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Clinico-etiological profile of Hyponatremia in elderly

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Abstract
Background: The incidence of hyponatremia is much more common in the elderly mainly owing to impaired ability to maintain water and electrolyte homeostasis in response to dietary and environmental changes. Reportedly common underlying causes of hyponatremia include pharmacotherapies, co-morbidities, fluid overload and volume depletion.
Aim: To assess the etiological factors responsible for hyponatremia among the elderly hospitalized patients and to describe the clinical manifestations associated with it.
Methodology: A prospective longitudinal study was conducted at General Medicine and allied specialities in Vinayaka Mission Kirupananda Variyar Medical College and Hospital, Salem for a period of one year between Jan 2016 to Dec 2016. All patients aged 65years and above with their serum sodium level less than 135meq/L were included in the study. A total of 235 patients were included in the study. Detailed history was obtained from the patients and a complete physical and blood examinations were done to assess the severity of hyponatremia.
Results: The mean age of the patients was 68.1 years. Majority of the patients are with moderate hyponatremia (46.8%) followed by severe grade (28.6%) and only 24.6%of them had mild hyponatremia. As the age of the patient increases the severity of hyponatremia also increases and this association was found to be statistically significant (P<.001). Patients with mild and moderate hyponatremia most of their presenting symptoms were non-neurological, whereas patients with severe hyponatremia majority of them presented with neurological symptoms. Hypertension followed by diabetes mellitus was the most common pre-existing illness present among the patients. Among the various aetiologies reported among our study subjects the most common aetiology was found to be drug induced hyponatremia. The second most common cause was reduced intake of sodium followed by SIADH, CCF, CNS lesions and renal diseases. 52% of the patients had more than factor influencing the occurrence of hyponatremia.
Conclusion: The most common cause of hyponatremia in elderly is diuretic (Thiazide) or its combination with antihypertensives. Studying the aetiology, risk factors and management of hyponatremia in hospitalized patients will help in reducing its incidence and minimize the complications associated with hyponatremia.

Keywords: hyponatremia, diuretics, neurological symptoms, euvolemia

Introduction

Hyponatremia is the most common electrolyte disorder encountered in clinical practice, occurring in up to 15% to 30% of both acutely and chronically hospitalized patients and when it comes to elderly studies had shown that the prevalence had increased up to 50% [1]. Significant hyponatremia can also be found in healthy individuals who participate in high endurance exercises such as marathon and iron man triathlons.[2] Although most cases are mild and relatively asymptomatic, hyponatremia is important clinically because acute severe hyponatremia can cause substantial morbidity and mortalityand rapid correction of chronic hyponatremia can lead to severe neurological deficit and death [3].

The incidence of hyponatremia is much more common in the elderly mainly owing to impaired ability to maintain water and electrolyte homeostasis in response to dietary and environmental changes [4]. The management of these cases needs modification due to physiological changes with age affecting the renal and other systems. Importantly euvolemic hyponatremia is more common among elderly. It is usually the result of an increase in free water with little change in body sodium. This condition is most commonly associated with non-osmotic vasopressin secretion. Causes of euvolemic hyponatremia include certain drugs (such as hydrochlorothiazide), glucocorticoid deficiency, hypothyroidism, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat syndrome [5].

According to the recent reports the commonest cause of hyponatremia is SIADH [6]. However, with the increased prevalence of hyponatremia in older people there is no corresponding increased prevalence of SIADH [7]. This raises concern that SIADH may be over diagnosed, particularly in hypovolemic older people. Reportedly common underlying causes of hyponatremia include pharmacotherapy (thiazide and loop diuretics, antidepressants, anticonvulsants, non-steroidal anti-inflammatories, and proton pump inhibitors), co-morbidities (congestive cardiac failure, renal failure, cirrhosis, respiratory infections), fluid overload and volume depletion [8-10].

Reports of the pharmacotherapy and polypharmacy associated hyponatremia are increasing [11]. Thiazide diuretic induced hyponatremia has been described as a "silent epidemic" due largely to the combination of their prescription, degenerate renal physiology and concomitant prescription of non-steroidal anti-inflammatories [12]. This is important because of the high prevalence of hypertension in the aging population and

widespread thiazide diuretic use. Similarly, the frequent prescribing pattern of other medications known to cause hyponatremia may be important contributing and easily treatable causes of the increased prevalence of hyponatremia in older people. Acknowledging the prevalence of polypharmacy in older patients Movig*et al* [13] report that concomitant diuretic and selective serotonin reuptake inhibitor (SSRI) therapy incurs a 13.5 increased odds ratio of developing hyponatremia compared to SSRI therapy alone.

As the symptomatology varies markedly the diagnosis of hyponatremia is difficult to establish. Thorough evaluation for hyponatremia mandates accurate history taking and clinical examination along with various investigations. Prompt recognition and optimal management of hyponatremia in hospitalized patients may reduce in-hospital mortality and symptom severity, allow for less intensive hospital care, decrease the duration of hospitalization and associated costs, and improve the treatment of underlying comorbid conditions and patient's quality of life.

Aim

To assess the etiological factors responsible for hyponatremia among the elderly hospitalized patients and to describe the clinical manifestations associated with it.

Methodology

A prospective longitudinal study was conducted at General Medicine and allied specialities in Vinayaka Mission Kirupananda Variyar Medical College and Hospital, Salem for a period of one year between Jan 2016 to Dec 2016. All patients aged 65years and above with their serum sodium level less than 135meq/L were included in the study. Trauma patients and patients with sodium replacement therapy (Vaptans) were excluded from the study. A total of 235 patients were included in the study. A detailed history was taken to clinically assess hyponatremia among the patients. The definition of symptomatic hyponatremia was based on a clinical assessment of symptomatology including the presence of altered sensorium, postural dizziness, lethargy and seizures. Sensorium changes comprised acute confusional states, memory disturbances stupor or coma, in the absence of dementia, psychiatric illness and substance abuse. Drugs that can increase the non-osmotic release of antidiuretic hormone (ADH) or potentiate its renal action (ADH stimulating drugs) were recorded. History of illnesses causing hyponatremia such as congestive heart failure, chronic kidney disease, chronic liver disease, hypothyroidism and other conditions which are associated with SIADH such as small cell lung carcinoma, CNS diseases, and pulmonary diseases were taken and recorded. History of fluid loss as in vomiting, diarrhoea, diuretic use, excessive sweating was taken.

Hydration status of the patient was determined by clinical examination. The signs ofhypovolemia included tachycardia, orthostatic falls in blood pressure, decreased skin turgor, dry mucous membranes and decreased peripheral perfusion with a delayed capillary refill more than three seconds. Hypervolemic state was defined by the presence of anasarca, ascites, symmetrical and pitting pedal edema and raised jugular venous pressure (JVP). Accordingly patients were divided into hypervolemic, hypovolemic and euvolemic states.

Following blood investigations were done CBC, platelet count, serum electrolytes, BUN and serum osmolality was calculated by using the formula 2([Na+] + [K+]) + RBS/18 + BUN/2.8 mOsm/L (RBS in mg/dl, BUN in mg/dl).

Patients with hyponatremia were classified based on serum sodium levels into following categories (i) Mild hyponatremia - 131 - 134 meq/L (ii)Moderate hyponatremia - 120 - 130 meq/L (iii) Severe hyponatremia - <120 meq/L.

All the data were entered and analysed by using SPSS version 21. For all the parametric variable mean and standard deviation was calculated. The association between two variables was analysed by using Pearson's chi-square test.

Results

Table 1 shows the age and gender wise distribution of the study population. It is seen from the table that majority of the study subjects were between the age group of 60 – 75 years with a minimum age of 60 and the maximum age was 84 years. The mean age was 68.1 years and there was almost equal distribution of males and females between all the age groups and male: female ratio is 1.11: 1. Based on the serum sodium levels the grading of hyponatremia was made as mild (131 - 134 meq/L), moderate (120 - 130 meq/L) and severe (<120 meq/L). Majority of the patients are with moderate hyponatremia (46.8%) followed by severe grade (28.6%) and only 24.6%of them had mild hyponatremia. As the age of the patient increases the severity of hyponatremia also increases and this association was found to be statistically significant (p<.001) (table 2). Based on the clinical features hyponatremia was classified as hypovolemia, euvolemia and hypervolemia. Majority of the patients had euvolemia (59.5%), followed by hypervolemia (23.4%) and hypovolemia (17%). There found to be no association between the grading of hyponatremia and the types of hyponatremia (table 3).

Table 1: Age and gender wise distribution of the study population:

Age in years	Gender		Total
	Male	Female	
60 – 65	32 (25.8%)	26 (23.4%)	58 (24.6%)
66 – 70	26 (20.9%)	24 (21.6%)	50 (21.2%)
71 – 75	28 (22.5%)	23 (20.7%)	51 (21.7%)
76 – 80	22 (17.7%)	19 (17.1%)	41 (17.4%)
>80	16 (12.9%)	19 (17.1%)	35 (14.8%)
Total	124 (100%)	111 (100%)	235 (100%)
Mean ± SD	68.2 ± 3.6	67.8 ± 3.8	68.1 ± 3.6

Table 2: Distribution of the study subjects based on the severity of hyponatremia

Age group	Severity of hyponatremia			Total	P value
	Mild	Moderate	Severe		
65	16 (27.5%)	33 (56.8%)	9 (15.5%)	58 (100%)	<.0001
66 – 70	15 (30%)	24 (48%)	11 (22%)	50 (100%)	
71 – 75	14 (27.4%)	20 (39.2%)	17 (33.3%)	51 (100%)	
76 – 80	9 (21.9%)	18 (43.9%)	14 (34.1%)	41 (100%)	
>80	4 (11.4%)	15 (42.8%)	16 (45.7%)	35 (100%)	
Total	58 (24.6%)	110 (46.8%)	67 (28.5%)	235(100%)	

P value derived by applying chi-square test

Table 3: Distribution of the study population based on the severity and types of hyponatremia

Severity of hyponatremia	Type of hyponatremia			Total
	Hypovolemia	Euvolemia	Hypervolemia	
Mild	16 (27.5%)	37 (63.7%)	5 (8.6%)	58 (100%)
Moderate	11 (10%)	63 (57.2%)	36 (32.7%)	110 (100%)
Severe	13 (19.4%)	40 (59.7%)	14 (20.8%)	67 (100%)
Total	40 (17%)	140 (59.5%)	55 (23.4%)	235 (100%)

Patients presented with various symptoms were classified into neurological and non-neurological symptoms. The neurological symptoms include ataxia, seizures, abnormal behaviour, delirium, confusion, irrelevant speech, hypo-responsiveness, drowsy, stupor and weakness of limbs. The non – neurological symptoms include vomiting, diarrhoea, lethargy and febrile illness, difficulty in breathing and reduced appetite. It is seen from table 4 that patients with mild and moderate hyponatremia most of their presenting symptoms were non-neurological, whereas patients with severe hyponatremia majority of them presented with neurological symptoms and this difference was found to be statistically significant.

Hypertension followed by diabetes mellitus was the most common pre-existing illness present among the patients. Heart diseases like congestive cardiac failure, neurological diseases like stroke and pulmonary diseases like pneumonia, fibrosis and pleural effusion were also present in few patients. Renal diseases related to diabetes were present in 9% of the study subjects. Carcinoma, hypothyroidism and rheumatoid arthritis constitute to 1% of the study subjects (table 5).

Among the various aetiologies reported among our study subjects the most common aetiology was found to be drug induced hyponatremia. The commonest drug used by the patients was diuretics alone or combination of diuretics with antihypertensive drugs. Thiazide diuretic followed by loop diuretics and potassium sparing diuretics were the most commonly. Few patients with CNS diseases had used SSRI's, eptoin and gabapentin. The second most common cause was reduced intake of sodium followed by SIADH, CCF, CNS lesions and renal diseases. 52% of the patients had more than one factor influencing the occurrence of hyponatremia. In our study it was also shown that there was no statistical significant association between any of the aetiological factor and the severity of hyponatremia (P>.05) (table 6).

Table 4: Distribution of the study subjects based on the presentation of symptoms

Severity of hyponatremia	Types of symptoms		Total	P value
	Neurological	Non – neurological		
Mild	13 (22.4%)	45 (77.5%)	58 (100%)	<.0001
Moderate	35 (32%)	75 (68%)	110 (100%)	
Severe	49 (73.1%)	18 (26.8%)	67 (100%)	
Total	106 (45.1%)	129 (54.8%)	235 (100%)	

Table 5: Distribution of the study subjects based on their pre-existing diseases

Pre-existing diseases	Frequency	Percentage
Diabetes mellitus	103	44%
Hypertension	148	63%
Liver disease	14	6%
Heart disease	56	24%
Renal disease	21	9%
Neurological disease	45	19%
Psychiatric illness	9	4%
Pulmonary disease	45	19%
Carcinoma breast	2	1%
Carcinoma lung	2	1%
Hypothyroidism	2	1%
Rheumatoid arthritis	2	1%

Table 6: Distribution of the study subjects based on the aetiology of hyponatremia

Aetiology	Grading of hyponatremia			Total (n=235)	P value
	Mild (n=58)	Moderate (n=110)	Severe (n=67)		
Drug induced hyponatremia	28 (48.2%)	46 (41.8%)	21 (31.3%)	95 (40.5%)	0.652
Congestive cardiac failure	8 (13.4%)	12 (10.9%)	11 (16.4%)	31 (13.1%)	0.846
CNS lesions /stroke	6 (10.3%)	9 (8.1%)	12 (17.9%)	27 (11.5%)	0.518
LRTI/pneumonia/fibrosis/effusion	6 (10.3%)	8 (7.2%)	5 (7.4%)	19(8%)	0.819
Renal disease	8 (13.4%)	16 (14.5%)	9 (13.4%)	33(8.5%)	0.683
Sepsis	3 (5.1%)	3 (2.7%)	8 (12%)	13(14%)	0.851
Poor intake	18 (31%)	34 (30.9%)	26 (38.8%)	78(33.1%)	0.914
Hypothyroidism	3 (5.1%)	5 (4.5%)	2 (2.9%)	10 (4.2%)	0.782
SIADH	12 (20.6%)	17 (15.4%)	14 (20.8%)	43 (18.2%)	0.916
Liver disease	1 (1.7%)	3 (2.7%)	2 (2.9%)	6 (2.5%)	0.834
Malignancy	1 (1.7%)	2 (1.8%)	3 (4.4%)	6 (2.5%)	0.691
Others	3 (5.1%)	1 (0.9%)	0	4 (1.7%)	0.319

Discussions

This study was undertaken keeping in view of frequent occurrence of hyponatremia in the elderly sick patients who are at higher risk of development of electrolyte disturbance as these people have age related physiological changes in the function of kidneys and other multiple co-morbid conditions. In our study the prevalence of hyponatremia was found to be almost similar in both males and females with a slight predominance among males. This is contrary to the literature report where females have outnumbered males in the hyponatremia group (52-70%) [14-16]. Males usually outnumber females in hospital admissions, which explains for the slight increase in number of male patients in the study. Studies have shown that female gender is an important risk factor for the development of severe complications [17].

In our study majority of the patients had moderate hyponatremia followed by severe and mild grade of hyponatremia and a similar type of results was also observed by the study done by M Y Rao *et al.* [18[and Aditya Mulgaonkar *et al.* [19] In our study euvolemic type of hyponatremia was found in 59.5% of the patients and a study done by Mittal M *et al.* [20] had quoted in his study that euvolemic hyponatremia constituted 61% among his patients and other hospital based studies have also found euvolemic hyponatremia as the commonest type.

In the present study neurological symptoms were reported among 45.5% of the patients in the form of confusions, delirium, abnormal behaviour and speech and only 6% of the patients had seizures, it is almost in par with the study done by M Y Rao etal[18] where only 4% of his patients had seizures. Studies have shown that both aging and male gender confers protection against hyponatremia induced seizures, although the reasons are unclear [21]. In our study most of the neurological symptoms were reported among patients with severe hyponatremia rather than mild and moderate grade of hyponatremia and this is similar to the work done by Clayton etal[8] and Nzerue *et al.* [22].

Most of the patients in our study had multiple co-morbid conditions of which hypertension and diabetes were the most common. Glucose being an osmotically active molecule, hyperglycemia can induce a fall in serum sodium levels by shifting water from intra-cellular to extra-cellular compartments. It has been calculated that serum sodium falls by 1.6 to 2.4 mmol/L for every 100mg/dl rise in serum glucose levels [23]. Hyponatremic hypertensive syndrome is a well-known entity, the most common association being in patients with essential hypertension receiving diuretics [24].

Though most of the studies had quoted that SIADH as the most predominant cause for hyponatremia among elderly in our study we found drug induced hyponatremia as the most common cause. In our study 63% were taking drugs which are known to cause hyponatremia. 9% patients were on diuretics alone. Diuretics with other antihypertensives were taken by 11% patients. Thiazide diuretics are a common cause of severe hyponatremia [25]. Upto a third of elderly patients taking a thiazide at hospital admission are hyponatremic and 14% of patients prescribed a thiazide diuretic in primary care have a sodium level below the normal range [26]. Severe hyponatremia occurs almost exclusively with thiazide rather than loop diuretics. Saeed *et al*, studied hyponatremia in hospitalized patients and in 19 out of 57 patients (33.3%) it was associated with diuretic use [27]. In a study by Sonnenblick *et al* majority of the patients who received thiazides, excess antdiuretic hormone activity, hypokalemia and excess water intake were accompanying findings which singly or together, appeared to contribute to the development of hyponatremia [28].

Though JNC VIII recommends diuretics as the first line drugs for treatment of hypertension, a word of caution should be maintained while prescribing diuretics in elderly and when required doses should be modified according to body weight and should begin with the lowest dose. Nowadays there is a widespread use of newer ARBs. In our study 21% patients were on ARBs. Most of the prescriptions were for diabetic hypertensives. The role of ARBs causing hyponatremia is not much studied. In a study by Turgutalp *et al* 43.8% of the patients with hyponatremia were on ARBs [29]. In another study by Yawas *et al* medicines accounted for 30% of cases of hyponatremia, of which diuretics, ARBs and ACE inhibitors were in the top list [30].

There are numerous reports of hyponatremia associated with antipsychotics and selective serotonin- reuptake inhibitors [31]. In this study 9% patients were taking SSRI or antipsychotics. Clayton *et al*. had concluded in their study that selective serotonin reuptake inhibitors (SSRIs) were a frequent cause of drug induced hyponatremia [8]. It is higher in women than in men and in persons 65 years of age or older than in younger persons. They had 12 (11.1%) patients out of 108 who were taking SSRI while in our study 3% patients had hyponatremia associated with SSRI use. Patients receiving multiple medications known to cause hyponatremia may also be at increased risk.

In our study 52% of the patients had multiple etiological factors for hyponatremia. In recent studies varying proportions of the patient have been associated with multiple aetiologies of

hyponatremia. In a study by Clayton etal[8] 75% of the patients of hyponatremia had multiple aetiologies while in the study by Nzerue *et al.* [32] only 10.9%of the patients had multiple etiological factors. These studies emphasize the importance of establishing the various factors responsible for hyponatremia in the patient so that relevant corrective measures are taken during the treatment.

In our study mortality was reported only in 5 patients with severe hyponatremia which accounts to only 2.1% which is highly contradicting to other studies. In 2005, Huda etal[14] in their study found that there was 27% mortality among patients of severe Hyponatremia; however mortality among these patients was not directly related to hyponatremia but to other concomitant comorbidities also. In a study by Nzerue *et al* mortality among patients with severe hyponatremia was 20.2% [32].

Conclusion

Hyponatremia being one the most common electrolyte disorder in hospitalized patients particularly in elderly. It is important to recognize it much early because of its potential morbidity, mortality and the economic impact on the patient and the health care. The most common cause of hyponatremia in elderly is diuretic (Thiazide) or its combination with anti hypertensives. Studying the aetiology, risk factors and management of hyponatremia in hospitalized patients will help in reducing its incidence and minimize the complications associated with hyponatremia. Caution should be exercised in prescribing diuretics/diuretic combination in elderly hypertensive or diabetic and also while advising strict salt restriction.

References

1. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006; 119(suppl 1):S30-S35.
2. Lien YH, Shapiro JI. Hyponatremia: Clinical Diagnosis and Management. Am J Med. 2007; 120:653-58.
3. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: Expert Panel Recommendations. Am J Med. 2007; 120(11A):S1-S21.
4. Clayton J.A., Le Jeune I.R., Hall I.P. Severe hyponatremia in medical in-patients: aetiology, assessment and outcome. QJ Med. 2006; 99:505-511.
5. Fried LF, Palevsky PM. Hyponatremia and hypernatremia. Med Clin North Am. 1997; 81:585-609.
6. Hannon, MJ, Thompson CJ. The syndrome of inappropriate antidiuretic hormone: Prevalence, causes and consequences. Eur. J. Endocrinol. 2010, 166. Doi: 10.1530/EJE-09-1063.
7. Soiza RL, Hoyle GE. Syndrome of appropriate antidiuretic hormone: Difficulties with diagnosing syndrome of inappropriate antidiuretic hormone in older people. Int. Med. J. 2011, 41. Doi:10.1111/j.1445-5994.2010.02388.x.
8. Clayton JA, Le Jeune, IR, Hall, IP. Severe hyponatremia in medical in-patients: Aetiology, assessment and outcome. QJM. 2006, 99:505-511.
9. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatremia in elderly hospitalized patients: Prevalence, aetiology and outcome. Int. Med. J. 2010; 40:574-580.
10. Cumming K, Hoyle GE, Hutchison JD, Soiza RL. Prevalence, incidence and aetiology of hyponatremia in elderly patients with fragility fractures. PLoS One 2014; 9:e88272.
11. Rosholm J, Nybo H, Andersen Ranberg K, Himmelstrup B, Skjelbo E, Christensen K, *et al.* Hyponatremia in Very Old Nonhospitalised People: Association with Drug Use. Drugs Aging. 2002; 19:685-693.
12. Mann SJ. The silent epidemic of thiazide-induced hyponatremia. J. Clin. Hypertens. 2008; 10:477-484.
13. Movig KLL, Leufkens HGM, Lenderink AW, Van Den Akker VGA, Hodiamont PPG, Goldschmidt HMJ, *et al*. Association between antidepressant drug use and hyponatremia: A case-control study. Br. J. Clin. Pharmacol. 2002; 53:363-369.
14. Huda MSB, Boyd A, Skagen K, Wile D, Van Heyningen C, Watson I, *et al.* Investigation and management of severe hyponatremia in a hospital setting. Postgrad Med J. 2006; 82:216-9.
15. Chow KM, Szeto CC, Wong TY, Leung CB, Li PK. Risk factors for thiazide-induced hyponatremia. QJM. 2003; 96:911-7.
16. Gill G, Huda B, Boyd A, Skagen K, Wile D, Watson I, *et al.* Characteristics and mortality of severe hyponatremia - a hospital-based study. ClinEndocrinol (Oxf). 2006; 65:246-9.
17. Ayus JC, Arieff Al. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA. 1999; 281:2299-2304.
18. MY Rao, U Sudhir, T Anil Kumar, S Saravanan, E Mahesh, K Punith. Hospital-Based Descriptive Study of Symptomatic Hyponatremia in Elderly Patients. JAPI. 2010; 58:667-69.
19. AdityaMulgaonkar, KhandeparkarAnar, Khandeparkar Viraj. Clinical profile of hyponatremic patients and associated risk factors in a tertiary care hospital in Goa.J. Evolution Med. Dent. Sci. 2016; 6(28):2311-14.
20. Mahim Mittal, Deepshikha, HunnyKhurana. Profile of hyponatremia in a tertiary care centre in North India. Int J Adv Med. 2016; 3(4):1011-1015.
21. Arieff Al, Kucharczyk J, Ayus JC. Age, gender and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. Am J Physiol. 1995; 268:143-152.
22. Naureen Tareen, David Martins, Glenn Nagami, Barton Levine, Keith C. Norris. Sodium Disorders in the Elderly. J NatI Med Assoc. 2005; 97:217-224.
23. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999; 106:399-403.
24. Agarwal M, Lynn KL, Richards AM, Nicholls G. Hyponatremic- Hypertensive Syndrome with Renal Ischemia: An Underrecognized Disorder. Hypertension. 1999; 33:1020-1024.
25. Adrogue HI, Madias NE. Aiding fluid prescription for the dysnatremias. Intensive Care Med. 1997; 23:309-16.
26. Byatt 'M, Millard PH, Levin GE. Diuretics and electrolyte disturbances in 1000 consecutive geriatric admissions. I R Soc Med. 1990; 83:704-8.

27. Saeed B O, Beaumont D, Handley G H, Weaver I U. Severe hyponatremia: investigation and management in a district general hospital. Clinical Pathol. 2002; 55:893-896.
28. Sonnenblick, Friedlander Y, Rosin AI. Diuretic induced hyponatremia. Chest. 1993; 103(2):601-6.
29. Turgutalp K, Ozhan O, Gok Oguz E, Horoz M. Clinical features, outcome and cost of hyponatremia associated admission and hospitalization in elderly and very elderly patients: a single centre experience in Turkey.International Urology and Nephrology. 2013; 45(1):265-73.
30. Yawas A. Hyponatremia: etiology, management and outcome. Coll. Physicians Surg. 2008; 18(8):467-71.
31. Movig KL, Leufkens HG. Association between antidepressant drug use and hyponatremia: a case control study. Br I Clin Pharmacol. 2002; 53:363-369.
32. Nzerue Chike M, Baffoe-Bonnie Henry, You Wei, Falana Babajide, Dai Shifan. Predictors of Outcome in Hospitalized Patients with Severe Hyponatremia. Journal of the National Medical Association. 2003; 95:335-343.