were not entirely unexpected (Forbes *et al.*, 1945; Coburn *et al.*, 1965; Shields, 1971). The fact that women eliminate their carbon monoxide faster than men, both at night and during the day, however, was surprising though agreeing with the results of Godin and Shephard (1972). A possible explanation for these results may be that men have more binding sites for carbon monoxide—that is, they have a larger myoglobin and haemoglobin mass. It follows, therefore, that a man will have a larger absolute amount of carbon monoxide than a woman for the same COHb level expressed as a percentage of the total haemoglobin.

Hence, a random COHb estimation shows the approximate mean COHb level which the subject maintains throughout 24 hours, and heavy smokers are continuously at risk from any adverse effects of carbon monoxide. They are therefore subjecting themselves to similar atherogenic stimuli as Astrup's experimental animals.

References

Armitage, A. K., and Turner, D. M. (1970). *Nature*, **226**, 1231.
Astrup, P. (1972). *British Medical Journal*, **4**, 447.
Castleden, C. M., and Cole, P. V. (1973). *Lancet*, **2**, 21.
Castleden, C. M., and Cole, P. V. (1974). In press.
Coburn, R. F. (1970). *Annals of the New York Academy of Sciences*, **174**, 11.
Coburn, R. F., Forester, R. E., and Kane, P. B. (1965). *Journal of Clinical Investigation*, **44**, 1899.
Cohen, S. I., *et al.* (1971). *Archives of Environmental Health*, **22**, 55.
Cole, P. V., Hawkins, L. H., and Roberts, D. (1972). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **79**, 782.
Forbes, W. H., Sargent, F., and Roughton, F. J. W. (1945). *American Joarnul of Physiology*, **143**, 594.
Godin, G., and Shephard, R. J. (1972). *Respiration*, **29**, 317.
Goldsmith, J. R., and Landaw, S. A. (1968). *Science*, **162**, 1352.
Lawther, P. J., and Commins, B. T. (1970). *Annals of the New York Academy of Sciences*, **174**, 135.
McIlvaine, P. M., Nelson, W. C., and Bartlett, D. J. (1969). *Archives of Environmental Health*, **19**, 83.
Russell, M. A. H. (1974). *Lancet*, **1**, 254.
Russell, M. A. H., *et al.* (1973). *British Medical Journal*, **4**, 512.
Shields, C. E. (1971). *Transfusion*, **11**, 89.

Studies on Whole-body Potassium in Non-ketoacidotic Diabetics Before and After Treatment

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Summary

Serial measurements of whole-body potassium were carried out in 28 diabetic patients, in 23 of whom diabetes had only recently been diagnosed. Eleven patients were treated with insulin, 12 with oral hypoglycaemic agents, and the rest were already on oral hypoglycaemic agents and had developed poor diabetic control; four of these required insulin. Whole-body potassium was measured before treatment was begun (or altered) and again one and six weeks later. Whole-body potassium (ratio of observed to expected) was initially reduced in most of the patients requiring insulin. After control of diabetes whole-body potassium increased significantly in the three groups. The increase in whole-body potassium in the individual patients varied over a wide range, and in patients who were treated with insulin it was often of a similar magnitude to that observed in patients in diabetic ketoacidosis.

Introduction

Metabolic balance studies have shown that patients in diabetic ketoacidosis may be severely depleted of potassium (Danowski *et al.*, 1949; Nabarro *et al.*, 1952). Less is known, however, about the potassium status of patients who have uncontrolled diabetes but are not ketoacidotic. Some information has been obtained through the studies of exchangeable potassium (Aikawa *et al.*, 1953; Telfer, 1966), a technique which has limitations not only because it is time consuming but also because it involves exposure of the subject to radiation.

Determination of the naturally occurring radioactive isotope of potassium-40 with the whole-body counter has certain advantages over both balance studies and exchangeable potassium techniques. It can be done quickly on an outpatient basis, thus making serial studies relatively easy, and because naturally occurring ^{40}K is measured radiation exposure is avoided. We have carried out serial measurements of whole-body potassium in non-ketoacidotic patients using the whole-body counter. The patients were newly diagnosed, untreated diabetics as well as established diabetics with poor control. The objectives of the study were to determine the potassium status of diabetic patients with uncontrolled diabetes, and to determine the effect of improvement of diabetic control on whole-body potassium.

Patients

Twenty-eight patients were investigated. Of these 23 were newly-diagnosed diabetics who had been referred to the diabetic clinic, diabetes being confirmed by a random blood sugar of over 200 mg/100 ml in association with symptoms of diabetes. Five patients who had established diabetes treated with oral hypoglycaemic agents were also investigated. In these cases symptoms of poor diabetic control had developed and heavy glycosuria had been present persistently for a month or more. No patient was clinically ketoacidotic and none had ketonuria. Each of the 28 patients had a whole-body potassium measurement before treatment was begun (or altered in the case of the patients already on treatment). The 23 new diabetics were then put on an appropriate carbohydrate-restricted diet and, using ordinary clinical criteria, 11 of them were treated with insulin and the remainder with oral hypoglycaemic agents (eight with sulphonylureas and four with biguanides). Of the five established diabetics who had uncontrolled diabetes four were put on insulin and one who was on sulphonylureas was given biguanides in addition. All patients had further whole-body potassium measurements one and six weeks later.

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During the course of the investigation no patient was on diuretics, digoxin, or any other drug thought to interfere with potassium balance. At the time of the third whole-body potassium measurement all patients were without diabetic symptoms. Postprandial urine specimens were regularly free from sugar in the patients on oral hypoglycaemic agents while random blood sugar estimations in the insulin-treated patients were all below 200 mg/100 ml.

Methods

Whole-body potassium was measured using the whole-body counter which had previously been calibrated by standard techniques (Hughes and Williams, 1967). The overall error in whole-body potassium measurement in this department is between 2·9% and 4·2%. Control values for whole-body potassium had previously been obtained from measurements carried out on 110 healthy volunteers (H. James, unpublished data). During these preliminary investigations it was found that whole-body potassium varied over a wide range and was related to body size. The best correlation between measured whole-body potassium and body size in the control studies was obtained by using the following equation:

$$\text{whole-body potassium} = a \times \text{weight} + b \times \frac{\text{total}}{\text{fat}} + c \times \text{height}^2 \times \frac{\text{shoulder}}{\text{width}} + d$$

where a, b, c, and d are constants (different for each sex) and were computed by applying least squares analysis to the controls' observed whole-body potassium, body weight, total body fat, height, and shoulder width. The use of this equation allows an estimate of the normal whole-body potassium expected for body size. The highest concentration of potassium is found in muscle tissue while adipose tissue is poor in potassium. We found that the correlation between whole-body potassium and the above equation is better than the correlation between whole-body potassium and lean body mass or body weight. We expressed most of the results as the ratio of the observed whole body potassium (Ko) to the normal whole-body potassium expected for body size (Ke). The mean normal Ko:Ke for our control group is, by definition, 1·00. The range—that is, ± two standard deviations—is 0·84-1·16.

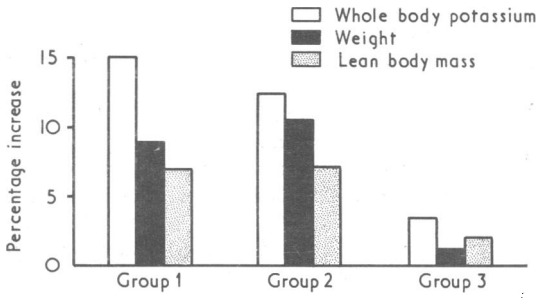
Total body fat was measured according to the method described by Fletcher (1962). Lean body mass was estimated by subtraction of the total body fat from the patient's measured body weight.

Results

For purposes of analysis the patients were divided into three groups. Group 1 consisted of newly-diagnosed diabetics who were treated with insulin, group 2 consisted of patients with established diabetes who had recently shown poor diabetic control, and group 3 consisted of newly-diagnosed diabetics treated with oral hypoglycaemic agents. The whole-body potassium and weight of each patient before and six weeks after starting treatment are shown in table I. The mean Ko:Ke for the three groups of patients is shown before treatment and after one and six weeks in table II. The significance of the difference between pretreatment Ko:Ke and the normal value was tested for the three groups using Students' paired *t* test. Before treatment the results for group 1 and group 2 were significantly below normal ($P < 0.001$ and $P < 0.05$ respectively). In addition, the mean value of Ko:Ke for group 1 was significantly lower than the value for group 3 ($P < 0.01$). After six weeks of treatment the mean Ko:Ke value for each of the three groups had increased, the increases of groups 1 and 2 being statistically significant ($P < 0.01$). At this stage, however, the value for group 1 was still below normal ($P < 0.05$) while the results for group 2 and group 3 were not significantly below normal.

The mean percentage changes in whole-body potassium, weight, and lean body mass in the three groups after six weeks of treatment are shown in the diagram. The increase in whole-body potassium was statistically significant in each of the groups (group 1, $P < 0.005$; groups 2 and 3, $P < 0.05$). The increase in lean body mass was statistically significant in group 1 ($P < 0.005$) and group 2 ($P < 0.05$), while the mean increase in body weight was statistically significant in group 1 only ($P < 0.001$).

The patients in group 1 had serum potassium measured before treatment was started. In no case was this below 3·5 mEq/l.



Mean percentage increase in whole-body potassium, body weight, and lean body mass in three groups after six weeks of treatment.

TABLE I—*Details of Three Groups of Patients including Observed Whole-body Potassium (Ko) compared to Whole-body Potassium expected for Body Size (Ke) Before and After Six Weeks of Treatment*

No. of Patients	Age	Sex	Before Treatment				After Treatment		
			Weight (kg)	Weight as % of Ideal Body Weight	Ko (g)	Ke (g)	Weight as % of Ideal Body Weight	Ko (g)	Ke (g)
			Group 1						
1	18	M.	52·3	77	92	124	90	128	129
2	19	M.	65·8	83	121	154	91	138	158
3	19	M.	54·4	85	115	126	95	115	129
4	21	M.	62·0	93	131	131	96	143	141
5	27	M.	66·5	92	127	143	96	160	149
6	37	M.	64·4	89	125	139	100	146	147
7	46	M.	56·8	75	114	129	81	128	132
8	60	M.	67·1	96	96	118	103	108	126
9	19	F.	62·0	112	92	100	126	101	106
10	20	F.	58·7	104	86	101	115	106	110
11	34	F.	44·8	81	66	79	83	68	80
			Group 2						
12	25	M.	84·6	116	130	148	121	142	150
13	31	M.	60·4	76	127	149	84	143	153
14	31	M.	68·7	98	130	133	103	144	137
15	33	M.	64·1	81	142	149	85	150	151
16	38	F.	45·1	67	85	93	84	105	102
			Group 3						
17	34	M.	79·2	106	138	142	103	139	143
18	42	M.	71·0	96	168	151	102	177	155
19	45	M.	56·2	85	118	124	85	121	123
20	46	M.	74·1	99	146	144	97	150	145
21	49	M.	68·7	100	135	124	104	135	127
22	56	M.	80·6	106	127	135	106	132	140
23	57	M.	81·4	111	138	144	115	141	147
24	57	M.	77·4	103	140	147	107	156	149
25	63	M.	88·3	122	140	147	124	154	146
26	63	M.	69·7	104	124	126	104	129	127
27	66	M.	101·6	139	157	159	141	150	157
28	70	F.	50·9	116	66	88	120	66	86

TABLE II—*Mean Ratio (± S.D.) of Observed Whole-body Potassium to Whole-body Potassium expected for Body Size Before and After One and Six Weeks of Treatment in Three Groups*

Group	Before Treatment	After Treatment	
		One Week	Six Weeks
1	0·87 ± 0·072	0·90 ± 0·072	0·95 ± 0·067
2	0·92 ± 0·056	0·93 ± 0·057	0·99 ± 0·051
3	0·97 ± 0·089	0·99 ± 0·068	0·99 ± 0·082

Discussion

Previous investigations of the potassium status of uncontrolled non-ketoacidotic diabetics have involved the use of exchangeable potassium techniques (Aikawa *et al.*, 1953; Telfer, 1966).

Aikawa *et al.*, (1953) concluded that the presence or absence of potassium deficit could be correlated roughly with the state of diabetic control. Most of their patients, however, received potassium supplements during the course of the study and so it is impossible to assess the effect on body potassium of solely improving diabetic control. More recently, Telfer (1966) observed that exchangeable potassium was significantly lower in patients with diabetes (controlled or uncontrolled) than in non-diabetic subjects. Surprisingly, no significant difference in exchangeable potassium was observed between the patients in whom diabetes was controlled and those in whom it was uncontrolled. Serial measurements were not performed and the effect of improving diabetic control was not examined.

Our study provides information on the potassium status of patients with uncontrolled, non-ketoacidotic diabetes in a variety of situations. The first conclusion is that whole-body potassium is reduced in most uncontrolled diabetics who require insulin. Twelve of the 15 patients in this study who were treated with insulin showed a significant reduction in whole-body potassium (see table I) while only two of the 13 patients who were treated with oral hypoglycaemic agents showed a significant reduction in body potassium. This reduction was greatest in the newly-diagnosed diabetics who required insulin and smallest in the newly-diagnosed diabetics who were treated with oral hypoglycaemic agents (see table II). The established diabetics who were poorly controlled occupied an intermediate position. These observations suggest that potassium depletion in uncontrolled diabetes is a graded phenomenon. It seems that the greatest potassium depletion occurs in patients who have the most severe disturbances of carbohydrate metabolism while subjects with lesser degrees of metabolic upset are less severely affected. There was no significant difference in the duration of symptoms or in the initial blood sugar level between the three groups. On the other hand, the mean body weights of the patients in groups 1 and 2 were considerably below the expected value before treatment, while the patients in group 3 had a mean body weight which was slightly in excess of the ideal value.

Control of the diabetes had a striking effect on the potassium status of most of the patients. The mean percentage increase in whole-body potassium with treatment for the three groups was in all cases significant. The mean whole-body potassium for the newly-diagnosed diabetics needing insulin, however, still remained below normal after six weeks of treatment. This group initially had the lowest whole-body potassium, and if good diabetic control was maintained and these patients had been followed up for longer whole-body potassium might have increased further.

Tissue breakdown and thereby loss of lean body mass is an important factor in the potassium depletion of ketoacidotic diabetic patients, but cellular depletion of potassium may be more important (Danowski *et al.*, 1949). In our patients, who were less severely ill, it is likely that both of these processes were involved though their relative importance may not be the same. The patients in groups 1 and 2 increased their lean body mass significantly after treatment and it seems that loss of body tissue may have accounted for much of the reduction in potassium observed. On the other hand, in these two groups the ratio of whole-body potassium to lean body mass also increased significantly with treatment, suggesting that there may have been some degree of cellular potassium depletion also. In contrast, the small change in whole-body potassium in new diabetics treated with oral hypoglycaemic agents and the insignificant change with treatment in the ratio of whole-body potassium to lean body mass suggest that there was no cellular potassium depletion in this group. Our findings and those of others (Danowski *et al.*, 1949) suggest that cellular potassium depletion in uncontrolled diabetes varies according to the severity of the diabetes. It is minimal in overweight new diabetics, of some importance in underweight diabetics requiring insulin, and of major importance in ketoacidotic patients. It is hoped that further studies of potassium and nitrogen depletion in uncontrolled diabetics currently in progress in our department may yield more definitive information on this subject.

Diabetic ketoacidosis is associated with substantial potassium depletion. Balance studies performed over eight to 12 days of intensive treatment by Nabarro *et al.* (1952) showed a retention of potassium of 8 mEq-582 mEq (mean 263 mEq). During the six-week period of our study newly-diagnosed non-ketoacidotic patients requiring insulin retained from 0 to 900 mEq of potassium (mean 400 mEq). The group of established uncontrolled diabetics retained 200 mEq-500 mEq of potassium (mean 325 mEq). The maximum gain in whole-body potassium among the newly-diagnosed diabetics treated with oral hypoglycaemic agents was 400 mEq of potassium, and the mean increase in whole-body potassium for the group was 120 mEq (table III). Potassium replacement is essential in the treatment of diabetic ketoacidosis (Beigelman, 1971; Soler *et al.*, 1972) and the question arises as to whether potassium supplements should form part of the initial treatment of underweight non-ketoacidotic diabetics requiring insulin. Our patients were not acutely ill and were treated with small daily doses of insulin. Their only source of potassium was that contained in their diet. Though deficient in whole-body potassium serum potassium was within the normal range in the patients in group 1. There seems to be an even stronger indication for potassium supplements in the treatment of uncontrolled non-ketoacidotic diabetics when there is a predisposition towards hypokalaemia. There may be such a disposition in patients who, though not ketotic, are markedly dehydrated and require intravenous fluid replacement. Patients on diuretics might also fall into this category.

TABLE III—*Mean Potassium Retention found by Various Workers in Diabetic Patients after Balance Studies*

Reference	Clinical State	Duration of Study	Mean (Range) K^+ Retention (mEq)
Danowski *et al.*, 1949	Ketoacidotic	About 4 days	241 (84–458)
Nabarro *et al.*, 1952	Ketoacidotic	8–12 days	263 (8–582)
Present study ..	Group 1	42 days	400 (0–900)
	Group 2	42 days	325 (200–500)
	Group 3	42 days	120 (−175–400)

A further interesting speculation is related to the possible effect of correction of potassium depletion on recovery of islet-cell function. It is not unusual to find that once good control has been achieved in a new diabetic needing insulin the insulin requirements may fall considerably, and occasionally insulin may not be necessary for some months. As potassium depletion impairs insulin secretion and repletion of potassium stores may reverse this abnormality (Gorden, 1973) it is possible that the increase in whole-body potassium temporarily improves endogenous insulin secretion.

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References

Aikawa, J. K., Felts, J. H., and Harrell, G. T. (1953). *Journal of Clinical Investigation*, **32**, 15.
Biegelman, P. M. (1971). *Diabetes*, **20**, 490.
Danowski, T. S., *et al.* (1949). *Journal of Clinical Investigation*, **28**, 1.
Fletcher, R. F. (1962). *Clinical Science*, **22**, 333.
Gorden, P. (1973). *Diabetes*, **22**, 544.
Hughes, D., and Williams, R. E. (1967). *Clinical Science*, **32**, 495.
Nabarro, J. D. N., Spencer, A. G., and Stowers, J. M. (1952). *Quarterly Journal of Medicine*, **21**, 225.
Soler, N. G., *et al.* (1972). *Lancet*, **2**, 665.
Telfer, N. (1966). *Metabolism*, **15**, 502.