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Impaired Homeostatic Mechanism of Potassium Handling After Acute Oral Potassium Load in Diabetes Mellitus

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Chronic stable diabetic patients (n = 6) were compared with healthy control subjects (n = 5) after acute oral intake of 50 mEq of potassium chloride (KCl) to investigate for possible derangements of homeostatic responses for acute term (3 hrs) to acute potassium load. Plasma renin activity (PRA), plasma aldosterone (PA), and transtubular potassium concentration gradient (TTKG) known as a useful semiquantative index of distal nephron potassium secretion were measured. All the baseline parameters were comparable between diabetic and non-diabetic subjects except for significantly reduced creatinine clearance in diabetics (mean ± SEM, 105 ± 4 vs. 85 ± 5 ml/min, p<0.05). Following acute oral KCl load, the peak increases of serum potassium changes from basal levels were noted at 2 hours in both groups, but were higher in diabetic subjects (mean ± SEM, 0.42 ± 0.06 vs. 0.62 ± 0.09 mEq/L). Also, 4 out of 6 diabetic subjects but none of the control subjects at 2 hours after oral KCl load became hyperkalemic (>5.0 mEq/L). PRA did not show any significant changes, whereas PA was increased simultaneously with increments in serum potassium in both groups, with blunted increases in the diabetics. Hower, TTKG was increased prominently in control subjects (8.18 from 4.98), but only slightly in diabetic subjects (4.55 from 4.18), with statistical difference between the two groups (p<0.01). These evidences led us to believe that diabetic patients, especially with renal insufficiency even with a mild degree and /or with basal hyperkalemia, should be given potassium administration carefully to avoid unexpected hyperkalemia. The impaired renal mechanism related to lack of aldosterone as well as distal tubular unresponsiveness to aldosterone has a role, at least partly, in inducing unexpected hyperkalemia to acute oral potassium load in diabetes mellitus, but further studies including a more large scale study are required to investigate the contributions of extrarenal mechanism, i.e., transcellular shifts of potassium related to insulin, catecholamines or both.

Key Words: *Potassium, Homeostasis, Transtubular Potassium Concentration Gradient, Renal Insufficiency, Diabetes Mellitus*

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INTRODUCTION

Diabetes Mellitus more than any other diseases, in the absence of advanced nephron mass reduction (GFR >20 ml/min), has been well known for an increased risk of hyperkalemia. This abnormality in diabetic

Patients atients is mostly attributed to impaired homeostatic mechanisms of potassium handling of either external balance of potassium by impairing renal excretion due to the underlying common problem of hyporeninemic hypoaldosteronism (DeLeiva et al., 1976; DeFronzo, 1980; Perez et al., 1977; Schambergam et al., 1972) or internal balance of it by interfering with transcellular shifting due to insulin deficiency, or acidosis, or hyperglycemia-induced hyperosmolality, and autonomic disturbances (DeLeiva et al., 1976; Epstein et al., 1983). Although, so far, frequent reports of the development of hyperkalemia in diabetic patients accompanied by these underlying disorders have been noticed after many medications, such as ACE inhibitors, some beta blockers, nonsteroidal anti-inflammatory agents, and potassium-sparing diuretics (Garella et al., 1984; Smoller et al., 1988; Walker et al., 1972), there is a paucity of studies regarding potassium handling in diabetic patients following oral potassium load except for a few reports (Perez et al., 1977; Smoller et al., 1988). Therefore, in this present study, we examined the incidence of hyperkalemia as well as renal potassium handling and changes of renin-aldosterone axis in response to oral potassium loading in a group of diabetic patients without overt clinical or laboratory findings of specific underlying causes of derangement of potassium homeostasis, such as hypoaldosteronism, but with a mild to moderate degree of renal insufficiency (creatinine clearance > 60 ml/min). As a diagnostic tool to evaluate potassium handling by the kidneys during this present study, a recently devised semiquantative index of the activity of the potassium secretory process in the cortical distal nephron known as the transtubular potassium concentration gradient (TTKG) was measured (Ethier et al., 1990).

SUBJECTS AND METHODS

Subjects. Six men of chronic stable diabetes mellitus (type 2, but insulin required) with mild to modest renal insufficiency (creatinine clearance > 60 ml/min), and five age, sex and body weight matched healthy volunteer men as the control group were evaluated (table 1). All diabetic patients were clinically stable before the study. Patients taking medications known to interfere with potassium homeostasis except once daily intermediate insulin injections were excluded. Duration of diabetes was 5.3 ± 0.8 years (range, 2.2 to 9 years). No discernible diabetic complication of autonomic neuropathy was found in any diabetic patient. All patients were adequately controlled in fasting blood sugars (range, 85 to 126 mg/dl) with normal range of hemoglobin Alc levels. Written informed consent was obtained from each study subject.

Study design. Diabetic subjects were evaluated as inpatients with regular uniform salt and potassium diet, and control subjects were put on same hospital foods with careful instruction of no additional food intake for 3 to 5 days before the study.

On the day of the oral potassium loading test, breakfast and insulin were withheld, and supine positions through studies except to void were kept. After insertion of indwelling polystylene catheter in an antecubital vein early morning, two one hour baseline urine samples for potassium, sodium and osmolality, and two baseline blood samples for potassium, sodium, creatinine, plasma renin activity (PRA), plasma aldosterone concentration (PA), and osmolality were obtained. Following baseline urine and blood collection, 50 mEq of KCl dissolved in 360 ml of diet-cola was administered orally to the study subjects, and then, urine collections were performed for 2 hours and blood specimens at 2 and 3 hours, respectively. Blood samples were drawn without tourniquet or fist-clenching and centrifuged at 4°C for 10 minutes and plasmas were stored at −20°C. Sodium and potassi-

tomated multiple analysis system using ion selective tomated multijple analysis system using ion selective electrode and other chemical procedures by automated bichromatic analysis system (Hitachi 736-20). Osmolality was measured by freezing point depression. PRA and PA were estimated by standard radioimmunoassay (kits from Abbott laboratory). Just before and 2 hours after oral KCl load, transtubular potassium concentration gradient (TTKG) was calculated by 1-hour urine collection and blood sample at the end of each urine collection using the formula: TTKG = [K] of urine/(urine osm./blood osm.)/[K] of blood (Ethier et al., 1990). Statistical analysis of the data was performed with the paired or unpaired Student's *t* test as appropriate, and p value less than 0.05 was considered statistically significant. Results are expressed as mean ± SEM.

RESULTS

Baseline characteristics of diabetic and control subjects (I) and (II) (table 1 and 2).

Between the patients and control subjects, there were no significant differences of mean value ± SEM in age and body weight, serum electrolytes and serum osmolality as well as urinary sodium (mEq/L) and potassium excretion (μEq/min) before oral KCl load. Ranges of serum potassium were from 4.2 to 4.8 mEq/L in diabetics and 4.3 to 4.6 mEq/L in controls.

Table 1. Baseline characteristics in diabetic and control subjects (I)

	Age	Wt	Serum Osm.	Serum K	Serum Na	Ccr
	(yr)	(kg)	(mOsm/kg water)	(mEq/L)	(mEq/L)	(ml/min)
Diabetics (n=6)	51±2	68±4	294±4	4.48±0.13	137±1	85±5
Controls (n=5)	48±4	65±6	290±3	4.50±0.05	139±1	105±4
p value	NS	NS	NS	NS	NS	<0.05

Osm., osmolality; K, potassium; Na, sodium; Ccr, creatinine clearance

Table 2. Baseline characteristics in diabetic and control subjects (II)

	Ccr	PRA	PA	Urine Na	Urine K•V	TTKG
	(ml/min)	(ng/ml/hr)	(pg/ml)	(mEq/L)	(μEq/min)	
Diabetics (n=6)	85±5	1.13±0.08	87±9	112±24	13±5	4.2±0.5
Controls (=5)	105±4	1.26±0.17	93±3	105±32	14±5	5.0±0.2
p value	<0.05	NS	NS	NS	NS	NS

Ccr, creatinine clearance; PRA, plasma renin activity; PA, plasma aldosterone: Na, sodium
Urine K•V, urinary potassium excretion rate; TTKG, transtubular potassium gradient

Mean values of PRA and PA as well as baseline TTKG were slightly lower in diabetics compared to controls, but without significance (PRA: diabetics, 1.13±0.08; controls, 1.26±0.17 ng/ml/hr; PA: diabetics, 87±9; controls, 93±3 pg/ml). Among these baseline parameters, the only statistically significant diference between the two groups was a modestly lower mean creatinine clearance in diabetics compared to controls (85±5 ml/min vs. 105±4 ml/min, $p < 0.05$).

Changes in mean levels of serum potassium (Fig. 1) and in individual serum potassium value of both groups (Fig. 2).

In both groups, there were significant increases in potassium levels from baseline values at 2 and 3hr after administration of 50 mEq of KCl load, respectively, but to a higher degree in diabetics and the values reached a peak at 2 hr (at 2hr: diabetics, 0.62±0.09, $p < 0.001$; controls, 0.42±0.06, $p < 0.001$; at 3hr: diabetics, 0.37±0.13, $p < 0.01$; controls, 0.1±0.11, $p < 0.05$). However, there were no significant differences in the hourly mean values of potassium level changes at 2 and 3 hr, respectively, between diabetics and controls. The analysis of peak potassium levels at 2hr after acute oral KCl load in individual control and diabetic subjects showed that none of the controls became hyperkalemic (serum potassium >5.0 mEq/L), in contrast, four out of six diabetic patients had peak levels greater than 5.0 mEq/L and tended to remain hypekalemic in three of these four patients up to 3 hr after acute oral KCl load.

Changes in mean values of plasma renin activity (PRA) and plasma aldosterone concentration (PA) (Table 3).

At 2 hr following oral KCl load, there was no change of PRA in controls and a slight but insignificant decrease of it in diabetics from baseline values of PRA. Along with significant increments in serum potassium levels in both groups (controls, 0.42±0.06; diabetics, 0.62±0.09 mEq/L; $p < 0.001$ in both), similarly PA levels in both groups increased significantly from baseline values, but to a relatively lesser degree in diabetics in view of greater serum potassium changes in diabetics than in controls (controls, 146±8 from 93±3, $p < 0.001$; diabetics, 122±13 from 87±9 pg/ml, $p < 0.05$). There was no statistically significant difference in PA between the diabetics and controls at 2hr.

Changes in urinary potassium excretion (Fig. 3) and TTKG (Table 3).

As described before (Table 2), though there was no difference in baseline urinary potassium excretion (Uk•V) and TTKG between diabetics and controls, Uk•V

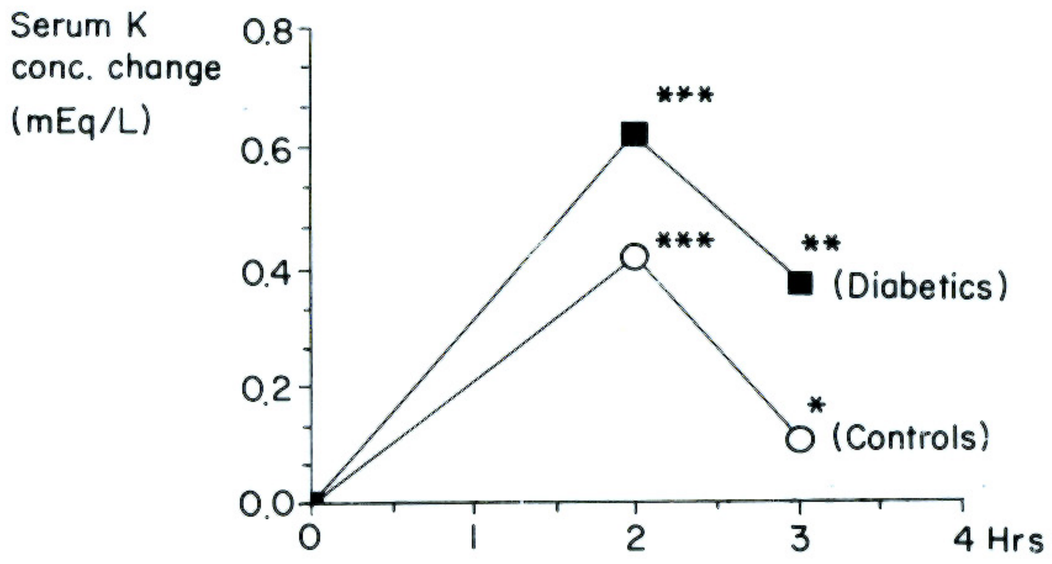
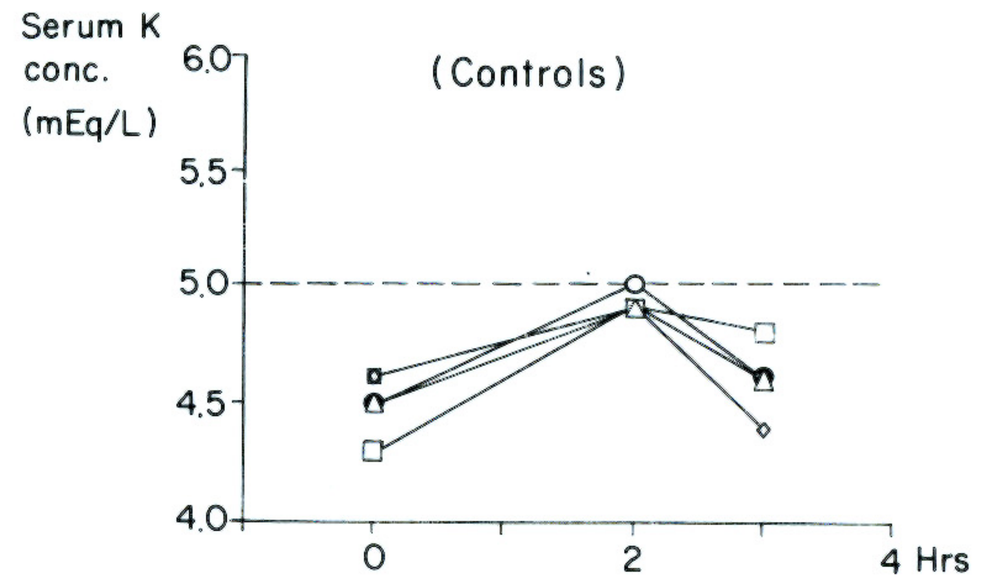


Fig. 1. Changes in mean values of serum potassium concentration on time course after oral potassium loading of 50mEq KCl to control (n=5) and diabetic groups (n=6). (*p < 0.05, **p < 0.01, ***p < 0.001 from baseline)



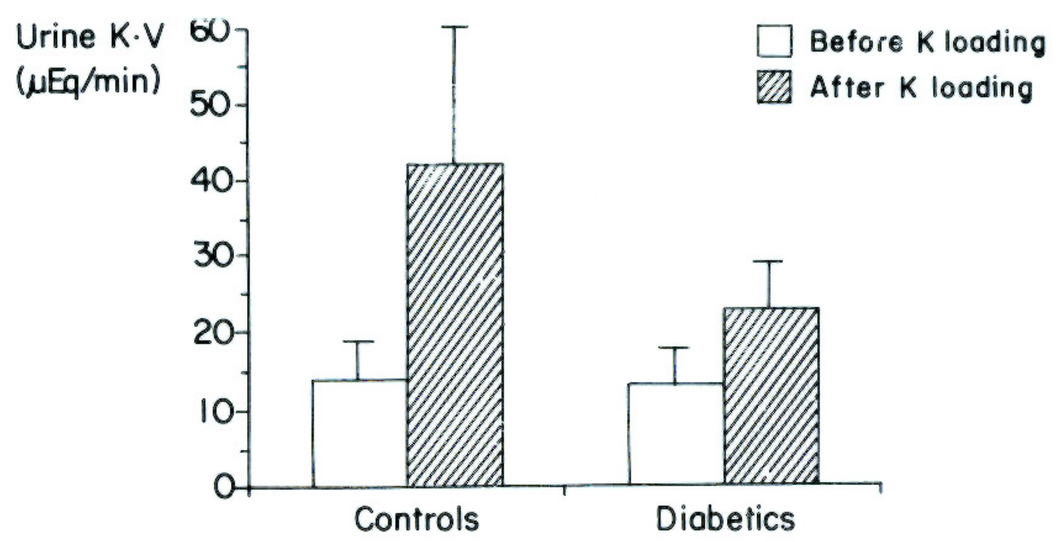


Fig. 3. Changes in urinary potassium excretion rate before and after oral potassium loading of 50 mEq KCl to control and diabetic subjects.
(Urine K•V, urinary potassium excretion rate)

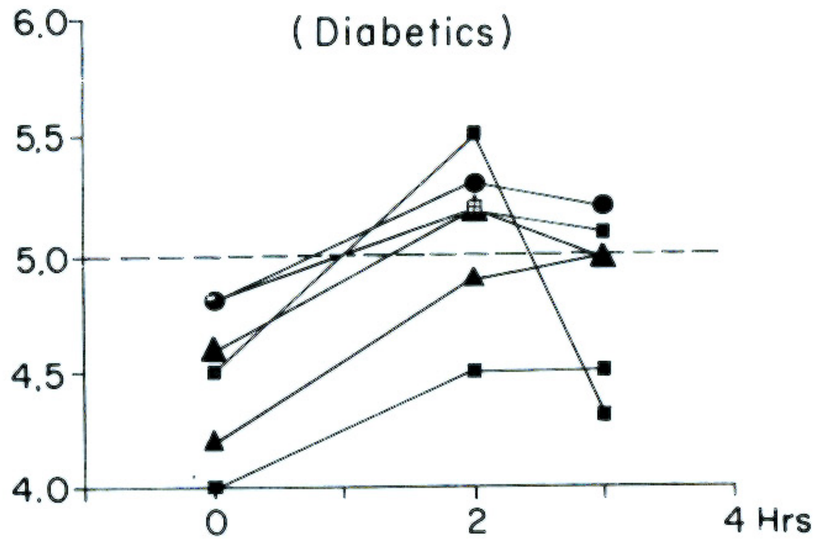


Fig. 2. Changes in serum potassium concentrations on time course after oral potassium loading of 50 mEq KCl to individual control and diabetic subjects. Dashed lines denote upper normal limit of serum potassium level, 5 mEq/L.

Table 3. Changes in mean values of serum potassium, plasma renin activity (PRA) and aldosterone (PA), urinary potassium excretion rate (Urine K•V), and TTKG before and after 2 hr of oral potassium loading (50 mEq of KCl)

	Controls		Diabetics	
	Baseline	2hrs	Baseline	2hrs
Serum K (mEq/L)	4.5±0.05	4.92±0.02***	4.48±0.13	5.10±0.14***
Serum K changes		0.42±0.06***		0.62±0.09***
PRA (ng/ml/hr)	1.26±0.17	1.26±0.2	1.13±0.08	0.98±0.1
PA (pg/ml)	93±3	146±8***	87±9	122±13*
Urine K•V (μEq/min)	14±5	42±18	13±5	23±6
TTKG	5.0±0.2	8.2±1.0*	4.2±0.5	4.6±0.3^^

^^P<0.01 from controls (2hrs), *p<0.05 from baseline, ***p<0.001 from baseline

K, potassium; PRA, plasma renin activity; PA, plasma aldosterone
Urine K•V, urinary potassium excretion rate; TTKG, transtubular potassium gradient

for 2 hrs after KCl load was almost two times higher in controls than in diabetics, but with no significance statistically (diabetics, 23±6; controls 42±18 μEq/min). At 2 hr following oral KCl load, TTKG increased significantly from 5.0±0.2 to 8.2±1.0 in controls ($p < 0.05$), in contrast, from 4.2±0.5 to 4.6±0.3 in diabetics showing almost no change from baseline value. There was a statistically significant difference between controls and diabetics at 2 hr after acute KCl load (8.2±1.0 vs 4.6±0.3, $p < 0.01$).

Correlation of changes in mean values of plasma aldosterone concentraions (PA) and TTKG (Fig. 4).

At 2 hr of oral KCl load, increase of PA was accompanied by increment of TTKG, an indirect index of the potassium secretory process in cortical distal nephron (Ethier et al., 1990), in controls. However, there was a very great discrepancy between the changes of PA and that of TTKG, namely, falling behind the degree of increase of PA in that of TTKG in diabetics.

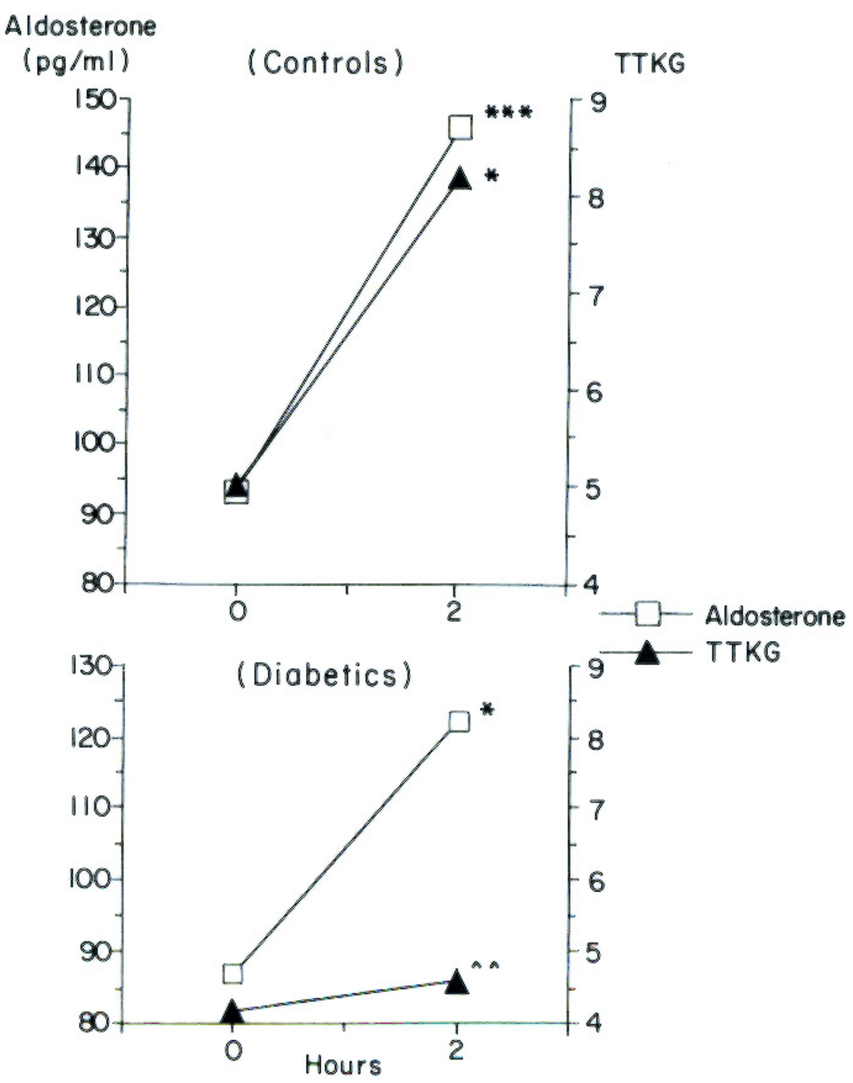


Fig. 4. Changes in serum aldosterone concentrations and TTKG before and after oral potassium loading of 50 mEq KCl to control and diabetic subjects. (*$p < 0.05$, ***$p < 0.001$ from baseline of each group, ^^$p < 0.01$ in comparison with controls) (TTKG, transtubular potassium gradient)

DISCUSSION

The acute potassium tolerances in previous studies have been tried in chronic renal failure (Gonick et al., 1971; Perez et al., 1983; Kahn et al., 1978) or diabetes mellitus with a modest degree of renal insufficiency (Perez et al., 1977; Smoller et al., 1988) to look for any abnormal responses in renal and extrarenal balances of potassium homeostasis which resulted in conflicting data. Blunted urinary potassium excretion and no difference in peak blood potassium levels following an oral potassium load between chronic renal failure (Gonick et al., 1971; Perez et al., 1983), or diabetic patients (Smoller et al., 1988) and controls were observed, supporting a major role for an extrarenal mechanism of potassium in these patients. On the other hand, significant increases in blood potassium levels and similar urinary potassium excretion in patients with chronic renal failure compared to those of controls were seen in the study of Kahn et al., 1978. In the present study, we evaluted potassium homeostasis, particularly renal handlings and the incidence of hyperkalemia after an acute oral potassium load in a group of chronic stable diabetic patients without a known clinical or laboratory history of hyporeninemic hypoaldosteronism, but with modestly reduced creatinine clearance more than 60 ml/min. For these investigations of potassium homeostasis during acute term for 3 hrs after acute oral KCl load, we studied the alteration of renin-aldosterone axis with measurements of the acute responses of plasma renin activity (PRA) and plasma aldosterone (PA), and calculation of TTKG suggested recently as a new vivo index of distal cortical potassium secretory system upon adequate distal sodium delivery (Ethier et al., 1990; West et al., 1986) not used in the previous studies.

We observed a greater increase in mean potassium levels in diabetics compared to those of controls (0.62±0.09 vs. 0.42±0.06 mEq/L at 2hr; 0.37±0.13 vs. 0.1±0.11 mEq/L at 3 hr, Fig. 1 and Table 3) as well as development of hyperkalemia greater than 5.0 mEq/L in the majority of diabetics (4 out of 6, Fig. 2) with reduced renal potassium excretion in view of lower excretion urinary potassium excretion shown as Uk·V (Table 3 and Fig. 3), and subnormal increase of TTKG (Table 3 and Fig. 4) on unrestricted diet compared to those of controls.

In the changes of PRA and PA to oral KCl load, our findings confirm that aldosterone responds promptly to even minor changes in blood potassium concentration as a positive feedback (Himathongkam et al., 1975). Nevertheless, blunted increase of aldosterone response to that of potassium in diabetics in comparison to controls was noticed in this study, a finding that provides a partial explanation for the above observed reduced renal potassium excretion and lesser increase of TTKG. Similar blunted aldosterone responses in diabetic subjects have been observed in previous

studies (Hayashi et al., 1984; Nicolis et al., 1981). Primary adrenal defect in aldosterone biosynthesis or release related to insulin lack in these diabetics could directly effect aldosterone secretion by reducing cellular influx of potassium at zona glomerulosa (Andres et al., 1962; DeFronzo et al., 1978), a suggestion known as one of the pathogenetic mechanisms of hyporeninemic hypoaldosteronism observed in diabetic patients with high prevalence (DeFronzo, 1980). PRA levels with increments of serum potassium after acute oral KCl load did not increase or even decreased in diabetics, and these results were consistent with the facts of suppression of renin secretion in resulting hyperkalemia with potassium intake (Brunner et al., 1970; Schneider et al., 1972).

The reasons for the decrease in urinary potassium in our chronic stable diabetic patients with no clinical evidence of total body depletion, or with lack of gastroparesis resulting in impaired gastrointestinal absorption of KCl load would be as follows. The possibility that blunted increment of aldosterone in diabetics compared to controls played a partial role in the impairment of urinary potassium excretion in acute term despite the well-known time delay intevening between the administration of aldosterone and the onset of a kaliuretic response (Ross et al., 1959). Also, the only significant variable between controls and diabetics in this study, the mild decrease in creatinine clearance with possible consideration of tubulo-interstitial disease in the diabetic group might work in concert with the reduced excretion of renal potassium due to the tubular resistance of distal cortical potassium secretory action of aldosterone in view of the discrepancy between increments of plasma aldosterone and TTKG. Though we did not measure the insulin levels in this study, it is also conceivable that residual exogenous or endogenous insulin activity known as decreasing urinary potassium (DeFronzo et al., 1975), albeit that the last insulin injection was 24 hrs before this study, and diabetes mellitus per se with relative deficiency of renal Na-K ATPase (Resh, 1983) might be associated with a defect in renal potassium excretion.

One of the reasons for the results of the greater increase in mean potassium levels of diabetics in our study could be the reduced renal handling of potassium excretion with the above described pathogenetic mechanisms. However, in this study, we did not investigate the degree of extrarenal potassium handling of transcellular potassium shifting (Perez et al., 1983; Smoller et al., 1988). Therefore, the difference between controls and diabetics in the degree of contribution of the amount of potassium translocation related perhaps to abnormal regulation by insulin or catecholamine, acidosis, or other specific transcellular transport defects (Bia et al., 1981; Kahn et al., 1978; Mitch et al., 1982) can not be speculated at present. Also, the discrepancy in the high incidence of hyperkalemia, more than 5 mEq/L in this study (67%) compared to that of previous similar study (50%) (Smoller et al., 1988), would be partly explained by the higher baseline blood potassium levels in the former (4.48 ± 0.13 vs. 4.19 ± 0.23 mEq/L).

In summary, since the present data showed that four out of six diabetic patients with a mild to moderate degree of renal insufficiency developed hyperkalemia for acute term following oral intake of 50 mEq of KCl, we should be cautious of supplying potassium to avoid unexpected hyperkalemia in diabetics in applicable situations despite the absence of advanced nephron mass reduction, especially, on baseline upper normal or above normal range of potassium level, or in any other accompanied clinical status interfering with renal and / or extrarenal mechanism of potassium homeostasis. In this study, the pathogenesis of this high incidence of hyperkalemia in diabetics after acute oral potassium load may be related to the coexistence of impaired secretion or biosynthesis of aldosterone and the distal tubular resistence at the sites of aldosterone action. However, further studies including a more large scale study are necessary to clarify the contributions of extrarenal mechanisms, such as transcellular shifting of potassium for hyperkalemia in diabetics.

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