Relationship Between the Basal Glucose Concentration, Glucose Tolerance and Forearm Glucose Uptake in Maturity-onset Diabetes

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SUMMARY

The relationship between the basal glucose concentration, glucose tolerance and peripheral glucose uptake has been studied in nonobese diabetic males not requiring insulin by determining forearm glucose uptake (FGU) during a 100 gm. oral glucose tolerance test (GTT) before and after carbohydrate restriction.

On a normal diet basal glucose concentrations were elevated and glucose tolerance was grossly impaired; the increment in FGU during the GTT (0 to 180 minutes) amounted to 52.8 mg./100 ml. forearm. After carbohydrate restriction basal glucose concentrations were reduced, the glucose tolerance curve was lowered and the increment in FGU rose to 76.5 mg./100 ml. forearm; glucose tolerance, however, expressed as the incremental area under the glucose tolerance curve (0 to 180 minutes), remained unchanged.

Serum insulin responses during the tests were low and uninfluenced by carbohydrate restriction. Blood lactate concentrations were increased by glucose loading before but not after carbohydrate restriction. FFA and β-hydroxybutyrate concentrations fell progressively after glucose loading while, conversely, acetoacetate concentrations were initially unchanged. During the GTT acetoacetate was taken up by the forearm while lactate and β-hydroxybutyrate were released.

In addition, the responses of three diabetics on a normal diet were compared with those of age-matched normal men; in each diabetic FGU was equal to or greater than that in the normal subjects, but nonetheless, the increment in glucose concentrations was several times greater.

The results suggest that in these patients with diabetes [1] the lowering of the glucose tolerance curve by carbohydrate restriction is not synonymous with an over-all improvement in tissue glucose disposal but is due primarily to a fall in the basal glucose concentration and [2] the impairment of glucose tolerance both before and after carbohydrate restriction is predominantly the result of a reduction in hepatic rather than peripheral glucose uptake.
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It is widely acknowledged that in diabetics a low carbohydrate diet results in a fall in the basal glucose concentration and a lowering of the glucose tolerance curve—effects to which the majority of authors refer as an "improvement in glucose tolerance."[1-5] There is reason to suspect, however, that in the past this interpretation has been frequently incorrect; the level of the basal glucose concentration profoundly influences the glucose concentrations which result after glucose loading and it is conceivable, therefore, that the lowering of the glucose tolerance curve by carbohydrate restriction is not necessarily indicative of "improved glucose tolerance" but merely an effect of the fall in the basal glucose concentration.

Changes in basal glucose levels and glucose tolerance

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are determined by largely unrelated processes and, accordingly, should be treated as separate entities. The former depends principally on the rate of gluconeogenesis,[6] while the latter refers primarily to those processes which determine the capacity for handling a glucose load, i.e. the capacity for glucose disposal and the restoration of basal glucose concentrations *after* glucose ingestion; these processes include the rate of pancreatic insulin release, the increase in hepatic glucose uptake, the suppression of hepatic glucose output and the increase in peripheral glucose uptake in the body as a whole.[7-9] Clearly, therefore, glucose tolerance is best expressed as the incremental area under the arterial glucose tolerance curve rather than as the total area since the former, but not the latter, eliminates the influence on the curve due solely to changes in the basal concentration.

The possibility that carbohydrate restriction, while reducing fasting hyperglycemia and lowering the glucose curve, may further impair glucose tolerance in some diabetics has been reported;[5] the study was confined, however, to measurement of concentrations and thus could not localize the site(s) of such impairment. Although Butterfield and Whichelow did study peripheral glucose uptake during oral glucose tolerance tests in diabetics after dietary restriction, they failed to interpret their findings in terms of glucose tolerance in the body as a whole.[10] In the present investigation we have studied forearm glucose uptake (FGU) during a 100 gm. oral glucose tolerance test (GTT) in diabetics before and after carbohydrate restriction in order to analyze the relationship between the change in glucose tolerance (defined in this study as the incremental area under the glucose tolerance curve) and the concomitant changes in the basal glucose concentration and peripheral glucose uptake.

SUBJECTS AND METHODS

Six nonobese,* diabetic males not requiring insulin were studied (table 1). None had hepatic or renal insufficiency or other endocrine disease, and all gave informed consent. Five subjects had fasting hyperglycemia and a low insulin response to glucose loading and will be reported together; the sixth subject (J.W.) is described separately. In each subject, an oral GTT was performed after ten days on a normal carbohydrate intake and again, with the exception of J.W., after seven days on a low carbohydrate diet, each individual acting as his own control. All subjects remained fully ambulant throughout. The composition of the diets, experimental design and analytical technics have been previously described.[11,12] Lactate, acetoacetate and β-hydroxybutyrate were estimated on blood precipitated immediately on withdrawal in ice-cold 0.6 M. perchloric acid. All therapy was withheld throughout the period of study, beginning at least ten days before the first (control) GTT, and was reinstituted only after completion of the second GTT.

RESULTS

Figure 1 shows that with a normal diet basal glucose concentrations were elevated, glucose tolerance was grossly impaired and the insulin response markedly reduced.[11,13-15] Mean FGU (expressed as the incre-

*Less than 120 per cent ideal body weight (Metropolitan Life Insurance Tables, 1959).

TABLE 1
Clinical data

Subject	Age	Height	Weight	Ideal body weight*	Total weight loss	Known duration of diabetes	Family history of diabetes	Previous therapy
	(yr.)	(cm.)	(kg.)	(%)	(kg.)	(yr.)		
V.P.	62	174	70.7	94	3.5	8	0	Chlorpropamide
T.R.	47	183	77.5	105	3.4	<1	+	Nil
P.R.	60	172	70.0	106	4.0	14	0	Chlorpropamide
K.P.	30	185	84.5	112	2.9	<1	+	Carbohydrate restriction
J.L.	55	163	69.8	110	2.4	<1	+	Clofibrate
J.W.	41	180	81.0	112	—	<1	0	Nil

* Metropolitan Life Insurance tables.

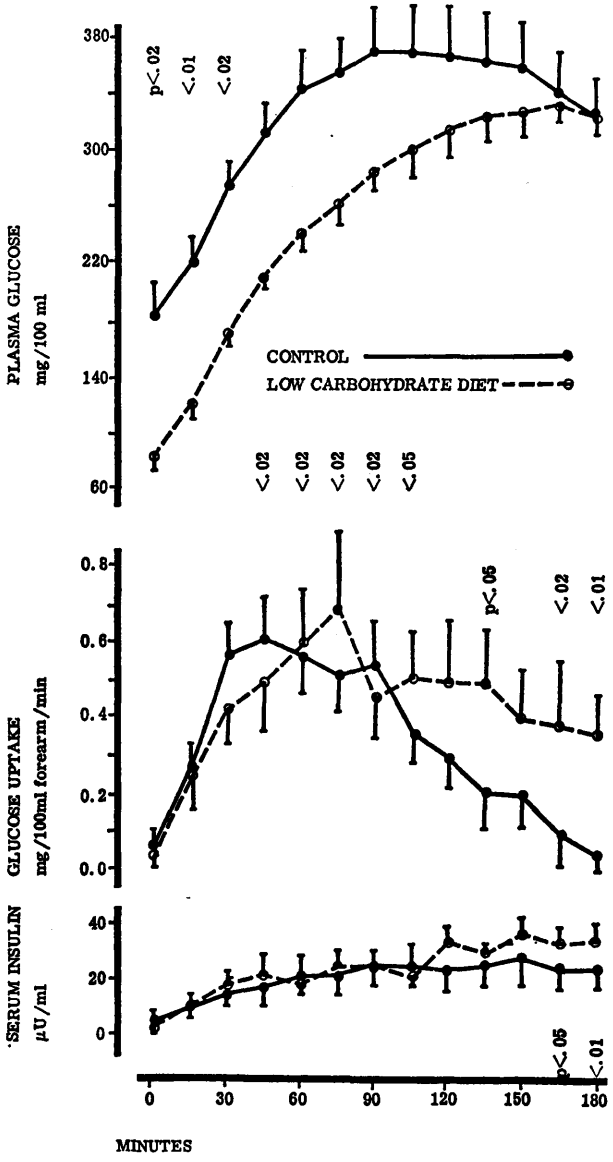

FIG. 1. Influence of carbohydrate restriction on the mean response following 100 gm. oral glucose load in maturity-onset diabetics (n = 5). The glucose curves illustrate the concentrations in arterialized venous plasma.

mental area) increased to reach peak levels forty-five minutes after glucose ingestion and declined thereafter; the rise in FGU (0 to 180 minutes) amounted to 52.8 mg./100 ml. forearm. After a low carbohydrate diet, basal glucose concentrations were strikingly reduced ($p < .01$) but the over-all increment in arterialized venous (AV) glucose concentrations after glucose loading (expressed as the incremental area 0 to 180 minutes) remained unchanged, as did the rise in serum insulin concentrations (figures 1 and 2). The increment in FGU (0 to 180 minutes) was increased to 76.5 mg./100 ml. forearm but this change was not statistically significant; when considered hour by hour, however, there was a significantly greater increase in both FGU ($p < .05$) and AV glucose concentrations ($p < .02$) between 120 and 180 minutes than occurred with a normal diet. Mean (± SEM) blood flow during the tolerance tests was significantly less ($p < .001$) after carbohydrate restriction, the levels being respectively 3.5 ± 0.2 and 2.6 ± 0.1 ml./100 ml. forearm per minute before and after the low carbohydrate diet. Serum potassium concentrations were not influenced by carbohydrate restriction.

With a normal diet, lactate concentrations tended

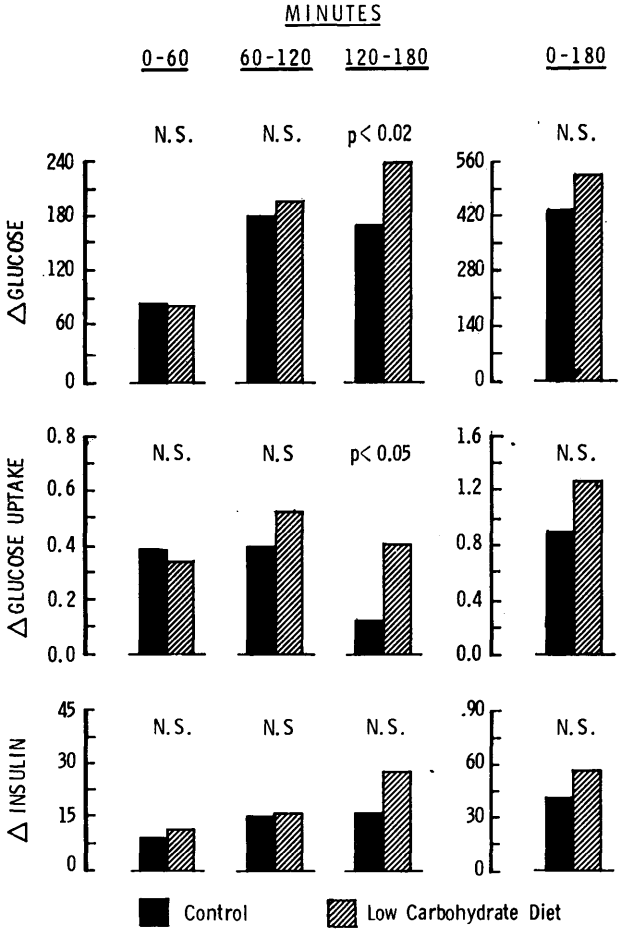

FIG. 2. Mean response following 100 gm. oral glucose load expressed as the incremental area (Δ) in five patients with diabetes.

to rise, though not significantly, in response to glucose loading (figure 3); AV and mixed venous (MV) levels were not significantly different. In contrast, following carbohydrate restriction, lactate levels tended to fall slightly; MV concentrations were significantly higher than corresponding AV levels at both thirty ($p < .05$) and sixty ($p < .05$) minutes. The basal AV lactate concentrations after carbohydrate restriction were lower but not significantly so.

Basal FFA concentrations rose in each subject after carbohydrate restriction and, as with the AV lactate levels, the failure of this change to achieve statistical significance is probably a consequence of having only five subjects in the study (table 2). FFA concentrations were reduced by glucose loading both before and after carbohydrate restriction. Serum growth hormone responses were not influenced by carbohydrate restric-

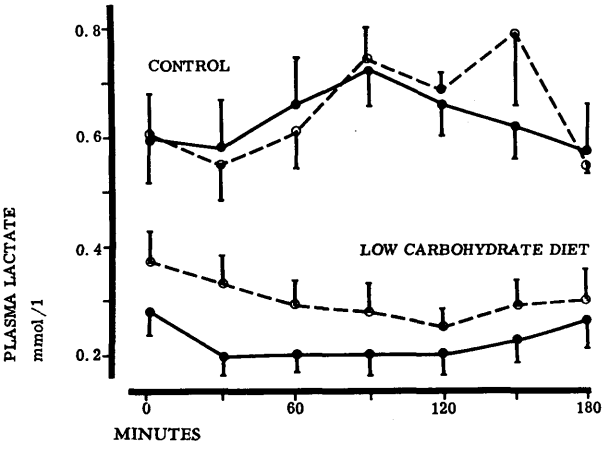

FIG. 3. Mean lactate concentrations following 100 gm. oral glucose load in arterialized venous (●—●) and mixed venous (o—o) plasma in maturity-onset diabetics (n = 4) before and after carbohydrate restriction.

TABLE 2

Oral glucose tolerance tests in nonobese diabetics before and after carbohydrate restriction

		Minutes 0	15	30	45	60	75
FFA	Before	576 ± 94*	—	571 ± 92	—	424 ± 58	—
μmol/L.	After	989 ± 107	—	880 ± 102	—	685 ± 103	—
	p†	N.S.		N.S.		N.S.	
Growth hormone	Before	6.4 ± 3.1	—	2.7 ± 0.9	—	2.0 ± 0.3	—
ng./ml.	After	17.4 ± 7.5	—	10.7 ± 4.1	—	3.8 ± 1.2	—
	p	N.S.		N.S.		N.S.	
Blood flow ml./ 100 ml. forearm/ min.	Before	2.5 ± 0.2	2.2 ± 0.3	2.3 ± 0.3	2.7 ± 0.2	3.2 ± 0.5	3.7 ± 0.8
	After	2.7 ± 0.1	1.8 ± 0.2	1.9 ± 0.2	2.3 ± 0.4	2.4 ± 0.5	2.8 ± 0.5
	p	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

* Standard Error of Mean.
† Significance of difference between means before and after carbohydrate restriction.

TABLE 2 *(continued)*

Oral glucose tolerance tests in nonobese diabetics before and after carbohydrate restriction

		Minutes 90	105	120	135	150	165	180
FFA	Before	374 ± 83*	—	291 ± 47	—	239 ± 43	—	278 ± 22
μmol/L.	After	571 ± 90	—	579 ± 80	—	597 ± 83	—	598 ± 88
	p†	N.S.		N.S.		N.S.		< .05
Growth hormone	Before	6.4 ± 5.0	—	3.7 ± 1.7	—	6.2 ± 2.1	—	6.2 ± 2.6
ng./ml.	After	3.5 ± 1.2	—	2.6 ± 0.9	—	3.1 ± 0.6	—	3.4 ± 0.6
	p	N.S.		N.S.		N.S.		N.S.
Blood flow ml./ 100 ml. forearm min.	Before	3.3 ± 0.4	3.6 ± 0.4	4.0 ± 0.6	4.0 ± 0.8	4.7 ± 0.6	4.6 ± 0.7	4.4 ± 0.7
	After	2.8 ± 0.4	2.8 ± 0.4	2.9 ± 0.4	2.8 ± 0.4	3.0 ± 0.5	3.0 ± 0.5	3.2 ± 0.4
	p	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

* Standard Error of Mean.
† Significance of difference between means before and after carbohydrate restriction.

tion and the high basal value is due to bias by the findings in one individual (T.R.).

After a normal carbohydrate intake, neither acetoacetate nor β-hydroxybutyrate were detectable in blood but basally, substantial ketonemia was observed after the low carbohydrate diet (figure 4). A clear dissociation was observed between the shapes of the acetoacetate and β-hydroxybutyrate response curves; thus, while β-hydroxybutyrate concentrations fell immediately ($p < .05$ at thirty minutes) and continued to decline throughout the GTT, acetoacetate levels remained unchanged for as long as ninety minutes, falling only thereafter. Both basally and after glucose loading, acetoacetate was taken up by the forearm while β-hydroxybutyrate was released. Statistically significant AV-MV differences were found for acetoacetate at zero ($p < .01$), thirty ($p < .01$), sixty ($p < .01$) and ninety ($p < .05$) minutes and for β-hydroxybutyrate at thirty ($p < .02$), sixty ($p < .02$) and ninety ($p < .02$) minutes.

Figures 5 to 7 compare the responses of each of three diabetics with those of age-matched normal male subjects. K. P. (figure 5) and T. R. (figure 6) had fasting hyperglycemia and a low insulin response to glucose challenge, while J. W. (figure 7) had fasting normoglycemia and a hyperinsulinemic response to glucose loading. Figure 5 shows that by ninety minutes the increments in FGU in K.P. and J.B. were 35.2 and 25.7 mg./100 ml. forearm respectively, yet the increment in plasma glucose concentrations in K.P. was 162 mg./100 ml. compared with only 31 mg./100 ml. in J.B.; although in the GTT as a whole the increments in FGU were virtually identical in the two subjects (47.3 and 45.0 mg./100 ml. forearm in K.P. and J.B.,

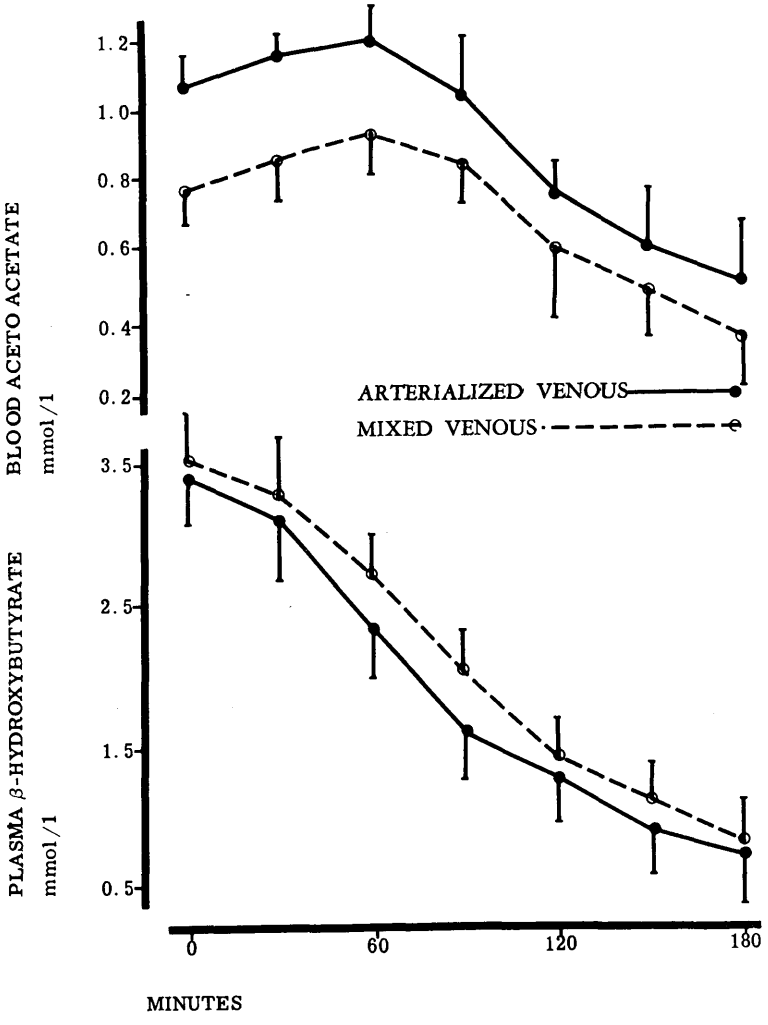

FIGURE 4

Influence of oral glucose loading on circulating ketone body concentrations in maturity-onset diabetics (n = 4) after carbohydrate restriction.

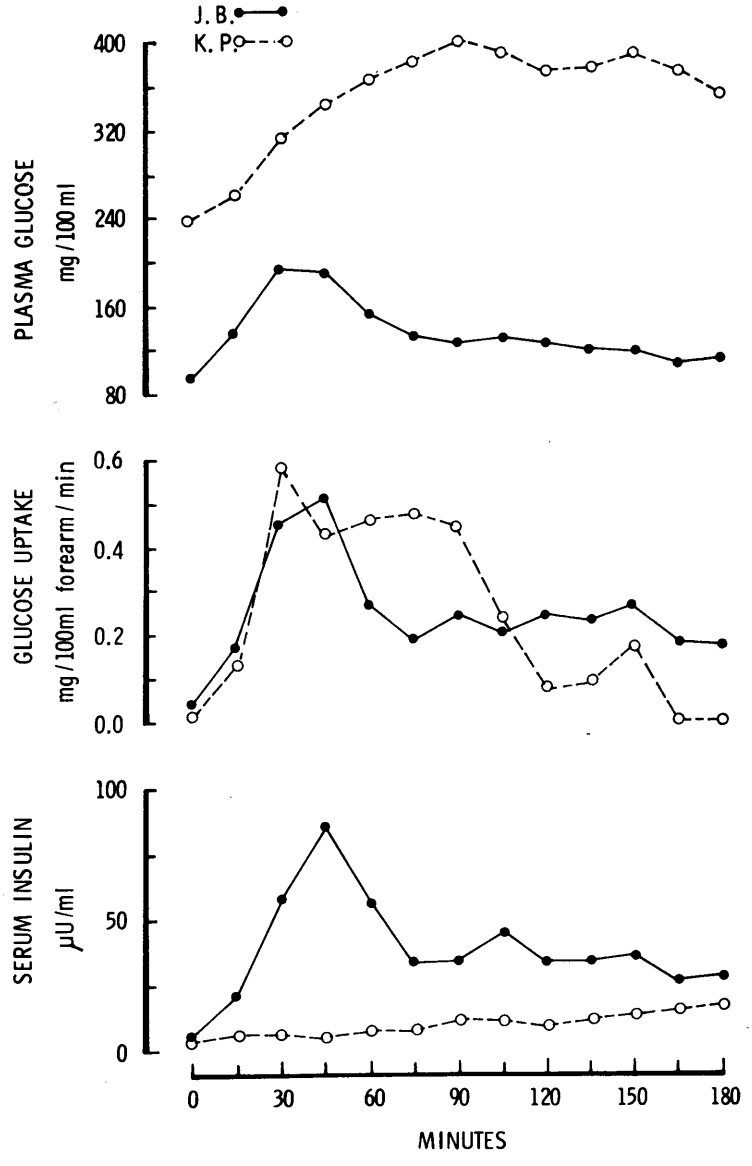

FIGURE 5

Comparison of the response following 100 gm. oral glucose load in diabetic K.P. (table 1) and J.B., a thirty year old normal male. The glucose curves illustrate concentrations in arterialized venous plasma.

respectively), the elevation in glucose concentrations remaining at 180 minutes was 119 mg./100 ml. in the diabetic as against only 17 mg./100 ml. in J.B., and the incremental area under the glucose curve in K.P. was 2.6-fold that in the nondiabetic. Figure 6 shows a similar pattern of disturbance in T.R., i.e. that while after 120 minutes the increments in FGU were practically identical in T.R. and T.P. (77.5 and 76.0 mg./100 ml. forearm, respectively), the corresponding elevations in glucose concentrations were 218 mg./100 ml. in T.R. but only 56 mg./100 ml. in T.P. In J.W. (figure 7) the increment in FGU (0 to 180 minutes) was 118 mg./100 ml. forearm compared with 74 mg./100 ml. forearm in A.P., yet in J.W. the incremental area under the glucose curve was 1.6-fold greater than that in the normal subject.

DISCUSSION

The present findings (figures 1 and 2) show that in our patients with diabetes carbohydrate restriction reduces basal glucose concentrations and lowers the glucose tolerance curve but does not influence over-all glucose tolerance (incremental area 0 to 180 minutes). When the responses are analyzed hour by hour, however, it emerges that the elevation in glucose concentrations in the third hour of the GTT was signifi-

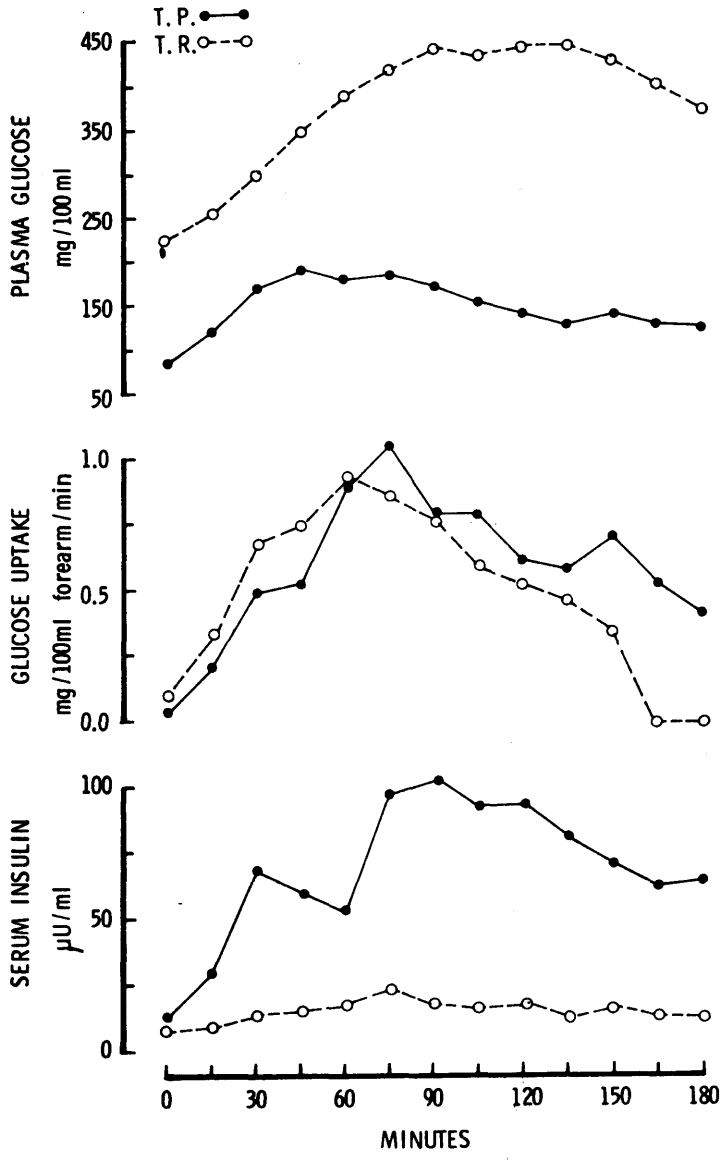

FIGURE 6

Comparison of the response following 100 gm. oral glucose load in diabetic T.R. (table 1) and T.P., a forty-seven year old normal male. The glucose curves illustrate concentrations in *arterialized venous plasma.*

cantly increased by carbohydrate restriction (figure 2); on this basis glucose tolerance is not improved by the dietary change but, on the contrary, is reduced even further. Since, therefore, the lowering of the glucose tolerance curve, was not associated with improved glucose tolerance, it must be attributed entirely to the fall in the basal glucose concentration—a response which, recent studies indicate, is essentially a reflection of an adaptive decrease in gluconeogenesis.[16-19]

As such, these findings confirm previous results[5] suggesting that in diabetics and nondiabetics, the effects of carbohydrate restriction on glucose tolerance differ not in nature but only in degree. Thus in each group there is both a fall in the basal glucose concentration and an impairment in the capacity for glucose disposal;[5,12] however, since the fall in basal glucose levels is the relatively greater change in diabetics, though not in nondiabetics, an over-all *lowering* of the glucose tolerance curve is the outcome.

Figure 2 shows that the incremental glucose area (120 to 180 minutes) was increased despite a significant rise in concomitant peripheral glucose removal. Thus in the light of the generally accepted view that ingested glucose is taken up in either liver or peripheral tissues,[9] and on the assumption that the response of the forearm tissues is representative of that for like

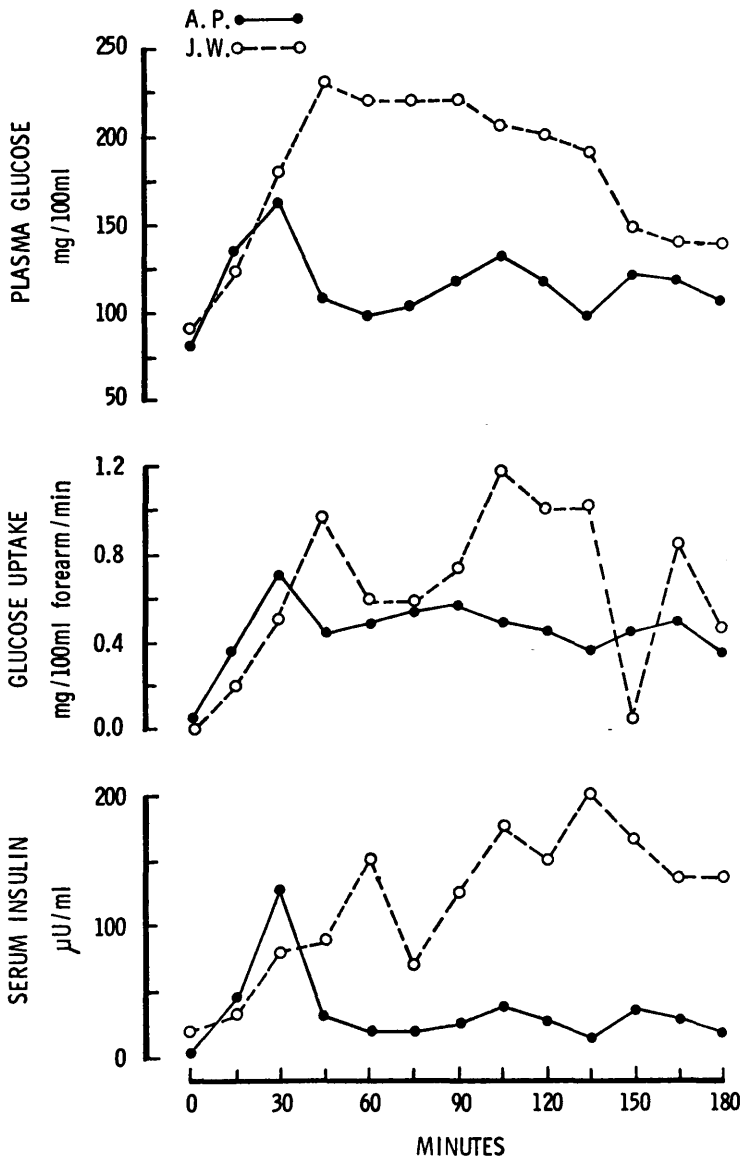

FIGURE 7

Comparison of the response following 100 gm. oral glucose load in diabetic J.W. (table 1) and A.P., a forty-one year old normal male. The glucose curves illustrate concentrations in arterialized venous plasma.

tissues throughout the body, our observations suggest that the further impairment of glucose tolerance following carbohydrate restriction is the result *not* of decreased peripheral glucose uptake but of diminished hepatic glucose conservation.[7]

From the current data the approximate disposition of the 100 gm. load in the body as a whole may be calculated.[11] With a normal diet some 29.8 gm. and 26.1 gm. are accounted for by increased peripheral glucose uptake and hepatic glucose conservation, respectively (table 3). After a low carbohydrate diet it is possible to account for the disposition of the entire glucose load without invoking any participation by the

TABLE 3

Disposition of 100 gm. oral glucose load in nonobese diabetics before and after carbohydrate restriction

	Diabetics	
	Before	After
Total peripheral glucose uptake	29.8 gm.	42.3 gm.
Remaining in glucose space after 180 minutes	30.4 gm.	51.2 gm.
Urinary loss*	13.7 gm.	6.5 gm.
Total hepatic glucose conservation	26.1 gm.	0.0 gm.
	100.0 gm.	100.0 gm.

* Glycosuria was quantitated in only two subjects, but since the glucose concentrations in these patients closely approximated those in the remaining three diabetics, we have used the mean figures of these two subjects to represent urinary loss during the glucose tolerance tests.

liver in glucose conservation. Thus, while peripheral glucose uptake is quantitatively preserved and, if anything, enhanced by carbohydrate restriction (presumably on a basis similar to that postulated for carbohydrate-deprived nondiabetics[12]), the hepatic response to glucose ingestion is totally ablated. It is clear from the foregoing that, since the glucose tolerance curve is in itself too nonspecific an entity with which to examine disturbed glucose homeostasis, the latter may be usefully analyzed only when, in addition, specific references to peripheral tissues and/or the liver are possible.

Figure 3 shows that blood lactate concentrations were increased by glucose ingestion before but not after carbohydrate restriction. Since the rise in lactate concentrations after glucose loading appears to be the consequence of increased hepatic glucose uptake and its metabolism to lactate by glycolysis,[11] the present responses support the conclusion that hepatic glucose uptake during the GTT was markedly impaired following the low carbohydrate diet.

It is clear, furthermore, that qualitatively the influence of carbohydrate restriction on the lactate and ketone body responses to glucose loading (figures 3 and 4) is similar in diabetics and nondiabetics.[12] The implications of these findings have been previously discussed.[12] Since lactate uptake in muscle is determined mainly by the arterial lactate concentration,[20] the failure to find significant AV-MV lactate differences across the forearm during the GTT before carbohydrate restriction is probably due to the fact that, as a result of the block to hepatic glucose uptake, AV lactate levels rose only insubstantially after glucose loading.

Although the available results do not yet allow a meaningful comparison of GTT data between diabetics and nondiabetics on a normal diet, certain tentative conclusions may be drawn. Figure 5 contrasts the response of K.P. (table 1) with an age-matched normal male subject (J.B.) and shows that, despite greater elevations in peripheral glucose removal in K.P. at both 90 and 180 minutes, glucose concentrations in the diabetic rose by increments five- to sevenfold greater than those in the nondiabetic. Similar remarks apply to the results shown in figure 6, since after 120 minutes the increments in peripheral glucose uptake were virtually identical in T.R. and T.P., yet in the diabetic (T.R.) the elevation in glucose concentrations prevailing at this time was 4.5-fold greater than that in the normal subject. Thus although for any given plasma glucose concentration, less glucose is utilized by peripheral tissues in the diabetics, the *absolute* amounts taken up within the context of the GTT were similar in the diabetics and nondiabetics; the results suggest, therefore, that in the former decreased glucose conservation by nonperipheral tissues, i.e. the liver, constitutes the major underlying disturbance. The latter applies equally to J.W. (figure 7); thus, since in J.W. the rise in peripheral glucose uptake after glucose loading exceeded the corresponding response in A.P. (and, indeed, fell at the upper extremity of the range for normal subjects[11]), the impairment in glucose tolerance can be explained only by postulating that the overriding defect was one in *hepatic* glucose conservation. More specifically, we may conclude that, since the ready suppressibility of hepatic glucose output by glucose and insulin administration appears to be retained in nonketotic diabetes,[21,22] the failure to augment hepatic glucose *utilization* after glucose loading is the major cause of the reduction in hepatic glucose conservation and, hence, in glucose tolerance.

The foregoing findings are consistent with several previous reports. Thus the central role of the liver as a major determinant of glucose tolerance was emphasized over thirty years ago by Soskin et al., who found in dogs that the production of a normal glucose tolerance curve, while not dependent on an intact pancreas, was dependent on the presence of a normal liver.[23] Ashmore et al. showed in vitro that both glucose phosphorylation and the rate of glucose degradation along glycolytic pathways was strikingly reduced in the diabetic liver.[24] Subsequently, Madison et al. demonstrated in vivo that the response of the liver to a glucose load is impaired in diabetic animals;[25,26] thus, although during glucose infusions hepatic glucose storage began at arterial glucose concentrations of 116 mg./100 ml. in normal dogs, this occurred in diabetic animals only when concentrations reached 200 mg./100 ml. and not at all in the more severely diabetic dogs, despite elevation of arterial glucose concentrations to levels approaching 500 mg./100 ml. These observations are consistent with more recent studies by Perley and Kipnis which show that, whereas glucose infusion of 31 gm. is sufficient to simulate the 100 gm. oral glucose tolerance curve in healthy subjects, some 50 gm. is required in nonobese diabetics;[13] these workers concluded that in diabetics a greater than normal proportion of ingested glucose reaches the peripheral circulation as a consequence of reduced hepatic glucose extraction. Finally, the current proposals are supported by the numerous studies of enzyme activity which indicate that

in the diabetic liver glucose utilization is markedly reduced.[9,27-30]

In contrast to the present findings (figures 5 to 7), reduced peripheral glucose uptake during the GTT in diabetics receiving a normal diet has been reported by Butterfield and Whichelow.[31,32] These observations[31,32] are difficult to interpret, however, since the authors did not measure insulin responses nor did they distinguish between insulin-requiring and noninsulin-requiring diabetics; it is conceivable, therefore, that while in some patients peripheral glucose uptake was reduced, in others it was equal to or greater than normal. Thus, while after glucose challenge arteriovenous (A-V) glucose differences across the forearm were greatly diminished or absent in some diabetics,[33-37] Somogyi[38] concluded that most patients exhibited A-V differences as great as and often greater than those in normal subjects. Indeed the largest A-V difference reported by Mosenthal and Barry[39] was 102 mg./100 ml. in a diabetic thirty minutes after glucose ingestion. Cavett and Seljeskog[40] on the other hand found that A-V differences were similar in diabetics and nondiabetics. Clearly, more comprehensive studies are required before many of the current problems can be finally resolved.

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