

# The Significance of Blood Lipid Alterations in Diabetes Mellitus

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Diabetics are known to develop vascular disease prematurely and with increased frequency when compared to nondiabetics. It has been suggested that the hyperlipemia<sup>1-6</sup> observed in nonketotic diabetics may be related to the increased incidence of vascular disease. Diabetics with vascular complications have been reported to have higher cholesterol<sup>1-4,7,8</sup> and triglyceride concentrations<sup>1,2,4,8</sup> than diabetics without complications. Plasma triglyceride was estimated indirectly in almost all of these previous studies. Gragnoli,<sup>8</sup> who used a direct chemical analysis of plasma glyceride, also observed that diabetics with complications had elevated levels.

In the present study, plasma triglyceride and cholesterol levels were measured in a large series of diabetic and nondiabetic subjects of all ages to evaluate the extent and significance of plasma lipid changes in diabetes. Results show that plasma triglyceride increases with age in diabetic, but not in nondiabetic, subjects, while cholesterol levels increase with age in both groups. High concentrations of plasma triglycerides and cholesterol were not correlated with clinically apparent complications in diabetics over fifty years, the age group in which most complications occur.

## METHOD

One hundred and ninety-five diabetic subjects, age five to eighty-five years, had been followed in either the diabetic clinic or pediatric metabolic clinic at The New York Hospital for six months to five years. The patients were seen at intervals not exceeding three months except in rare instances; medical history and physical findings were carefully documented. Urine glucose, acetone and albumin were determined at each visit; blood glucose and blood urea nitrogen determinations were made at intervals. All patients had radiographic examinations of the chest and most patients in the adult group had yearly electrocardiograms. One

hundred and fifty-eight patients were maturity onset diabetics and thirty-seven were juvenile diabetics (onset prior to age fifteen).

During the study period an effort was made to keep the patients at normal weight, their urine free of acetone and to keep them free of hypoglycemia and symptomatic glycosuria. Low-calorie diets were prescribed for those patients who were above their ideal weight. Other patients took an ad libitum diet with the omission of concentrated carbohydrate. Low-fat diets were not prescribed during the period of study.

Oxalated venous blood was obtained from patients who had fasted overnight and omitted their morning dose of insulin or oral hypoglycemic agent. Plasma triglyceride was determined by the method of Van Handel and Zilversmit,<sup>9</sup> cholesterol in the carbon tetrachloride extract by the method of Forbes<sup>10</sup> and blood sugar by the method of Haden.<sup>11</sup>

Repeated determinations were made on plasma samples from many patients but for the statistical analyses involving group comparisons only first values have been used. Correlation coefficients were determined, using all values.

One hundred and forty-eight nondiabetic subjects, age one to eighty-six years, had been examined at The New York Hospital. Those patients who showed clinical evidence of coronary artery disease, peripheral vascular disease, renal disease or liver disease were rejected from this control group. Only that portion of the data relating serum lipid levels to age, to clinically apparent complications and to duration of diabetes has been analyzed for the present study.

Statistical significance was tested as follows:

1. (a) The mean values obtained from the data were compared by the Student's *t* test. (b) The values were converted to their logarithms which normalized the skewed distribution of triglyceride values observed in the primary data (*g* *t* test).<sup>12</sup> The skewed distribution of triglyceride in the present series confirms observations of Carlson<sup>14</sup> and Albrink.<sup>17</sup> The means obtained from the logarithm converted data were compared by the Student's *t* test. The mean triglyceride values obtained from the antilogarithms did not differ signifi-

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cantly from means calculated from the nontransformed data. However, by conversion to logs, the standard deviations from the mean were reduced to about 10 per cent of that obtained from the nontransformed data.

2. The Wilcoxon rank test,<sup>13</sup> which is not based on the assumption of a normal distribution.

The tests for significance using either the nontransformed data, logarithm conversion data or the Wilcoxon rank test, all gave similar results. In the tables, only the results of analysis of the nontransformed data are presented.

RESULTS

Plasma triglyceride concentration increased with age in diabetics but not in nondiabetics (figure 1). The mean triglyceride level for diabetics over age thirty was significantly higher than that for diabetics under thirty ( $p < .001$ ) (table 1). This difference in triglyceride levels was not apparent in the nondiabetics under and over thirty years of age ( $p > .10$ ). On the other hand, plasma cholesterol increased with age in both diabetics and nondiabetics (figure 2). Patients over age thirty had significantly higher cholesterol levels than those under thirty in both the diabetic group ( $p < .001$ ) and the nondiabetic group ( $p < .001$ ) (table 1). However, cholesterol values appeared to reach a plateau after age fifty in both diabetics and nondiabetics (figure 2). The apparent increase in triglyceride and cholesterol levels in nondiabetics age forty to fifty was not statistically significant when compared to nondiabetics of all other ages.

A comparison of diabetics and nondiabetics in the same age groups (figures 1 and 2) (table 2) revealed that: (a) Diabetics up to age thirty did not have higher triglyceride levels than nondiabetics up to age thirty. (b) Diabetics over age thirty had higher triglyceride levels than nondiabetics over thirty. (c) Diabetics un-

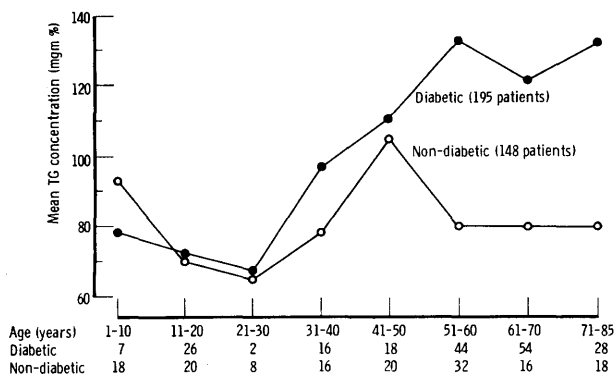


FIG. 1. Plasma triglycerides related to age of diabetic and nondiabetic subjects.

TABLE 1

Change in plasma triglyceride and cholesterol concentration with age in diabetics and nondiabetics

Age	Number of patients	Triglyceride (mg./100 ml.)		Cholesterol (mg./100 ml.)	
		Mean ±S.D.	p	Mean ±S.D.	p
Under 30 yrs.	46	79 ±44		150 ±47	
Over 30 yrs.	102	85 ±41	>.10	213 ±71	<.001
<b>Diabetics</b>					
Under 30 yrs.	35	73 ±46		181 ±59	
Over 30 yrs.	160	123 ±84	<.001	235 ±69	<.001

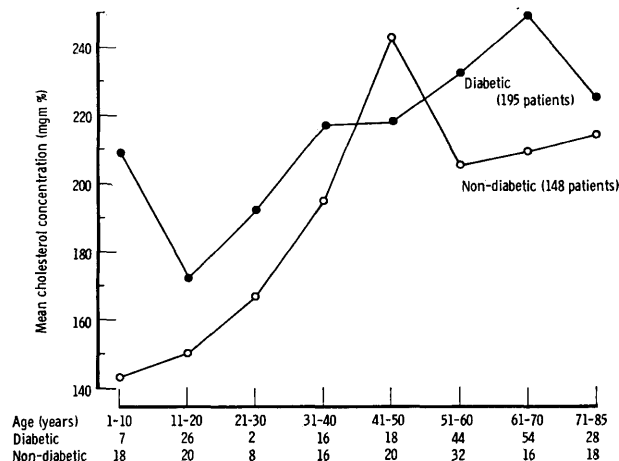


FIG. 2. Plasma cholesterol related to age of diabetic and nondiabetic subjects.

der age thirty and over thirty years had higher cholesterol levels than nondiabetics.

Subdivision of the diabetic group on the basis of presence or absence of clinically evident complications (retinopathy, myocardial infarction, peripheral vascular disease, neuropathy and diabetic nephropathy) revealed that most complications occur in older patients (table 3) (figure 3). Only in the age group thirty-one to fifty years did diabetics with clinically demonstrable complications have higher triglyceride levels than those without demonstrable complications. Diabetic complications were not associated with higher triglyceride values in those diabetics under age thirty or over age fifty. Plasma cholesterol levels in patients with and without complications were not significantly different in any age group (table 3) (figure 4).

Individual complications rarely appeared singly and in most patients there were multiple complications. However, no single complication was associated with elevated plasma triglyceride and cholesterol concentration when patients with that disorder were compared to those diabetics free of any apparent complication in the same age group (table 4). The only complication that appeared in diabetics under thirty years of

TABLE 2

Comparison of plasma triglyceride and cholesterol concentration in diabetics and nondiabetics in the same age groups

	Total number of patients	Number of patients	Triglyceride (mg./100 ml.)		Cholesterol (mg./100 ml.)	
			Mean ±S.D.	<i>p</i>	Mean ±S.D.	<i>p</i>
Diabetic	195	114	±81		225	±95
Nondiabetic	148	83	±42	<.001	194	±71
Under 30 yrs.						
Diabetic	35	73	±46		181	±59
Nondiabetic	46	79	±44	>.10	150	±47
Over 30 yrs.						
Diabetic	160	123	±84		235	±69
Nondiabetic	102	85	±41	<.001	213	±71

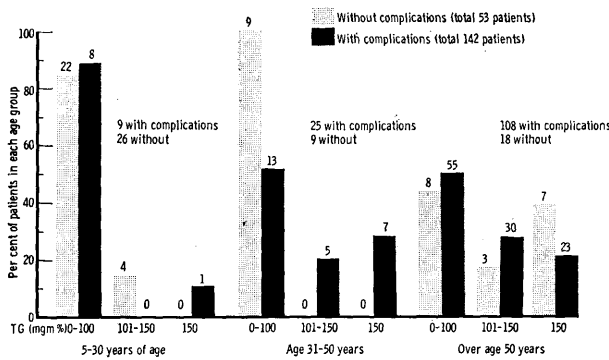


FIG. 3. Plasma triglyceride related to the presence or absence of evident complications of diabetes.

age was retinopathy. In this age group triglyceride levels in patients with retinopathy did not differ from the levels of either those diabetics without any apparent complications or nondiabetics. On the other hand, diabetic patients with myocardial infarction, all of whom were over age thirty, did have higher triglyceride levels than nondiabetics, but those levels did not differ from diabetics free of clinically apparent complications

TABLE 3

Comparison of plasma triglyceride and cholesterol concentration in diabetics with and without complications in the same age groups

	Number of patients	Triglycerides (mg./100 ml.)			Cholesterol (mg./100 ml.)		
		Mean	±S.D.	<i>p</i>	Mean	±S.D.	<i>p</i>
Diabetics—5-30 yrs.							
with complications	9	96	±70		192	±73	
without complications	26	65	±33	>.10	177	±55	>.10
Diabetics—31-50 yrs.							
with complications	25	118	±57		221	±51	
without complications	9	68	±27	<.001	206	±47	>.10
Diabetics—over 50 yrs.							
with complications	108	124	±85		235	±69	
without complications	18	149*	±36	<.05	262*	±93	>.10
Total number diabetics							
with complications	142	121	±80		230	±67	
without complications	53	94	±80	<.05	211	±78	>.10

\*Note—mean is higher for those without complications.

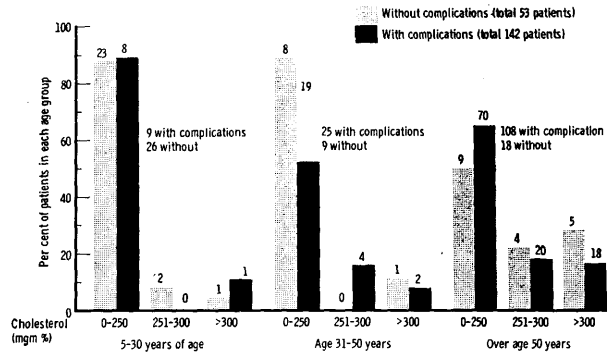


FIG. 4. Plasma cholesterol related to the presence or absence of evident complications of diabetes.

in the same age group.

Known duration of diabetes did not affect plasma triglyceride or cholesterol concentration (figure 5). The mean triglyceride and cholesterol values for diabetics whose known duration of disease was over or under ten years did not differ (table 5).

In both diabetics and nondiabetics neither plasma cholesterol nor plasma triglyceride values was correlated with blood sugar ( $p > .10$ ). However, a high degree of correlation existed between triglyceride and cholesterol ( $r = .392$ ;  $p < .001$ —diabetics) ( $r = .252$ ;  $p < .01$ —nondiabetics).

DISCUSSION

These results show that in diabetes hyperglycemia does occur but is present only in subjects over thirty years of age, while hypercholesterolemia is present throughout the life span. The increased level of plasma triglyceride and cholesterol observed in older diabetic subjects cannot be attributed to long duration of clinically apparent diabetes. In accord with previous observations,<sup>1,7</sup> these results indicate that the known dura-

TABLE 4

Plasma triglyceride and cholesterol concentration in diabetics with different vascular complications compared to those in diabetics without complications

	Number of patients	Triglycerides (mg./100 ml.)		Cholesterol (mg./100 ml.)	
		Mean	Difference*	Mean	Difference*
All patients over 30 yrs. of age					
Diabetics with retinopathy	43	112		240	
Diabetics without complications	27	122	Not significant	244	Not significant
Diabetics with myocardial infarction	47	148		240	
Diabetics without complications	27	122	Not significant	244	Not significant
Diabetics with peripheral vascular disease	58	128		251	
Diabetics without complications	27	122	Not significant	244	Not significant
Diabetics with neuropathy	25	130		232	
Diabetics without complications	27	122	Not significant	244	Not significant
Diabetics with diabetic nephropathy	6	107		219	
Diabetics without complications	27	122	Not significant	244	Not significant
All patients under 30 yrs. of age					
Diabetics with retinopathy	6	75		168	
Diabetics without complications	26	65	Not significant	175	Not significant

\* $p > .10$  for all.

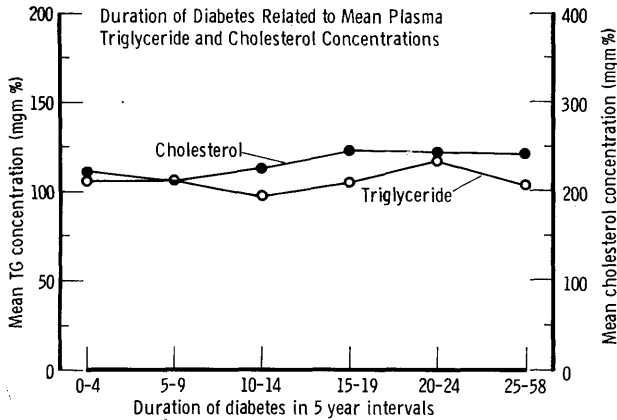


FIG. 5. Known duration of diabetes related to mean plasma triglyceride and cholesterol concentrations.

TABLE 5

Duration of diabetes related to plasma triglyceride and cholesterol concentration

	Number of patients	Triglyceride (mg./100 ml.)		Cholesterol (mg./100 ml.)	
		Mean $\pm$ S.D.	$p$	Mean $\pm$ S.D.	$p$
Under 10 yrs.	116	116 $\pm$ 90		217 $\pm$ 63	
Over 10 yrs.	79	111 $\pm$ 64	$>.10$	237 $\pm$ 79	$>.10$

tion of diabetes does not affect plasma triglyceride or cholesterol concentration.

In nondiabetic subjects, results of other studies have indicated that there is a slight rise in plasma triglyceride concentration with age.<sup>14-17</sup> In this study a slight but insignificant rise was noted only in the fourth decade in nondiabetics ( $p > .10$ ), a phenomenon noted by others.<sup>7,14,15,17</sup> With increasing age, plasma triglyceride concentration in nondiabetics showed no significant change but the cholesterol rose and tended to level off after age fifty.

The present data do not clearly establish a relationship between elevated serum triglycerides and clinically apparent complications in most diabetics. In the older age group (over fifty), which was the largest group of patients, the observed hyperglycemia was not related to the increased occurrence of complications. However, the studies do show a relationship between complications and elevated plasma triglyceride concentration in younger diabetics aged thirty-one to fifty. It is of interest that nondiabetics in this middle age group were found to have elevated triglyceride levels which have been correlated with the early development of ischemic heart disease.<sup>15,18</sup>

Although plasma cholesterol is higher in diabetics than in nondiabetics, it does not appear to be useful in differentiating those diabetics with complications from those without complications.

In this study the lack of correlation between plasma triglyceride levels and complications observed in most diabetics differs from the results of others.<sup>1,2,4,7</sup> This difference may be related to differences in analytical methods, size of series, and variations in therapy. Thus, from results obtained in this study, it appears that measurement of plasma triglyceride concentration cannot be used as an index to the development of clinically apparent complications in the older diabetic.

SUMMARY

1. Plasma triglyceride (measured by a direct analysis) and cholesterol concentrations were compared in a large diabetic and nondiabetic population ranging in age from one to eighty-six years. Plasma triglyceride levels increased with age in diabetics but not in nondiabetics. Plasma cholesterol concentration in both nondiabetics and diabetics increased with age.

2. Diabetics over age thirty had higher plasma tri-

glyceride levels than nondiabetics, while under age thirty the two groups did not differ. Plasma cholesterol level of diabetics was higher than that of nondiabetics throughout the life span.

3. In the age group thirty-one to fifty, diabetics with clinically apparent complications had higher plasma triglyceride concentration than those without apparent complications. In contrast, diabetics under age thirty and over fifty with complications did not have elevated plasma triglyceride levels. In all age groups the plasma cholesterol concentration in diabetics with and without complications did not differ.

4. Neither the plasma cholesterol nor triglyceride concentration was related to the known duration of diabetes.

#### SUMMARIO INTERLINGUA

##### *Le Signification de Alterationes del Lipidos Sanguineae in Diabete Mellite*

1. Le concentrationes in le plasma de triglycerido (mesurate per un analyse directe) e de cholesterol esseva comparate in un grande population diabetic e non-diabetic de etates de inter un e octanta-sex annos. Le nivellos de triglycerido in le plasma montava con le etate in le subjectos con diabete sed non in le non-diabeticos. Le nivellos de cholesterol in le plasma montava con le etate in le subjectos con diabete e etiam in le non-diabeticos.

2. Diabeticos de plus que trenta annos de etate habeva plus alte nivellos de triglycerido in le plasma que non-diabeticos del mesme gruppo de etate, durante que infra le etate de trenta annos, le gruppos diabetic e non-diabetic non differeva. Le nivellos de cholesterol in le plasma esseva plus alte in diabeticos que in non-diabeticos durante le curso total del vita.

3. In le gruppo de etate ab trenta-un ad cinquanta annos, diabeticos con clinicamente apparente complicationes habeva plus alte concentrationes de triglycerido in le plasma que diabeticos sin clinicamente apparente complicationes. Del altere latere, diabeticos de minus que trenta annos e de plus que cinquanta annos de etate, mesmo in le presentia de complicationes, non habeva elevate nivellos de triglycerido in le plasma. In omne le gruppos de etate, le concentration de cholesterol in le plasma non differeva inter diabeticos con e diabeticos sin complicationes.

4. Ni le concentration de cholesterol in le plasma ni illo de triglycerido esseva relationate con le cognoscite duration del diabete.

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