Abstract

Aim: The aim of this study is to compare oral signs, symptoms and oral lesions type and prevalence, in end stage renal disease (ESRD) with non-end stage renal disease (NESRD) in diabetes mellitus (DM) patients. Methodology: Two groups of DM patients were studied, Group 1 includes 100 patients with ESRD, who were under hemodialysis therapy, and Group 2 includes 100 patients with NESRD whose serum creatinine level is <2.0 mg/dl. The DM status and other laboratory investigations were recorded, with the patients consent and thorough oral examination was performed and the findings were recorded. All the data were entered into Microsoft Excel sheets. Statistical analysis including Pearson’s correlation analysis, Chi-square test, and t-test were done using SPSS software SYSTAT version 7.0. Results: On thorough clinical examination, the prevalence of oral lesions was found to be higher in ESRD patients. The most common lesions such as saburral tongue ($P \leq 0.002$), petechiae/ecchymoses ($P \leq 0.000$), pale mucosa ($P \leq 0.000$), stomatitis medicamentosa ($P \leq 0.043$) fissured tongue, smooth tongue, candidiasis, dry and fissured lips, angular cheilitis, uremic stomatitis, signs such as uremic fetor ($P \leq 0.000$), xerostomia and symptoms like burning tongue, unpleasant taste are noted. Conclusion: The high prevalence of uremic fetor, saburral tongue, pale mucosa, and petechiae/ecchymoses in ESRD patient group can be considered as a possible sign of undiagnosed advanced stage of renal disease in other diabetic patients.

Key words: Diabetes mellitus, diabetic nephropathy, pale mucosa, saburral tongue, uremic fetor

Introduction

End stage renal disease (ESRD) is the final stage of chronic kidney disease (CKD), and ESRD usually results from a progressive and irreversible loss of renal function and is defined by a glomerular filtration rate of <15 ml/min. In CKD, the pre-ESRD is termed as non-end stage renal disease (NESRD) or nondialysis-dependent CKD.$^{[1]}$ In fact, diabetic nephropathy has become the major cause of ESRD.$^{[2]}$

The most common causes of ESRD were chronic hypertension, glomerulonephritis, polycystic kidney disease, renovascular disease, and diabetes mellitus (DM).$^{[1]}$ DM is a major health problem in today’s society as the number of patients with diabetes is growing continuously. As diabetic nephropathy progresses to ESRD and impose enormous medical, economic and social costs on both the patients and the health-care system, it deserves greater social concern. Hence, it is felt the need to identify the disease at an early stage based on the oral manifestation in NESRD-DM patients to avoid the complication and for suitable treatment. Based on the studies, done by de la Rosa García et al.$^{[3]}$ a study has been undertaken to detect the oral manifestation in already diagnosed ESRD-DM and NESRD-DM patient and to compare them in both the conditions.

Methodology

This study was conducted between June 2010 and May 2011 in the Department of Oral Medicine and Radiology of Ragas Dental College and Hospital, and Voluntary health services, Chennai, Tamil Nadu, India. Two hundred DM patients were screened for this study. In ESRD group, 100 DM patients who were undergoing hemodialysis [Figure 1] were included and in NESRD
group, 100 DM patients who were not under any dialysis with serum creatinine level ≤2.0 mg/dl were included. Patient in the age group of 12 years and above were included in both ESRD and NESRD groups, the only exclusion criteria for both ESRD and NESRD groups is patients with HIV infection. All the patients were examined [Figure 2] for the presence of intraoral lesions, signs and symptoms. Data were collected from individuals fulfilling the following criteria.

**Clinical criteria for diagnosis**

Saburral tongue [Figure 3] is identified when the patient had a yellowish-white plaque on tongue dorsum, which could not be scraped off by a blunt instrument. Slightly elongated filiform papillae were found.[3] Fissured tongue is characterized by grooves that vary in depth and were noted along the dorsal and lateral aspects of the tongue. Purpura [Figure 4] is the appearance of red or purple discolorations on the skin that do not blanch on applying pressure. They were caused by bleeding underneath the skin/mucosa. Purpura measure 0.3–1 cm (3–10 mm), whereas petechiae measure <3 mm, and ecchymoses >1 cm.[4]

Smooth tongue [Figure 5] is a condition characterized by a smooth glossy tongue that is often tender/painful. The atrophy of papillae will result in a smooth tongue. The tongue may be pale or erythematous and may appear small or enlarged. Burning tongue is a condition characterized by a burning or tingling sensation on the lips, tongue, or entire mouth. Pain typically is low or nonexistent in the morning and builds up over the course of the day.[5]

An acute rise in blood urea nitrogen (BUN) (>150 mg/dl) may result in uremic stomatitis [Figure 6] which disappear 2–3 weeks after medical intervention and consequent decrease in BUN. Uremic stomatitis is considered as a kind of chemical burn. Usually, the red burning mucosa is covered with gray exudates and would be ulcerative later. Four types[6] of uremic stomatitis have been described:

1. Erythemo-Pultaceous Form
2. Ulcerative
3. Hemorrhagic and
4. Hyperkeratotic.

The Erythemo-pultaceous form is characterized by red, burning mucosa covered with a gray exudates and pseudomembrane. The ulcerative form is characterized by frank ulceration with redness and a pultaceous covering.[7,9] Hemorrhagic form is characterized by gingival bleeding, petechia, and ecchymosis develop in labial and buccal mucosa, soft palate and tongue borders, hyperkeratotic form is characterized by clinically, adherent white lesions arise on the dorsal, ventral, and lateral parts of the tongue, as well as in the buccal, labial, or retromolar areas.[10] However, some patients may have
an exudate from the oral mucosa, together with ulcerative lesions of the skin.\(^6\)

Uremic fetor was identified when the patient had a urine odor breath in persons with uremia.\(^3\) The odor occurs from the smell of ammonia, which is created in the saliva as a breakdown. Denture stomatitis, form of candidiasis seen in chronic denture users is considered. Xerostomia is confirmed by tongue blade sign.

**Investigations required**

A volume of 5 ml of venous blood was drawn and the serum was separated by centrifugation, at 3000 rpm for 10 min to remove particulate materials. This freshly obtained serum was used immediately for biochemical analysis; modified Jaffe’s Kinetic method\(^{11}\) was used to estimate the levels of creatinine in serum. Modified Berthelot method\(^{12}\) was used to estimate the levels of urea level in serum. Glucose oxidase-peroxidase method\(^{13}\) was used to estimate the levels of Fasting blood glucose in serum. The cyanmethemoglobin method\(^{14}\) was used to estimate the levels of hemoglobin (Hb) in blood.

**Statistical analysis**

All the data were entered into Microsoft Excel sheet. Statistical analysis including Pearson’s correlation analysis, Chi-square test, and t-test were done using SPSS software SYSTAT version 7.0 (Chicago, IL).

**Results**

In the present study, out of the 100 ESRD patients, 41 patients were male and 59 female, 22 were between 12 and 40 years, 59 were between 41 and 60 years, 17 were between 61 and 80 years, 2 were between 81 and 100 years. Sixty patients did not have any habits, 22 patients have smoking habits, and 18 patients have tobacco-related habits. Twenty-nine patients were on renal diet, 68 patients were on vegetarian diet and three patients were on nonvegetarian diet. Seventeen were insulin dependent diabetes mellitus (IDDM) patients, and 83 were non-insulin-dependent diabetes mellitus (NIDDM) patients. Twenty-four patients had family history of DM, and 76 patients did not have any family history of DM. Twenty-six patients were hypertensive patients, and 74 were normotensive. The Hb level, in 56 patients was found to be <10 mg/dl, 41 patients were between 10 and 15 mg/dl, and 3 patients were more than 15 mg/dl. The serum creatinine levels in 91 patients were between 2 and 10 mg/dl, 9 patients were more than 10 mg/dl. The blood urea level, in 37 patients was found to be <50 mg/dl, 40 patients were between 50 and 100 mg/dl, 23 patients were more than 100 mg/dl. Fifty-two patients had taken metformin, 40 patients had taken sulphonylurea, and 8 patients had taken insulin.

Among the 100 NESRD patients, 38 patients were male and 62 patients were female, 50 patients were between 12 and 40 years, 42 patients were between 41 and 60 years, 7 patients were between 61 and 80 years, 1 patient was between 81 and 100 years. Eighty-one patients did not have any habits, 13 patients have smoking habits, and 6 patients have tobacco-related habits. Seventy-seven patients were on renal diet, 23 patients were on vegetarian, 22 were IDDM patients, and 78 were NIDDM patients. Twenty-two patients had family history of DM and 78 patients did not have any family history of DM, 14 patients were hypertensive and 86 were normotensive. The Hb level, in 7 patients was found to be <10 mg/dl, 87 patients were between 10 and 15 mg/dl, 6 patients were more than 15 mg/dl. The serum creatinine level, in all patients were found to be <2 mg/dl, the blood urea level, in all patients were found to be <50 mg/dl. Six patients had taken metformin, 55 patients had taken sulphonylurea, and 39 patients had taken insulin.

Among the 200 patients [Graph 1 and Table 1], 24 patients had saburral tongue (P ≤ 0.002), 4 patients had fissured tongue, 18 patients had smooth tongue, 23 patients had burning tongue, 51 patients had candidiasis [Figure 7], 44 patients had dry and fissured lips [Figure 8], 20 patients had petechiae/ecchymoses (P ≤ 0.000), 13 patients had angular cheilitis, 1 patient had uremic stomatitis, 53 patients had uremic fetor (P ≤ 0.000), 82 patients had xerostomia, 8 patients had herpes labialis, 5 patients had aphthous ulcer, 59 patients had pale mucosa (P ≤ 0.000), 86 patients had unpleasant taste, 4 patients had stomatitis medicamentosa (P ≤ 0.043), and 11 patients had lichen planus [Figure 9].

Among 100 ESRD patients, 19 had saburral tongue, 2 had fissured tongue, 11 had smooth Tongue, 13 had burning tongue, 23 had candidiasis, 22 had dry and fissured lips, 18 had petechiae/ecchymoses, 4 had angular cheilitis, 1

| Oral lesions/signs/symptom          | ESRD | NESRD | Total | P   |
|------------------------------------|------|-------|-------|-----|
| Saburral tongue                    | 19   | 5     | 24    | 0.002 |
| Fissured tongue                    | 2    | 2     | 4     | 1   |
| Smooth tongue                      | 11   | 7     | 18    | 0.3  |
| Burning tongue                     | 13   | 10    | 23    | 0.5  |
| Candidiasis                        | 23   | 28    | 51    | 0.4  |
| Dry and fissured lips              | 22   | 22    | 44    | 1   |
| Petechiae/ecchymoses               | 18   | 2     | 20    | 0.001 |
| Angular cheilitis                  | 4    | 9     | 13    | 0.15 |
| Ulcerative or uremic stomatitis    | 1    | 0     | 1     | 0.3  |
| Uremic fetor                       | 52   | 1     | 53    | 0.001 |
| Xerostomia                         | 42   | 40    | 82    | 0.77 |
| Herpes labialis                    | 5    | 3     | 8     | 0.47 |
| Aphthous ulcer                     | 1    | 4     | 5     | 0.174|
| Unpleasant taste                   | 46   | 40    | 86    | 0.39 |
| Lichen planus                      | 7    | 4     | 11    | 0.35 |
| Pale mucosa                        | 45   | 14    | 59    | 0.001 |
| Stomatitis medicamentosa           | 4    | 0     | 4     | 0.04 |

ESRD=End stage renal disease, NESRD=Non-end stage renal disease
patient had uremic stomatitis, 52 had uremic fetor, 42 had xerostomia, 5 had herpes labialis, 1 had aphthous ulcer, 45 had pale mucosa, 46 had unpleasant taste, 4 had stomatitis medicamentosa, and 7 had lichen planus.

Among 100 NESRD patients, 5 had saburral tongue, 2 had fissured tongue, 7 had smooth tongue, 10 had burning tongue, 28 had candidiasis, 22 had dry and fissured lips, 2 had petechiae/echymoses, 9 had angular cheilitis, no

Discussion

Gall et al.\textsuperscript{[15]} found that males had 2.6 times greater risk of developing incipient or overt nephropathy, Choy et al.\textsuperscript{[16]} found that for ESRD patients, the male/female ratio was reported to be about 1:1 for diabetes patients. In our study, with respect to sex, the female patients were more because of greater possibility of small sample size.
Thorman et al.\textsuperscript{[17]} on 101 patients and found 43 were women and 58 were men with a mean age of 50.0 ± 12.3 years, Hsu et al.\textsuperscript{[18]} found the prevalence of chronic renal insufficiency among older adults was 10-fold that of younger individuals. However, younger individuals with chronic renal insufficiency were about 3-fold more likely to progress to ESRD. In this study, the mean age group affected by ESRD is 50.77; the mean age group affected by NESRD is 40.82. A positive correlation ($P \leq 0.000$) between the ESRD and NESRD groups with respect to age in the distribution.

Ayodele et al.\textsuperscript{[19]} found that smoking ($P \leq 0.001$) is associated with an accelerated loss of renal function, cessation of smoking alone may reduce the risk of progression by 30% in patients with Type 2 Diabetes. In the present study, an incidental finding was observed that is there is a positive correlation ($P \leq 0.003$) between the ESRD and NESRD groups with respect to age in the distribution.

Gross et al.\textsuperscript{[20]} found in 108 patients, that dietary protein restriction slowed the progression of diabetic nephropathy in patients with Type 1 diabetes. More recently, a 4-year randomized controlled trial in 82 patients with Type 1 diabetes with progressive diabetic nephropathy showed that a moderately low-protein diet (0.9 g/kg/day) reduced the risk of ESRD or death by 76%. In the present study, an incidental finding was observed that is that 106 patients were on renal diet (low or no sodium, phosphorous, and protein diet), 91 patients were on vegetarian diet and 3 patients were on non-vegetarian diet. There is a positive correlation ($P \leq 0.000$) between the ESRD and NESRD groups with respect to renal diet in the distribution.

Kovács\textsuperscript{[21]} found that patients who have Type 1 diabetes with nephropathy and hypertension, 50% will go on to develop ESRD within 10 years. About 80% of people who have Type 1 diabetes and microalbuminuria will progress to overt nephropathy, whereas only 20%-40% of those with Type 2 diabetes over a period of 15 years will progress.

Newsome et al.\textsuperscript{[22]} on 87,094 patients, found a history of hypertension ($P \leq 0.01$) was statistically significant. In the present study, an incidental finding was observed that there is a positive correlation ($P \leq 0.03$) between the ESRD and NESRD groups with respect to hypertension in the distribution.

Vesterinen et al.\textsuperscript{[23]} in CKD patients with DM had poor glycemic control as expected (mean HbA1C) 8.0% the normal value being 5.9%, with a $P < 0.01$. In the present study, There is a negative correlation between the two groups with respect to fasting blood sugar level in the distribution. The mean value for the fasting blood sugar level in ESRD patients is 161.63 mg/dl. The mean value for the fasting blood sugar level in NESRD patients is 153.18 mg/dl.

Francois Madore et al.\textsuperscript{[24]} found the dose of dialysis and urea reduction ratio was significantly associated with Hb concentration ($P < 0.001$). In the present study, there is a positive correlation between the two groups with respect to Hb level in the distribution ($P < 0.000$). The mean value for the Hb level in ESRD patients is 9.81 mg/dl. The mean value for the Hb level in NESRD patients is 12.3 mg/dl.

A study was conducted by de la Rosa García et al.\textsuperscript{[3]} in 2006, evaluated 229 individuals, and categorized patients with serum creatinine <2.0 mg/dl as NESRD-DM. Agarwal et al.\textsuperscript{[25]} who stated that serum creatinine persistently >1.8 mg% for 8–12 weeks in the absence of any reversible factor was the criterion to diagnose chronic renal failure (CRF). El Nahas et al.\textsuperscript{[26]} stated that plasma urea concentration rose to 110 during the high protein diet and subsequently fell to forty during the low protein diet ($P < 0.025$).

In the present study, there is a positive correlation between the two groups with respect to the concentration of serum creatinine level and blood urea level ($P < 0.000$) in the distribution with the mean value for the serum creatinine in ESRD patients is 4.334 mg/dl. The mean value for the serum creatinine in NESRD patients is 0.945 mg/dl. The mean value for the blood urea level in ESRD patients is 73.72 mg/dl. The mean value for the blood urea level in NESRD patients is 28.66 mg/dl.

Gross et al.\textsuperscript{[20]} stated that Metformin should not be used when serum creatinine is >1.5 mg/dl in men and >1.4 mg/dl in women due to the increased risk of lactic acidosis. Sulfonylureas (SUs) and their metabolites except glimepiride, were eliminated through renal excretion and should not be used in patients with decreased renal function. Thus, most Type 2 diabetic patients with diabetic nephropathy should be treated with insulin.

Nisbet et al.\textsuperscript{[27]} found that life-threatening lactic acidosis can occur, caused by the accumulation of metformin, and that risk factors for this include renal impairment, old age and doses over 2 g/day. The estimated prevalence of life-threatening lactic acidosis is one to five cases per 100,000 with mortality in reported cases up to 50%.

Choudhury and Luna-Salazar\textsuperscript{[28]} suggested the use of metformin and the first-generation SU agents chlorpropamide, tolbutamide and tolvazamide, as well as the α-glucosidase inhibitors acarbose and miglitol, should be avoided in patients with advanced CKD or ESRD, in light of their association with metabolic acidosis and prolonged hypoglycemia.

Abe et al.\textsuperscript{[29]} stated that Conventional oral hypoglycemic agents, such as SU, were not suitable due to the risk of prolonged hypoglycemia; furthermore, metformin is contraindicated for moderate to advanced CKD. Yale\textsuperscript{[30]} found that Insulin also can be used safely in renal failure.
In this study, an incidental finding was observed that there is a positive correlation between the two groups with respect to medication for DM in the distribution. In this present study also, patients who have been having serum creatinine level ≥2.0 mg/dl have been under the medication of metformin, and sulfonylurea.

Chuang et al.[31] found that the incidence of uremic odor in CRF patients with DM (27.9%). The incidence of mucosal petechia/ecchymosis was 20.9% in CRF patients with DM. De La Rosa Garcia E et al.[3] evaluated 229 individuals, found that the high prevalence of uremic fetor, xerostomia, saburral tongue, and candidiasis in ESRD, could be tried as warning signs on the possibility of nondiagnosed advanced renal disease in DM patients. Mosannen Mozaffari et al.[9] stated that one of the early symptoms may be a bad metallic taste and unpleasant odor in the mouth particularly in the morning. This uremic fetor, an ammoniacal odor is a typical sign of all uremic patients. Four of 300 patients with uremia were observed to have probable uremic stomatitis in the 1930s, while in 1964 another four affected patients were reported from a group of 262 patients with renal disease.

Udayakumar et al.[32] conducted a study on one hundred patients with CRF on hemodialysis and found oral changes including macroglossia with teeth markings (35%), xerostomia (31%), ulcerative stomatitis (29%), angular cheilitis (12%), and uremic breath (8%). Ulcerative stomatitis seen in 29% is reported to occur in patients with blood urea level more than 150 mg/ml. Sowell,[7] Carl and Wood,[8] Hovinga et al.[9] found Uremic stomatitis is often a clinical finding in cases of advanced disease. Gavaldá et al.[33] examined the oral mucosa of individuals with CRF and noted several mucosal lesions, uremic stomatitis, and Candida infections in 37% of these patients.

Al-Attas and Amro[34] conducted a study on 150 diabetics. They found that the number of patients with candidal carriage from the oral cavity was higher in patients with Type 1 diabetes than in Type 2 ($P = 0.003$).

In the present study, there is a positive correlation between the ESRD and NESRD groups with respect to the prevalence of oral mucosal lesions in the distribution. The lesion which were found predominantly in both ESRD and NESRD patients were saburral tongue ($P \leq 0.002$), smooth tongue, burning tongue, candidiasis, dry and fissured lips, petechiae/ecchymoses ($P \leq 0.000$), ulcerative or uremic stomatitis, herpes simplex, angular cheilitis, uremic fetor ($P \leq 0.000$), xerostomia, pale mucosa ($P \leq 0.000$), and stomatitis medicamentosa ($P \leq 0.043$).

**Conclusion**

It is to be pointed out that ESRD-DM patients had a significantly higher prevalence of signs, symptoms and oral lesions, as compared to NESRD-DM patients. Oral manifestations were barely symptomatic when present, or were probably less of trouble for the NESRD patient as compared to other manifestations of ESRD. Those frequently found conditions of uremic fetor, unpleasant taste, xerostomia, pale mucosa, burning tongue, dry fissured lips, candidiasis, saburral tongue or smooth tongue in our study group, could be tried as warning signs for undiagnosed kidney disease in other diabetic patients. The diagnosis and treatment of oral lesions will contribute to improve the quality of life of the ESRD-DM patient.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002;39 2 Suppl 1:S1-266.

2. Filser D, Haller H. Nephropathie bei diabetes mellitus type 2 (nephropathy in type 2 DM). Internist 2000;41:1363-73.

3. de la Rosa Garcia E, Mondragón Padilla A, Aranda Romo S, Bustamante Ramírez MA. Oral mucosa symptoms, signs and lesions, in end stage renal disease and non-end stage renal disease diabetic patients. Med Oral Patol Oral Cir Bucal 2006;11:E467-73.

4. Shulman JD, Beach MM, Rivera-Hidalgo F. The prevalence of oral mucosal lesions in U.S. adults: Data from the Third National Health and Nutrition Examination Survey, 1988-1994. J Am Dent Assoc 2004;135:1279-86.

5. Prabhur SR, Wilson DF, Daftary DK and Johnson NW. Oral diseases in tropics, Oxford University Press, 1992. 1st edition, 1993. p. 25-125.

6. Mozaffari MP, Amirchaghmaghi M, Mortazavi H. Oral Manifestations of Renal Patients Before and After Transplantation: A Review of Literature. DJH 2009;1:1-6.

7. Sowell SB. Dental care for patients with renal failure and renal transplants. J Am Dent Assoc 1982;104:171-7.

8. Carl W, Wood RH. The dental patient with chronic renal failure. Quintessence Int Dent Dig 1976;7:9-15.

9. Hovinga J, Roodvoets AP, Gaillard J. Some findings in patients with uremic stomatitis. J Maxillofac Surg 1975;3:125-7.

10. Taylor GW, Borgnakke WS. Periodontal disease: Associations with diabetes, glycemic control and complications. Oral Dis 2008;14:191-203.

11. Groop PH, Thomas MC, Moran JL, Watden J, Thorn LM, Mäkinen VP, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 2009;58:1651-8.

12. Orsonneau JL, Massoubre C, Cabanes M, Lustenberger P. Simple and sensitive determination of urea in serum and urine. Clin Chem 1992;38:619-23.

13. Basak A. Development of a rapid and inexpensive plasma glucose estimation by two-point kinetic method based on glucose oxidase-peroxidase enzymes. Indian J Clin Biochem 2007;22:156-60.

14. Berninger H, Smith R. A modification of the spectrophotometric determination of carbon monoxide in blood enabling direct determination of per cent hemoglobin saturation. Clin Chem 1959;5:127-34.
15. Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: Prospective, observational study. BMJ 1997;314:783-8.

16. Choy BY, Ho YW, Chau KE, Leung CB, Tsang WK, Lui SF. Renal replacement therapy for patients with diabetes mellitus in Hong Kong. Hong Kong J Nephrol 2001;3:89-96.

17. Thorman R, Neovius M, Hylander B. Prevalence and early detection of oral fungal infection: A cross-sectional controlled study in a group of Swedish end-stage renal disease patients. Scand J Urol Nephrol 2009;43:325-30.

18. Hsu CY, Vittinghoff E, Lin F, Shlipak MG. The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency. Ann Intern Med 2004;141:95-101.

19. Ayodele OE, Alebiosu CO, Salako BL. Diabetic nephropathy – a review of the natural history, burden, risk factors and treatment. J Natl Med Assoc 2004;96:1445‑54.

20. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: Diagnosis, prevention, and treatment. Diabetes Care 2005;28:164‑76.

21. Kovács GL. Diabetic Nephropathy. eJIFCC. 2009;20:41-53.

22. Newsome BB, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med 2008;168:609-16.

23. Vesterinen M, Ruokonen H, Furuholm J, Honkanen E, Meurman JH. Clinical questionnaire study of oral health care and symptoms in diabetic vs. non-diabetic predialysis chronic kidney disease patients. Clin Oral Investig 2012;16:559-63.

24. Madore F, Lowrie EG, Brugnara C, Lew NL, Lazarus JM, Bridges K, et al. Anemia in hemodialysis patients: Variables affecting this outcome predictor. J Am Soc Nephrol 1997;8:1921-9.

25. Agarwal SK, Dash SC, Irshad M, Raju S, Singh R, Pandey RM. Prevalence of chronic renal failure in adults in Delhi, India. Nephrol Dial Transplant 2005;20:1638-42.

26. El Nahas AM, Masters-Thomas A, Brady SA, Farrington K, Wilkinson V, Hislon AJ, et al. Selective effect of low protein diets in chronic renal diseases. Br Med J (Clin Res Ed) 1984;289:1337-41.

27. Nisbet JC, Sturtevant JM, Prins JB. Metformin and serious adverse effects. Med J Aust 2004;180:53-4.

28. Choudhury D, Luna-Salazar C. Preventive health care in chronic kidney disease and end-stage renal disease. Nat Clin Pract Nephrol 2008;4:194-206.

29. Abe M, Okada K, Soma M. Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: Metabolism and clinical practice. Curr Drug Metab 2011;12:57-69.

30. Yale JF. Oral antihyperglycemic agents and renal disease: New agents, new concepts. J Am Soc Nephrol 2005;16 Suppl 1:S7‑10.

31. Chuang SF, Sung JM, Kuo SC, Huang JJ, Lee SY. Oral and dental manifestations in diabetic and nondiabetic uremic patients receiving hemodialysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:689-95.

32. Udayakumar P, Balasubramanian S, Ramalingam KS, Lakshmi C, Srinivas CR, Mathew AC. Cutaneous manifestations in patients with chronic renal failure on hemodialysis. Indian J Dermatol Venereol Leprol 2006;72:119-25.

33. Gavlăd C, Bagán J, Scully C, Silvestre F, Milián M, Jiménez Y. Renal hemodialysis patients: Oral, salivary, dental and periodontal findings in 105 adult cases. Oral Dis 1999;5:299-302.

34. Al-Attas SA, Amro SO. Candidal colonization, strain diversity, and antifungal susceptibility among adult diabetic patients. Ann Saudi Med 2010;30:101-8.