TG 204 mg/dl.

Comment: This patient is not a totally straight-forward example of diabetic lipemia because she was receiving Premarin which may have aggrevated her hyper-lipidemia. Furthermore, we were not rigorous in documenting her therapeutic response only to insulin but instead, we instituted several changes (↑ insulin dose, diet, Atromid-S, and stopped Premarin) because we were concerned about the abdominal pain and the very real possibility that she might develop pancreatitis. Nevertheless, she does illustrate an example in which poor diabetic control eventuates in marked hyperlipidemia, eruptive xanthomas, lipemia retinalis, and hepatomegaly. Occasionally, pancreatitis may also occur (59-63).

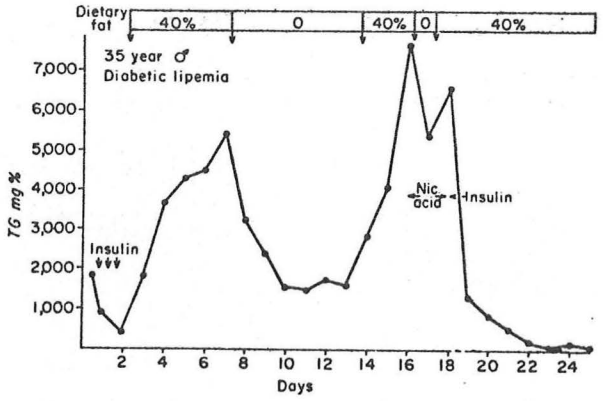
The essential clinical features of Diabetic Lipemia are as follows:

1) Gross Hyperglycemia for weeks to months.
2) Insulin levels are reduced but not absent.
3) ± ketosis but without metabolic acidosis.
4) Elevated plasma FFA.
5) Hepatomegaly, eruptive xanthomas, lipemia retinalis.
6) Mixed Hyperlipemia - chylomicrons and VLDL are elevated
7) Lipoprotein Lipase Activity is low.

At first glance this disorder might be considered as a less extreme example of events that occur in hyperlipemia associated with diabetic ketoacidosis but there are two essential differences: (1) The lipids are generally higher in the patients with diabetic lipemia and may approach 25,000 mg/dl and (2) the patient with diabetic lipemia tends to be resistant to the development of diabetic acidosis although they may have ketosis (58).

The pathophysiology of the hyperlipidemia is fairly well established and helpful clues came from experiments in rats which demonstrated that acute insulin deficiency was followed by a drop in adipose tissue lipoprotein lipase (64,65).

Bagdade and co-workers (61,62) investigated this problem in some detail. As shown in Fig. 4, these investigators found that patients with this syndrome experience a reduction in plasma TG when insulin is administered. A reduction of TG also occurs when fat is removed from the diet but the TG levels do not drop as far as they do with insulin treatment.



Response of Fasting Plasma Triglyceride Concentration (TG) to Dietary Changes, Nicotinic Acid Administration and Insulin Treatment in Case 1.

Fig. 4 Ref. (61).

To estimate the adipose tissue lipoprotein lipase activity, the investigators administered a dose of intravenous heparin and measured the lipolytic activity present in plasma - Post-Heparin Lipolytic Activity or PHLA.

Fig. 5 indicates the rate at which metabolic changes occur when insulin therapy is started (61). After 4 hours of insulin therapy, PHLA had not increased and plasma TG had not dropped. After 24 hours of treatment, PHLA had increased to the normal range and TG had dropped considerably. After 5 days the plasma TG was normal.

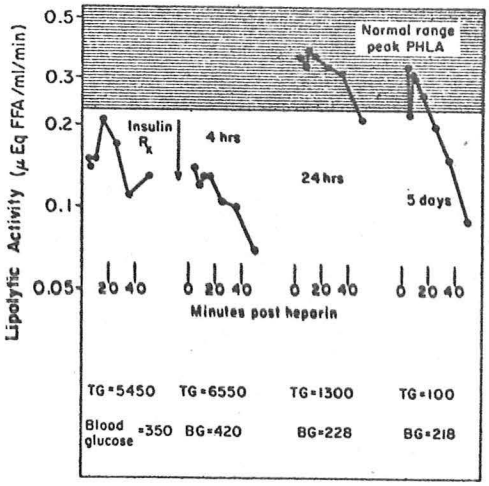
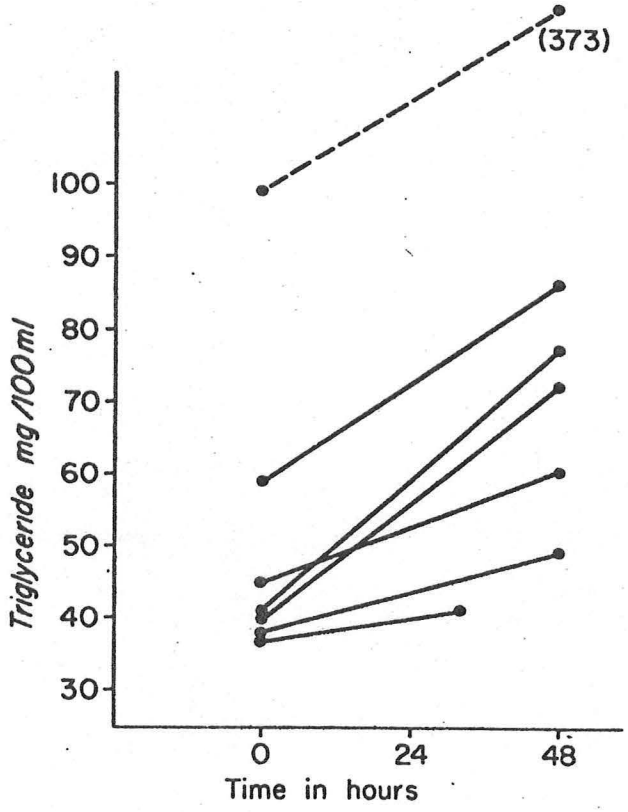


Fig.5

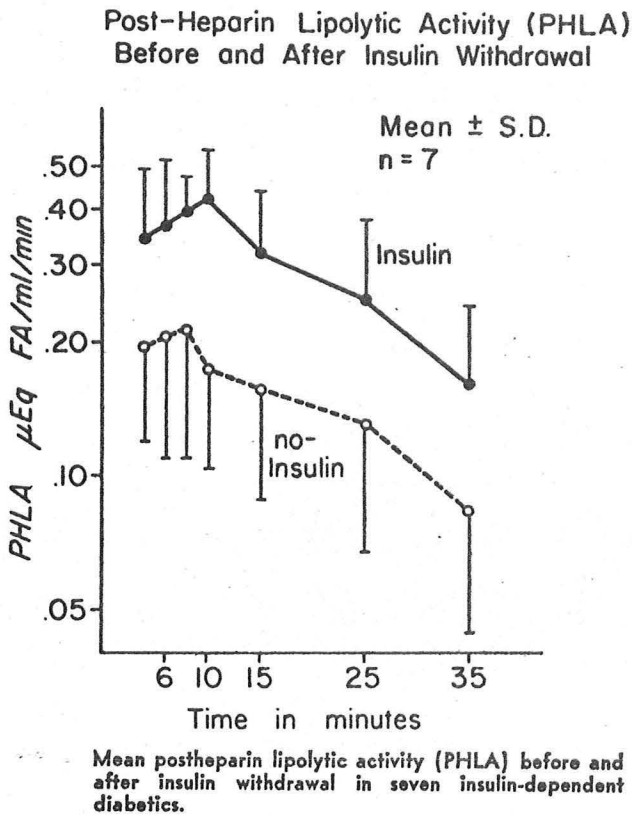
Postheparin Lipolytic Activity (PHLA), Plasma Triglyceride Concentration (TG) and Blood Glucose Levels before and after Insulin Treatment in Case 1.
The range of normal activity (10 minute values[8]) is shown in the crosshatched area.

To determine how rapidly PHLA might change following acute withdrawal of insulin, these workers discontinued insulin therapy in 7 volunteer, uncomplicated diabetic subjects while they were monitored on a metabolic ward and recorded changes in plasma glucose, FFA, TG, and PHLA over the next 48 hours. The results for plasma TG and PHLA are illustrated in figures 6 and 7 (62).



Plasma triglyceride concentrations before and after insulin withdrawal in seven insulin-dependent diabetics.

Fig.6

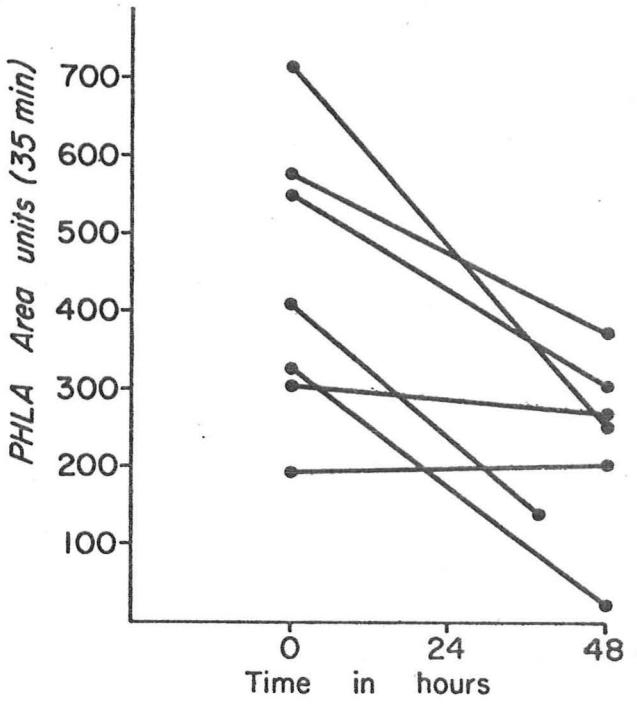


Mean postheparin lipolytic activity (PHLA) before and after insulin withdrawal in seven insulin-dependent diabetics.

Fig 7

It was observed that following insulin withdrawal, PHLA dropped fairly quickly (Figures 7 and 8) and was associated with a rise in plasma TG (Figure 6). Plasma FFA levels also rose during this period.

Since diabetic lipemia represents a more chronic state of underinsulinization, the predominant mechanism producing the hyperlipemia is a defect in lipoprotein removal (49,50,66).



Individual changes in postheparin lipolytic activity (PHLA) before and after insulin withdrawal in seven insulin-dependent diabetics.

Fig. 8

Treatment: Treatment involves reestablishing adequate insulin replacement. During treatment, the lipoprotein patterns often progress from 5 → 4 → 2 → normal (41). As initial treatment, a low fat diet may help to produce a more prompt reduction in plasma lipids but this maneuver is usually not necessary and an ADA diet may usually be employed at the outset. After 2-3 months of treatment, a repeat measurement of the fasting plasma cholesterol and triglyceride is indicated. If the repeat values remain outside the desirable range, specific therapy of the hyperlipidemia should be considered.

3. Glucose intolerance or mild diabetes mellitus with hypertriglyceridemia and obesity.

Case #3: 35 year old, white female with coronary heart disease documented by cardiac catheterization. Cardiac risk factors included hyperlipidemia, hypertension, mild obesity, fasting hyperglycemia, and cigarette smoking. Ht 65½ inches, Wt 156 lbs. At the time she was first seen (11/5/75) she had been instructed to follow a calorie-restricted, low saturated fat, low cholesterol, low salt diet, but she was not successful in losing weight.

Because of her young age and the presence of coronary disease with angina pectoris, a fairly aggressive program was started in an attempt to lower her cardiac risk factor profile. Treatment of her hypertension and angina will not be discussed.

Lab data and treatment are summarized below:

Date	Chol mg/dl	TG mg/dl	FBS mg/dl	Wt lb	Treatment
3/10/75	-	-	142		Diet
11/26/75	257	300	124	154	Diet + Atromid-S
4/ 7/76	320	297	145	170	Diet + Atromid-S

At this point, Atromid-S was discontinued because of general fatigue and unexplained leg cramps although muscle enzymes were not increased. Nicotinic Acid was started.

6/23/76	232	247	190	163	Nicotinic Acid
7/21/76	200	139	200	164	Nicotinic Acid

Nicotinic Acid was discontinued due to rise in SGOT and alk. phos. along with increased FBS. Atromid-S was restarted without difficulty.

3/23/77	328	894	181	177	Atromid-S
5/18/77	203	730	192	172	Atromid-S + Orinase started.
8/ 2/77	260	328	160	169	Nicotinic Acid 500 mg/t.i.d. added to therapy.
11/16/77	214	163	147	160	Wt down to 160.

The patient now feels generally well. In retrospect she did not have Atromid-S induced myopathy. Her marked increase in lipids coincided with a significant weight gain and her improvement now may be due mostly to weight loss. The use of Atromid-S and Nicotinic Acid together is purely empirical -- there is a "clinical impression" among some lipidologists that this combination sometimes works when Atromid-S alone is ineffective and when full therapeutic doses of Nicotinic Acid alone are not well tolerated. Thus, the use of a full dose of Atromid-S with a smaller dose of Nicotinic Acid seems to be effective in some patients but one could not prove the point in this case because of the associated weight loss. This approach is not generally recommended because it lacks experimental validation in clinical trials.

Her 4 children are normolipidemic. Her mother was diabetic and died of a dissecting aortic aneurysm at age 53. Her father died of lung cancer at age 58. Her 40 year-old brother is alive and well but was not available for a blood test.

Case #4: 50 year old, white female with a strong family history of heart disease (three brothers died in their mid-50's of myocardial infarctions). The patient was taking Premarin but had also gained 45 lb in 18 months. Prior to this weight gain, her chol. was 222 mg/dl, TG 618 mg/dl, and FBS 140 mg/dl. Upon admission to the hospital in 3/77, her chol. was 960 mg/dl, TG 9,380 mg/dl, and FBS was 195 mg/dl. Her hyperglycemia was asymptomatic but she had eruptive xanthomas. Her subsequent course is outlined. Ht 5 ft, Wt 184 lb

Date	Chol mg/dl	TG mg/dl	FBS mg/dl	Wt lb	Comment
3/77	960	9380	195	184	Admission
4/10/77	382	3740	144	-	Atromid-S, 1200 caloric diet, 30% fat.
8/17/77	235	2147	205	199	Orinase started.
10/19/77	233	859	130	200	

This patient has relatively mild diabetes but severe hyperlipidemia and may therefore have a familial form of hyperlipidemia along with diabetes (vida infra).

These two cases are examples of a frequently encountered clinical situation in our Parkland Lipid Clinic. The fasting hyperglycemia or mild diabetes is often associated with varying degrees of hypertriglyceridemia and almost invariably with obesity. Since diabetes mellitus (or glucose intolerance), obesity, and

hypertriglyceridemia are not individually well understood in terms of pathophysiology and underlying biochemical derrangements, their actions in concert are even more confusing to understand.

We will consider the problem from four different points of view.

A) Genetic Factors.
B) Competitive use of fuels - the glucose-FFA cycle.
C) Defects in triglyceride clearance - adipose tissue LPL.
D) Insulin Resistance.

A) Genetic Factors: Patients with diabetes mellitus do not invariably have hyperlipidemia and patients with primary hyperlipidemias do not invariably have diabetes.

In patients who have both disorders, it is not clear if: (1) the disorders are controlled by two separate genes that are closely linked, (2) the two genes segregate independently but happen to co-exist by chance or (3) the disturbed metabolism in diabetes mellitus produces secondary hyperlipidemia or vice versa.

There is not a great deal of information to help solve this problem but two studies deserve comment. Goldstein et al. (67) estimated the frequency of risk factors in Normolipidemic and Hyperlipidemic survivors of a myocardial infarction and their findings are listed in Table 9.

Diabetes was most common in the hypertriglyceridemic survivors but the frequency of 18.6% was not significantly different from the 11.1% found in normal survivors or the 11.5% found in

Table 9

Frequency of Risk Factors in Normolipidemic and Hyperlipidemic Survivors‡

Risk factor	Frequency: All survivors (n = 500)	Normolipidemic survivors (n = 343)	Hypercholesterolemic survivors§ (n = 78)	Hypertriglyceridemic survivors§ (n = 118)
		%		
Diabetes mellitus‖	12.6	11.1	11.5	18.6
Hypertension¶	15.4	13.4	16.6	21.2*
Obesity**	17.2	14.0	25.5*	*24.5*
Hyperuricemia‡‡	13.8	13.1	14.1	19.5
Excessive smoking§§	39.5	38.5	44.0	40.8

* Denotes statistical level of significance at 0.05 (italicized number denotes 0.01) using Chi-square test to compare proportion with risk factor in hyperlipidemic with that in normolipidemic group.
‡ 95th percentile values used to define hyperlipidemia.
§ Independent of level of other plasma liquid.
‖ Diagnosed if one of two criteria fulfilled: (*a*) survivor taking either insulin or an oral antihyperglycemic medication; or (*b*) fasting plasma glucose >120 mg/100 ml.
¶ Considered present if past history of specific treatment with antihypertensive drug therapy. Frequency of hypertension by same criterion in controls was 6.2%.
** Weight in excess of 125% of ideal body weight by criteria of Metropolitan Life Insurance Company tables (51). Frequency of obesity by same criteria in controls was 16.8%.
‡‡ Plasma uric acid ≥7.0 mg/100 ml in women and ≥8.0 mg/100 ml in men (52).
§§ More than 20 cigarettes per day. Frequency of excessive smoking by same criterion in controls was 10.0%.

hypercholesterolemic survivors. Thus, in this select group of patients who survived a myocardial infarction, diabetes was not more frequent in the patients with hypertriglyceridemia although a trend suggested this might be so.

No such trend was found, however, when Brunzell et al. reported their findings on the frequency of diabetes mellitus in adult first degree relatives of patients with familial forms of hypertriglyceridemia (68). For this study diabetes mellitus was defined as being on treatment with insulin or oral sulfonylurea agents for previously detected fasting hyperglycemia and sporadic hypertriglyceridemia was diagnosed if a hypertriglyceridemic patient had no hypertriglyceridemic first degree relatives and at least four normolipidemic adult first degree relatives. The results are shown in Table 10 for the analysis in families with familial hypertriglyceridemia.

Table 10

Prevalence of Diabetes in Genetic Hypertriglyceridemia

	Diabetes	No Diabetes	Total
Hypertriglyceridemic Propositi	*n* = 25	*n* = 66	*n* = 91
Relatives >39 yr old			
Hyperlipidemic	3/23 (13.0%)	5/80 (6.2%)	8/103 (7.8%)
Normolipidemic	5/34 (14.7%)	5/125 (4.0%)	10/159 (6.3%)
Total	8/57 (14.0%)	10/205 (4.9%)	

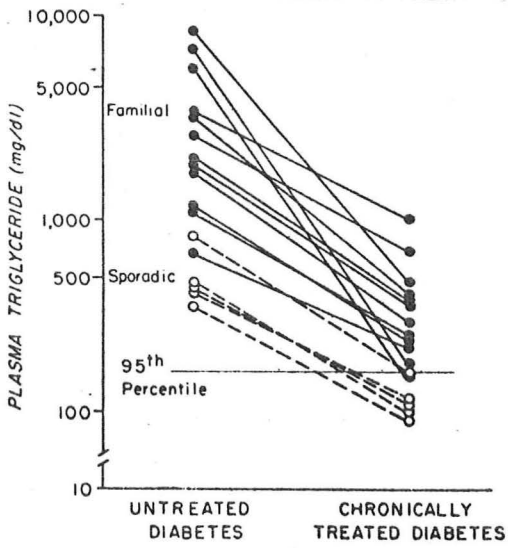
Prevalence of diabetics in spouse controls 4/232 (1.8%).

In the families of propositi with both familial hypertriglyceridemia and diabetes, diabetes occurred with equal frequency in the normolipidemic (14.7%) and hyperlipidemic (13.0%) relatives.

Similar findings were observed in the analysis of families of propositi with only hypertriglyceridemia but in these families the overall frequency of diabetes in the relatives was lower. These findings suggest that while diabetes is frequently associated with hypertriglyceridemia, genetic hypertriglyceridemia.

per se, does not carry an increased risk of diabetes. Thus, diabetes and genetic forms of Familial Hypertriglyceridemia appear to be independent entities.

These investigators also evaluated diabetic patients with either familial forms or sporadic forms of hypertriglyceridemia with regard to their response to diabetic treatment (Fig. 9).



Plasma triglyceride levels in index diabetic subjects before and after long-term therapy with oral sulfonylureas or insulin. e—e: Index subjects with concomitant familial form of hypertriglyceridemia. o---o: Index subjects with non-familial hypertriglyceridemia. Age-adjusted plasma triglyceride in log scale on ordinate compared to value for 95th percentile (horizontal line) of spouse control population.[14]

Fig. 9

They noted that the triglyceride levels before diabetic treatment were much higher in patients with coexistent familial hypertriglyceridemia as compared to those with the sporadic form. After chronic diabetic treatment, the plasma TG levels in patients with sporadic hypertriglyceridemic often returned to normal while those in the patients with Familial Hypertriglyceridemia remained elevated. The patients originally described by Adlersberg and Wang as having a syndrome of Idiopathic Hyperlipemia, Mild Diabetes Mellitus and Severe Vascular Damage (71) are very similar clinically to the patients with diabetes mellitus and Familial Hypertriglyceridemia described by Brunzell and co-workers.

Our fourth patient may therefore have a familial form of hypertriglyceridemia based on the response of her plasma lipids to diabetic treatment but this

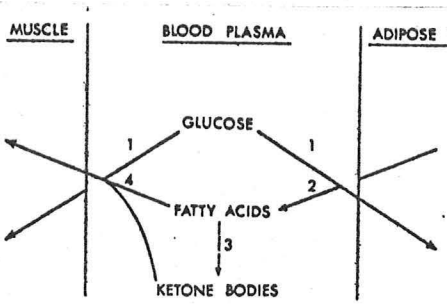
evidence can only be considered circumstantial in her case since we haven't tested for hypertriglyceridemia in any of her first degree relatives.

Glueck et al. examined the frequency of glucose intolerance in patients with hyperlipidemia classified by lipoprotein phenotyping and observed glucose intolerance in one-third of type 2 and type 3 patients, one-half of type 4 patients, and 80% of type 5 patients (69). A similar high prevalence of glucose intolerance or diabetes in Type 5 Hyperlipoproteinemia was recently reported by Greenberg et al. (70). Since the criteria for glucose intolerance were too low (3) and the lipoprotein phenotypes included patients with multiple genetic disorders (67), the significance of the results are highly questionable.

Without specific markers for diabetes and hypertriglyceridemia, such genetic studies will not be conclusive (44). At this time, however, there is no evidence to indicate that diabetes mellitus and familial hypertriglyceridemia are closely linked genetically.

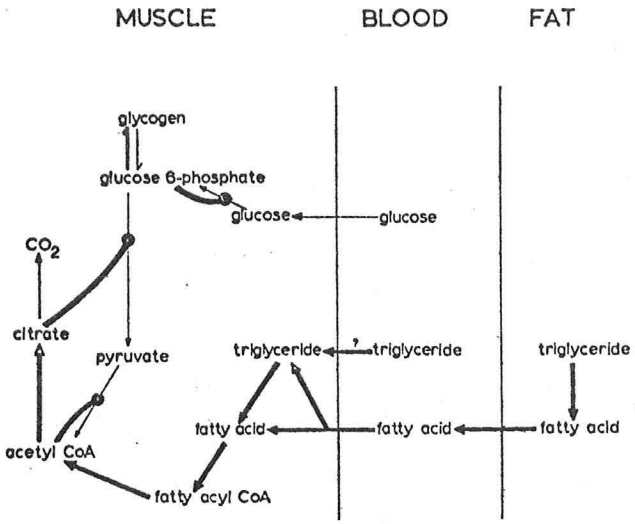
B) Competitive Use of Fuels: The glucose-FFA cycle.

In 1963, Randle and co-workers put forth the concept of a glucose-fatty acid cycle (72). According to this concept, increased plasma levels of FFA derived from adipose tissue would lead to increased uptake of FFA by muscle (Figure 10). The metabolic intermediates generated from fatty acid oxidation would then serve to inhibit glycolysis in muscle which would in turn serve to inhibit glucose uptake by muscle (Fig. 11).



—Glucose fatty-acid cycle, blood phase.
1. Uptake of glucose by muscle and adipose tissue.
2. Release of fatty acids from adipose tissue to plasma albumin.
3. Formation of ketone bodies from fatty acids by liver.
4. Uptake of fatty acids and ketone bodies by muscle.

Fig. 10



Modifications in the interrelationships of carbohydrate and lipid metabolism in the alloxan-diabetic rat

Reactions of feedback inhibitions which are accentuated are indicated by thick lines. Reproduced by courtesy of Recent Progress in Hormone Research.

Fig. 11

The cycle would be beneficial because it would operate to conserve glucose for tissues that cannot utilize FFA for fuel (eg. brain, RBC's).

During periods of fasting, adipose tissue would release FFA which would be preferentially taken up by skeletal muscle. Since this process would lead to inhibition of glucose uptake by the muscle tissue, more glucose would be available for use by the glucose-requiring tissues. The impaired uptake of glucose by the muscle would be reflected as insulin resistance. The cycle

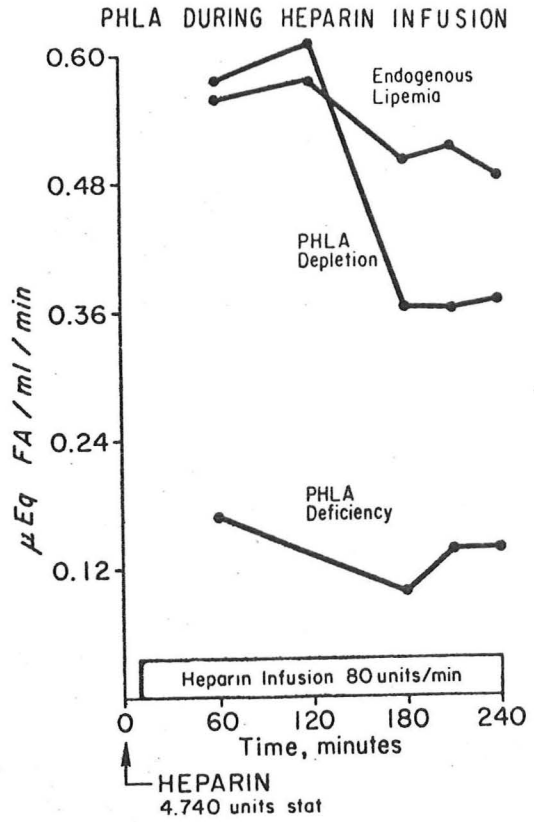
is then visualized as a primitive mechanism which, independent of hormonal control, will tend to maintain a constant plasma glucose concentration in animals that feed intermittently. This topic has been reviewed extensively (21,29,30) and there is a large body of indirect evidence to suggest that this cycle is operative in man. The extent of its impact on the metabolic derrangements observed in patients with mild diabetes, hypertriglycdridemia, and obesity is difficult to quantify because the hormonal changes in these patients may greatly override any metabolic influence exerted by the glucose-fatty acid cycle, per se.

C) Defects in triglyceride clearance - altered adipose tissue lipoprotein lipase activity.

Recent studies of adipose tissue LPL in patients with mild diabetes indicate that reduced LPL levels may also occur with lesser degrees of insulin deficiency than those observed in Diabetic Lipemia. Earlier studies that measured Post-Heparin Lipolytic Activity (PHLA) in the plasma shortly after an intravenous heparin injection indicated that no qualitative defect in PHLA was apparent in diabetic subjects with mixed hyperlipidemia (chylomicrons and VLDL) as compared with normal subjects (74). PHLA following a low heparin dose is the same in diabetic and normal subjects (75) but if a continuous heparin infusion is given, the late phase of release of PHLA is reduced in Diabetic subjects (75).

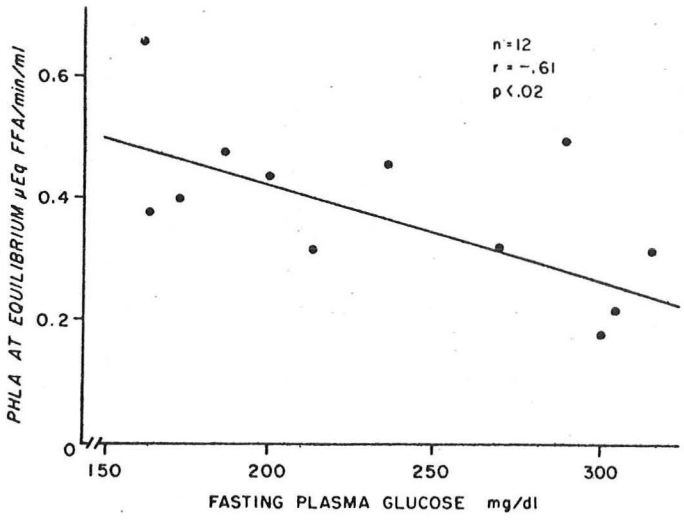
In these studies, a low stat dose of Heparin was given to test the immediate release of PHLA. Subsequently, a constant heparin infusion was started and PHLA was measured repeatedly during that time (Fig. 12). The subjects studied included normal controls, non-diabetic hypertriglyceridemic subjects and both treated and untreated diabetic hypertriglyceridemic subjects.

Both normals and non-diabetic hypertriglyceridemic subjects had very similar early and late phase (equilibrium) PHLA (late phase was the last hour of the infusion). Untreated diabetics had the same early phase PHLA as the other groups but the late phase PHLA was markedly reduced (PHLA depletion in Fig. 12). The late phase PHLA was inversely related to the fasting plasma glucose (Fig. 13).



A composite representation of the types of PHLA response during prolonged constant infusion of large doses of heparin.

Fig. 12



Relationship between postheparin lipolytic activity at equilibrium of heparin infusion and fasting plasma glucose levels in untreated diabetic subjects with elevated fasting plasma glucose levels.

Fig. 13

It was also noted that the late phase PHLA was not restored promptly when diabetic therapy was instituted but in eight subjects studied after 6 months of therapy with either insulin or sulfonylurea, late phase PHLA was the same as that in non-diabetic subjects. It is noteworthy that chronic sulfonylurea or insulin therapy in the untreated diabetics reduced the mean plasma TG from 3310 ± 2850 mg/dl to 373 ± 304 mg/dl. Thirteen of 15 non-diabetic hypertriglyceridemic subjects had first degree relatives with hypertriglyceridemia while 9 of the 11 untreated diabetics had non-diabetic relatives with significant hypertriglyceridemia. The diabetics with a genetic form of hypertriglyceridemia had higher plasma triglyceride levels than the non-diabetic hypertriglyceridemic patients and the hypertriglyceridemia did not completely reverse with diabetic treatment. In contrast, the plasma lipids in the untreated diabetics with non-familial hyperlipidemia were initially lower and then became normal with diabetic treatment (Table 11).

Table 11

	Non-diabetic Hypertriglyceridemia	Diabetes with Genetic Hypertriglyceridemia	Diabetes with Non-familial Hypertriglyceridemia
Plasma TG	703 ± 759 mg/dl	4234 ± 2703 mg/dl	538 ± 259 mg/dl

In an effort to determine if the PHLA reflected LPL activity in adipose tissue, this group of investigators then studied factors influencing adipose tissue LPL in three groups of subjects (untreated diabetics, normal controls, and non-diabetic hypertriglyceridemic subjects). The tissue LPL was measured in a sample of subcutaneous buttock adipose tissue obtained by needle aspiration. Results are summarized in the tables below (77):

Table 12

	Adipose tissue LPL (heparin-releasable)
Control	2.7 ± 1.2 neq FFA/10^6 cells/min
Untreated Diabetic	1.0 ± 0.5 neq FFA/10^6 cells/min

Long term treatment of the diabetes (10-12 weeks) produced the following changes:

Table 13

Effect of long-term treatment of Diabetes on Adipose Tissue LPL, Plasma Glucose, and Plasma TG

	Adipose Tissue LPL Heparin-releasable neq FFA/10^6 cells/min		Plasma Glucose mg/dl		Plasma TG mg/dl	
	before	after	before	after	before	after
mean ± S.D. n=5	0.9±0.5	3.5±2.9	248±47	140±33	1849±2190	684±372
% change		+257±161		-43±14		-51±31
P<		0.025		0.01		0.025

Thus, earlier observations in the PHLA system were essentially confirmed when adipose tissue LPL was measured.

It was also interesting to note that adipose tissue LPL increased in control subjects within 6 hours after eating a high carbohydrate meal but not after eating a 40% fat formula diet. The adipose tissue LPL of diabetic subjects did not increase after carbohydrate feeding.

Thus, it is evident that adipose tissue LPL activity is influenced by dietary feeding in normal subjects and is subject to fairly dynamic change. Furthermore, non-ketotic diabetics with hypertriglyceridemia have low adipose tissue LPL

activity before treatment and this low activity is converted nearly to normal after chronic diabetic treatment with either insulin or sulfonylurea. It must be emphasized that LPL is also found in skeletal muscle, heart, lactating mammary gland, and lung (78) and it is not known whether the changes of LPL activity in diabetic adipose tissue also occur in other diabetic tissues (79).

Furthermore, PHLA reflects the sum of the activities of Hepatic Lipase and Lipoprotein Lipase and it is now known that hepatic lipase activity is the same or slightly increased in diabetics as compared to controls (79).

D. Insulin Resistance

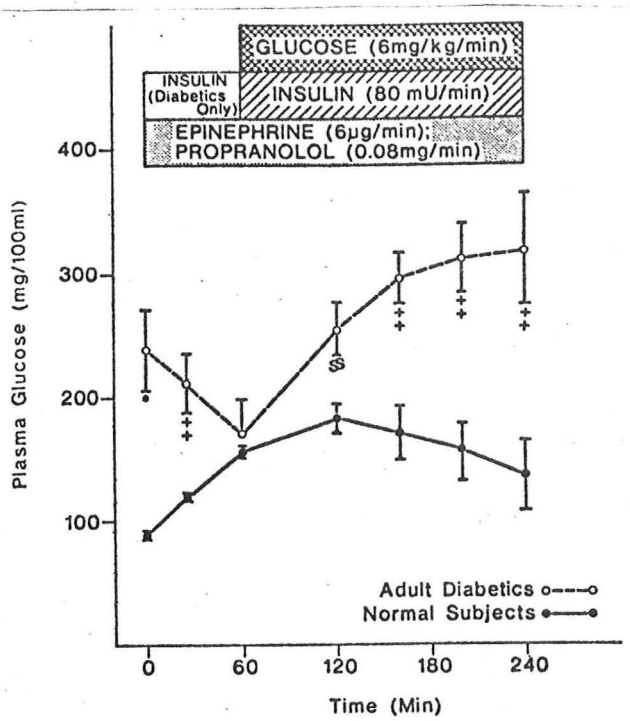
A series of observations during recent years has led to a formulation of the hypothesis that hyperinsulinemia leads to hypertriglyceridemia by increasing triglyceride secretion from the liver. Only a few of the studies will be cited for this discussion. Davidson and Albrink studied the response of plasma FFA and blood glucose to a standardized intravenous insulin injection in a variety of patients (normal, obese, fasting hyperglycemic, hypertriglyceridemic) and noted that the immediate decline in blood glucose was correlated with the plasma triglyceride concentration (the higher the triglyceride, the slower the response to insulin). These findings were taken as evidence for insulin resistance in patients with hypertriglyceridemia (80). Subsequently, Farquhar et al. studied dietary carbohydrate induction in patients with hypertriglyceridemia and noted that the dietary-induced rise in plasma TG was proportional to the post-prandial hyperinsulinemia following a test meal (81). Topping and Mayes later demonstrated that the secretion of VLDL from the perfused rat liver was enhanced when insulin was added to the perfusate (82), thereby providing in vitro evidence that insulin was capable of stimulating hepatic TG production and secretion. The following

scheme was gradually developed to try to explain the role of insulin in the production of hypertriglyceridemia:

Cellular Insulin Resistance → Compensatory Hyperinsulinemia →

↑ hepatic VLDL-TG production → Hypertriglyceridemia

Olefsky, et al. re-examined this hypothesis in 1974 in a group of 34 patients described as having only chemical diabetes or endogenous hypertriglyceridemia (84). No attempt was made to study specific genetic forms of hyperlipidemia. Insulin resistance was measured by a method based upon the suppression of both endogenous insulin secretion and hepatic glucose output by the continuous infusion of epinephrine, propranolol, glucose and exogenous insulin. This method specifically measures the ability of similar plasma levels of exogenous insulin to promote glucose uptake and an example of one such study is given in Fig. 14 (83). In addition, these workers measured insulin and glucose responses to a test meal, fasting plasma TG levels, and the VLDL-TG turnover rate in their patients. They then set about searching for correlations and their search yielded the following:



The mean (±SE) plasma glucose levels of four adult onset diabetic and four normal subjects whose plasma glucose concentrations were equalized at an intermediate level before receiving the basic 180-min infusion of glucose (6 mg/kg/min), insulin (80 mU/min), epinephrine (6 μg/min), and propranolol (0.08 mg/min). All subjects were infused with epinephrine and propranolol for the first 60 min and, in addition, the diabetic subjects received varying amounts of intravenous insulin. Under these conditions, the fasting plasma glucose level of the normal subjects had risen modestly after 60 min while the fasting plasma glucose concentration of the diabetics had decreased to a similar level at that time. All subjects then received the basic infusion mixture for an additional 180 min with frequent blood samples obtained for measurement of plasma glucose levels. *$P < 0.001$; ‡$P < 0.01$; §$P < 0.05$.

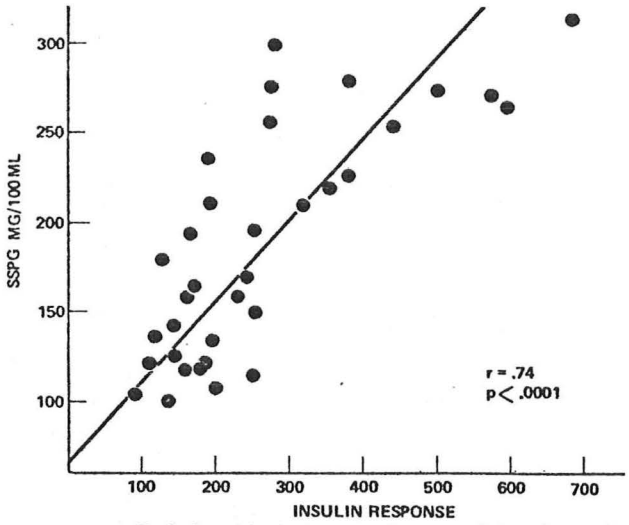
Fig. 14

1. There was a positive correlation between the insulin resistance measured by the infusion test and the plasma insulin response to a test meal.

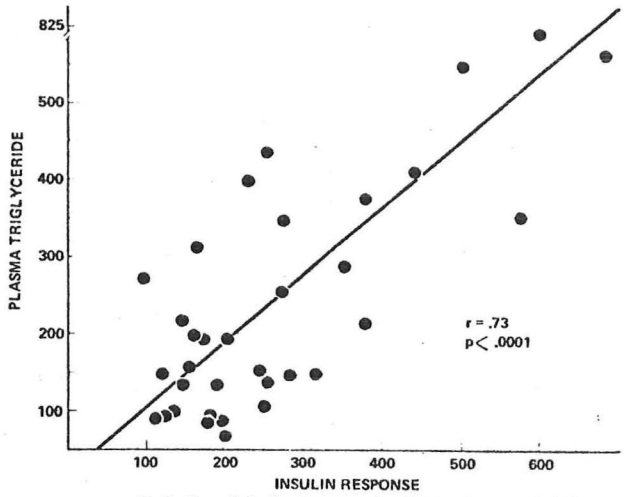
2. There was a positive correlation between the fasting plasma triglyceride level and the insulin response to a test meal.

3. There was a positive correlation between the VLDL-TG production rate and the insulin response to a test meal.

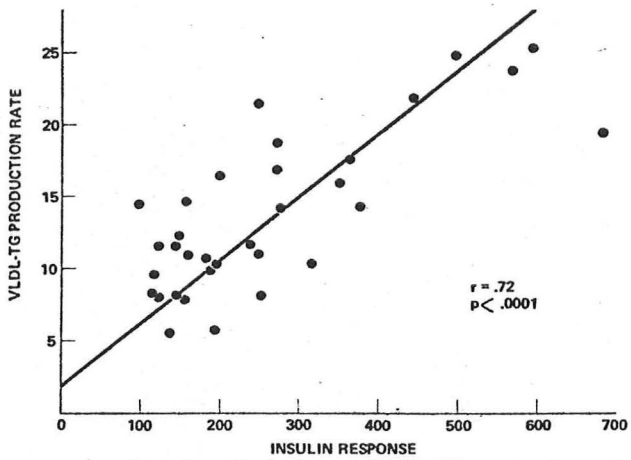
4. There was a positive correlation between the VLDL-TG production rate and the fasting plasma TG level



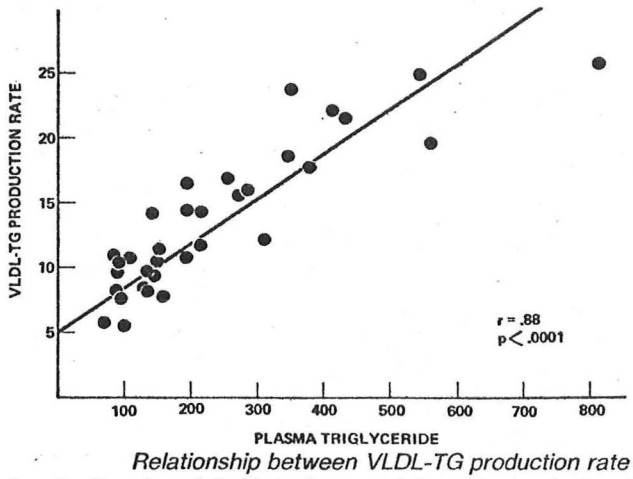
Relationship between degree of insulin resistance (SSPG) and insulin response to formula. Degree of insulin resistance (mg/100 ml) expressed as the mean of the seven plasma glucose measurements during the steady state (see "Methods"), and insulin response is expressed as the total area under the 3 hour response curve (mean of two tests).



Relationship between fasting plasma triglyceride levels (mg/100 ml) and insulin response to formula. Plasma triglyceride levels are expressed as the mean of at least three separate determinations and insulin response is expressed as the total area under the 3 hour response curve (mean of two tests).



Relationship between VLDL-TG production rate (mg/kg/hour) and insulin response. VLDL-TG production rate is measured using the ^{3}H-glycerol technic (see "Methods") and insulin response is expressed as the total area under the 3 hour response curve (mean of two tests).



Relationship between VLDL-TG production rate (mg/kg/hour) and fasting plasma triglyceride levels (mg/100 ml). VLDL-TG production rate is measured using the ^{3}H-glycerol technic (see "Methods"), and plasma triglyceride levels are expressed as the mean of at least three separate determinations.

Fig. 15

Since the investigators demonstrated highly significant positive relationships for each step of their proposed scheme, they concluded that the overall hypothesis was strengthened.

Unfortunately, the demonstration that hyperinsulinemia and hypertriglyceridemia are highly correlated in a group of patients does not establish that they are causally related. In addition, insulin resistance is not well understood biochemically and while this phenomenon is correlated with reduced numbers of insulin receptors on membranes of certain body cells (eg. lymphocytes and adipocytes), the reduced number of receptors may secondarily reflect primary abnormalities of certain metabolic processes within the cell (85-87) and the primary abnormalities in cells may differ from organ to organ. It is also not known if insulin resistance develops uniformly in all tissues or if different organs develop insulin resistance at differing rates. The scheme that implicates hyperinsulinemia in the pathogenesis of hypertriglyceridemia requires the assumption that the liver remains sensitive to the effects of insulin at least with regard to triglyceride metabolism but no experimental data supports this assumption. Finally, hypertriglyceridemia is not invariably observed in patients with apparent insulin resistance as is illustrated by the data kindly provided me by Dr. Barbara Howard and Dr. Peter Savage at the USPHS Center in Phoenix, Arizona. The figures below are the mean figures for the indicated parameters in a group of non-diabetic Pima Indians separated by quartiles according to the fasting plasma insulin level.

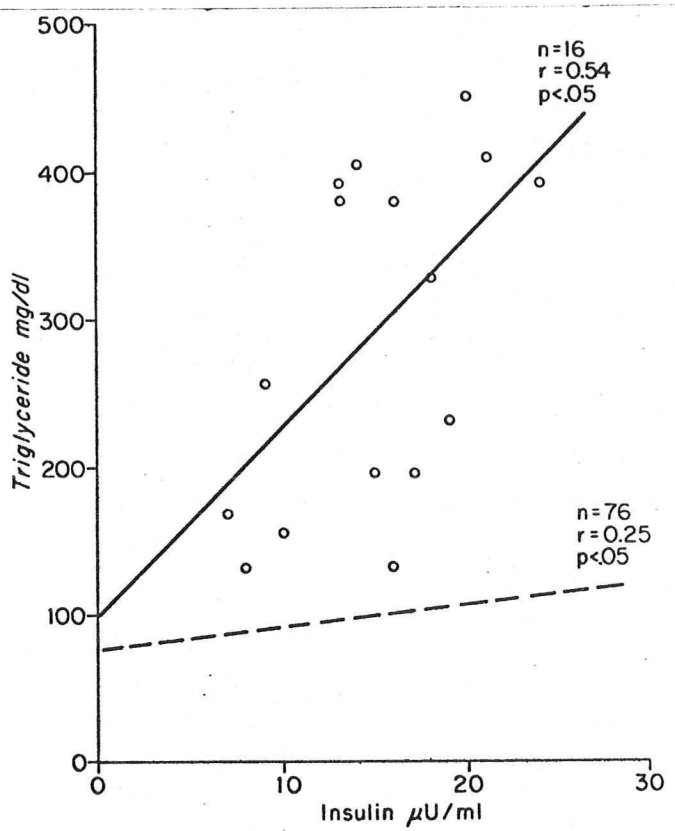
Carbohydrate, Lipid, and Insulin Parameters
in Non-Diabetic Pima Indiana

		Mean Values							
Quartile	No.	Age yrs	Wt. % of ideal	Fasting Insulin µU/ml	Fasting Glucose mg%	2hr PC Plasma Glucose mg%	1 hr Insulin Response µU/ml	TG mg%	Chol mg%
1	37	46	125	12	94	116	42	126	160
2	38	38	143	28	90	120	131	100	123
3	40	37	153	35	93	130	169	80	104
4	36	30	153	48	92	132	316	100	132

Thus, in this genetically homogenous population where the fasting insulin varies 4-fold in the non-diabetic members, there is no difference in the fasting plasma TG values.

In a recent brief communication, Brunzell and Bierman (88) compared the fasting insulin and fasting TG levels in normal and affected individuals from families with either familial hypertriglyceridemia or familial combined hyperlipidemia since hypertriglyceridemia occurs in both diseases. While there was a positive correlation between the triglyceride level and the insulin level in both the normal subjects and the hypertriglyceridemic patients from families with familial hypertriglyceridemia, the hypertriglyceridemic relatives had higher triglyceride levels than the normolipidemic relatives for the same insulin levels (Fig. 16). No relation between triglyceride and insulin levels was found in hypertriglyceridemic patients with familial combined hyperlipidemia. These authors concluded that insulin modulates TG levels in hypertriglyceridemic subjects with familial hypertriglyceridemia as it does in control subjects but

that the abnormal mechanism inherited in Familial Hypertriglyceridemia appears to be more sensitive to the regulatory effects of insulin than in normal subjects. This study gives us no more insight into the mechanisms producing hypertriglyceridemia but it does indicate that the role of insulin is not universal based on the lack of correlation between insulin levels and plasma TG in patients with combined hyperlipidemia.



Relation between fasting plasma triglyceride levels and insulin levels in affected relatives with familial hypertriglyceridemia ($y=12.7x + 98.3$). Presence of hypertriglyceridemia in relatives was ascertained by age-adjusted values (12) but are reported in the figure as nonadjusted values. Dotted line represents best fit of data from normolipidemic relatives ($y= 1.62x + 75.6$) (individual data points not shown).

Fig. 16

Summary: There is no clear understanding of the pathophysiology that leads to the syndrome of mild diabetes mellitus, hypertriglyceridemia, and obesity. With regard to genetic factors, there is no proof that any of the monogenic forms of hyperlipidemia are closely linked genetically to diabetes mellitus. Any association of a familial form of hyperlipidemia with diabetes appears to be a random event. The idea that hyperglycemia occurs when glucose uptake by muscle is inhibited in the presence of abundant plasma triglyceride (glucose-FFA cycle) has a certain

logical appeal but hormonal changes probably override any metabolic influence exerted by the substrates alone and there is no direct evidence that this cycle operates in man.

Mounting evidence indicates that diabetics have a defect in adipose tissue lipoprotein lipase which may cause impaired clearance of VLDL-TG from the plasma. This defect in LPL activity can be corrected with insulin or sulfonylureas.

Finally, in the presence of insulin resistance, hyperinsulinemia is thought to exert a stimulatory effect on the liver to produce and secrete VLDL-TG at an abnormally high rate.

All things considered, it is most likely that the hypertriglyceridemia in this group of diabetics occurs as a result of both overproduction of VLDL-TG by the liver and impaired catabolism by the peripheral tissue, specifically adipose tissue. If there is insulin resistance in the tissues of these patients, LPL activity would become impaired and lipolysis in adipose tissue would be accelerated via activation of hormone-sensitive lipase. The newly-released FFA would then be transported to the liver where they would be used to produce VLDL-TG. These patients do not become ketotic because insulin activity is still present.

A number of investigators have performed VLDL-TG turnovers in such patients to determine if the hypertriglyceridemia was caused by overproduction and(or) impaired catabolism. Results of such studies have generally yielded variable results (43,89) but two recent reports indicate that both overproduction and impaired clearance of VLDL occur in patients with hypertriglyceridemia and insulin resistance. FFA flux was also found to correlate directly with VLDL turnover, implying that FFA flux to the liver drove VLDL production. These results then support the above suggestion that overproduction and impaired catabolism together play a role in the development of hypertriglyceridemia in these patients (90,91).

Treatment: In any given patient, it is not always easy or possible to determine if a genetic hyperlipidemia is complicating the diabetes. In the hyperlipidemic diabetic subject, treatment should first be directed toward control of the diabetes. After a period of 3 months, the plasma lipids should be retested and if they remain elevated, therapy for the hyperlipidemia should be started.

Normal plasma lipid levels are not easily defined because the statistical normal values for cholesterol in the American Population are higher than the values found to be ideal in terms of cardiovascular risk (92). Thus, there is a trend toward accepting the value for a plasma cholesterol as "ideal" if it is equal to or less than 220 mg/dl. The plasma triglyceride, however, does not appear to be as strong a risk factor as cholesterol (12,14) and for that reason, there is a growing tendency to accept the normal value derived by statistical means and this figure is 200 mg% (67,70).

Since most patients are obese, weight reduction should be a major goal of therapy. The role of obesity in the aggrevation of carbohydrate intolerance and lipemia has been well stressed (93) and weight reduction has been shown to reduce the plasma lipid, glucose, and insulin levels in patients with both hyperlipemia and hyperglycemia (94).

Overweight patients with asymptomic hyperglycemia (fasting plasma glucose $\geq$ 140 mg/dl) and hyperlipemia are given the calorie-restricted prudent diet as outlined by the American Heart Association. In this diet, 45% of the calories come from carbohydrate, 35% from fat, and 20% from protein. The total cholesterol content is reduced (<300 mg/day) and the polyunsaturated fats are relatively enriched. In the patient with symptomatic hyperglycemia, the American Diabetes Association low fat diet is prescribed and is similar to the one used by the AHA except that the food portions are more rigorously measured out in the ADA diet. Obviously, the symptomic patient will also require either insulin or

a sulfonylurea agent.

If hyperlipidemia remains after 3 months of adequate diabetic therapy, a hypolipidemic drug may be employed. The first choice at the present time is clofibrate (Atromid-S) in a dose of 1 gram b.i.d. This drug has reportedly produced improved glucose tolerance (95,96) and elevated PHLA levels (97,98) in diabetic subjects. It does not appear to be uniformly effective, however. Nicotinic acid in doses up to 3 grams per day is an effective hypolipidemic agent but since it appears to impair glucose tolerance and aggrevate diabetes mellitus (99,100), it is generally not recommended for use in this particular group of patients. We have treated a few insulin-requiring diabetic patients with this drug and achieved a significant reduction in plasma lipids without a measureable worsening of their diabetic control. An exception, however can be found with Case No. 3 whose blood sugar increased during nicotinic acid therapy.

Since both diabetes mellitus and hyperlipidemia are considered major risk factors for the development of premature atherosclerosis (101-103), one is hopeful that control of these risk factors with appropriate treatment will be beneficial in lowering the risk of heart disease in these patients. Whether or not treatment does any good is still an open question but a clue may come from studies of the Pima Indians which show that these people have a low prevalence of coronary heart disease (CHD) but an extraordinarily high prevalence of diabetes mellitus (104,105). Despite the presence of diabetes, these Indians have plasma lipid levels much lower than those encountered in Caucasian and black Americans. While there are other major differences between the Pimas and other groups of Americans that could influence the prevalence of CHD, the possible benefit of low plasma lipids in reducing CHD risk in diabetic patients should not be overlooked.

The following topics will not be discussed but references, if available, have been provided.

4. Lipoatrophic Diabetes Mellitus (20,106-113).
5. Hyperlipidemia, Chronic Pancreatitis, and Resultant Diabetes Mellitus (125).

For information on the role of glucagon in hyperlipidemia consult the following references (31-33, 114-124).

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