Oral Glucose Tolerance and Related Factors in a Normal Population Sample

II. Interrelationship of Glycerides, Cholesterol, and other Factors with the Glucose and Insulin Response

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Summary: The data available from the previous paper have been analysed to determine the interaction between the blood sugar and plasma insulin responses to oral glucose and a number of other biological variables. The total sugar and insulin responses were derived by calculating the total area and the incremental area under the curves.

The blood sugar area was significantly correlated with age in both men and women, particularly the former. A striking degree of correlation was found in men between the level of fasting glycerides and the blood sugar area. There was a significant correlation also in women, but this was entirely due to the presence of the older, postmenopausal individuals. A lower degree of correlation was found in both sexes between fasting glycerides and the insulin area.

Obesity, as defined by three interrelated factors—ponderal index, triceps fat-fold thickness, and arm girth—was significantly correlated with the insulin area (the association being stronger in the men) and with the blood sugar area only in men.

The fasting cholesterol level was correlated with obesity in both sexes but with the blood sugar area and the insulin area only in men.

Introduction

There is only fragmentary information about factors related to or determining the blood sugar response to oral glucose in normal individuals. The response is known to be related to age and sex (Boyns *et al.*, 1969) and to the time of day (Bowen and Reeves, 1967; Jarrett and Keen, 1968). The hormonal changes of menstruation and pregnancy are associated with changes in glucose tolerance (O'Sullivan, 1961; Jarrett and Graver, 1968); severe dietary carbohydrate restriction alters the form of the response (Himsworth, 1935), which is rapidly returned to normal by a few days of increased carbohydrate intake (Wilkerson *et al.*, 1960).

Although obesity is commonly held to be associated with diabetes mellitus, there is little acceptable evidence concerning the true relationship between variation in body weight and the response to glucose in the population at large. Perley and Kipnis (1967) showed a clear link between obesity and a hyperinsulinaemic response to glucose, independent of blood sugar levels, but it is not known whether this relationship holds across the whole range of adiposity.

Sampling of populations has shown that oral glucose tolerance is continuously distributed, merging imperceptibly from the "normal" into the "diabetic" response (Butterfield, 1964; Gordon, 1964; Keen, 1964; Sharp, 1964). Because of this,

interpretation of glucose tolerance tests in the intermediate area can be very difficult. It is reasonable to suppose that knowledge of other factors quantitatively related to glucose tolerance would aid this interpretation and might also throw some light on the aetiology of diabetes. We have therefore used the data in the previous paper, together with other biological data available, to examine their interaction in an epidemiologically acceptable normal population sample.

Material and Methods

The data available for analysis included the following: (1) standing height (in inches) and weight (in pounds) from which the ponderal index ($\text{height}^3/\text{weight}$) was derived; (2) triceps fat-fold thickness measured to the nearest mm. with the Harpenden skin calliper on the left arm at the mid-triceps position; (3) arm girth (in mm.) measured on the right upper arm at the point of maximum circumference, with the arm hanging loosely by the side at rest; (4) blood sugar levels in mg./100 ml. measured fasting and at 30-minute intervals for two hours after 50 g. of oral glucose; (5) plasma insulin levels in $\mu\text{u.}/\text{ml.}$ at the same five time points; (6) blood sugar "area" and plasma insulin "area"; these indices were derived from 4 and 5 in two ways: (a) "area" = $a + 2b + 2c + 2d + e$ and (b) "incremental area" = $(b + c + d + e) - 4a$, where a is the fasting value and $b, c, d,$ and e are the succeeding values during the test; (7) fasting plasma glyceride level (in mg./100 ml.); (8) fasting total plasma cholesterol level (in mg./100 ml.); (9) age in years; and (10) sex.

Data analysis was carried out with the IBM 360/65 computer at University College, London, by frequency distribution plots, linear correlation, and multiple partial correlation analysis. Sex differences were found in most of the biological variables, therefore the analyses are presented separately for each sex. The frequency distribution of values of blood sugar area, insulin area, arm girth, ponderal index, plasma glycerides, and plasma cholesterol was reasonably normal. The distribution of fat-fold thickness was positively skewed, but was normalized by logarithmic transformation. Following conventional practice, log fat-fold thickness was therefore used for the analysis.

Results

Blood Sugar and Plasma Insulin.—The correlation coefficients relating each and all blood sugar levels and log insulin values are shown in Table I. If blood sugar and insulin values at the same time point only are compared, it can be seen that all the correlations are significant, except those for the fasting values in women and the 30-minute values in men. In both sexes the highest degree of correlation was found between the levels at 90 and 120 minutes respectively.

Fat-fold Thickness, Arm Girth, and Ponderal Index.—The mean, standard deviation of the mean, and range of values for these three measurements are shown in Table II. The mean triceps fat-fold thickness of the women is almost twice that of the men, though the mean arm girth is almost identical.

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Thus the proportion of subcutaneous fat in the upper arm of the women is greater than that of the men, though this may well not be representative of total body fat (Albrink and Meigs, 1964). However, the mean values of ponderal index, which gives a measure of the degree of rotundity and hence a measure of obesity, were similar in the two sexes.

TABLE I.—Correlation Coefficients of Log Insulin with Blood Sugar at Five Sampling Times of the Glucose Tolerance Tests

Blood Sugar	Log Insulin					Sex
	0	30	60	90	120	
0	0.227	0.096	0.281	0.383	0.385	M
	0.164	0.128	0.152	0.115	0.132	F
30	0.129	0.197	0.319	0.291	0.203	M
	0.129	0.363	0.410	0.321	0.200	F
60	0.067	-0.124	0.387	0.460	0.380	M
	0.143	0.049	0.437	0.427	0.310	F
90	0.073	-0.113	0.194	0.668	0.557	M
	0.173	0.093	0.248	0.580	0.448	F
120	0.180	0.010	0.152	0.525	0.650	M
	0.201	0.026	-0.009	0.301	0.555	F

$r \geq 0.195 = P < 0.05$
 $r \geq 0.254 = P < 0.01$
 $r \geq 0.321 = P < 0.001$ } where $n = 100$

TABLE II.—Mean (and Standard Deviation) and Range of Values of Triceps Fat-fold Thickness, Arm Girth, and Ponderal Index

	Men				Women			
	Mean	S.D.	Range	n	Mean	S.D.	Range	n
Triceps fat fold ..	10.4	4.2	4-21	100	20.3	7.6	7-38	110
Arm girth ..	29.6	3.3	23-37	100	27.8	3.5	18-35	110
Ponderal index ..	12.50	0.73	11.06-14.03	109	12.29	0.80	10.07-14.12	111

Blood Sugar Area and Plasma Insulin Area.—Analyses were performed with both area and incremental area. The results were almost identical; therefore only the results with calculated area are presented. The blood sugar area (Table III) increases with age in both sexes, a tendency which is more apparent in the men (see also Table V). The mean area is greater in the men at all ages except in the youngest age group, where the women significantly exceeded the men. By contrast, Table IV shows that the mean plasma insulin area of the women exceeded that of the men in every age group. No clear trends with age were apparent.

TABLE III.—Mean Blood Sugar Area (With Standard Deviation) by Age and Sex

Age	Blood Sugar Area					
	Men			Women		
	Area	S.D.	n	Area	S.D.	n
< 24	672.1	98.0	24	743.8	116.5	22
25-34	731.9	136.7	22	718.0	101.5	22
35-44	806.2	116.3	20	762.5	178.7	20
45-54	843.6	176.9	22	804.9	185.6	23
55+	902.7	186.0	21	828.3	152.0	24
Overall mean	787.8	165.6	109	773.0	153.2	111
Range ..	509-1,441			499.0-1,250.0		

TABLE IV.—Mean Plasma Insulin Area (with Standard Deviation) by Age and Sex

Age	Plasma Insulin Area					
	Men			Women		
	Area	S.D.	n	Area	S.D.	n
≤ 24	323.1	97.3	24	514.5	372.0	22
25-34	356.9	141.9	22	392.8	203.0	22
35-44	397.6	158.7	20	449.4	274.5	20
45-54	401.7	192.1	22	425.3	178.0	23
55+	361.8	155.6	21	451.4	235.3	24
Overall mean	366.9	151.3	109	446.5	258.5	111
Range	148-1,039			130-1,702		

Fasting Glycerides and Fasting Cholesterol.—These have been considered in the preceding paper (Boyns *et al.*, 1969).

Interrelations

Table V shows the results of the correlation analysis of blood sugar area, insulin area, log fat-fold thickness, arm girth, ponderal index, plasma glycerides, plasma cholesterol, and age in men and women separately. Three factors—log fat-fold, arm girth, and ponderal index—are highly interrelated, and each is in some degree an indicator of obesity. All three are significantly related in men with the insulin area, the highest correlation being between the latter and ponderal index. In women the degree of correlation was smaller, the relation between log fat-fold and insulin area failing to achieve significance.

TABLE V.—Partial Correlation Coefficients Obtained by Multiple Correlation Analysis

Sex	Insulin Area	Log Fat Fold	Arm Girth	Ponderal Index	Glycerides	Cholesterol	Age	
M	0.322±	-0.078	0.171	-0.310†	0.734±	0.475±	0.480±	Blood sugar area
F	0.315±	-0.068	-0.016	-0.130	0.376±	0.184	0.226*	Insulin area
V		0.353±	0.319†	-0.396±	0.296†	0.255*	0.099	Log fat fold
F		0.163	0.200*	-0.283†	0.214*	0.067	-0.078	Arm girth
M			0.742±	-0.603±	0.046	0.160	-0.033	Ponderal index
F			0.752±	-0.683±	0.111	0.227*	0.171	Glycerides
M				-0.758±	0.186	0.222*	0.093	Cholesterol
F				-0.709±	-0.106	0.186	0.339±	
M					-0.364±	-0.341±	-0.328±	
F					-0.131	-0.245*	-0.285†	
M						0.573±	0.418±	
F						0.320†	0.205*	
M							0.555±	
F							0.527±	

* $P < 0.05$. † $P < 0.01$. ± $P < 0.001$.

Glyceride levels, which have been related to obesity by a number of authors (Albrink and Meigs, 1964; Sailer *et al.*, 1966), correlated poorly with the three obesity factors in this group, achieving statistical significance only in respect of ponderal index in the men. Cholesterol levels correlated rather better with the three obesity factors, correlating significantly with log fat-fold in women, arm girth in men, and ponderal index in both sexes. Of the three only ponderal index showed a significant correlation with blood sugar area, and that was limited to the men.

Insulin area was significantly correlated with the glyceride level in both sexes, with the cholesterol level in men only.

TABLE VI.—Correlation of Glycerides with Blood Sugar Area

Age	Men				Women			
	Mean Glycerides	Mean Area	r	n	Mean Glycerides	Mean Area	r	n
≤ 29	79.2	699.7	0.395	32	75.7	738.1	0.030	36
≥ 30	100.1	836.5	0.726	68	85.6	776.6	0.515	60
≤ 34	80.1	698.2	0.403	40	74.4	728.2	0.087	42
≥ 35	102.3	855.7	0.746	60	87.8	788.6	0.483	54
≤ 39	83.8	724.1	0.517	49	76.9	735.3	-0.002	53
≥ 40	102.7	858.6	0.750	51	88.0	795.2	0.697	43
≤ 44	85.2	735.4	0.465	58	78.5	736.3	0.088	59
≥ 45	104.8	871.9	0.815	42	87.4	803.4	0.712	37
≤ 49	85.3	739.2	0.497	65	80.1	755.8	0.256	67
≥ 50	108.6	892.0	0.802	35	86.1	776.9	0.655	29
All	93.4	792.7	0.713	100*	81.9	762.2	0.375	96*

* Glyceride levels were not available for 24 individuals, and these were necessarily omitted from this analysis.

Not surprisingly, when previous results are considered, blood sugar area was significantly correlated both with age and with insulin area. There was a striking degree of correlation ($r = 0.734$) in men between the glyceride level and the blood sugar area. Because of the cross-correlations between glycerides, age, and blood sugar area, a further analysis was performed correlating glycerides and blood sugar area above and below consecutive age levels (Table IV). It is apparent from this analysis that the significant relationship between glycerides and blood sugar area in the women depends on the presence of the older women,

specifically the age group above 45 years. In this group the age of the menopause, where it had been reached, lay between 44 and 49 years, and no woman above 49 years of age was still menstruating. In men the younger group at each age stratification showed the lower degree of correlation, but this was nevertheless highly significant, even in the under-30 age group.

The data were finally subjected to multiple regression analysis with the use of Program 03R of the Biomedical Computer Programs (Dixon, 1965). Variables which did not reach significance at the 5% level, as judged by a T test (where $T = \frac{\text{regression coefficient}}{\text{standard error of regression coefficient}}$),

were deleted to obtain the final regression equation. The results are given in Table VII.

TABLE VII.—Results of Multiple Regression Analysis (See Text)

Dependent Variable	Variables Contributing Significantly	All		Men		Women	
		r	P	r	P	r	P
Blood sugar area	Insulin area	0.255	<0.001			0.284	<0.01
	Glycerides	0.482	<0.001	0.649	<0.001	0.336	=0.001
	Age	0.233	<0.01	0.294	<0.01		
Insulin area	Blood sugar area	-0.263	<0.001	-0.250	<0.02	-0.260	<0.02
	Ponderal index	0.303	<0.001	0.298	<0.01	0.390	<0.001
	Arm girth	-0.344	<0.001	-0.391	<0.001		
Glycerides	Age					0.298	<0.01
	Blood sugar area					0.297	<0.01
	Insulin area	0.525	<0.001	0.682	<0.001	0.281	<0.01
	Log fat fold	-0.159	<0.05			0.210	<0.05
	Arm girth					0.356	<0.001
	Ponderal index	-0.172	<0.05			-0.415	<0.001

r = Partial correlation coefficient. P = Probability.

Discussion

The blood sugar response to oral glucose, as defined by the blood sugar area, was related in men to the fasting plasma glycerides, age, fasting plasma cholesterol level, insulin area, and ponderal index, in descending order of statistical significance. In women it was related only to the fasting plasma glycerides, insulin area, and, weakly, to age. The relationship with ponderal index could be due to age interaction, for age and ponderal index are also related. However, the very strong relationship between glyceride levels and glucose tolerance in men is only partly due to age interaction, as shown in Tables VI and VII. This relationship is the most striking one to emerge from this study.

There is a considerable literature demonstrating the interrelationship of carbohydrate and lipid metabolism, but the data presented in this study provided the clearest indication yet of a strong statistical association between fasting glyceride levels and the response of the blood glucose and plasma insulin to an oral glucose load. This may well be due to the fact that the population studied was an acceptable sample of the normal, free from the uncertainties introduced by diagnostic grouping.

The only comparable studies are those of Ostrander *et al.* (1967) at Tecumseh, Michigan, and Harlan *et al.* (1967) at Pensacola, Florida. In the former the analysis of the relationship was restricted to that between hyperglycaemia and hyperglyceridaemia, and was confined to four small selected groups. Among these, high serum glyceride levels and glucose tolerance indexes tended to cluster in the same persons, but this was only due to the inclusion of a group with both coronary artery disease and hyperglycaemia. However, it is not possible to determine from their data whether a stronger association might have been obscured by the inclusion of premenopausal women, among whom we found no significant associations. The study of Harlan *et al.* (1967) was confined to men, former naval aviation cadets, who were largely middle-class and who were middle-aged (average age 48) at the time of examination. In this group there was a significant correlation between the fasting

serum glycerides (and the Sf fractions 20–400) and the blood sugar measured two hours after 100 g. of oral glucose. Albrink and Meigs (1964), studying an all-male group, looked only at fasting blood sugar, but found a just significant correlation ($P < 0.05$) between this and the level of fasting glycerides.

The associations between the blood sugar and plasma insulin responses to oral glucose and the level of fasting plasma glycerides are capable of several interpretations. It is conceivable that the level of the plasma glycerides determines, in some way, the response to oral glucose. However, the experiments of Farquhar *et al.* (1966) and Reaven *et al.* (1967) provide strong evidence for an alternative explanation. These authors found that, in a group of patients with normal fasting blood sugar, the glucose and insulin responses to oral glucose correlated significantly with the subsequent fasting plasma glyceride response to a period on a high carbohydrate intake. In a second group of patients, including both hyperglycaemic and frankly diabetic individuals, only the insulin response to oral glucose was significantly correlated with the subsequent glyceride response to a high carbohydrate diet. The lack of correlation with the blood glucose response in this group of patients appeared to be due to the fact that many of the more hyperglycaemic individuals had low insulin responses.

Reaven *et al.* (1967) proposed that “in most patients the degree to which a high carbohydrate diet stimulates hepatic triglyceride production and secretion is directly related to the insulin response produced by that diet.” This hypothesis, modified and provisional, may be applied to our own data. Thus the prevailing insulin levels of an individual, as indicated by the response to oral glucose, may determine the level of fasting glycerides.

The means by which insulin regulates glyceride levels are probably complex. The acute effect of glucose or insulin in the postabsorptive state is to lower glyceride levels (Havel, 1957; Schlierf and Kinsell, 1965), probably by facilitating peripheral clearance of glycerides by an increase in lipoprotein lipase activity (Kessler, 1962). Insulin also suppresses fatty acid release by adipose tissue (Mahler *et al.*, 1964), which might be expected to reduce hepatic triglyceride synthesis by limiting the supply of substrate. Salans and Reaven (1966), however, presented some experimental evidence that insulin increases hepatic triglyceride production. Insulin may therefore have a dual role, the balance being affected by other factors, perhaps including the blood glucose level.

The association between glucose and insulin levels on the one hand and glyceride and cholesterol levels on the other may provide a link in the previously demonstrated association between hyperglycaemia—often unrecognized and of moderate degree—and the presence of vascular disease (Keen *et al.*, 1965; Ostrander *et al.*, 1965). In a sample of the moderately hyperglycaemic group described by Keen *et al.* (1965), hyperinsulinaemia was also demonstrated (Chlouverakis *et al.*, 1967). An association of hyperglycaemia, hyperlipidaemia, and hyperinsulinaemia could provide conditions favouring the development of atherosclerotic vascular changes. The relative immunity of premenopausal women to these changes (Oliver and Boyd, 1959) may be a consequence of the quite different relation between plasma glycerides and the glucose and insulin response to oral glucose shown in this study.

The last and perhaps the most important link in this chain of associations is diet. Keen and Rose (1958) compared the diets of a group of patients having atherosclerotic disease with that of matched controls and found that the patients consumed more calories than the controls. Four risk factors for the development of arterial disease—obesity, hyperglycaemia, hyperglyceridaemia, and hypercholesterolaemia (Epstein, 1967)—can all be linked in some way to the amount or type of diet. For example, the common form of hyperglyceridaemia is carbohydrate-dependent (Ahrens *et al.*, 1961), and the nature of the plasma lipid response is modified by the type of carbohydrate ingested (Macdonald, 1967).

We cannot directly relate the findings in this study to the development of clinical arterial disease, for its prevalence was low and the group was small. The provocative relations which have emerged, however, justify a speculative attempt to link the biochemical changes in the normal population sample with a disease which is so common in our society.

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ADDENDUM: Since these papers were accepted for publication we have learned of the work of Timms *et al.* (1968). These authors showed that the estimation of triglycerides in rat serum by Lofland's semi-automated method gave consistently higher values than two other methods. They suggest that this discrepancy is due to "contamination of the isopropanol extracts by glucose or other carbohydrates." However, we consider it highly unlikely that this phenomenon plays any part in the relationships discussed in our papers for the following reasons: (1) only a very small proportion of the variation in fasting glyceride levels could be accounted for by variation in the accompanying levels of fasting blood sugar, (2) the mean fasting glyceride level is significantly different in the two sexes (men 93.4, women 81.9; $0.01 > P > 0.001$), whereas the mean fasting blood sugar levels are almost identical (men 83.06, women 81.22); (3) although the fasting blood sugar is highly correlated with the fasting glycerides in the men ($r=0.36$), it is not in the women ($r=0.07$); and (4) despite a clear correlation between age and fasting glycerides in both sexes (men, $r=0.42$; women, $r=0.21$), the correlation between age and fasting blood sugar is not significant in women ($r=0.07$) and significant only at the 5% level in men ($r=0.24$).

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Effect of Oestrogens and Progestogens on Liver Function in the Puerperium

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Summary: A modified bromsulphthalein test has been used to detect alterations in liver function in puerperal women taking either a synthetic oestrogen, stilboestrol, or a pure progestogen, megestrol acetate. The oestrogen appreciably reduced the ability of the liver to excrete dye into the bile. It also reduced significantly the equivalent liver volume and the plasma clearance of dye. The progestogen did not have this effect. In so far as these results represent liver dysfunction they are due to the oestrogen component of the combined preparation.

Introduction

Many authors have commented on alterations in liver function in women taking oral contraceptives (Ockner and Davidson, 1967). Some have attempted to elucidate whether such changes

are due to the oestrogen or the progestogen in any combination tablet (Adlercreutz and Ikonen, 1964; Eisalo *et al.*, 1964, 1968). This is not an easy task, because most of the progestogens used are 17 α -alkynyl substituted derivatives of nortestosterone which may to a small extent be metabolized to oestrogens (Brown and Blair, 1960; Paulsen *et al.*, 1962). Further difficulty arises because the conventional liver function tests are relatively insensitive and may not be significantly altered by the functional changes induced by these drugs. In this work an attempt has been made to determine the more subtle changes by using the modified bromsulphthalein (B.S.P.) test described by Richards *et al.* (1959). A group of conventional liver function tests have also been performed on each patient. For reasons mentioned above only two drugs have been studied: a pure synthetic oestrogen, stilboestrol, and a pure progestogen, megestrol acetate. By making use of the puerperium it has been possible to administer much larger doses of these than are normally used for gynaecological or contraceptive purposes and to accentuate any stress they may place on the liver. Megestrol acetate is 6-methyl,17 α -acetoxy progesterone, and, unlike the nortestosterone derivatives, is not metabolized to oestrogenic compounds. At present it is used in three oral contraceptives.

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