Carbohydrate Metabolism in Hyperadrenocorticism

Armando Aguiar Pupo, M.D., Bernardo L. Wajchenberg, M.D., and José Schnaider, M.D., São Paulo, Brazil

SUMMARY

Investigations of tolerance to oral and intravenous glucose, intravenous and intra-arterial insulin, intravenous tolbutamide, and to subcutaneous glucagon were made in twelve patients with hyperadrenocorticism. The findings varied among patients, but certain trends were apparent.

Fasting blood sugar concentrations tended to he low. The results of oral glucose tolerance tests were diabetic in eleven patients. The rate of glucose disappearance during glucose loading was normal or increased in all. Intravenous tolbutamide caused prolonged hypoglycemia in three of five patients. Hypoglycemia after intravenous and intra-arterial insulin was decreased. Depression of serum phosphorus was less than normal. Glucagon caused a rise in blood sugar above that of normals.

The findings suggest that there is a normal or even increased rate of glucose utilization in clinical endogenous hyperadrenocorticism. The data are compatible with the view that the action of insulin on muscle tissue may be decreased with shift to other areas, perhaps adipose tissue. DIABETES *15*:24-29, January, 1966.

In recent years there have been many studies of the effects of adrenocortical hormones on carbohydrate metabolism. Much of the investigation has been in vitro, however, and clinical observations have been limited usually to detailed studies in single cases, or single observations in groups of cases. In the past six years we have had opportunity to examine carbohydrate metabolism in twelve patients with endogenous hyperadrenocorticism, and the results are reported herein.

METHODS AND RESULTS

Patient material

In table 1 are given the age, sex, and duration of known hyperadrenocorticism of the twelve patients. The adrenals were examined histologically in each and were characterized by adenoma in two patients and hyperplasia in the remainder. In three instances hyperplasia was related to pituitary adenoma. The adenoma was demonstrated at autopsy in two, and was diagnosed on the basis of an enlarged sella and optic nerve compression in the third.

Assay of adrenal function was made with ACTH stimulation in all, with 9-alpha fluorohydrocortisone or dexamethasone suppression in ten, and metopirone suppression in eight (table 1). In patient CGP the urinary steroid values were minimally abnormal according to the criteria of this laboratory, but determination of plasma ACTH yielded a high value of 8 mU./100 ml.* The values in patient RF were also only minimally abnormal, but he is included because adrenal hyperplasia and a chromophobe pituitary adenoma were found at necropsy. In patient WAN the urinary 17-ketosteroids (17-KS) were elevated and the 17-hydroxycorticosteroids (17-OHCS) only suggestively elevated. Virilism was absent, but hyperplasia of the zona fasciculata of the adrenals was found.

Chemical analyses

The urinary 17-OHCS were determined according to Butt et al.,[1] the urinary 17-KS according to Drekter et al.,[2] blood sugar by the Somogyi-Nelson method,[3] and serum inorganic phosphorus according to Fiske and Subbarow.[4] Regression lines and confidence limits of data were calculated by methods in current usage.[5]

Oral glucose tolerance

Oral glucose tolerance tests (GTT) were conducted in eleven patients following daily intake of 300 gm. carbohydrate for three days. Venous blood for glucose determination was obtained fasting and at intervals of 30, 60, 90, 120, and 180 min. after ingestion of 1.75 gm. of glucose per kilogram of body weight. The results are shown in table 2. All curves are in the range of those of diabetes except for that of patient VM, in whom only the 2-hr. sugar concentration is elevated. In two patients (AVB and FTA) the fasting

From the Diabetes and Adrenal Unit, First Medical Clinics, Hospital das Clinicas of the University of Sao Paulo.

*Assay obtained through the courtesy of Dr. Don H. Nelson of the Department of Medicine, University of Southern California, School of Medicine.

blood sugars (FBS) were elevated, and diabetes persisted after alleviation of hyperadrenocorticism. In the remaining ten patients the FBS were in the low normal range. In three patients the serum inorganic phosphorus was measured during testing and the maximum decreases were 1.2, 0.9, and 1.3 mg. per 100 ml.

Intravenous glucose tolerance

Intravenous GTT's were performed by the method of Amatuzio et al.[6] in nine of the patients with hyperadrenocorticism and in nine apparently normal subjects. Twenty-five grams of glucose in 50 per cent solution were given intravenously in 4 min., and capillary samples of blood obtained by finger puncture before injection, 4 min. after injection and thereafter at 8-min. intervals for 72 min. for glucose analysis (table 2). The rate constants of glucose disappearance were calculated as the slopes of the regression lines of the logarithm of the blood sugar concentration on time. The rate constants were listed as increased or decreased respectively when they were beyond the 95 per cent confidence limits of the mean slopes of the normal men and women.[7] Despite the occurrence of hyperglycemia, the disappearance rates were within normal range in three, increased in five, and decreased in one only. In the patient with decreased disappearance, the levels of blood glucose during glucose loading, orally or intravenously, exceeded those of the other patients, and genetic diabetes with insulin deficiency may have been present.

Intravenous insulin tolerance

Intravenous insulin tolerance tests were performed in nine of the patients with hyperadrenocorticism and thirteen apparently normal subjects. Glucagon-free insulin (0.1 U. per kilogram body weight) was injected intravenously in the fasting patient, and venous blood obtained before and 15, 30, 45, 60, 90, and 120 min. after injection for blood glucose and serum inorganic phosphorus analysis (table 3). The mean decrease in sugar concentration of 46 per cent from the initial level in the patients was less ($p<0.01$) than that of 65 per cent noted in the normals. The decrease in phosphorus concentration was also less ($p<0.01$) than in the normal subjects. Accordingly, the findings suggest that antagonism to insulin action was present.

Intra-arterial insulin tolerance

The procedure of Galbraith et al.[8] was used to study the peripheral utilization of glucose after insulin injection into the brachial artery. These workers have found that the effect of "immediately fixed" insulin can be expressed by the difference between

$$\frac{A\text{-}V_1}{A} \text{ and } \frac{A\text{-}V_c}{A}$$

in which A represents arterial glucose concentration, V_1 represents venous glucose concentration in the injected forearm and V_c venous glucose concentration in the contralateral forearm. Accordingly, 2 U. of soluble insulin were injected into a brachial artery of patients who had fasted sixteen hours, and samples of arterial and venous blood were obtained simultaneously through indwelling needles from the artery and both antecubital veins.

The results in three patients with hyperadrenocorticism and six apparently normal subjects are shown in table 4. In patient MS the values were low but within the normal range. In patient ELP the values were also in the lower limit of normal with the exception of that obtained at fifteen minutes which was below the confidence interval. In the other patient, ACF, there was a significantly low value at 30 min.

Despite the general absence of significant differences between the responses of the patients and those of healthy individuals, the effect of circulated insulin

$$\frac{A\text{-}V_c}{A}$$

was different in cases MS and ACF. While in the controls there was a decrease in blood sugar from the 5-min. to the 30-min. sample, in the patients the effect was opposite with values greater at 30 min. than at 5 min. These findings suggest a delayed response to insulin. In patient ELP the pattern of response was similar to the normal, however.

Intravenous tolbutamide tolerance

The intravenous tolbutamide tolerance test was performed in twenty apparently normal subjects (ten men and ten women) and five patients with adrenal hyperactivity. One gram of sodium tolbutamide diluted in 10 ml. of distilled water was administered intravenously over a period of 4 min., and samples of blood were obtained for glucose determination before and at 10, 20, 30, 40, 50, 60, 75, 90 and 120 min. after the injection. The results in the normal subjects and the patients are shown in table 5. In two patients, ACF and CGP, the blood sugar values were within the normal range. In the remaining three patients the sugar levels at 40, 50, 60, and 90 min. were below the mean values of the normals by more than two standard deviations.

Glucagon tolerance

The blood sugar response to glucagon was investi-

TABLE 1 (*continued on page* 27)

Adrenal function in twelve patients with hyperadrenocorticism (values are mg. of urinary excretion in twenty-four hours)

Patient	Age	Sex	Known duration of hypercorticism	Adrenal pathology	After ACTH (25 mg. intravenously, 8 hrs.)						After 9-alpha fluorohydrocortisone (2.5 mg. q 6 hrs.)			
					Basal		Day 1		Day 2		Basal		Day 4	
					17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS
C.G.P.	36	F	84 mos.	Hyperplasia	12.52	14.94	36.6	30.46	42.2	42.23	11.26	15.67		
W.A.N.	20	F	60 mos.	Hyperplasia	10.05	21.4	21.88	37.1	24.3	46.7	10.25	14.2		
A.V.B.	22	F	48 mos.	Hyperplasia (adenoma pituitary)	27.0	7.6	66.0	12.2	44.4	7.3	13.2	3.64	3.64	2.5
R.F.	20	M	48 mos.	Hyperplasia (adenoma pituitary)	11.24	19.5	20.39	37.4	30.1	69.8	12.4	12.8		
E.F.	18	F	24 mos.	Hyperplasia (adenoma pituitary)	42.33	15.59	124.7	32.48	144.95	52.28	55.08	17.46	45.4	15.85
F.T.A.	35	F	12 mos.	Hyperplasia	20	17.5	39.6	23.2	76.7	20.0				
M.M.M.	26	F	8 mos.	Hyperplasia	19.2	13.7	54.5	24.3	63	28.4				
M.S.	28	F	7 mos.	Hyperplasia	14.7	21.8	40.1	30.5	59.7	34.25	12.16	16.5	15.81	
R.X.M.	19	F	7 mos.	Adenoma	18.66	13.4	54.5	21.5	36.36	16.71	12.9	7.4		
A.C.F.	26	F	7 mos.	Adenoma	10.43	2.7	18.56	5.4	22.56	6.4	20.84	4.5		
E.L.P.	18	F	7 mos.	Hyperplasia	20.47	26.6	47.67	55.4	53.21	64.3	14.8	17.3		
V.M.	20	M	4 mos.	Hyperplasia	22.0	30.0	51.0	78.8	55.1	85.3		20.0		8.0

gated in four apparently normal subjects and three patients with hyperadrenocorticism. Thirty micrograms of glucagon per kilogram body weight were injected subcutaneously as suggested by Van Itallie and Bentley.[9] Capillary blood samples for glucose analysis were obtained before injection and subsequently every 8 min. for 72 min.

The findings are shown in figure 1 as the mean of the increments of the blood sugar values in relation to the fasting blood sugar. The increase in blood sugar in the patients was well above that of the control subjects.

In the same subjects a small amount of epinephrine (3 μg. per kilogram body weight) was administered

TABLE 2

Oral and intravenous glucose tolerance tests in patients with hyperadrenocorticism

Patient	Oral GTT Venous blood sugar (mg. per 100 ml.) Min. after glucose ingestion						Intravenous GTT Capillary blood sugar (mg. per 100 ml.) Min. after glucose ingestion										Disappearance rate k	Comparison to normal k
	0	30	60	90	120	180	0	8	16	24	32	40	48	56	64	72		
C.G.P.	72	220	205	200	205	144												
W.A.N.	78	207	243	335	303	136	70	422	368	311	248	225	205	179	154	148	0.0216	Increased
A.V.B.	246	330	382	330	350	262	292	547	510	450	441	420	390		359	312	0.0083	Decreased
E.F.	66		274		179	57	73	310	226	224	208	158	123	96	84	66	0.237	Increased
F.T.A.	154	198	256	276	279	202	117	327	287	250	210	187	180	175	170	160	0.0113	Normal
M.M.M.	80	112	158	162	168	163	84	336	302	235	213	196	185	148	134	130	0.0152	Normal
M.S.	89	171	241	238	224	95	87	296	233	224	172	156	133	122	115	107	0.0159	Normal
R.X.M.	50	89	107	190	144	112	49	217	171	144	132	112	105	91	72	57	0.0285	Increased
A.C.F.	67	137	218	391	195	115	92	366	298	247	208	163	154	125	117	96	0.0209	Increased
E.L.P.	52	101	182	241	196	154												
V.M.	70	78	79	85	117	96	69	202	190	157	123	108	83	78	65	72	0.0214	Increased
Normal men*																	0.0165 ± 0.0035	
Normal women*																	0.0145 ± 0.0035	

*Mean ± 95 per cent confidence limits

TABLE 1 *(continued from page 26)*

Adrenal function in twelve patients with hyperadrenocorticism (values are mg. of urinary excretion in twenty-four hours)

After dexamethasone (0.5 mg. q 6 hrs.)				After dexamethasone (2.5 mg. q 6 hrs.)				After metopirone (750 mg. q 4 hrs.)					
Basal		Day 4		Basal		Day 4		Basal		Day 1 (Rx)		Day 2 ($\bar{p}$ Rx)	
17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS	17-OHCS	17-KS
		8.33				8.53	9.74	14.35	13.9	14.86	19.9	23.8	14.9
		3.99	6.69			3.52	0.87	11.84	29.1	17.88	23.67	20.7	37.8
		8.8	16.9			8.4	10.4	12.5	21.4	14.5	23.9	12.9	19.7
								11.9	16.8	30.2	29.5	40.9	49.3
		14.6	6.5			14.3	5.1	19.1	17.8	11.0	5.0	9.3	3.6
		20.0	5.9			24.8	5.5	21.5	6.1	18.2	4.2	15.85	7.7
		7.81	22.0				12.4	14.18	20.7	15.18	23.1	29.3	57.9

subcutaneously, 10 min. prior to glucagon injection, as suggested by Van Itallie and Bentley.[9] With this dose the epinephrine effect on liver glycogenolysis is negligible, but glycogenolysis and subsequent inhibition of peripheral glucose uptake occur in muscle.[10,11] The addition of epinephrine had no effect in the patients with hyperadrenocorticism, while the glucose concentrations in the normal subjects achieved higher levels than when glucagon alone was given (figure 1).

DISCUSSION

The findings exemplify the various alterations in carbohydrate metabolism observed in patients with hyperadrenocorticism. Loss of carbohydrate tolerance has

TABLE 3

Insulin tolerance tests (0.1 U./kg. body weight) in normal subjects and patients with hyperadrenocorticism

Patient	Blood sugar (mg. per 100 ml.) Min. after insulin injection							Serum inorganic P (mg. per 100 ml.) Min. after insulin injection							Maximum ΔP	Maximum ΔP compared to normal
	0	15	30	45	60	90	120	0	15	30	45	60	90	120		
C.G.P.	76	44	44	57	76	70	65									
W.A.N.	75	75	34	36	50	60	73									
E.F.	64	48	32	40	44	53	68	3.2	3.0	2.9	2.9	3.2	3.6	3.7	0.3	Decreased
M.M.M.	70	53	37	32	50	55	64	3.1	2.7	2.5	2.5	2.6	2.8	3.1	0.6	Normal
M.S.	89	75	56	56	70	75	100	3.5	3.2	3.1	3.2	3.3	3.4	3.5	0.4	Decreased
R.X.M.	54	36	21	23	32	44	50									
A.C.F.	90	85	65	68	69	78	84	3.3	3.9	3.0	2.9	2.9	3.1	3.3	0.4	Decreased
E.L.P.	63	41	30	22	45	53	62	3.6	3.5	3.4	3.6	3.6	3.6	3.6	0.2	Decreased
V.M.	85	32	43	62	64	73	86	3.4	2.9	2.8	2.7	2.6	2.7	3.3	0.7	Normal
Mean	74	54	40	44	56	62	72	3.3	3.2	2.9	2.9	3.0	3.2	3.4	0.4	
Normal mean* (13 subjects)	88 ±21	38 ±19	33 ± 8	41 ±23	45 ±15	61 ±23	82 ±25								1.3 ±0.7	

*± 95 per cent confidence interval for single values

TABLE 4

Effects of intra-arterial insulin in normal subjects and two patients with hyperadrenocorticism

$\frac{A\text{-}V_1}{A}$

Patient	Min. after insulin injection 0	5	15	30	45	60
M.S.	0.02	0	0.03	0.10	0	—0.07
A.C.F.	0.05	0.06	0.06	0.02	0.04	0.06
E.L.P.	0.02	—0.12	—0.04	0.09	0.05	—0.01
Mean*	+0.11	+0.09	+0.09	+0.08	+0.09	+0.08
	±0.1	±0.18	±0.30	±1.2	±0.4	±0.63

$\frac{A\text{-}V_c}{A}$

Patient	Min. after insulin injection 0	5	15	30	45	60
M.S.	0.08	0.08	0	0.07	0	0
A.C.F.	0.10	—0.08	0	0.12	0.02	0.14
E.L.P.	0	0.13	0.07	0.06	0.05	0.07
Mean*	+0.13	+0.14	—0.06	—0.13	+0.06	+0.17
	±0.09	±0.08	±0.38	±0.34	±0.01	±0.09

$\frac{V_c\text{-}V_1}{A}$

Patient	Min. after insulin injection 0	5	15	30	45	60
M.S.	—0.06	—0.08	0.03	0.03	0	—0.07
A.C.F.	—0.05	0.11	0.06	—0.10	0.01	—0.07
E.L.P.	0.02	—0.25	—0.11	—0.03	—0.045	—0.08
Mean*	—0.02	—0.05	+0.15	+0.21	+0.03	+0.01
	±0.08	±0.20	±0.20	±0.21	±0.11	±0.10

*±95 per cent confidence limits.

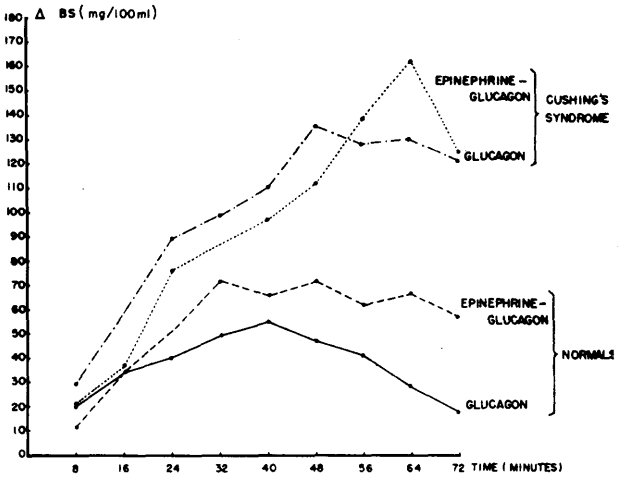

FIG. 1. △ Blood sugar means in normal controls and patients with Cushing's syndrome after glucagon and epinephrine-glucagon.

been emphasized in previous reports, and all but one of the present patients had GTTs compatible with that of genetic diabetes. The one patient with normal tolerance had the shortest known duration of hyperadrenocorticism. It is noteworthy that the fasting blood sugar of patient RXM was consistently low, and during insulin tolerance testing the response resembled that of adrenal insufficiency.

The normal or increased rates of glucose disappearance during intravenous glucose loading suggest that carbohydrate utilization may not only be normal but even increased in hyperadrenocorticism. The hyperglycemia occurring during oral glucose loading could be explained by inadequate liver uptake of glucose in relation to increased liver gluconeogenesis. Consequently, a greater load of glucose would be presented to periph-

TABLE 5

Intravenous tolbutamide tolerance tests in twenty normal subjects and four patients with hyperadrenocorticism

Patient	Blood sugar (mg. per 100 ml.) Min. after tolbutamide injection 0	10	20	30	40	50	60	75	90	120
C.G.P.	72	91	56	48	42	48	58	62	62	62
W.A.N.	59	52	45	39	29	24	37	30	30	50
E.L.P.	73	64	52	41	31	28	31	35	41	50
R.X.M.	52	46	46	34	26	23	23	23	30	59
A.C.F.	74	78	63	43	48	66	65	60	66	68
Mean of normal subjects* (20)	85 ±30	76.95 ±27	62.55 ±29	51.85 ±28	50.20 ±20	52.30 ±12	57.05 ±16	56.65 ±16	61.65 ±19	66.55 ±17

*±95 per cent confidence limits.

eral tissues.[12] The blood sugar levels during oral glucose tolerance testing were elevated, but the curves were unusual in that the FBS was elevated in two cases only and low, below 70 mg. per 100 ml., in five. Thus, they differed somewhat from the curves usually observed in genetic diabetes in that higher fasting levels would have been expected in view of the high post-loading levels.

It is possible that increased rate of glucose utilization could have been due to increased rate of insulin secretion. Hypertrophy and hyperplasia of islets and degranulation of beta cells have been described in Cushing's syndrome,[13,14] and during experimental cortisone treatment of rats,[15] guinea pigs,[16] and rabbits.[17,18] A persistence of hypoglycemia occurred in three of the patients receiving intravenous tolbutamide. Evidence for an increased production of insulin has been reported with the finding of high plasma immunoreactive insulin content in Cushing's syndrome following glucose loading.[19] In patient AVB with decreased tolerance during intravenous glucose loading, islet cell exhaustion may have ensued with development of permanent diabetes.

The small decrease in serum phosphorus concentration during glucose loading is difficult to explain. Impairment of some aspect of insulin action is suggested by the reduction of effect of "immediately fixed" insulin as evidenced by the intra-arterial insulin tolerance tests.[20] Perhaps glucose utilization was impaired in muscle, and excessive in adipose tissue. Such a condition might account for the normal or increased glucose utilization with decreased phosphorus uptake.

The hyperglycemic response to glucagon was greater than that observed by Weisenfeld and Goldner.[21] This could be related to increased liver glycogen present in hyperadrenocorticoid states. Still, the addition of epinephrine failed to increase the blood sugar as was observed in the normal subjects. The reasons for this are unknown, and speculation as to mechanisms is not warranted at this time.

ACKNOWLEDGMENT

This study was supported by a grant from The Lilly Research Laboratories, Indianapolis, Indiana.

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