STUDIES IN SERUM ELECTROLYTES. IX. THE CHANGE IN TOTAL QUANTITY AND OSMOLAL CONCENTRATION OF GLUCOSE AND CHLORIDE IN THE SERUM AFTER THE INGESTION OF GLUCOSE BY DIABETIC PATIENTS

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Under certain conditions observers have reported an inverse relationship in the concentration of sugar and of chloride in the blood. Herrick (1) in 1924 observed it following the ingestion of 100 grams of glucose in six individuals. Ni (2) obtained the same relationship following the removal of the pancreas or the administration of insulin in dogs which he regarded as a manifestation of osmotic compensation. Sunderman, Austin and Williams (3) observed it following the administration of insulin to diabetic patients,—the increase in serum chloride being associated with an increase of total fixed base. Their freezing point data suggested that the increased concentration of electrolytes in the serum did not entirely compensate osmotically for the decreased concentration of sugar. They found the change usually accompanied by a higher specific gravity and an increased concentration of the total solids of the serum.

Changes in the concentration of blood sugar are usually associated with changes in the water content of the blood and tissues. The intravenous administration of hypertonic solutions of glucose is used clinically to produce dehydration and diuresis. Following the administration of hypertonic solutions of either saccharose or glucose intravenously in dogs, Keith (4) found the plasma volume diminished and both the viscosity of the blood and the concentration of hemoglobin increased. Drabkin, Page and Edwards (5) and Drabkin (6) demonstrated that administration of insulin to dogs produces not only a lowering of the blood sugar but also anhydremia which manifests itself in increase of the concentration of hemoglobin and erythrocyte count, and reduction of plasma volume.

Change in the concentration of a solute may result from addition or removal of either solute or solvent. Moreover, in solutions such as blood or serum which contain a high concentration of solids, the distinction between concentration of solute per unit of solution and per unit of solvent is important. The concentration of solute is commonly estimated in relation to volume of solution in clinical studies. It is, however, the concentration of solute per unit of solvent which perhaps has more physicochemical significance.

The present study was designed to determine in the diabetic patient to whom glucose was administered the *changes* in the concentration of glucose and chloride in serum in relation to the *change* in the amount of water circulating in the serum, and from these data to estimate the *change* in the total quantity and in the osmolal concentration of both glucose and chloride in serum.

MATERIAL AND METHODS

Venous blood was withdrawn under oil from 18 fasting patients who were attending the Metabolic Clinic at the Pennsylvania Hospital for diabetes mellitus. The serum was obtained from the centrifuged specimen of the clotted blood by the technique described elsewhere (7). Seventy-five grams of glucose dissolved in 200 cc. of water flavored with lemon juice were then ingested, and after an interval of ninety minutes serum was again obtained for analysis.

Glucose in the serum was measured by Benedict's method (8) within 20 minutes after the collection of the blood. The Wilson and Ball procedure (9) was employed for the measurement of the serum chloride. The specific gravity of the serum was measured at 20° C. with pyknometers of 2 ml. capacity. The total residue of the serum was obtained by drying the serum at 100° C. to constant weight. Freezing point measure-

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TABLE I

Effect of ingestion of glucose by diabetic and normal individuals on the glucose and chloride concentrations of serum

Case	Specific gravity	Chloride	Glucose	Solids	Chloride	Glucose	Δ [Glucose] − Δ [Chloride]	Chloride	Glucose	Water	Solution transferred to serum after glucose					
											Chloride	Glucose	Water	Chloride	Glucose	π_{ex}
	20/20°	m. Eq./L	mM./L	grams/kgm.	m. Eq./kgm. H_2O	mM./kgm. H_2O		m. Eq./kgm. R	mM./kgm. R	grams/kgm. R	m. Eq./kgm. R	mM./kgm. R	grams/kgm. R	m. Eq./kgm. H_2O transferred	mM./kgm. H_2O transferred	mm.
1 (f)	1.0290	103.0	8.9	91.55	110.2	9.5	4.77	1189.5	102.7	10796						
(g)	1.0283	101.2	18.5	89.10	108.0	19.8		1228.6	224.7	11372	39.1	122	576	67.9	211.8	347.6
2 (f)	1.0285	97.8	16.4	88.00	104.3	17.5	3.99	1195.3	200.9	11463						
(g)	1.0268	95.4	28.2	82.00	101.2	29.9		1296.5	382.9	12816	101.2	182	1353	74.8	134.5	284.1
3 (f)	1.0281	99.9	17.4	90.25	106.8	18.6	4.46	1192.0	207.8	11160						
(g)	1.0273	96.6	32.9	88.00	103.1	35.2		1225.5	417.8	11887	33.5	210	727	46.0	288.9	380.9
4 (f)	1.0276	102.4	9.3	92.00	109.7	9.9	3.73	1178.7	106.9	10740						
(g)	1.0269	99.9	21.0	85.80	106.4	22.4		1272.9	268.0	11963	94.2	161.1	1223	77.0	131.7	285.7
5 (f)	1.0304	100.9	12.7	95.90	108.3	13.7	3.11	1113.4	140.3	10280						
(g)	1.0302	97.3	24.3	94.70	104.3	26.0		1112.1	277.5	10658	−1.3	137.2	378	−3.4	363.0	356.2
6 (f)	1.0291	100.1	8.5	93.95	107.3	9.1	4.51	1120.8	94.7	10442						
(g)	1.0268	98.2	19.4	87.10	104.8	20.7		1224.4	242.4	11689	103.6	147.7	1247	83.1	118.4	284.6
7 (f)	1.0274	100.4	7.8	88.80	107.2	8.3	3.89	1195.7	92.5	11150						
(g)	1.0262	96.8	23.4	83.80	103.0	24.9		1271.8	308.0	12353	76.1	215.5	1203	63.3	179.1	305.7
8 (f)	1.0255	108.6	8.7	80.65	115.2	9.2	3.34	1451.6	115.5	12600						
(g)	1.0253	106.3	16.4	80.10	112.7	17.4		1457.0	224.7	12928	5.4	109.2	328	16.5	332.9	365.9
9 (f)	1.0286	101.9	16.7	90.65	109.0	17.8	4.40	1209.0	197.0	11096						
(g)	1.0285	99.9	27.4	86.90	106.4	29.2		1270.8	348.4	11948	61.8	151.4	852	72.5	177.7	322.7
10 (f)	1.0275	106.3	11.2	86.25	113.2	11.9	4.34	1322.4	138.9	11678						
(g)	1.0271	103.9	23.2	82.90	110.3	24.7		1387.3	310.4	12577	64.9	171.5	899	72.2	190.8	335.2
11 (f)	1.0258	103.9	12.4	80.55	110.2	13.2	3.35	1398.2	167.1	12691						
(g)	1.0260	101.1	22.5	79.35	107.0	23.8		1414.0	314.7	13217	15.8	147.6	526	30.0	280.6	340.6
12 (f)	1.0308	102.8	13.3	98.20	110.6	14.3	3.49	1107.9	143.2	10015						
(g)	1.0290	100.6	22.7	92.45	107.8	24.3		1181.5	266.4	10964	73.6	123.2	949	77.6	129.8	285.0
13 (f)	1.0268	98.5	11.5	88.45	105.2	12.3	2.35	1186.3	138.7	11278						
(g)	1.0255	97.2	15.7	83.20	103.3	16.7		1264.5	203.7	12238	78.1	65.0	960	81.4	67.7	230.5
14 (f)	1.0254	98.2	12.9	78.90	104.0	13.7	3.45	1348.1	177.3	12965						
(g)	1.0257	94.4	26.5	77.75	99.8	28.0		1359.6	381.8	13620	11.5	204.5	655	17.6	312.2	347.4
15 (f)	1.0295	105.3	7.7	94.20	112.9	8.3	2.95	1177.4	86.2	10426						
(g)	1.0286	103.6	14.4	88.50	110.5	15.4		1257.6	174.9	11381	80.2	88.7	955	84.	92.9	260.9
16 (f)	1.0268	104.8	6.0	85.55	111.6	6.4	3.83	1299.6	74.5	11644						
(g)	1.0258	102.7	15.3	81.85	109.1	16.2		1365.5	202.9	12522	65.9	128.4	878	75.1	146.2	296.4
17 (f)	1.0263	102.1	9.8	84.50	108.6	10.4	4.38	1292.1	123.8	11894						
(g)	1.0261	100.3	19.7	80.00	106.3	20.9		1380.2	271.4	12990	88.1	147.6	1096	80.4	134.7	295.5
18 (f)	1.0258	105.4	10.8	84.20	112.2	11.5	3.44	1346.5	137.6	12002						
(g)	1.0250	103.5	20.0	79.15	109.7	20.2		1444.7	266.3	13175	98.2	128.7	1173	83.7	109.7	276.8
Normal																
FWS (f)	1.0269	101.3	5.7	89.00	108.3	6.1	∞	1200.2	67.1	11084						
(g)	1.0268	101.3	4.7	89.15	108.3	5.0		1194.9	52.2	11032	5.3	12.0	52	102.1	231.5	435.1
ESW (f)	1.0270	102.2	5.1	85.05	108.8	5.5	3.43	1270.4	64.0	11680						
(g)	1.0271	102.9	2.9	85.40	109.5	3.1		1267.6	35.9	11572	2.8	28.1	109	25.8	259.4	311.0

ments were made by means of the Stadie-Sunderman apparatus (10).

CALCULATION OF RESULTS

The concentrations of glucose and chloride in serum before and after the glucose administration have been expressed as moles per liter of serum; as moles per kilogram of serum water; and as moles per kilogram of dry residue exclusive of the glucose and chloride. It is the second of these, the molality of a solute in serum which is most simply related to changes in the osmotic equilibrium, thermodynamic potential, or activity of the solute. If it be assumed as a plausible approximation for these experiments, that, excluding the glucose and the chlorides, the remaining solids of the serum remain constant during the ninety minute period of the experiment, then from the ratios of glucose, chloride, and water to solids the percentile change in the total quantities of these three components may be calculated.

The following equations were employed in our calculations (those for glucose being analogous to those for chloride).

SYMBOLS

Sp = specific gravity at 20° C.
H_2O = water in grams
S = solids in grams
Gl = glucose in millimoles
Cl = chloride in millimoles
L = liters of serum
K = kilograms of serum
[ ] = concentration per kilogram of water
R = residual solids in kilograms. (Solids exclusive of glucose and chloride as NaCl)
π_{ex} = osmolal concentration of glucose and chloride in the fluid calculated as exchanged
subscript f = fasting
subscript g = after glucose

$$\frac{\mathrm{Cl/L}}{\mathrm{Sp}} = \mathrm{Cl/K}; \quad \frac{\mathrm{H_2O/L}}{\mathrm{Sp}} = \mathrm{H_2O/K} = 1000 - \mathrm{S/K}, \quad (1)$$

$$\frac{1000\ \mathrm{Cl/K}}{1000 - \mathrm{S/K}} = [\mathrm{Cl}], \quad (2)$$

$$\mathrm{Cl/R} = \frac{1000\ \mathrm{Cl/L}}{\mathrm{Sp\ (S/K)} - 180\ \mathrm{Gl/L} - 58.45\ \mathrm{Cl/L}}, \quad (3a)$$

$$\mathrm{H_2O/R} = \frac{\mathrm{Sp} \times 10^6 - \mathrm{Sp\ (S/K)} \times 10^3}{\mathrm{Sp\ (S/K)} - 180\ \mathrm{Gl/L} - 58.45\ \mathrm{Cl/L}}. \quad (3b)$$

Transference of H_2O, Cl, and Gl to the serum after glucose administration.

$$\Delta\ \mathrm{Cl/R} = (\mathrm{Cl/R})_g - (\mathrm{Cl/R})_f, \quad (4a)$$

$$\Delta\ \mathrm{H_2O/R} = (\mathrm{H_2O/R})_g - (\mathrm{H_2O/R})_f. \quad (4b)$$

Concentrations of Cl and Gl (expressed as mM. per kilogram of water added) in the solution entering serum after glucose administration are as follows:

$$\Delta\ \mathrm{Cl}/(\Delta\ \mathrm{H_2O} \times 10^{-3}) = \frac{1000\ \Delta\ \mathrm{Cl/R}}{\Delta\ \mathrm{H_2O/R}}. \quad (5)$$

Estimated osmolal concentration of chloride and glucose in the fluid calculated as exchanged (π_{ex}) assuming 1.9 as the osmolal equivalence of a mole of electrolyte.

$$\pi_{ex} = 1.9\ \Delta\ \mathrm{Cl}/(\Delta\ \mathrm{H_2O} \times 10^{-3}) + \Delta\ \mathrm{Gl}/(\Delta\ \mathrm{H_2O} \times 10^{-3}). \quad (6)$$

RESULTS

The data pertinent to this paper have been recorded in Table I.

Relationship between the concentrations of glucose and chloride in serum on a water basis

From calculations made from the data in this paper and in a previous paper (11) there was no significant correlation between the concentration of glucose and chloride in either the serum or corpuscles in the blood of different patients. However, following the ingestion of glucose in diabetic patients there was a striking correlation between the *change* in the concentrations of glucose and chloride in the serum when these were expressed on a water basis.

In the serum of each of the diabetic patients following the administration of glucose there was a decreased concentration of chloride as well as the anticipated increased concentration of glucose. The increase in the glucose concentration in moles per kilogram of water was accompanied by a decrease in the chloride concentration in moles per kilogram of water in the mean ratio of 3.77 $\pm$ 0.45 to 1.

In Figure 1 the increase in the milliosmolal concentration of glucose in the serum is plotted against the decrease in the milliosmolal concentration of chloride. The statistically calculated regression line of chloride on glucose is:

$$-\Delta\ \pi_{\mathrm{Cl}} = 0.369\ \Delta\ \pi_{\mathrm{glucose}} + 1.50.$$

If the osmolal decrease in concentration of chloride were equal to the osmolal increase in glucose the curve would follow the dotted line. The increase in the concentration of glucose when greater than about 3 mM. per kilogram of water is thus not entirely compensated for osmotically by the decrease in the concentration of chloride.

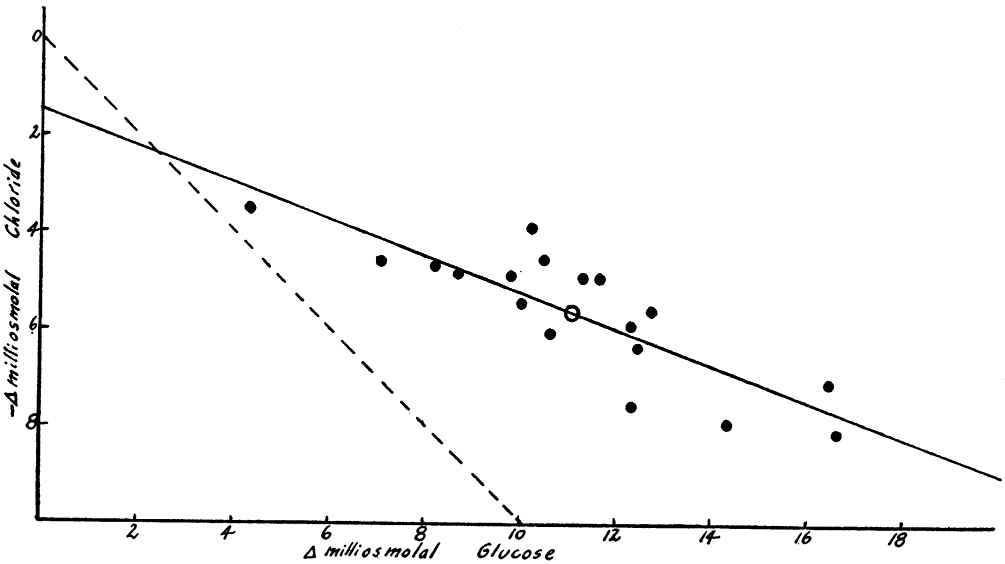

FIG. 1. INCREASE IN OSMOLAL CONCENTRATION OF GLUCOSE PLOTTED AGAINST THE DECREASE IN OSMOLAL CONCENTRATION OF CHLORIDE.

TABLE II

Effect of ingestion of glucose by diabetic individuals on the total base and freezing point of serum

Case	Freezing point	Total base	Glucose	H_2O
	° C.	*m. Eq./kgm. H_2O*	*mM./kgm. H_2O*	*grams/kgm. serum*
19 (f)..	− 0.544	158.8	7.73	901.45
(g) .	− 0.552	157.5	12.66	904.65
20 (f)..	− 0.527	156.1	7.66	909.40
(g) .	− 0.533	151.0	17.19	913.65

In Table II are given concentrations of total base and glucose in relation to the water in the serum of two diabetic patients. With increase of serum glucose the total base was diminished in the serum of both of these patients. It would appear thus that the decrease in the concentration of chloride was probably accompanied by a decrease in the concentration of total base.

The composition of the serum after ingestion of glucose

The concentrations of glucose and chloride in each sample of serum obtained before and after the administration of glucose are given in Table I and are expressed per unit of volume, per unit of water, and per unit of residual solids. Although the concentration of chloride per liter and per kilogram of serum water was decreased in all of the cases following glucose, the amount of chloride per kilogram of residual solids in the serum, with the exception of Case 5, was increased. In Case 5, as in the others, there was a greater amount of glucose and water present in the serum after the administration of glucose than before.

In the upper part of Figure 2 is given the percentile increase in the water of the serum per kilogram of solids. In the lower part of the graph the open columns represent the osmolal concentration of the increment of glucose and the hatched columns the osmolal concentration of the increment of chloride calculated as if they were in the increment of water. The analyses indicate that in 17 of the 18 cases, the increment in chloride was from 5.4 to 103 m. Eq. per kilogram of increment of water. In Case 5 the calculation indicates a slight loss of chloride from the serum. The estimated osmolal concentration of the fluid increment with both chloride and glucose included was on the average higher than that of the fasting serum. This is consistent with the observed increase in the freezing point depression in the serum after glucose ingestion (Cases 19 and 20).

In Table I and Figure 2 are given the measurements obtained from similar analyses in two normal individuals following the ingestion of glu-

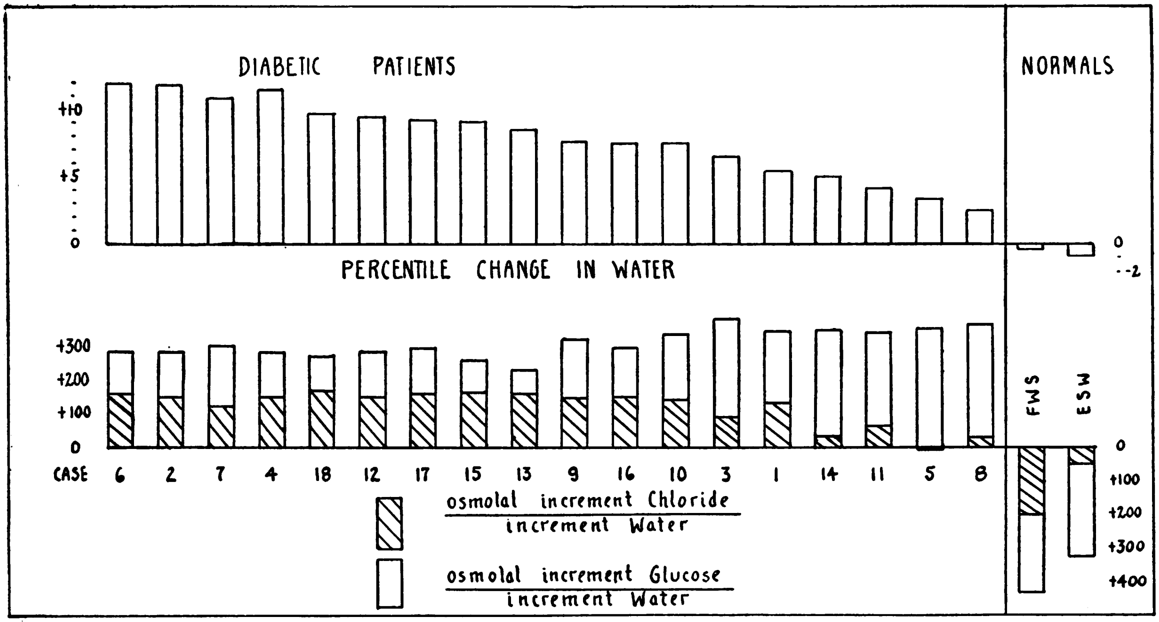

FIG. 2. CHANGES IN SERUM AFTER GLUCOSE INGESTION.

cose. If the same assumption be made that there is no change in the total solids (excepting glucose and chloride) in the serum of the normal individuals after the ingestion of glucose then it will be observed that there was an outflow of water as well as of glucose and of chloride. The changes of volume and composition of the serum in normal individuals were just the reverse of those observed in the diabetic patients.

While there are many studies in the literature giving changes in concentration of solutes per liter of serum following hemorrhage, plasmapheresis, intravenous injection of hypotonic or hypertonic solutions, etc., few studies contain in addition, measurements of specific gravity and dry weight. It is, therefore, impossible to calculate from them the changes of solute per kilogram of water or to estimate the sign or the approximate ratio, Δ solute/Δ H_2O.

SUMMARY

Blood was removed from fasting diabetic patients before and 1½ hours after the ingestion of glucose. The increase in the concentration of glucose in the serum as moles per kilogram of water was accompanied by a decrease in the concentration of chloride in the same units in approximately the ratio of 3.8 to 1.

The assumption was made that the amount of solids in the serum, excepting glucose and chloride, remained constant during the brief period of an experiment and the amounts of glucose, chloride and water present in the serum before and after the administration of glucose were calculated in relation to these residual solids. The results of these calculations indicated that after the ingestion of glucose there was not only an increase in the total quantity of glucose in the serum but also an increase in the total quantities of chloride and water present. The increase in the total quantity of chloride was from 0 to 103 m. Eq. per kilogram of added water. The increment in glucose plus chloride calculated in relation to the increment of water gave, on the average, a value representing a higher osmolal concentration than that of the fasting serum. The final results obtained after the ingestion of glucose by diabetic individuals, therefore, were an increase in glucose concentration, a decrease in chloride concentration, an increase in the osmotic pressure, and an increase in the total quantities of glucose, chloride, and water of the serum.

In the serum of the diabetic patient the disturbance resulting from the uptake of glucose is distributed among at least three other variables: serum volume, osmotic pressure, and chloride con-

centration. The experiments illustrate the fact that a change in concentration induced with respect to a single component, such as glucose, tends to disturb the concentration of other components of the serum and to induce transfers of some of them to or from the serum.

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