Fractional excretion of sodium (FENa): A paraphernalia in incipient nephropathy versus overt nephropathy in Type I Diabetes Mellitus

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Abstract

An estimated 40% of patients diagnosed with Type I diabetes and 5 - 15% of patients with Type II diabetes eventually develop ESRD and diabetes has become the leading cause (44%) of end-stage renal disease in India. There is substantial evidence that early treatment will delay or prevent the onset of diabetic nephropathy, or diabetic kidney disease. In its earliest stage Diabetic nephropathy manifests with low levels of albumin (microalbuminuria) in the urine. This often is referred to as incipient nephropathy. With the progress of disease, urine albumin levels will increase until overt nephropathy (defined as more than 300 mg per 24 hours or more than 200 mcg per minute). The present hospital based observational descriptive study was conducted in Siddhartha Medical College, Vijayawada and Bhaskar Medical College & General Hospital, Moinabad from June 2014 to February 2016. 94 type I diabetes patients on Insulin therapy for 5 years as subjects along with 30 normal people as controls were enrolled in the study. T1D-Overt exhibit significantly increased FENa compared with T1D-Incipient, T1D-normal and Control subjects. Our study illustrates the importance of tubule-glomerular feedback as a major pathway of renal sodium handling in T1D-Overt as well as the important role of ambient glucose levels in kidney functioning. Future studies should determine the clinical role of blocking proximal tubular sodium reabsorption with SGLT2 inhibitors, because these agents have the potential to reduce hyper filtration and blood pressure predominantly in T1D-H, thereby protecting against the initiation and progression of diabetic nephropathy. Early identification of incipient nephropathy in Type I Diabetics with FENa may substantially assist in the early management and prevention of delaying end stage renal disease in Diabetics thus reducing morbidity.

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-6377.2016.00027.7

Introduction

An estimated 40% of patients diagnosed with Type I diabetes and 5 - 15% of patients with Type II diabetes eventually develop ESRD, although the incidence is substantially higher in certain ethnic groups.[(1)] Because of the large prevalence of diabetes in the general population, diabetes has become the leading cause (44%) of end-stage renal disease in India.[(2)] There is substantial evidence that early treatment will delay or prevent the onset of diabetic nephropathy, or diabetic kidney disease. In its earliest stage Diabetic nephropathy manifests with low levels of albumin (microalbuminuria) in the urine. This often is referred to as incipient nephropathy.[(3)] With the progress of disease, urine albumin levels will increase until overt nephropathy (defined as more than 300 mg per 24 hours or more than 200 mcg per minute). Overt nephropathy often occurs in conjunction with a hyperfiltrative period, in which the creatinine clearance and glomerular filtration rate are high. The elevated clearance is deceptive, however, because it is followed by a gradual decrease in glomerular filtration rate that ultimately leads to kidney failure.[(4)] Microalbuminuria rarely develops in patients with Type I diabetes during the first few years of the disease. For this reason, the American Diabetes Association (ADA) recommends that screening begin only after the patient has had Type I diabetes for five years.[(5)] Because of the long duration of abnormal glucose metabolism that often precedes diagnosis, patients with Type II diabetes are more likely to have microalbuminuria (or overt nephropathy) at diagnosis. Thus, patients with Type II diabetes should be screened at the time of diagnosis for the presence of microalbuminuria.[(6)] The ADA guidelines suggest that two of three tests for microalbuminuria need to be positive in a three- to six-month period to diagnose diabetic nephropathy correctly.[(7)] Testing Patients with overt nephropathy do not need screening for microalbuminuria because the level of protein in the urine is high enough to be detected easily on routine

urinalysis. Changes in renal hemodynamic function characterized by glomerular hyperfiltration may play a role and have been primarily attributed to activation of neurohormonal pathways such as the renin-angiotensin-aldosterone system (RAAS).[8,9] Hyperfiltration is common, affecting about 50% of Type I-Diabetes patients, defined by a glomerular filtration rate (GFR) ≥135 mL/min/1.73 m^2[10]. The fractional excretion of sodium (FENa) measures the percent of filtered sodium that is excreted in the urine. FENa depends on sodium intake, effective intravascular volume, GFR, and intact tubular reabsorptive mechanisms.[11] This calculation is widely used to help differentiate prerenal disease (decreased renal perfusion) from acute tubular necrosis (ATN) as the cause of acute kidney injury (AKI, formerly called acute renal failure). Patients with uncomplicated Type I-Diabetes exhibit lower FE_{Na} under euglycemic conditions. Increased FE_{Na} is seen in Type I Diabetes-Hyperfilterative but not Type I-Diabetes-Normal suggests that the mechanisms responsible for increased sodium reabsorption leading to hyperfiltration can be saturated.[12] The aim of the current study was therefore to compare the fractional sodium excretion (FE_{Na}) in incipient nephropathy versus overt nephropathy and DM type I patients with normal kidney functions and healthy control (HC) subjects.

Materials and Methods

The present hospital based observational descriptive study was conducted in Siddhartha Medical College, Vijayawada and Bhaskar Medical College & General Hospital, Moinabad from June 2014 to February 2016. 94 type I diabetes patients on Insulin therapy for 5 years as subjects along with 30 normal people as controls were enrolled in the study. Patients with Incipient diabetic nephropathy (defined as persistent urinary albumin excretion rate [AER] of 20 to 200 micrograms/min) and overt nephropathy were identified. Twenty-four-hour urine collections classified all patients correctly.[13] Patients were classified into four groups, AER in type I diabetics with normal AER (n = 34), incipient (n = 28) and clinical or overt (defined as persistent AER greater than 200 micrograms/min) nephropathy (n = 32), and in healthy controls (n = 30). 24 hour urine samples were collected and blood samples collected at the end. Screening for microalbuminuria was done using turbidimetry immunoassay by measurement of antigen-antibody reaction by the end point method, urine and serum creatinine was estimated by Jaffe's method, fasting and postprandial blood glucose levels were estimated by GOD-POD method after 8 hours of fasting and 2hours after meal respectively. All were measured on chem5 (Transasia). Serum and urine sodium was measured using Ion selective electrode method. FENa was determined using formula.[14]

$$\text{FENa Percent} = \frac{\text{UNa} \times \text{SCr}}{\text{SNa} \times \text{UCr}} \times 100$$

Data are presented as mean±SD. ANOVA with post hoc Tukey tests was used to assess for between-group differences, a paired student t test was used, and $P < 0.05$ was considered significant. Linear regression analysis was performed to determine the relationship between albumin and change in FENa. All statistical analyses were performed using IBM SPSS Statistics v22.0. Ethical committee approval from both medical colleges was taken prior to the study and informed consent was taken from the subjects before enrolment into the study.

Results

Participants were healthy without any co-morbid conditions, with urinary sodium reflective of adherence to the prescribed diet. All participants were normotensive.

Sex: The male to female ratio was equal in controls, males dominated in Type I diabetes-Normal group with P>0.05. Male to female ratio was near equal with slight female preponderance in Type I diabetes-incipient without any statistical significance P>0.05. Females predominated in overt nephropathy with P<0.05. (Table1, Fig. 2)

Age: majority of the controls and Type I Diabetes-Normal were in the age group of 30 to 50 years, whereas both the incipient and overt nephropathy showed a trend towards older age group with P < 0.001.(Table 1, Fig. 1)

Blood glucose levels & HBA1C: The three diabetes groups exhibited similar diabetes duration and HbA1c and glucose levels were similar in T1D-N, T1D-incipient versus T1D-overt which showed slight increase in its mean values of fasting, post prandial and HBA1C with P<0.001. **(Table 1)**

Urine Microalbumin: The values in both control and Type I Diabetes-normal were less than 30 mg/day and their means were almost comparable with Type I Diabetes-normal being slightly more. Values in incipient nephropathy ranged between 30 to 300 mg/day with mean of 167.96 mg/day and mean in overt nephropathy was 1681.96. (**Table 1)**

Serum Creatinine: Means of controls, T1D-normal and T1D-incipient were within normal range, whereas the mean of overt nephropathy was significantly higher with P<0.001. **(Table 1, Fig. 4)**

Urine Creatinine: There was significant difference (P<0.001) between means of Overt nephropathy versus incipient, normal T1D and controls. **(Table 1, Fig. 3)**

Serum Sodium: There was no significant difference (P>0.001) between any group and all means were within normal range. **(Table 1, Fig. 3)**

Urine Sodium: There was no significant difference (P>0.001) between means of controls, T1D-normal and T1D-incipient, but there was significant difference between incipient and overt nephropathy with P<0.001. **(Table 1, Fig. 3)**

FENa: there was no significant difference (P>0.001) between means of controls, T1D-normal and T1D-incipient, but there was statistically significant difference between incipient and overt nephropathy with P<0.001. **(Table 1, Fig. 4)**

Table 1: comparison of parameters between different groups

Parameter	Controls	T1D-normal	T1D-incipient	T1D-overt	P value
Sample size	30	34	28	32	
Males	15	21	13	14	>0.001
Females	15	13	15	18	<0.001
Age < 30 years	2	6	2	0	>0.001
Age 30-50 years	24	25	16	18	>0.001
Age > 50 years	4	3	10	14	<0.001
FBS(mg/dl)	71.23±13.17	111.33±12.7	108.24±15.24	122.02±13.11	<0.001
PLBS(mg/dl)	124.12±14.14	147.27±13.22	144.89±17.17	157.91±15.48	<0.001
HBA1C	5.81±0.77	6.91±0.81	6.97±1.17	7.75±1.11	<0.001
Microalbumin (mg/day)	12.23±7.42	13.26±3.88	167.96±77.66	1681.96±824.42	<0.05
Serum Creatinine(mg/dl)	0.83±0.17	1.01±0.14	1.21±0.15	1.91±0.14	<0.001
Urine Creatinine(mg/dl)	58.73±1.89	59.47±2.07	58.42±2.15	50.87±6.05	<0.001
Serum Sodium(mmol/l)	138.70±3.39	139.26±3.50	138.25±3.38	135.84±3.24	>0.001
Urine Sodium(mmol/l)	67.90±7.94	69.85±7.96	70.32±7.90	80.06±7.11	<0.001
FENa	0.69±0.17	0.85±0.17	1.05±0.16	2.25±0.17	<0.05

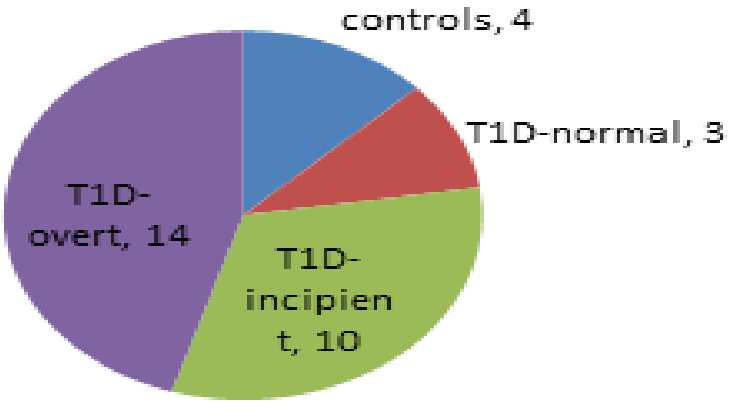

Fig. 1: >50 years age distribution in various groups

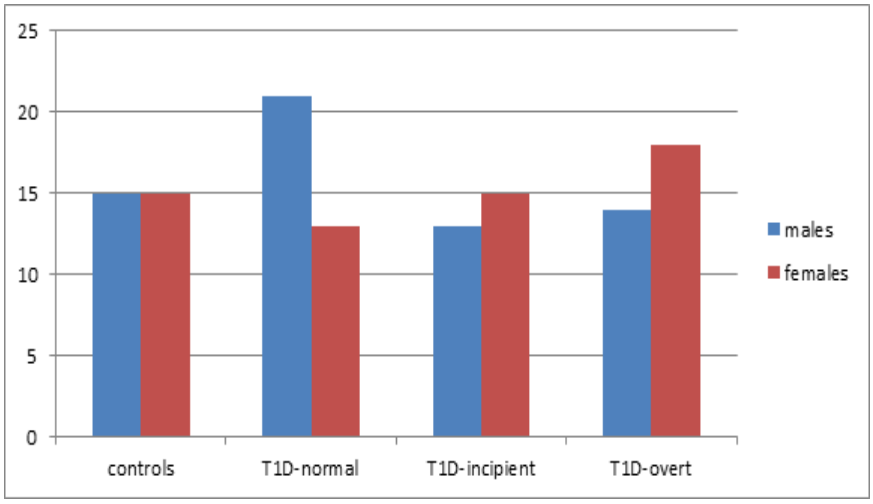

Fig. 2: Sex distribution in groups

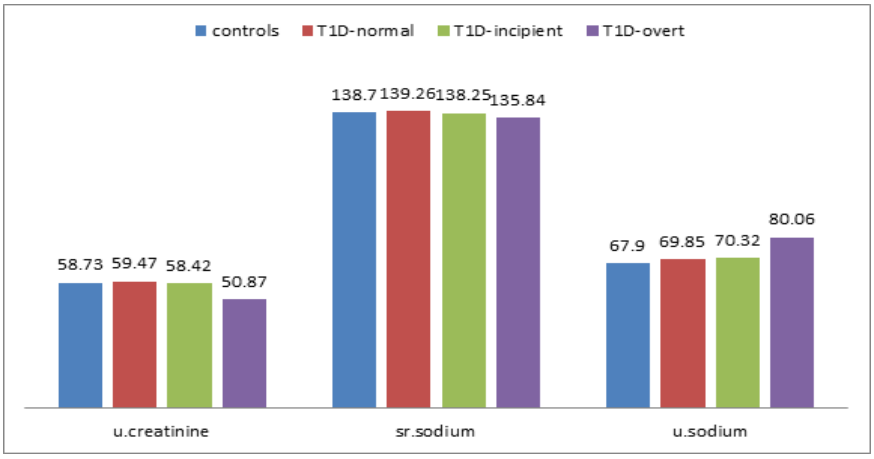

Fig. 3: Urine creatinine and sodium and serum sodium distribution in groups

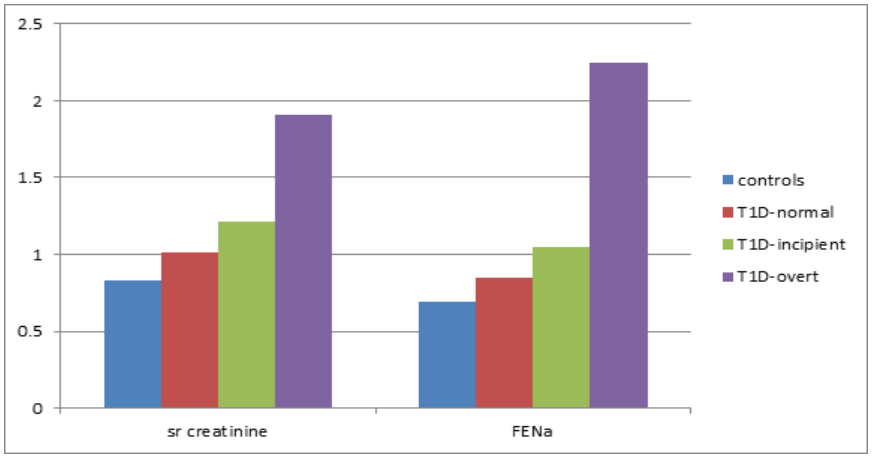

Fig. 4: Serum creatinine and FENa in groups

Discussion

The first novel observation in this study was that T1D-Overt had higher FENa levels compared with T1D-Normal, T1D-Incipient and Control subjects. The decrease in sodium delivery to the distal tubule could lead to renal hyper-filtration through reduced sodium transport by macula densa cells, causing less adenosine to be generated, leading to reduced tubule-glomerular feedback and afferent vasodilatation in incipient nephropathy which precedes a stage of hyper-filtration.[15] In overt Nephropathy as a result of hypo-filtration as well as decreased sodium absorption in

exchange for protons in proximal convoluted tubule there is increased excretion of sodium. This difference in FENa between T1D-Incipient and T1D-Overt is, however, expected under steady-state conditions because the two groups exhibited similar salt intake, serum sodium levels, and comparable 24-h sodium excretion. Therefore, the higher GFR in T1D-Incipient must be associated with a level of higher sodium re-absorption and lower FENa to maintain total body sodium equilibrium. It is apparent that conclusions about segmental tubular sodium re-absorption in intact human organs are limited, but future human mechanistic studies might consider the use of sodium/lithium clearance techniques to gain further insight. We observed an increase in FENa with T1D-Overt and minimal change in T1D-Incipient with no change in T1D-Normal. In addition, an increase in GFR under hyperglycemic conditions was only observed in T1D-Normal. This finding may seem counterintuitive because increased tubular delivery of glucose due to ambient hyperglycemia should increase SGLT2 function and result in increased proximal sodium reabsorption and further elevations in GFR.[16] Although our observation that FENa is lower in T1D-Incipient is consistent with up regulated SGLT2 activity, the increase in FENa during Overt Nephropathy suggests that other factors become important under these conditions. First, if proximal tubular sodium reabsorption was maximal in T1D-Incipient under euglycemic conditions, further delivery of glucose may result in increased glycosuria and subsequent higher FENa, as suggested by the larger but statistically non-significant glucosuric response in T1D-Incipient. Such a phenomenon has been suggested in studies involving healthy dogs, because the mechanisms responsible for diabetes-induced reductions in FENa are saturable.[17] A similar effect may occur in T1D-Overt patients under euglycemic conditions, leading to elevated FENa compared with Control and incipient groups.[18] Our study results support the theory that T1D-Overt exhibit a state of tubular sodium excess supporting the tubular hypothesis for hyper filtration and the increase in FENa suggests that mechanisms responsible for increased sodium reabsorption leading to hyper filtration can be saturated. We also observed that females were more prone for both incipient and overt nephropathy and age showed a positive risk factor in the development of nephropathy in Type I Diabetes.

Further studies are required for better understanding of the intricate relationship among glucose, FENa, and GFR and may aid in the development of more practical methods of identifying hyper filtration in patients with T1D. As 24-h sodium excretion was similar between the controls and T1D-normal and T1D-incipient groups and the patients were kept on a similar high-salt diet, based on the need to maintain salt balance, one would expect the higher GFR in T1D-Incipient to be associated with a higher fractional tubular sodium re-absorption. To better assess whether T1D-Incipient retain more sodium and thereby contributing to volume expansion and higher blood pressures, measures of total body water and sodium content should be measured in future studies. Short fall in the study was that Salt intake before the dietary control period was not measured as part of our study, and it is possible the T1D-Normal normally exhibited a lower sodium intake than that in the prescribed study diet. Given the effect of high salt intake on reducing GFR, T1D-Normal may only appear to "normofilter" during this experimental setting. Finally, although we have attributed changes in FENA to increased SGLT2 activation causing hyper filtration, we recognize that other mechanisms may also be operative such as primary proximal tubular cell hypertrophy due to ornithine decarboxylase, leading to increased primary sodium reabsorption via SGLT2 and sodium-hydrogen exchange.[19] We believe that it is unlikely that the filtered load of sodium made a significant contribution to differences in FENA: although serum sodium was higher in T1D-Incipient and T1D-Overt versus T1D-Normal and Control subjects, suggesting a greater filtered sodium load, FENa was only higher in T1D-Overt. This suggests that filtration status was a more important determinant of FENa rather than filtered sodium load.

Conclusion

T1D-Overt exhibit significantly increased FENa compared with T1D-Incipient, T1D-normal and Control subjects. Our study illustrates the importance of tubule-glomerular feedback as a major pathway of renal sodium handling in T1D-Overt as well as the important role of ambient glucose levels in kidney functioning. Future studies should determine the clinical role of blocking proximal tubular sodium reabsorption with SGLT2 inhibitors, because these agents have the potential to reduce hyper filtration and blood pressure predominantly in T1D-H, thereby protecting against the initiation and progression of diabetic nephropathy. Early identification of incipient nephropathy in Type I Diabetics with FENa may substantially assist in the early management and prevention of delaying end stage renal disease in Diabetics thus reducing morbidity.

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