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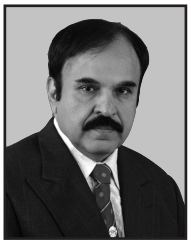

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Editor's Note

Dear colleagues,

Greetings of the season!

The objective of TAPIJ is to publish up-to-date, quality original research papers alongside relevant and insightful reviews. I am delighted to present last issue of TAPIJ of 2017, which has several informative articles, which covers various aspects of Medical sciences and unusual case reports.

This issue has interesting original article on "Gender difference among T2DM patients with Diabetic nephropathy" and a review article on "A new era has started in anti-diabetics; welcome SGLT2 inhibitors" which highlights the importance of SGLT2 inhibitors among Type 2 Diabetes.

This issue has three interesting case reports, first case report shows the An interesting case of Pulmonary Embolism with Type 2 Diabetes and Cushing Syndrome, second case report is on unexplained Hypokalemia & unusual arrhythmia and the third case report focused on Case Report of a model patient with controlled Diabetes Mellitus over a period of 33 years was discussed in detail.

Besides these, we have our usual articles on ECG, Dermatology and toxicology sections presents the valuable articles. This edition comes as a combination of various specialties to enlighten the readers and will add food for thought.

I am sure that this issue of TAPIJ with its articles on various aspects of medicine will explore both clinical and academic knowledge.

With warm regards,

Dr. Vijay Viswanathan

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Original article

TAPI Journal Vol. 9, Issue 3, Sep – Dec 2017

Gender difference among T2DM patients with Diabetic nephropathy

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Abstract:

Aim: The aim of the current study was to determine the gender difference among T2DM patients with Diabetic nephropathy.

Methods: A total of 4431 (2289:2142) subjects with T2DM who underwent estimated Glomerular Filtration Rate (eGFR) and renal function test for assessing renal function were included in the cross - sectional study. Based on eGFR and albuminuria, patients were grouped into Low Risk (LR), Moderately increased Risk (MR), High Risk (HR) and Very High Risk (VHR) categories as per KDIGO classification. Demographic, anthropometric, and biochemical details were recorded accordingly.

Results: Among the study population (n=4431), 63.07% were in LR group (ie., without Diabetic Nephropathy), followed by 50.48% in MR, 31.60% and 17.90% in HR and VHR group respectively. The mean age of the study population was 53.2 years in males and 52.8 years in females, with diabetic duration of 15.3 years and 14.8 years. The prevalence of diabetic nephropathy was 36.92%. The prevalence of DN was more in female (20.71%) when compared to male (16.20%) with significant difference ($p<0.0001$). However, the percentage of males in HR and VHR was more when compared to females.

Conclusion: Gender difference plays a major role in the progression of target organ damage among T2DM patients with vascular and renal damage. The current finding highlighted that the prevalence of diabetic nephropathy tends to be higher in women with diabetes. However the severity of the disease was more in men. This might be due to the imbalance in hormones associated with diabetes.

Keywords: KDIGO, gender difference, Diabetic nephropathy

Introduction:

Globally among women diabetes is ninth leading cause of death, and second highest in south Asian mortality in women with diabetes. There is remarkable gender discrimination in assessing the health care services and support for diabetes which lead to increased rate of mortality and morbidity in diabetic women. The long term burden of diabetes falls inexplicably on women and they experience higher mortality and morbidity due to complications of diabetes than their male counterparts. The risk of diabetes among women was high due to the increased life span, inequalities and gender differences. The mortality and morbidity was high in women with diabetes due to diabetes related complications (1). WHO reported that about 55% of diabetes deaths occur in women (2). In South Asian community, diabetes is four times more likely to develop due to genetic predisposition (3) and also the risk of developing cardiovascular disease and renal problems was high among this population (4). Diabetic women in reproductive age potentially affects the next generation. Further, the risk of gestational diabetes was also higher among Asian women, thereby increasing the risk of T2DM among their children later in life (5).

Diabetes and diabetic complication among women is much neglected area, which requires attention from global and regional perspective. Due to various reasons diabetes among women is unique and its regional prevalence is also increasing along with the added burden of insulin resistance from puberty that predisposes women to long term ill health from a young age (6). There is a paucity of data pertaining

to the gender difference among diabetic nephropathy in South Indian T2DM patients. Thus the present study aimed to determine the gender difference among T2DM patients with Diabetic nephropathy.

Research Design and Methods:

The cross sectional study was conducted among T2DM patients, who attended the outpatient Diabetes clinic during the study period of October 2016 to October 2017 in a tertiary care hospital in India. All patients included in the study had undergone eGFR and albumin creatinine ratio for assessing renal function. The study population included all patients aged above 25 years and were screened for laboratory investigations, medications, demographic and anthropometric details. All the subjects were on treatment with oral hypoglycemic agents, some were on insulin, and few were known hypertensive's and were on antihypertensive medication. Patients with Type1 Diabetes and gestational diabetes and those with incomplete laboratory data were excluded from the study.

Demographic and anthropometric details such as age, gender, duration of diabetes, family history of diabetes were recorded accordingly. Biochemical parameters such as fasting and postprandial glucose, HbA1c, urea, creatinine, urinary protein and urinary albumin values were recorded. All biochemical parameters were estimated using BS400 biochemistry auto analyzer, HbA1c was measured using HPLC method using variant turbo equipment (Bio-Rad). Creatinine was estimated by Jaffe's kinetic method, urinary albumin was estimated by immuno-turbidimetric procedure. Urinary protein was determined using pyrogallol method. The eGFR was calculated based on CKD - EPI equation, which gives the best estimation of GFR (7).

Study population was grouped into Low Risk (LR), Moderate Risk (MR), High Risk (HR) and Very High Risk (VHR) categories according to KDIGO classification, based on eGFR and urinary albumin values (8). Data was analyzed using SPSS (version 16.0, Illinois, USA) software. Mean and standard deviation for continuous variables and percentages for categorical variables are reported accordingly. Chi-square test or t-test were performed as applicable for comparing the variables between different groups, and a P value < 0.05 was considered to be statistically significant.

Results:

In the present study a total of 4431 T2DM patients were included, of which 51.65% were males and 48.35% were Females. The mean age of the study population was 53.2 years in males and 52.8 years in females, with diabetic duration of 15.2 years and 13.4 years respectively (Table 1). Based on the KDIGO classification, 63.07% were in LR group (ie., without Diabetic Nephropathy), followed by 50.48% in MR, 31.60% and 17.90% in HR and VHR group respectively.

Table 1: Demographic details of the study population

Variables	**Male**	**Female**
Gender	2289	2142
Age (years)	53.2±7.4	52.8±9.52
BMI (Kg/m^2)	26.8±4.7	27.5±4.5***
Diabetes Duration (years)	15.3±6.2	14.8±5.6*
Systolic BP (mmHg)	126.6±16.3	143.1±21.4 ***
Diastolic BP (mmHg)	82.6±7.6	83.5±11.9*
HbA1c %	8.2±1.91	9.8±1.93***

** Significant at 0.05 level; ** Significant at 0.01 level; *** Significant at 0.001 level*

Table 2: Gender difference in Diabetic nephropathy among T2DM patients, based on KDIGO classification.

Variables	**Over all n = 4431**	**Male n = 2289**	**Female n = 2142**	**P value**
No DN (LR)	2795 (63.07)	1571 (35.45 %)	1224 (27.62 %)	0.0001*
DN (MR, HR, VHR)	1636 (36.92)	718 (16.20%)	918 (20.71 %)	

** Values represent in n (%); Values are significant using chi – square test (P<0.0001).*

Among the study population the overall prevalence of Diabetic nephropathy was 36.92%. The prevalence of DN was more in female (20.71%) when compared to male (16.20%) with significant difference ($p<0.0001$) (Table 2). However based on risk stratification (Fig 1.), higher percentages of HR (34.67%) and VHR (20.33%) was seen in males, when compared to that in females (HR - 29.19% and VHR - 16.01%).

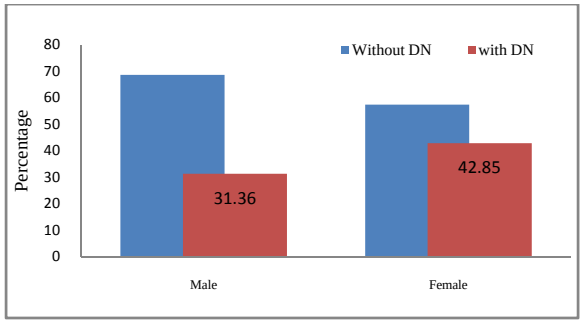

Fig 1a

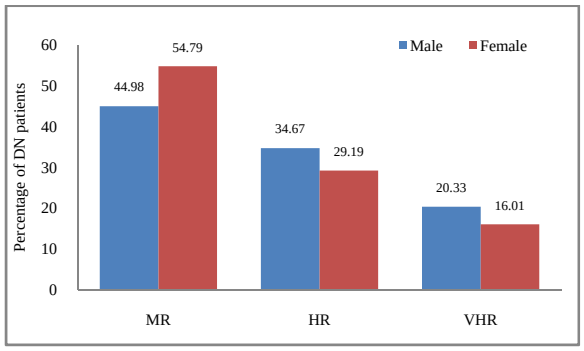

Fig 1b

Fig 1a: Diabetic Nephropathy among Male and Female T2DM patients; Fig 1b: Severity of Diabetic Nephropathy among genders.

Discussion:

Gender difference plays a major role in the progression of target organ damage among patients with insulin resistance and highlighted that the vascular and renal damage is increased in women especially women with diabetes than men (9). The current study finding emphasizes that the prevalence of diabetic nephropathy tends to be higher in women with diabetes than men with diabetes. Indian based population study highlighted that the prevalence of overt nephropathy was 26.9% (10). In a previous study renal risk was stratified using eGFR and albuminuria based on KDIGO classification and showed that there is significant association between the Diabetic retinopathy and the renal risk categories (11).

Current study finding highlighted that, although the prevalence of DN was high in females, the severity of the disease is found to be more in male. Earlier study showed that the progression of DN is faster in men and also often undergoes dialysis; perhaps the mortality risk is higher among women with diabetic nephropathy than diabetic men during chronic dialysis treatment (12). The glycemic control was poor among T2DM women and is less likely to reach target HbA1c (13). Further women with diabetes showed high incidence of microalbuminuria. This might be due to the imbalance in hormones associated with diabetes (14). Preclinical evidences suggested the estrogen protects against nephropathy, as it inhibits the rennin - angiotensin – aldosteron system, perhaps testosterone up regulates this system (15). Obesity also plays a major role in developing CKD among women than men (16). In addition genetic factors might influence the risk of developing nephropathy in women and men (17, 18).

The major limitation of the study is that the renal biopsies were not performed, as it is difficult to carry out these procedures in population-based studies due to logistic and ethical reasons. Further a prospective multicentre study focusing on the gender difference in diabetes related complications and its associated risk factors has to be evaluated. This study highlighted the importance of growing epidemic of T2DM in South Indian population and gender differences in diabetic nephropathy.

Conclusion:

To conclude the present study highlighted that the prevalence of the diabetic nephropathy was higher in female when compared to males, however the severity of the disease was higher in males when compared to females. Thus there is

need to focus on the diabetes awareness and control program to manage the potential economic burden owing to diabetic nephropathy in India.

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Review Article

TAPI Journal Vol. 9, Issue 3, Sep – Dec 2017

A New era has Started in Anti-Diabetics; Welcome SGLT2 Inhibitors

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Introduction

The prevalence of Diabetes is increasing worldwide very rapidly. In 2015, International Diabetes Federation estimated 415 million peoples are diabetic around the globe and 78 million peoples are from South- East Asian region (SEA). India is contributing at major with 69 million (1). In 2004, it was estimated that India would have 79 million peoples with diabetes by 2030 but in 2015 India is almost close to that estimate (2). In last two decades there are several anti-diabetic agents including DPP4i have been developed and launched in India, but practically there is not so much improvement in Diabetes prevalence rate (3). Recently in 2014-15, SGLT2i, a newer class of oral anti-diabetic agent approved and launched in India and Indian perspective need to evaluate should we welcome it or not? (4)

Unmet need in India in Diabetes:

As per IDF 2015 data, out of 69 million of diabetes patients, 66.9% patient failed to achieve glycemic target irrespective of therapeutic management. (5) So, why such challenges in outcome? Does Indian need different approach to treat diabetes? Before that it is important to explore the basic challenges. Indians are having certain characteristics which are actually helps to develop metabolic complication, that may denote as Indian phenotype, refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels etc (6). Along with these, Indians are also having lower insulin sensitivity, higher insulin resistance level, and low level of glucose disposal rate in skeletal muscle, high leptin level and triglycerides in serum including genetically predisposition. (7-8)

Hence, focusing only on glucocentric approach is not enough to treat Type 2 diabetes in India. As most of the guidelines are recommending HbA1c reduction along with blood pressure and weight reduction as comprehensive management to treat diabetes (Table 1). (9) Out of all existing anti-diabetic agent's only GLP-1a addresses all these three parameters (9-10). As per Indian context, using GLP-1a agents are a challenging as these are costly and injectable too (11). So, this is important to

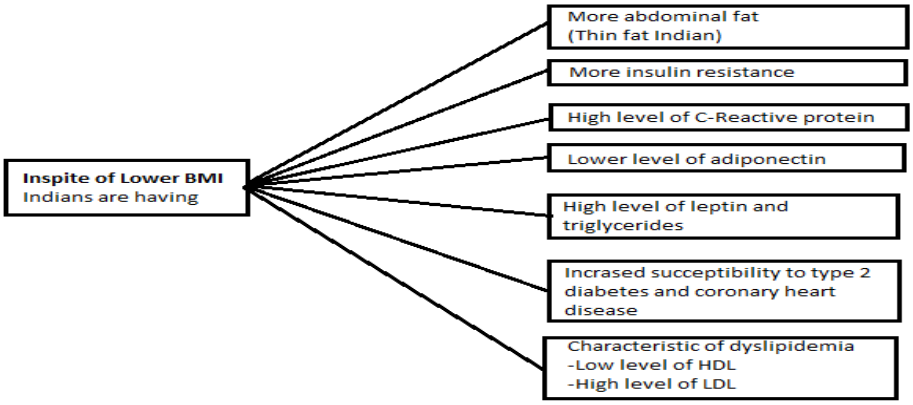

Figure 1: Characteristic of Indian phenotype
BMI- Body mass index, HDL-High density lipoprotein, LDL- Low density lipoprotein

Guidelines	Glycaemic Control	Weight (Kg)		Blood pressure
	HbA1c	BMI (Kg/Sqm)	Waist Cirm cm (in)	mmHg
WHO 2006	<7.0%	<25 (M) <24 (F)		<130/80
EASD-ESC 2007	≤6.5%	<25 (M)	<94 (37 In) (M) <80 (32 In) (F)	<130/80
ADA 2012	<7.0%	≤25 (M)	-	<130/80
ADA 2011	≤6.5%	-	-	<130/80
CDA 2008	≤7.0%	<25 (M)	<102 (40 In) (M) <88 (35 In) (F)	<130/80

Table 1 : Comprehensive anti-diabetic management suggested by guidelines
HbA1c - Glycosylated hemoglobin, BMI-Body mass index, M-Male, F- Female
WHO-World Health Organisation, EASD-European Association for the Study of Diabetes
ESC-European Society of Cardiology, ADA-American Diabetes Association
CDA-Candian Diabetes Association

evaluate SGLT2i in these parameters whether these agents meet the unmet need as per requirement.

What is SGLT2i and how does it work?

Kidney plays an important role in glucose homeostasis. It plays mainly by two ways, one by producing glucose by approximately 15-55 gm/ day and also by re-absorbing glucose in proximal convoluted tubule (PCT) which is approximately ~ 180 gm/day. (12) Sodium glucose co-transporters (SGLTs) play an important role in renal glucose re-absorption process. SGLT2 which is situated at PCT -segment 1 and it is responsible for ~ 90% of glucose reabsorption and rest ~10 % by SGLT 1 which is situated at PCT segment 3 (Figure 2) (13).

In Type 2 diabetes mellitus there is over-expression of SGLT2 and SGLT1 co-transporter which leads to enhancement of renal threshold upto ~250 mg/dl from ~180 mg/dl that leads to ~75 mg/min excess glucose re-absorption through both kidneys which actually causing enhanced hyperglycaemia (14-15). SGLT2 inhibitors are group of anti-diabetic molecule which works through inhibiting glucose re-absorption at proximal convoluted tubule in nephron which leads to excretion of excess glucose through urine and that leads to reduction of hyperglycaemia. This urine excretion of glucose of ~70 gm/ day leads to ~280 kcal calorie loss along with ~400 ml/day of water by osmotic diuresis. (15-16)

SGLT2i: Glycaemic and extra-glycaemic benefit: A comprehensive anti-diabetic management.

In India, only three SGLT2 inhibitors, Canagliflozin, Dapagliflozin and Empagliflozin have been launched so far (17). In terms of pharmacokinetic and pharmacodynamics, profiles all these molecules are almost similar to each other (Table 2.) (18-29).

There is no head to head trial within SGLT2 inhibitors, but still regarding glycemic efficacy in 24 weeks, add on to metformin therapy, with Canagliflozin 100 mg and 300 mg, mean HbA1c reductions are ~0.79 and ~0.94

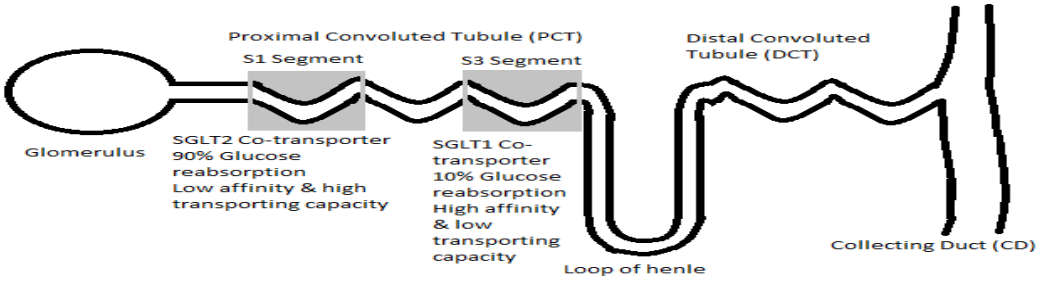

Figure 2: Structure of nephron and position and function of Sodium Glucose Co Transporter (SGLT)

respectively against baseline value of 7.9 and 8.0. Similarly with Dapagliflozin 10 mg, mean HbA1c reduction ~0.84 against baseline value of 7.9 and with Empagliflozin 10mg and 25 mg, mean HbA1c reductions are ~0.7 and ~0.77 respectively against baseline value of 7.9 in Empagliflozin 10 mg and 25 mg arm (30-32). With SGLT2i, it is not only reducing HbA1c but also reducing blood pressure and body weight. Regarding body weight reduction with SGLT2 inhibitors, there is approximately ~2kg to ~2.5kg placebo corrected weight reduction in add on to metformin therapy in 2 years and that effect is sustained over 4 years (30-33). Most importantly SGLT2 inhibitor associated with 2/3rd fat mass loss and only 1/3rd of lean mass loss which resulted in reduction of weight circumference. (34) That means SGLT2 inhibitors truly works as comprehensive management by addressing glycaemic benefit as well as blood pressure and body weight reduction. SGLT2 inhibitors also address the core modifiable challenges of Indian phenotype characteristics like improve glucose disposal rate in skeletal muscle, improve beta cell function, reduce serum triglycerides and leptin (35-37). Apart from GLP-1a and DPP4 inhibitors, SGLT2 inhibitor also protects against glucotoxicity-induced apoptosis of pancreatic ß-cells (38). Thus in 2016 guideline of American Association of Clinical Endocrinology, SGLT2 inhibitor has been positioned ahead of DPP4 inhibitor after metformin as oral anti diabetic agent. (10)

Advantage of SGLT2 inhibitor in Type 2 Diabetes management:

SGLT2 inhibitor works through insulin independent pathway (39). In addition to this, its' efficacy also depends on serum glucose level which leads to have very less chances of having hypoglycaemia due to this molecule (40). SGLT2 co-transporters express also at alpha cell in pancreas and inhibition of this co-transporter leads to slight increase of serum glucagon level within physiological range that resulted into mild increase endogenous glucose production in liver (15, 41). SGLT2 inhibitor can be used as mono-therapy, add on to metformin, sulphonylurea, insulin, thiazolidinedione etc., as second and third line of anti-diabetic agent with comprehensive diabetes management outcome. (39)

Myth and Reality about SGLT2i:

There are certain myths with SGLT2i thus in clinical practice sometime it could have some challenges to welcome this molecule, but it will be helpful if the reality can be revealed for SGLT2i.

a) SGLT2i and its' action on T2DM pathology

As its' primary mechanism of action by reducing excess glucose through urine leads to

Table 2	Dapagliflozin	Canagliflozin	Empagliflozin
Tmax	~ 2 hours	1-2 hours	1-3 hours
Cmax	Dose-dependent increase in C_{max} and AUC	Dose-dependent increase in C_{max} and AUC	Dose-dependent increase in C_{max} and AUC
Mean Plasma terminal half life	12.9 hours (DAPA 10 mg)	10.6 hours (CANA 100 mg) and 13.1 hours (CANA 300 mg)	10.8 to 19 hours
Bioavailability	78% (DAPA 10 mg dose)	65%, dose not specified	-
Protein binding	91%; no diff in Hepatic Impairment or Renal Impairment	99%; no diff in hepatic or renal impairment	-
Dosage	10mg 5mg	100mg 300 mg	10mg 25mg
Kidney impairment dosage	eGFR upto 45ml/min/1.73m2= 10mg	Upto 60 eGFR=300 mg 45 to 60 eGFR=100 mg	Upto 60 eGFR=25mg 45 to 60 eGFR=10 mg
Selectivity	SGLT1 IC_{50} = 400–1400 SGLT2 IC_{50} = 1–6	SGLT1 IC_{50} = 684–710 SGLT2 IC_{50} = 3–4	SGLT1 IC_{50} = 8300 SGLT2 IC_{50} = 3
Route of elimination	75% excreted in urine, 21% in feces	33% excreted in urine, 41.5% excreted in feces, negligible enterohepatic circulation	21.4%–22.3% excreted in urine

Table 2: Pharmacokinetic & pharmacodynamic differences of dapagliflozin, canagliflozin and empagliflozin

reduction of development of glucotoxicity induced hyperglycaemic complication. Regarding action at ominous octet, core pathology of type 2-diabetes mellitus, SGLT2 inhibitor directly reduces glucose reabsorption in kidney and increase glucagon level due to action at alpha cell at pancreas. In addition to this, indirectly it improves beta-cell function in pancreas, increase endogenous glucose production in liver, increases lipid oxidation in adipose tissue and improve insulin sensitivity in skeletal muscle and induce more glucose utilization. Thus like as DPP4i and GLP-1a, SGLT2 inhibitor also have impact at diabetes pathology; Ominous Octet (15).

b) SGLT2i and Urinary Tract infection or Genital mycotic infection

Diabetes patients are at risk of developing bacterial or fungal infection. These infections are more common in uncontrolled diabetes patient. Lower urinary tract infection (UTI) is common in type 2 diabetes patients; has been reported up to 22% (42). Infection risk in patients with diabetes was directly related to glycaemic status of that individual (glycated haemoglobin (HbA1c) level; the risk was approximately 2-fold greater (adjusted RR, 1.76; 95% CI, 1.30–2.38) for patients with HbA1c levels in the highest quintile despite therapy with anti-hyperglycaemic agents. (43) Not even the bacterial infection, even for mycotic infection diabetes is an established risk factor for not only vaginal candida colonization but also development of *Valvovaginal candidiasis* (VVC), particularly in women with uncontrolled glycaemia. Risk of developing vulvovaginal infection is 81% greater in patient with T2DM (adjusted relative risk [RR], 1.81; 95% CI, 1.64–2.00). This is due to diabetes patient having diminished immune function in host (inhibiting neutrophil function, antigen presenting cell response etc). If hyperglycemia gets corrected, then there could be improvement in host immune defense mechanism. That could be reason behind rate of infection is more in uncontrolled glycemic patients than that of in controlled one (43). With SGLT2 inhibitor therapy, most of the events are mild to moderate in intensity, mostly responded at initial course of anti-biotic or anti-fungal therapy and once uncontrolled hyperglycemia gets corrected rate of recurrence rate is very less (44-45).

c) SGLT2i and Hyponatremia or electrolyte imbalance

Due to its' mechanism of action, SGLT2 inhibitor blocks sodium glucose co-transporter 2 in proximal convoluted tubule in nephron leads to stop entering glucose and sodium (Na+) into lining tubular cell. Apart from this SGLT pathway, there are several other pathways are responsible for sodium reabsorption in nephron. Sodium - hydrogen anti-port plays major role in sodium reabsorption.

About 60-70% of sodium reabsorption is happening through proximal convoluted tubule and just <5% of Na uptake along the PCT would

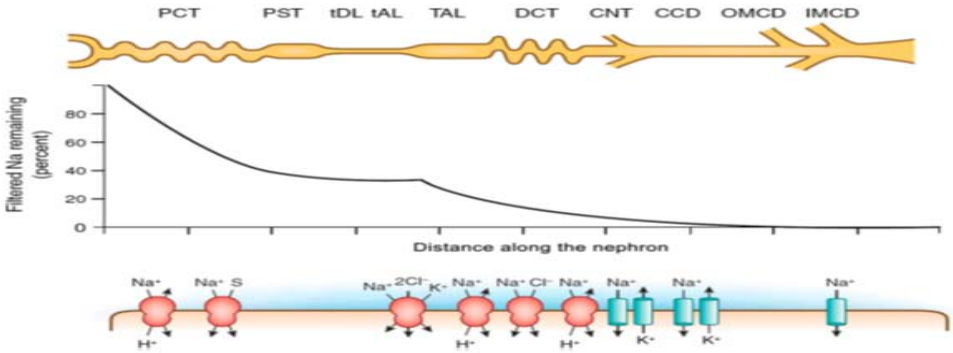

Figure 3: Na transport along the nephron.
CCD, cortical collecting duct; CNT, connecting tubule; DCT, distal convoluted tubule; IMCD, inner medullary collecting duct; OMCD, outer medullar collecting duct; PCT, proximal convoluted tubule; PST, proximal straight tubule; S, solute (various); tAL, thin ascending limb; TAL, thick ascending limb; tDL, thin descending limb

Image source: Lawrence G. Palmer and Jurgen Schnermann; Clin J Am Soc Nephrology: 2014

be mediated by the sodium glucose co-transporter SGLT2 (Figure 3.) (46). In 13 placebo controlled trial with Dapagliflozin, (Phase 2b and 3), mean change of serum potassium from baseline over 24 weeks is similar with placebo arm which merely have any clinical outcome due to sodium and potassium (46-47).

d) SGLT2i and Diabetic Keto-acidosis (DKA)

Risk of DKA among patients with T2DM on SGLT2i is quite low, probably numbering less than one in 1000 to one in 10,000. (48) There are two types of diabetic keto-acidosis, one is with raised blood glucose level and another is with normal blood glucose level (<300 mg/dl) that may be referred a euglycaemic diabetic keto-acidosis (euDKA). This is due to lesser amount of insulin secretion leads to use of glucose as substrate to generate energy is less, that leads to breakdown of fat to produce fee fatty acid and then followed by ketogenesis to enter inside kerbs cycle to produce energy. Thus it is very critical to select SGLT2 inhibitor patient. If patient is on insulin, the insulin dose can be reduced as per demand when in combination with SGLT2 inhibitor but should not be withdrawn along with this should not be prescribed in type 1 diabetes patient till the time of approved indication is available (Figure 4) (49).

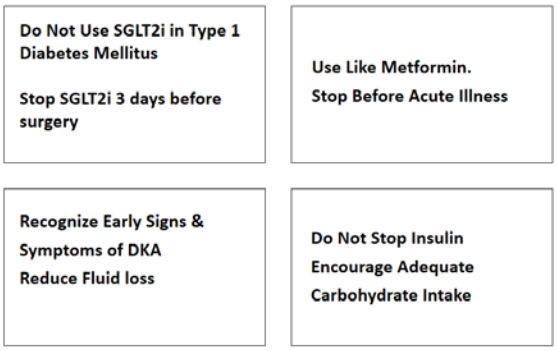

Figure : 4 Measure to prevent Diabetic ketoacidosis (DKA) with SGLT2i

e) SGLT2i and acute kidney injury (AKI)

In May 2016, FDA has come up with acute renal failure warning against Canagliflozin and Dapagliflozin based on 101 reported case from period from March 2013 to October 2015 reported at FDA adverse effect reporting system out of 1.5 million SGLT2 inhibitor usages. 73 cases were due to Canagliflozin and 28 cases due to Dapagliflozin. No case was reported for Empagliflozin. In US, Canagliflozin was launched in March 2013 followed by Dapagliflozin was launched in January 2014 and Empaglifloxin was officially launched in September 2014 and product was available from December 2014 onwards (50-53).

Of the 101 cases, 51 reported concomitant ACE inhibitor use, 26 reported concomitant diuretic uses, and 6 reported concomitant nonsteroidal anti-inflammatory drug (NSAID) use. A prior history of chronic kidney disease was reported in 10 of the 101 cases. In some cases, dehydration or hypotension was reported (50).

In clinical trial with SGLT2 inhibitors there were some case reported either as acute renal failure or acute kidney injury or more than 50% fall of eGFR from base line. In phase 2b/3 trial, 5 cases and 4 cases of were reported with canagliflozin 100 mg and 300 mg respectively; 1 case each were reported with dapagliflozin 2.5 mg and 5 mg respectively; 9 cases and 10 cases were reported with Empagliflozin 10 mg and 25 mg respectively. Empa-REG trial, CVOT (Cardiovascular Outcome trial) with Empagliflozin, 26 cases and 19 cases of acute kidney injury were reported with Empagliflozin 10 mg and 25 mg respectively (51-54).

Regarding renal safety with SGLT2 inhibitors, in phase 2b/3 trial, eGFR data is available with Canagliflozin, Dapagliflozin and Empagliflozin. For Canagliflozin, 2 years data, for Empagliflozin 1 year data and with Dapagliflozin both 2 and 4 years data of eGFR are available. In Empa-REG trial, 4 years eGFR data is available with Empagliflozin. In all across the trial with SGLT2 inhibitors, there were initially drop of eGFR within 1-2 weeks of initiation of treatment and later it normalizes (33, 54-57).

The drug safety communication stated that health care professionals should consider certain factors, including state of dehydration;

chronic kidney insufficiency; congestive heart failure; and taking other medications such as diuretics, anti-hypertension medication like angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs) (50).

f) SGLT2i and bone fracture & amputation.

The SGLT-2 inhibitor dapagliflozin, there is no significant alteration of bone turnover markers or bone mineral density in men as well as postmenopausal women with T2DM after 50 weeks (58) and 102 weeks of follow-up. There is no increase in fractures was observed in pooled data from patients with normal to mildly impaired renal function across the dapagliflozin clinical studies (52). In CANVAS study, there is more incidence of toe amputation was observed with Canagliflozin compared to placebo and if we can look the patient background, the people who had prior history of amputation, there risk of further amputation is high (51). In May 2017, USFDA FDA Drug Safety Communication confirms increased risk of leg and foot amputations with the diabetes medicine Canagliflozin based on new data from two large clinical trials (60). With Empagliflozin, in phase 2b/3 data, fracture incidence is comparable in both empagliflozin and placebo arm (3.9% vs 3.8%) (53) So overall with SGLT2i, incidence of fracture 3 per 1000 patients (52,57,61). There is no signal so far regarding this effect can assumed to be as class effect.

g) SGLT2i and hypovolemia or dehydration:

SGLT2 inhibitor works as osmotic diuretic and due to its mechanism of action there could be fluid loss of ~400 ml/day which is just one extra void of urine. (15) This urine output is spread throughout the day, and does not cause nocturia. However, in Indian climate presents health challenges in the form of heat exhaustion, hypovolemia and electrolyte imbalance to some extent.

Counselling must include advice to maintain adequate fluid and electrolyte intake, and awareness about symptoms of dyselectrolytemia. One should also ensure that SGLT2i are not co-prescribed with loop diuretics. There is no need to monitor serum electrolytes or renal function tests in persons on chronic SGLT2i management (62).

To choose a medicine, safety and efficacy plays an important role and if these are important than even the pioneer molecule like metformin is also having safety issue like lactic acidosis, sulphonylurea is having issues like hypoglycaemia, weight gain, other anti-diabetic and anti-hypertensive every molecules are having some pros and cons and as physician, it is a basic need to understand the balance between safety and efficacy that is where right selection of patient for SGLT2 inhibitor play an important role (63-64).

Which SGLT2 inhibitor is best?

Differentiation within the class of SGLT2 inhibitors is inconclusive. First of all, there is no head to head trial so far, but in safety analysis data of all these three SGLT2i available in India, Empa-Reg trial of Empagliflozin has published so far but that is also with patient of whom more than 99% had prior cardiovascular event earlier (54). Now for other two, with CANVAS trial for Canagliflozin and DECLARE -Timi 58 trial for Dapagliflozin are ongoing which consists of varying number of patient with prior history of cardiovascular event or earlier or are at risk of cardiovascular disease as primary prevention which are actually true representation of common patient time of day to day diabetic clinical practice. Recently CANVAS study has published which met the primary objective of 3P MACE which has proven superiority as well (51). So, as of now, the phase 2b/3 cardiovascular meta-analysis are available for Dapagliflozin which looks similar trends of what Empa-Reg & CANVAS study had shown, which shows cardiovascular benefit could be an class effect. Keeping that in mind any SGLT2 inhibitor can be added at initial course of anti-diabetic management across disease spectrum (51-52, 65-66).

Right selection of patient for SGLT2 inhibitor

SGLT2 inhibitor works through insulin independent pathway and this can be given all across disease spectrum of type 2 diabetes mellitus. As most of the guidelines are suggesting it can be added as add on to metformin, sulphonylurea, insulin etc as second or third line agent only few thing to be checked as should not be given in below 45 ml/min eGFR patient, type 1 diabetes, patient on acute surgery or acute illness, at severe dehydration, elderly patient or patient with history of recurrent infection. It can be given all across the patient of any category of body mass index (BMI) as glycaemic benefit result is similar irrespective of baseline BMI (67-69).

Conclusion

SGLT2i are the class of oral anti-diabetic agent which actually working as poly-pill, with glycaemic control it can also reduce blood pressure and weight which are actually an objective of comprehensive anti-diabetic management as suggested by most of the guidelines across. Out of all anti-diabetic agents available so far, all of them including DPP4 inhibitor have shown either cardiovascular neutrality or failed to show cardiovascular neutrality, but only this class of oral anti-diabetic molecule has shown cardiovascular benefit in two of the CVOT trial (EMPA-Reg and CANVAS) result published so far (51,54). This class of molecule has proven to have a positive effect in some of those modifiable factors towards developing challenging metabolic disease outcome which is nothing but addressing the unmet need of Indian phenotype. Keeping that comprehensive management in mind as per Indian context it is the high time that SGLT2 inhibitors should be added in all across the type 2 diabetes patient as an early add on anti-diabetic agent in appropriate patient profile as selection of right patient is the key to win in that race.

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Case Report

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An interesting case of Pulmonary Embolism with Type 2 Diabetes and Cushing Syndrome

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Abstract:

An unusual case of pulmonary embolism in a young male who presented with respiratory distress with a background of steroid treated bronchial asthma. None of the known risk factors including thrombophilia could be found. Newly discovered type 2 diabetes mellitus, steroid use, opiate abuse were considered to be unusual risk factors for his venous thromboembolism.

Introduction:

Pulmonary embolism is a life threatening condition, warranting prompt diagnosis and treatment. Young people usually have inherited risk factors like Factor V Leiden and prothrombin gene mutation. With no recognizable risk factors, the diagnosis is likely to be delayed.

Case summary:

A 36 year old male presented with dyspnoea and tremors for 10 days. He had no history of cough, orthopnoea, chest pain or haemoptysis. He was a known case of bronchial asthma for 10 years, on T. Prednisolone 10 mg daily for 2 years. An interesting past history was that the patient developed left leg pain a year back followed by generalized arthralgia and myalgia. The patient was seen by a local doctor, who without further evaluation started the patient on T. Aceclofenac, followed by T. Tramadol. Two months earlier, the patient was switched to T. Tapentadol (opioid analgesic) which he has been taking above the prescribed limit. General examination showed tachypnoea, SpO2 of 93% on room air, and signs of cushing syndrome like round facies, proximal weakness of limbs, 'buffalo hump' and striae. Cardiovascular examination showed sinus tachycardia with no signs of heart failure. Respiratory examination showed bilateral rhonchi. Neurological examination was unremarkable except for fine tremors.

He was clinically diagnosed to have acute exacerbation of bronchial asthma with chest infection. He was started on intravenous antibiotics, nebulisation, steroids and continuous oxygen. Chest x-ray showed upper mediastinal widening. His condition deteriorated with dropping oxygen saturation and he was immediately transferred to the ICU. 2D Echo showed an ejection fraction of 60%, mildly dilated right atrium, right ventricle, mild haziness noted in right pulmonary artery suggestive of thrombus and mild pulmonary hypertension. Then, computerized tomography (CT) thorax was done which showed partial pulmonary embolism involving almost all of bilateral segmental and sub segmental pulmonary arteries, dilated main pulmonary artery and patchy ground glass density over both upper lobes suggestive of atypical infective aetiology / pulmonary embolism. Lower limb doppler showed deep vein thrombosis (DVT) in the left leg involving left superficial femoral, popliteal and anterior tibial vein with no evidence of DVT in the right leg.

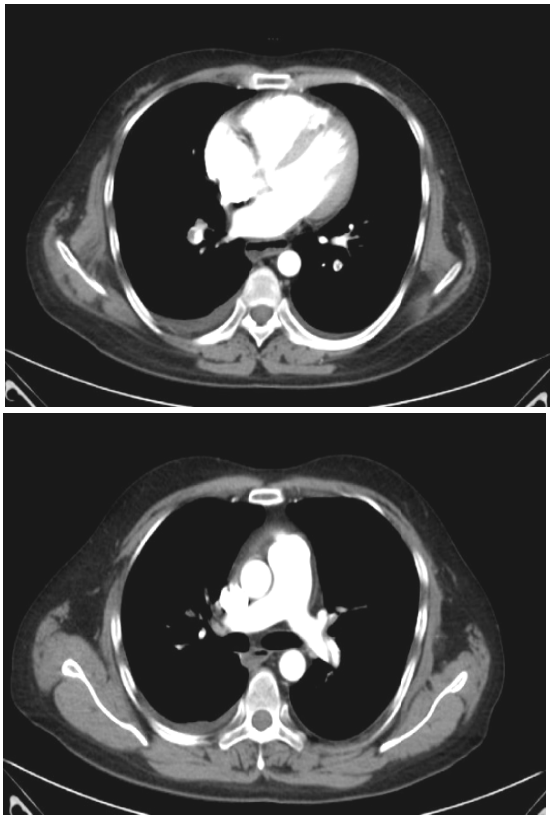
Other notable investigations include HbA1c - 6.9%, FT4 - 1.39 ng/dl, TSH - 2.9 miu/L, Serum cortisol - 8.58, BUN - 15mg/dl, Creatinine - 0.7 mg/dl, LFT - Normal, Antinuclear antibodies - negative, Homocysteine level - normal, D-Dimer - 2.39, FDP - positive, thrombophilia screen - Proteins C, Protein S, antithrombin and factor V Leiden mutation analysis report were negative and BNP - 239.5.

Type 2 Diabetes was discovered incidentally. He was started on low molecular weight heparin (LMWH) and T. Acitrom

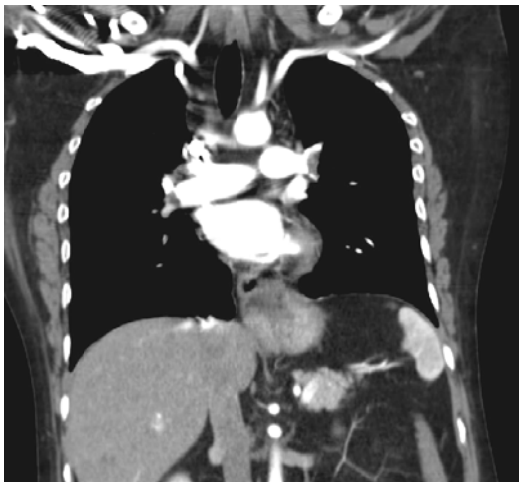
(Phenindione) and monitored to keep the INR >3. Patient improved well and was discharged with T. Phenindione, T. Prednisolone, and bronchodilators. Acitrom diet and Diabetic diet was recommended and advised to follow up for INR and blood sugar monitoring.

Images:

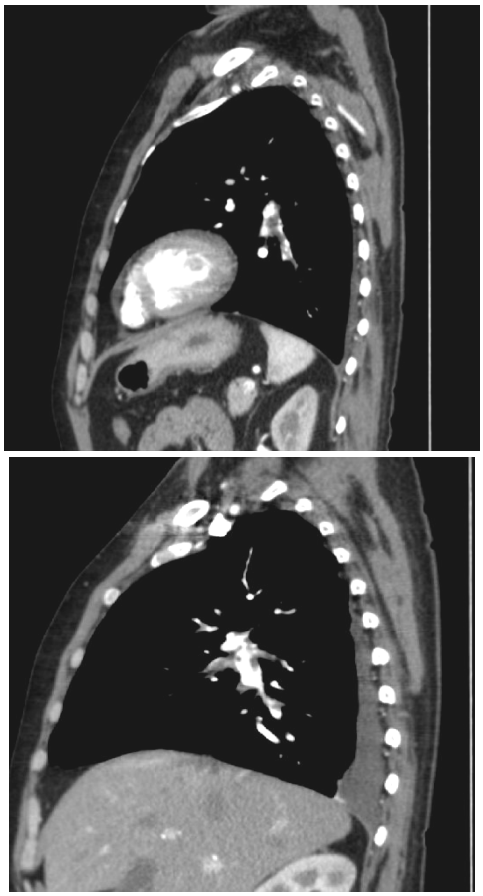
1. CT Thorax (Axial Section)



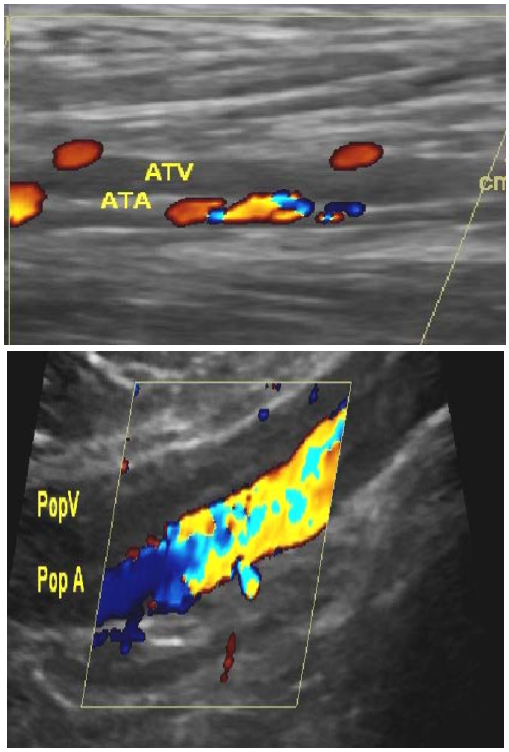
2. CT Thorax (Coronal Section)

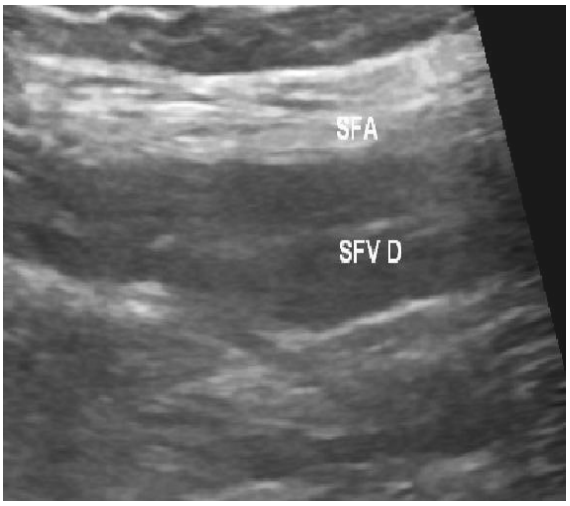


3. CT Thorax (Sagittal Section)



4. Left Lower Limb Doppler





Discussion:

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE) are common vascular conditions with well established risk factors [9,10]. There are acquired, genetic and mixed risk factors. Acquired risk factors include age, recent surgery, active cancer, immobilisation, hyperthyroidism, polycythemia, hormone therapy, obesity and heavy cigarette smoking. Inherited risk factors include antithrombin, protein C, protein S deficiency, factor V Leiden and the prothrombin G20120A mutation. Mixed causes include hyperhomocysteinemia.

In our case, the patient did not have any of the common risk factors associated with VTE. Several epidemiological studies have reported associations between obesity, metabolic syndrome and type 2 diabetes with VTE [2,3,4,5]. Probably dehydration and endothelial dysfunction in diabetes may contribute to thrombosis. Studies have shown that use of glucocorticoids can increase the risk for venous thromboembolism. It is likely to occur within last 90 days of use [6,7,8].

Another significant factor playing a role was the inability of the primary physician to evaluate the patient based on his complaints of left lower limb pain a year back. This forced the primary to give steroids and later opioid analgesics to symptomatically manage the patient. The nontraditional risk factor 'opioid abuse' was also considered in our case and there is literary evidence to suggest the same [11,12].

Highlights/Conclusion:

- The primary physician failed to evaluate the symptoms but instead started the patient on pain management.
- The patient is a young male with none of the well established risk factors.
- Diabetes and abuse of steroids and opiates might have contributed to the VTE.
- The therapeutic decision of duration of anticoagulant therapy is challenging.

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Unexplained Hypokalemia & unusual arrhythmia

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Abstract:

We had a 50 yr old lady, not a known diabetic so far, presented with 15 days of constipation, general weakness & loss of weight. Clinically she had mild abdominal distension and irregular pulse. Investigations revealed moderate hypokalemia, random blood glucose 238mg% with HbA1c 10.8% and ECG changes of hypokalemia with premature atrial contractions changing to atrial bigeminy. After correcting K and controlling Blood glucose, the rhythm reverted to normal sinus and constipation was relieved. Abdominal distension reduced. We are discussing the possible causes for the constipation and hypokalemia. And we presume that atrial bigeminy is a rare entity with hypokalemia. We discussed the cause & mechanism for these abnormalities, and emphasize the need for detecting Diabetes in the community.

Keywords: Hypokalemia, Atrial Bigeminy, Constipation

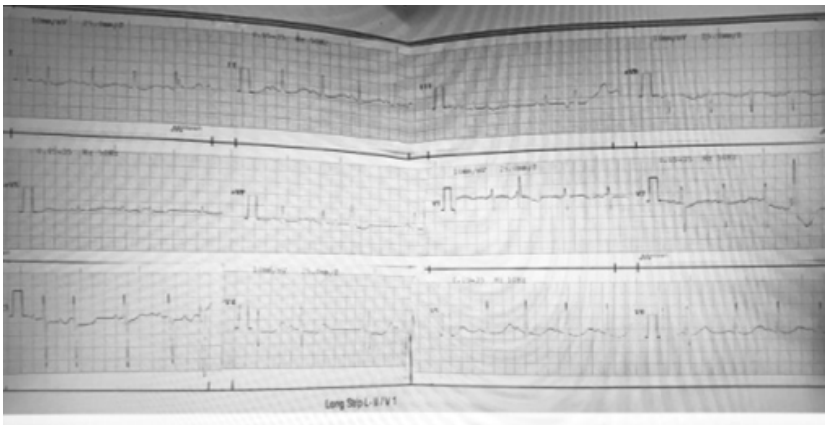
Introduction:

General weakness, constipation, loss of appetite and loss of weight are very common day to day complaints encountered daily by every practitioner. When we investigated a patient with all these complaints, we came to understand that one very common disorder may produce these symptoms. Surgical conditions of constipation can be easily diagnosed and we ruled out those causes. Weight loss is a frequent presentation of Diabetes Mellitus (DM). Increase in appetite is mostly associated with DM but our patient had loss of appetite. After investigations and treatment we have one explanation for all these symptoms that is the hypokalemia and we discuss the pathogenesis.

Case presentation:

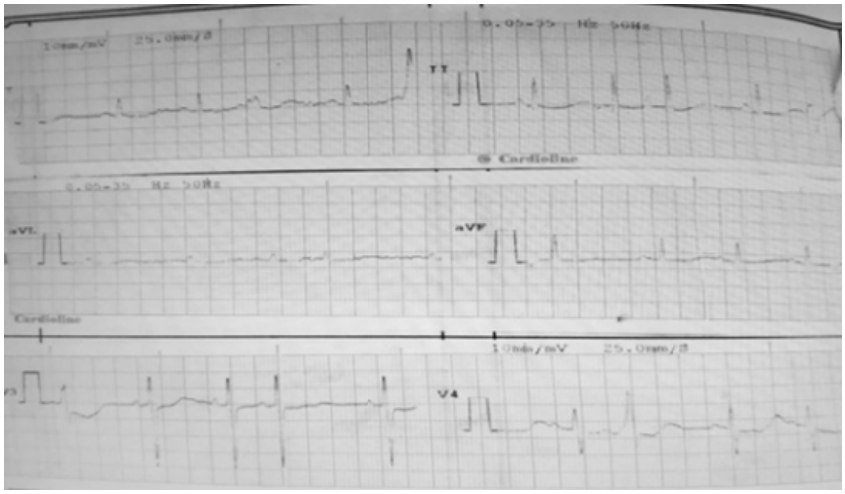
A 50 year old lady, Mrs. Kanniyammal came with complaints of Loss of appetite, Loss of weight -2 months, general weakness and constipation for 15 days. Patient was apparently normal before 2 months; developed loss of

Fig 1. Interpretation of ECG - 1 On 24/10/17



NSR; HR- 88/min; 5 to 7 atrial premature complexes seen in many leads; One with aberrant conduction. Patient was started on Diabetic diet, Tab. Metformin 500 1 tds; Syp. KCl 10ml TDS, Syp. Sucralfate 5mL TDS, T. Dulcolax 5mg 0-0-1

Fig 2. Interpretation of ECG -2 On 27/10/17



SR - 68/mt; Multiple atrial premature complexes; More in number than previous ECG; T wave flat all leads; U wave V4 V5 & V6.

appetite and lost 3 kg weight in 2 months. H/o constipation for 2 weeks but she has been passing flatus and scanty stools. There is no h/o nausea, vomiting, passing blood in stools, or alternating with diarrhea; neither there is any h/o fever, nor any drug intake. She denied h/o Polyuria or increased thirst. She is not a known case of DM, hypertension or thyroid disorder.

General examination: Patient was conscious and oriented; moderately built and nourished. She was not anemic and mildly dehydrated. There was no pedal oedema.

Vitals signs:

BP: 110/70mm Hg; Pulse: 82/min**,** irregular pulse, Temp: 97.6^0 F, RR: 20 cycles/min

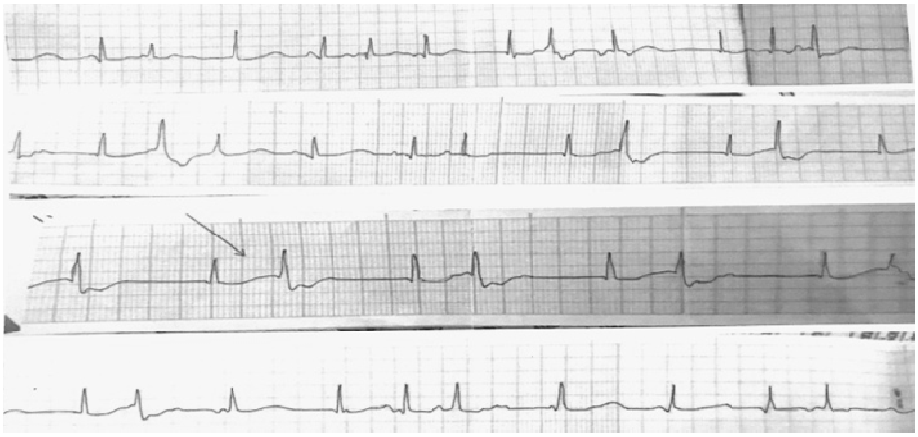
Systemic examination:

Abdomen: Soft, mild tenderness over the epigastric region; Abdominal distension was there; *Adb. Circumference:* 76cm; Bowel sounds heard sluggishly; CVS: S1, S2 heard; no murmurs; *RS*: NVBS heard bilaterally and *CNS:* normal.

Investigations:

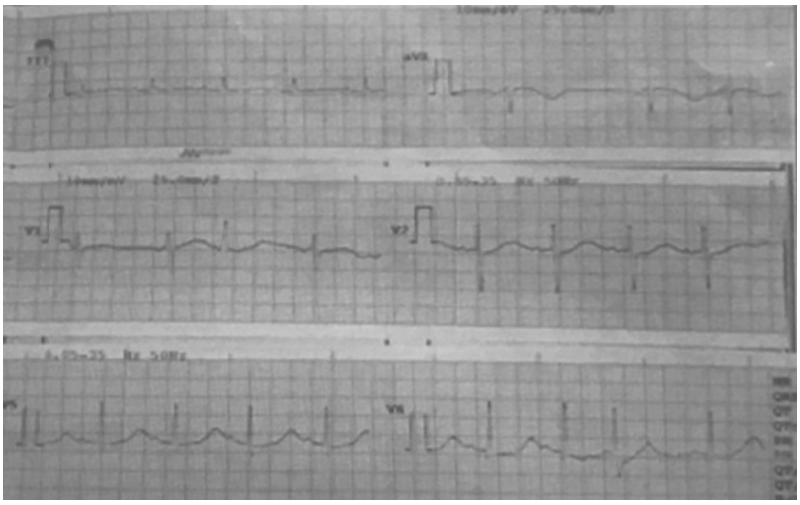
On 24/10/2017, Hb: 11.9%. PCV: 35.8%. WBC: 6920/cu mm, Random Blood Glucose: 228.5mg/dL, Tot. Bilirubin: 1.5 mg/dL, Direct Bilirubin: 0.6mg/dL, Indirect Bilirubin: 0.9 mg/dL, Tot proteins: 6.6g/dL; Albumin: 3.2g/dL, SGOT, SGPT, ALP: normal; Blood urea: 29

Fig: 3 Interpretation of ECG - 3 On 28/10/17



Sinus rhythm with atrial bigeminy. HR – 83/mt

Fig: 4 Interpretation of ECG - 4 on 30/10/17



NSR ; HR – 88/MT; Bigeminy reverted; Few APCs seen in avF, V1, V6

mg/dL, Serum Creatinine:1.3 mg/dL, Uric acid: 6.6mg/Dl; Urine routine:Sugars [+]; Proteins [+]

On 25/10/2017, FBS: 184mg/dL; **HbA1c: 10.5%**

On 26/10/2017; Sodium: 132mEq/L, Potassium: **2.5mEq/L,** Chloride: 97mEq/L; USG abdomen: Imp: Fatty liver

On 28/10/2017; T3: 107.91ng/dL (ref value 70-204); T4: 17.5µg/dL (ref value 5.10-14.1); TSH: 0.49µIU/mL (ref value 0.27-4.2).

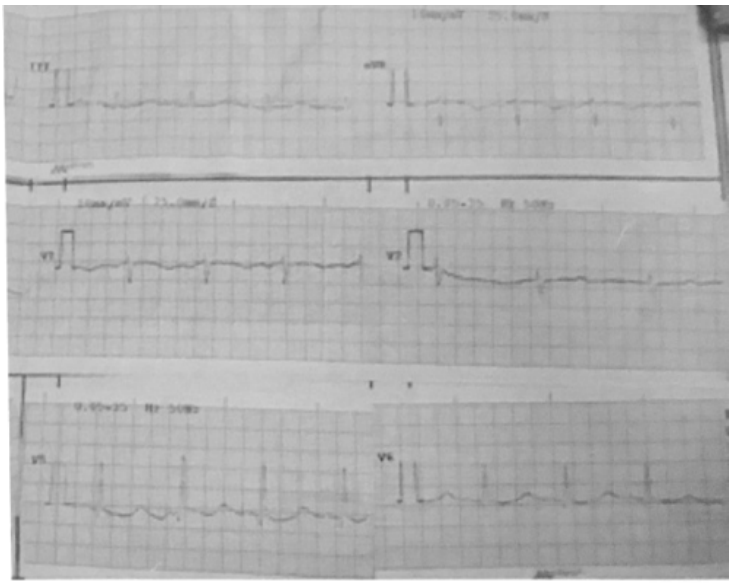
Patient was started on T. Digoxin 0.25mg ½ -0-0, Inj. Heparin 5000U IV sc 6th hourly; Continued with Syp. KCl, OHAs and other drugs; Soap water enema was given.

On discharge Pt was stable comfortable with pulse rate of 82/mt; regular BP 140/82 mmHg, Passed stools with abdominal circumference of 72 cm.

Discussion:

Constipation is a very common complaint, frequently treated by every practitioner. In the vast majority of cases (probably >90%)

Fig: 5 Interpretation of ECG - 5 on 01/11/17



NSR; HR – 60/mt; No APCs

there is no underlying cause[2]. The major surgical causes like GIT obstruction due to malignancy or benign mass are rare and medical causes are common. Our patient is not a known Diabetic, presented with loss of appetite for 2 months, general weakness and constipation for 2 weeks duration. We admitted her and investigated to find out the causes for her symptoms and treated accordingly. We noted her Random Blood Glucose was 228.5mg/dL and the Gly.HbA1c was 10.5%! This indicates that she must have been a diabetic for more than 2 months. During the previous weeks of admission, they celebrated Diwali, and surely she would have consumed lot of sweets and increased her glucose load and blood glucose might have increased to very high levels, resulting in several clinical and metabolic complications.

Diabetic patients can develop constipation by various ways,[1]. Diabetic enteropathy and autonomic neuropathy[4,7] are few mechanisms. Because of loss of appetite, she might have been taking less food, lacking in fiber content and bulk which could cause constipation. Another biochemical finding we noted is the hypokalemia (Table 1). Hypokalemia is also a cause for constipation[4,7,9]. Hypokalemia is classified according to the serum potassium concentration.

Table 1. Serum Potassium level

Date	Sr. Potassium level
24/10/2017	2.5
26/10/2017	2.5
28/10/2017	2.5
29/10/2017	4.2
01/11/2017	2.5

**(ref value: 3.5-5.1mEq/L)*

Hypokalaemia is defined as a serum concentration of potassium <3.5 mmEq/K or mmol/L (Table 2). Serum potassium level of 2.5–3 meq/l (Normal: 3.5–5.0 meq/l), may cause muscle weakness, myalgia, muscle cramps and constipation (from disturbed function of smooth muscle) [8, 10, 11].

Table 2. Hypokalemia is classified as follows [6].

Severity	Level of potassium (mEq/dL)
Mild	3 to 3.5
Moderate	2.5 to 3
Severe	Less than 2.5

On examination we noted her pulse was irregular and ECG (Fig.1) showed multipe atrial extrasystoles. The characteristic hypokalemic changes[3] (Table 3.) were seen.

Table 3. The usual ECG changes in hypokalemia[3].

S.No	ECG manifestation
1.	Progressive diminution with eventual disappearance of the T wave
2.	Progressive increase in the amplitude of the U wave
3.	Fist and second-degree AV block
4.	Depression of the ST segment

Abdomen was distended (78cm girth) which could be due to disturbed function of smooth muscles & partial intestinal paralysis known to occur with hypokalemia[9]. At potassium <2.5 mmol/L, serious neuromuscular problems emerge. To remember the common causes of hypokalemia easily, the mnemonics "D" reasons (Table - 4) is useful[2,9].

Table 4. Causes of hypokalemia - the mnemonics "D" reasons[2,9]

1.	Diet	Not taking fruits, fresh vegetables, eating disorders such as anorexia nervosa and bulimia, DASH diet,
2.	Drinks	Alcohol, excessive cola
3.	Diarhoea	Vomiting, diarrhea, RT aspiration, GIT fistulas
4.	Dialysis	Renal failure, renal tubular acidosis, Dialysis
5.	Drugs	Diuretic, Dulcolax-Laxatibe abuse, Dilators of bronchi,

		Digitalis, amphotriin B, Beta agonists and Insulin
6.	Diaphoresis	Excessive sweating due to any cause
7.	Diueresis	Any polyuria, diabetes insipedes
8.	Diabetes Mellitus	Any polyuria, diabetes insipedes
9.	Ductless gland disorders	Cushing's syndrome, cortisone therapy, hypothyroidism
10.	Deficiencies	Magnesium, Folic acid

General weakness, loss of appetite, constipation, distension of abdomen and ECG irregularities are all could be explained as due to hypokalemia.

What is the exact cause of hypokalemia? We searched the literatures and discuss in this article.

In Type 2 Diabetes very high blood glucose may cause Insulin resistance and hyper-insulinemia. The excess endogenous insulin can provoke hypokalemia[2]. Insulin resistance may lead to, fat cells liberating fatty acids which are converted to ketones. The ketonemia and accompanying acidosis can lower the extracellular potassium, shifting potassium into the cells causing hypokalemia[1,2]. As levels of insulin increase in the blood due to resistance, more potassium is driven into cells; therefore, hyper-insulinemia, can be associated with hypokalemia. Hyperglycemia induced osmotic diuresis can deplete potassium, leading to hypokalemia [1]. The cause of hypokalemia in our case could be multifactorial.

Hypokalemia is not an uncommon condition. Since we don't do the serum electrolytes test routinely, several cases of hypokalemia are missed. Clinical features of exhausted feeling, muscle cramps, constipation and abdominal distension are indications for serum electrolyte test. The causes of hypokalemia in diabetics include: (1) redistribution of potassium [K^+] from the extracellular to the intracellular fluid compartment (shift hypokalemia due to insulin administration); (2) gastrointestinal loss of K^+ due to mal-absorption syndromes (diabetic-induced motility disorders, bacterial overgrowth, chronic diarrhea states) and (3) renal loss of K^+ (due to osmotic diuresis and/or

Figure 1.1: Summary of Dietary Recall over the years.

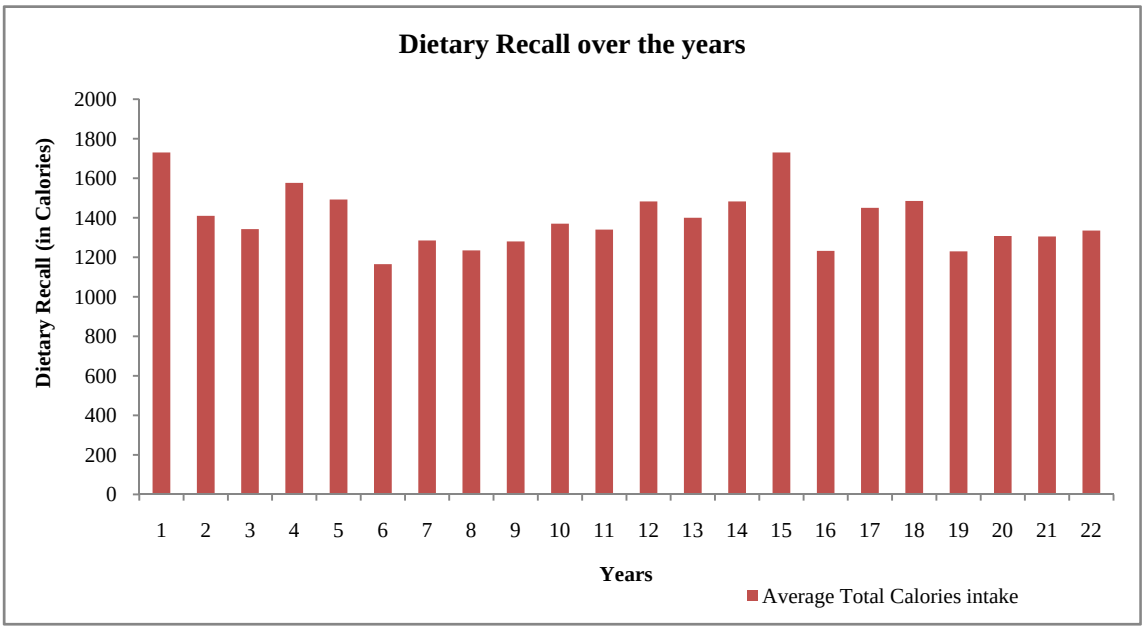
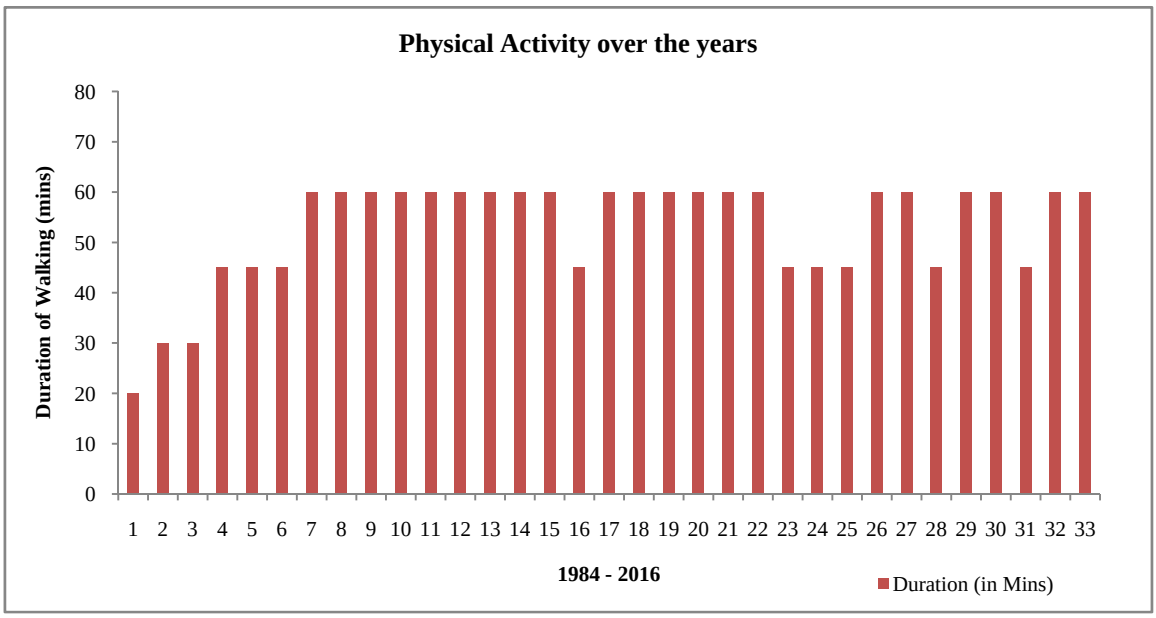


Figure 1.2: Summary of Physical Activity over the years.



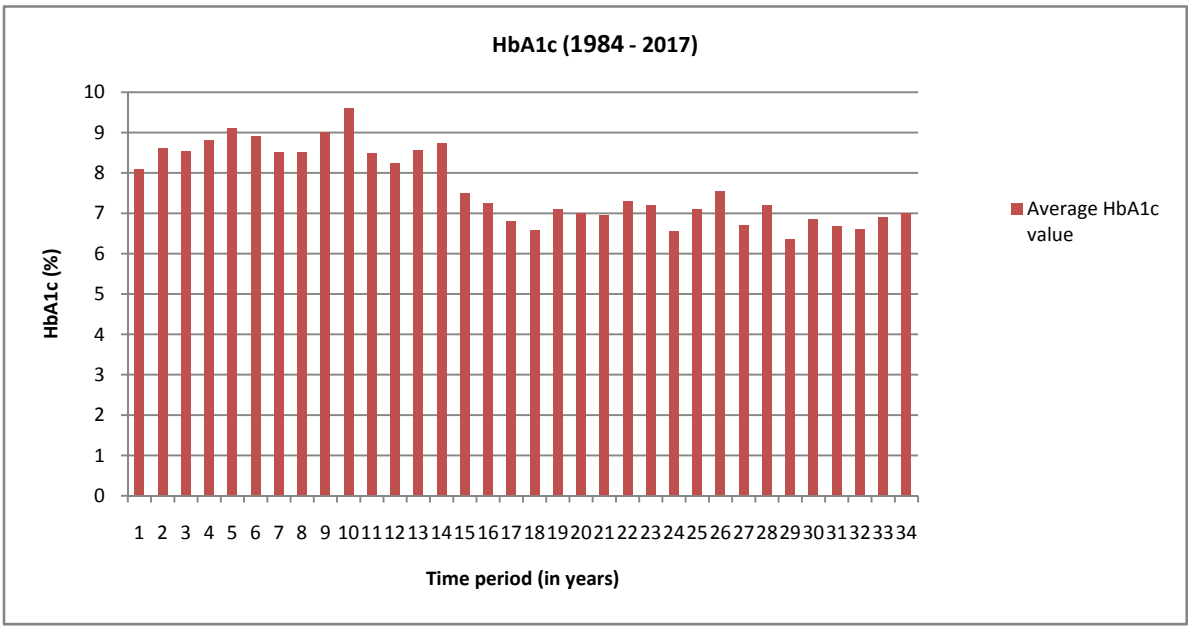
coexistent hypomagnesemia[8,9].

In our case the hypokalemia could also be due to very low or nil dietary source (One of the causes of low serum potassium). The usual ECG changes in hypokalemia are seen in one ECG (fig.2). Hypokalemia can aggravate the cardiac arrhythmic tendency [2].Atrial fibrillation is a common event in hypokalema[6]. Lower potassium levels in the extracellular space cause hyper polarization of the resting membrane potential. This delayed re-polarization may promote reentrant arrhythmias[4,2]. Our patient had multiple atrial premature complexes, ultimately developed atrial bigeminy. This is due to the phenomenon of "Rule of Bigeminy".

The rule of Bigeminy[3]:

Extra systoles tend to follow long RR intervals – this is the rule of bigeminy. Bigeminy is

Figure 1.3: Summary of Glycated Haemoglobin (HbA1c) over the years.



a heart rhythm problem in which there is a continuous alternation of long and short heart beats. Most often this is due to ectopic beats occurring so frequently that there is one after each sinus beat. A long cycle or R-R interval precipitates an ensuing ventricular extrasystole. (Premature complex) The compensatory pause of the extra systole in turn constitutes another long R-R interval which tends to precipitate a further extrasystole. This process is thus self-perpetuating, resulting in bigeminal rhythm[13].

Some conditions (differential diagnosis) causing Bigeminy3:

1. Alternate ventricular premature complexes (common) – ventricular bigeminy
2. Alternate atrial or nodal extrasystoles – Atrial or juntional bigeminy
3. Any form of 3:2 AV block
4. Atrial flutter with alternating 4:1 and 2:1 AV block

Hypokalemia is associated with a 10-fold increase in hospital mortality due to the adverse effect on the cardiac rhythm, blood pressure and cardiovascular morbidity. [2]

Conclusion:

We present this case report mainly to stress on screening necessity for electrolytes in situations of general weakness, loss of appetite and constipation especially in diabetics. On scrutinizing the literature, it is seen that atrial bigeminy is a rarer incidence than ventricular bigeminy[5,6]. But in our case we noted atrial bigeminy**.** It is seen in this case that the entire problem eventually points to Diabetes Mellitus. The patient was totally unaware of Diabetes and developed complications. There are so many patients of Diabetes in the community, not knowing that they are Diabetics. Unless we screen the individual, they may go for complications. We emphasize the need for detecting diabetes at any available opportunity. Whenever a patient comes for medical aide it is mandatory to r/o diabetes

Acknowledgement:

Our sincere Thanks to the Management, Dean and Medical Superindendent of Karpagam Faculty of Medical Sciences & Research, Coimbatore – 641032 for permitting us to publish this article to "The Journal of the Association of Physicians of India" (Tamil Nadu State Chapter).

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Case Report of a model patient with controlled Diabetes Mellitus over a period of 33 years

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Abstract:

Excellent compliance to treatment plan is the key to achieving long lasting glycemic control over a period of 33 years.

Introduction:

Patients with Diabetes Mellitus (DM) are encouraged to follow a healthy lifestyle consisting of proper, timely and balanced dietary intake; regular physical activity (walking, yoga, or aerobics); routine self-monitoring of blood glucose (SMBG); hygienic personal habits (no smoking, alcohol or tobacco) and regular medications as per the treatment and management plan. Improper, reduced or no adherence to the treatment plan will result in poor glycemic control and increased financial burden to the patient (1).

Case Presentation:

A female aged 82 years with a history of T2DM since 1984. Initially IGT diagnosed, she was diagnosed as a T2DM patient during a pre-op glycemic control check for cataract surgery of the right eye.

On routine once in three months examination - her vitals were found to be stable with a blood pressure of 120/80. Her physical examination showed a normal healthy Body Mass Index (BMI) of 19.95kg/m^2 (Height = 1.58m and Weight = 49.8kg) with a waist circumference of 30cm and 35 percentage of body fat. On history collection - her family history for DM was positive (Siblings), while that of HTN and IHD was negative. She had a positive history of Dyslipidemia since 2010 and had Diabetic Peripheral Neuropathy since 2007. She underwent cataract surgery of the left eye three years prior to T2DM diagnosis and also Arthoplasty of the right shoulder in 2007. She is currently on the medication regimen of Glipizide 5mg+Metformin 500mg and Voglibose 0.2mg twice a day for diabetes control, Rosuvastatin 5mg for cholesterol, also on multivitamins – Neurobion Forte and Bon K2 HD.

Periodic dietary counseling indicated an adequate intake of total calories in the range of 1100 to 1300 kilocalories with a Total CHO = 174.3, Total Protein = 37.25g and Total Fat = 22.20g. She followed a 5 meal pattern with all meals taken on time and no deviation from the diet chart given on her first visit to the tertiary care centre in 1984. Furthermore, patient has been on pure vegetarian diet since 2004. The following was observed during the routine Education counseling – timely OHA medications, regular physical activity (1 hour walking daily) and regular Self-Monitoring Blood Glucose (SMBG) especially daily FBS.

While her blood sugars showed proper glycemic control with following test results – Fasting glucose = 120mg/dl, Post Prandial glucose = 118mg/dl, HbA1c (three month average blood sugar) = 6.8; her kidney profile showed normal kidney functioning with Serum Urea = 35, Serum Creatinine = 0.8, Estimated Glomerular Filtration Rate (eGFR) = 69 and Renal Function Tests showed a normal Albumin/Creatinine ratio (A/C ratio) of 8. Her lipid profile showed a clear nature of serum with Triglycerides of 127mg/dl, Total Cholesterol of 148 mg/dl, HDL Cholesterol of 48 mg/dl, LDL Cholesterol of 78 mg/dl and Non-HDL Cholesterol of 100mg/dl. Patient's electrolytes report was also normal with following results – Sodium = 138, Potassium = 4.2, Chloride = 102,

Bicarbonate = 27, Anion Gap = 9 and Ionized Calcium of 1.1. Furthermore, Liver Function Test indicated normal functioning with Total Bilirubin = 0.7, Total Protein = 7.1g, Serum Albumin = 4.4, Serum Globulin = 2.7, S.G.O.T = 23, S.G.P.T = 16 and Alkaline Phosphatase = 132. Eye test report indicated no Diabetic Retinopathy.

Discussion:

The patient presented with controlled T2DM and co-morbidity of Dyslipidemia, which was also in control as a result of her proper management plan and medications. The summarization of her healthy lifestyle over the years is presented in Figure 1.1 and 1.2. On patient's first visit a dietary recall of 2060 calories was calculated and she was advised to maintain a total intake of 1600 calories. The patient stated that strict control over her intake, proper meal timings, five meal pattern, inclusion of healthy intermediate snacks and regular exercise (walking for 1 hour daily) made it possible for her to manage her diabetes in a healthy manner. The importance of diet and regular exercise has been mentioned in the American Diabetes Association and European Association for the Study of Diabetes, Guidelines as part of the treatment plan for patients with T2DM (2).

It is important to understand that Compliance and Adherence are two different concepts often used in place of the other. Compliance is defined as 'the extent to which a person's behavior coincides with medical advice' (3); while Adherence stands for 'active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result' (4). The patient's compliance to the plan advised by her consultant and the team of health care personnel was the key towards her achieving the Target 7% goal. Also, over the years, patient was regular with her Oral Hypoglycemic Agents (OHA) medications. As shown in Figure 1.3, the aforementioned factors helped her in maintaining HbA1c levels in the range of 6.5 to 7.5%.

Conclusion:

Regular follow-up of once in three months, adherence to the medication regimen, self management of blood glucose and maintaining a healthy lifestyle are the cornerstones of lifelong proper glycemic control.

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TAPI Journal Vol. 9, Issue 3, Sep – Dec 2017

Dermatology photo feature

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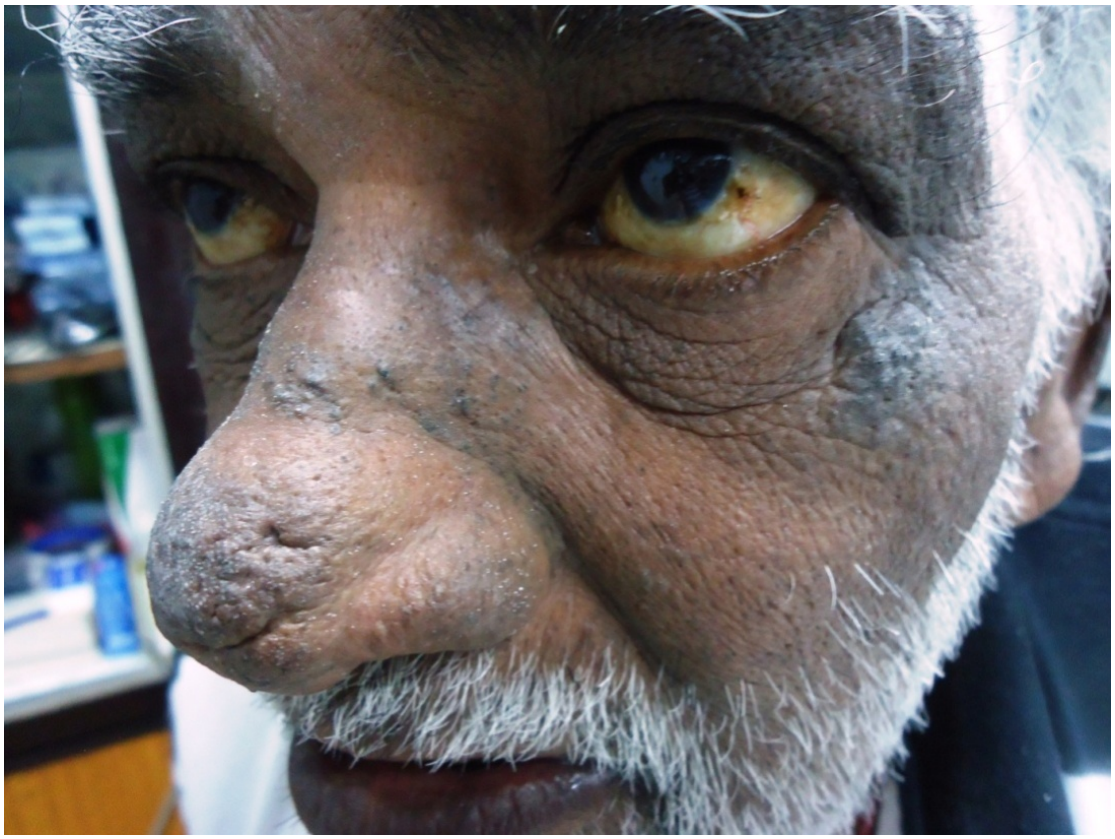

A 55 year old male presented with a 10 year history of multiple raised lesions over the face especially over the nose. He had history of aggravation on exposure to heat and alcohol consumption. He also had complaints of disfigurement of the nose. He is a known alcoholic with abundant consumption of alcohol since the last 20 years. He is a known diabetic on treatment since the last 10 years. On examination there were multiple erythematous to pigmented plaques over the face with nasal predominance. Multiple open comedones were seen over the nose and the nasolabial region. Pitting, scarring and a few telangiectasias on closer examination along with bulbous disfigurement of the nose were also seen.

Diagnosis: Rhinophyma

Pathogenesis:

Rhinophyma has multifactorial etiology. The primary etiology is superficial unregulated vasodilatation. Unregulated superficial vasodilatation leads to vascular instability and further leads to extravasation of fluids resulting in prolonged edema of the interstitial dermis leading to localized inflammation. Increased mast cell infiltration and macrophage and keratinocyte activation leads to the up regulation of fibrosis promoting matrix metalloproteinases.

The enlarged blood vessels lead to induration of skin. The edema and inflammation leads to the erythematous and swollen appearance of the nose. Fibrosis leads to scar formation

subsequently leads to an irregular nodular appearance and scar formation. There is also hypertrophy and hyperplasia of the sebaceous glands. Prominent pores and oozing of sebum may also be seen. Alcohol and caffeine consumption may aggravate the condition due to local vasodilatation caused by these substances.

Description/ Clinical picture:

Rhinophyma is a finding seen in advanced stages of stage IV rosacea. The other names for this condition are copper nose, bulbous nose, beer drinker's nose and brandy nose. It is a benign skin condition with tumorous growth in which an erythematous, large and bulbous appearing nose is seen. It is more commonly seen in men and in the fifth to the seventh decade of life.

In the first stage of rosacea facial flushing is seen. This then leads to the second stage in which persistent facial erythema, telangiectasias and thickened skin is seen. This is then followed by erythematous pustules and papules over the face. Rhinophyma is the fourth and final stage in which the skin over the nose is erythematous with telangiectasias. Fissuring and scarring is also seen. As the condition progresses the nasal tip becomes enlarged and the skin over the nose hypertrophies. This leads to distortion of the nasal architecture leading to a bulbous appearance. Tumorous growths can develop in the late nodular forms of the condition. Secondary airway obstruction may also be seen. The bony and cartilaginous frameworks remain unaffected in majority of cases. Few non melanoma skin carcinomas have been reported in cases of long standing rhinophyma. Certain changes such as rapid growth pattern, ulceration and drainage should be considered as suspicious factors for malignancy.

Management:

Avoidance of sun exposure, cessation of alcohol consumption, reduction of caffeine consumption, and reduction of consumption of spicy food, avoidance of exposure to heat and avoidance of strenuous exercise is necessary to prevent aggravation of the condition. Usage of PABA free sunscreens with both UVA and UVB protection is required. Physical sunscreens such as those containing zinc or titanium oxide is preferred.

Rhinophyma responds poorly to medical lines of therapy and it needs surgical management although rosacea in the early stages respond to topical antibiotics and retinoids. The main purpose of surgical treatment is to remove tissue outgrowths and reshape a disfigured nose thus improving the cosmetic appearance of the patient.

The various procedures which can be done include microdermabrasion, cryotherapy, electrocautery, radiofrequency ablation and heated scalpel. Fractional lasers such as Erbium-YAG laser and fractional Co2 laser can also be used. Ablative lasers such as unfractionated Co2 laser are not preferred in Indian skin types due to the side effects of hypo or depigmentation or hyper pigmentation although aggressive ablative laser treatment may be required in advanced cases.

Surgical modalities such as tangential excision, scissor sculpting, excision with skin grafting and even rhinoplasty may also be needed in more severe cases. A combination of procedures usually yields better results. In case of malignant pathology Moh's excision or full thickness nasal skin excision with nasal reconstruction may be required.

TAPI Journal Vol. 9, Issue 3, Sep – Dec 2017

Narrow QRS tachycardia in a young female

Dr. T.R. Muralidharan*, Dr. Subash Chandhar T**

**Head of the department, **Department of Cardiology, Sri Ramachandra University*

A 31 year old lady came to the hospital for paroxysmal palpitation. On casual examination she was noted to have a pulse rate of 160/min. She was otherwise asymptomatic, systemic examination revealed no abnormalities. Hence an ECG was done as the next step of evaluation. ECG done showed features of narrow complex regular tachycardia with no obvious discernible P waves, with a heart rate of around 180/min. Her thyroid profile and electrolyte panel were within normal range. Now the possibilities entertained are:

(i) AVNRT;

(ii) Atrial tachycardia

(iii) Junctional tachycardia and

(iv) Sinus tachycardia.

Note: *Refer page 35 for Answer and Explanations – ECG Section*

TAPI Journal Vol. 9, Issue 3, Sep – Dec 2017

Toxicology clinics-bench to bed side Allergy, Anaphylaxis and Angioedema -I

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Introduction:

Allergic reactions and anaphylaxis are potentially life-threatening processes that present with a variety of clinical symptoms. Clinicians must be able to recognize these presentations and make prompt clinical decisions regarding management of a patient's airway, treatment options, and disposition of a patient who improves after initial presentation. Furthermore, clinicians may be faced with patients who have atypical presentations or require special consideration, such as high-risk patients with comorbid conditions and patients who do not respond to first-line treatments.

1. What is meant by Allergy?

It is defined as a misguided reaction by the immune system to allergens, especially a particular food, pollen, fur, or dust that are harmless for most people to which it has become hypersensitive.

2. What is meant by Anaphylaxis?

It is defined as acute onset of severe, life-threatening, generalized or systemic hypersensitivity reaction.

3. What are the clinical criteria's to be fulfilled for Anaphylaxis?

According to the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

A. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

B. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence);
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

C. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

4. Will Anaphylaxis present without any urticaria or mucosal signs?

Yes, based on the definition patient can have anaphylaxis without any urticaria or mucosal

signs. Furthermore, in the patient with known allergies, anaphylaxis may present as isolated hypotension.

5. Can an allergic reaction cause hypertension?

Yes, during an allergic reaction the body comes under a lot of stress which can contribute towards high blood pressure. This is particularly true if the allergy is undiagnosed and the body is in a constant state of allergen 'fighting', i.e. because of a specific food.

6. Can abdominal pain and/or vomiting without other symptoms will it be a feature of anaphylaxis due to insect allergy?

Yes, abdominal pain and/or vomiting to a food or medication, this is considered as mild to moderate symptom. However, if someone experiences abdominal pain and/or vomiting after being stung or bitten by an insect, this is a symptom of anaphylaxis and the adrenaline autoinjector should be administered.

7. Does allergy run in families?

The tendency to be allergic runs in families. If one family member has a food allergy (father, mother or a child), then all children in the immediate family will also be susceptible to allergies and could possibly become allergic to something. This will not necessarily be an allergy to the same foods as others in the family, and it does not necessarily follow that if one family member has an allergy that is severe, any other allergies in the family will also be severe.

8. Is anaphylaxis same as an anaphylactoid reaction?

Anaphylaxis is a severe response by the immune system to a specific substance and has the potential to be life-threatening. An anaphylactoid reaction (sometimes called 'pseudoanaphylaxis') has similar symptoms to anaphylaxis but is not caused by the immune system. Anaphylactoid reactions are more commonly referred to as non-immune anaphylaxis and occur due to cell degranulation.

9. What are the usual triggers of anaphylaxis?

Food is the most common trigger of anaphylaxis in children, especially peanuts and tree nuts. Other foods include shellfish, fish, milk, eggs, soy and sesame. Medications and arthropod stings are the other important triggers.

10. What is the role of investigations for anaphylaxis in the emergency setting?

The diagnosis of anaphylaxis is made clinically, and immediate treatment is necessary. Serum markers may be helpful for long-term management when the diagnosis of anaphylaxis is unclear.

11. What is the serum markers estimated for long-term management?

Histamine level, it is rarely performed, peak at 10 minutes and back to baseline at 1 hour; and Serum tryptase usually taken at 1, 6 and 24 hours.

12. How to interpret the Serum tryptase levels?

The serum tryptase assay is highly specific for anaphylaxis and can be used retrospectively to confirm the diagnosis where it was unclear. However, a negative result does not exclude the diagnosis when clinical manifestations are compelling. The normal Serum tryptase is less than 1ng/mL and incase of non-specific and anaphylactoid reactions the levels will be 1-15ng/mL. The levels of more than 15ng/mL is noted in true anaphylaxis levels.

13. What are biphasic reactions?

Biphasic reactions refer to the recurrence of anaphylaxis symptoms soon after the initial episode. It occurs about 5% of the time and may occur even 24 hours after the initial episode. It is usually less severe than the initial episode and mainly due to delayed administration of adrenaline or slow response to adrenaline.

14. What are the Differential diagnoses of conditions that mimic anaphylaxis?

- Idiopathic urticaria
- Isolated angioedema
- Serum sickness
- Phaeochromocytoma
- Systemic mastocytosis
- Asthma
- Panic disorders
- Globus hystericus
- Vocal cord dysfunction

15. What dose of IM adrenaline is used in anaphylaxis? How and when should you give it IV?

The dose of IM adrenaline for anaphylaxis is adrenaline 1:1000 (1 mg/mL) 0.01 mg/kg to a maximum of 0.3-0.5 mg IM. This can be repeated every 3-5 minutes if life-threatening symptoms of hypotension, respiratory distress or stridor persist. IV adrenaline may be given if there is no resolution despite multiple doses of IM adrenaline — 0.1-5.0 micrograms/kg/min.

16. Why should you give IM adrenaline to patients with evidence of anaphylaxis?

Multiple studies have found IM adrenaline administered to the lateral thigh is absorbed faster than SC adrenaline.

17. What is the role of antihistamines in the treatment of anaphylaxis?

There may be some benefit in reducing cutaneous manifestations, based on a study showing the superiority of combined H1 and H2 blockers over H1 blockers alone in the treatment of mild allergic reactions. Avoid first-generation antihistamines like promethazine that are more likely to contribute to hypotension.

18. What is the role of corticosteroids in the treatment of anaphylaxis?

Prednisolone is often given to prevent the risk of a biphasic reaction. There is essentially no good evidence to support this practice. There is no evidence to guide dosing or duration. However, ACLS advises hydrocortisone 4 mg/kg IV or IM then 2-4mg q6h.

19. What is the role of glucagon in anaphylaxis?

Patients on beta blockers who experience anaphylaxis may have a hypertensive response to adrenaline and suboptimal clinical improvement, and may require 1 to 3mg of IV glucagon once or glucagon by continuous infusion until anaphylaxis is controlled. IV glucagon makes most people vomit and one must prepare for that when using it.

20. Will anaphylaxis develop later in life?

Yes, anaphylaxis and allergic reactions can develop at any point in a person's life and at any age, although they're more commonly diagnosed in childhood. People with asthma, people with allergy-related skin conditions (such as eczema) and people who have suffered serious reactions in the past are most likely to develop anaphylaxis.

21. I am a village health nurse who administers immunizations in nursing homes and other community settings – do I need to carry oxygen and the equipment to administer it?

Anaphylaxis after immunization is very rare - less than 1 in a million immunizations. Based on a risk assessment oxygen would not be routinely needed by nurses to enable them to administer immunizations in the community.

22. How long do you need to admit/ observe a patient with anaphylaxis for?

At least 6 hours (in most cases; according to expert consensus guidelines). However, admission should be considered for higher risk situations.

23. What is required prior to discharging a patient with anaphylaxis?

Prior to discharge provide appropriate discharge instructions (e.g. written action plan) and teach how to use of adrenaline auto-injector.

Pearls for anaphylaxis:

- The progression of anaphylaxis from itching to urticaria to death is unpredictable. Patients with these symptoms should be treated as soon as they occur.
- Patients with anaphylaxis may present with hypotension alone and no cutaneous or pulmonary findings. Acute diarrhoea can also be an isolated finding.
- Adrenaline should be administered IM, not subcutaneously.
- There is no absolute contraindication to the use of adrenaline in patients with heart disease who experience anaphylaxis.

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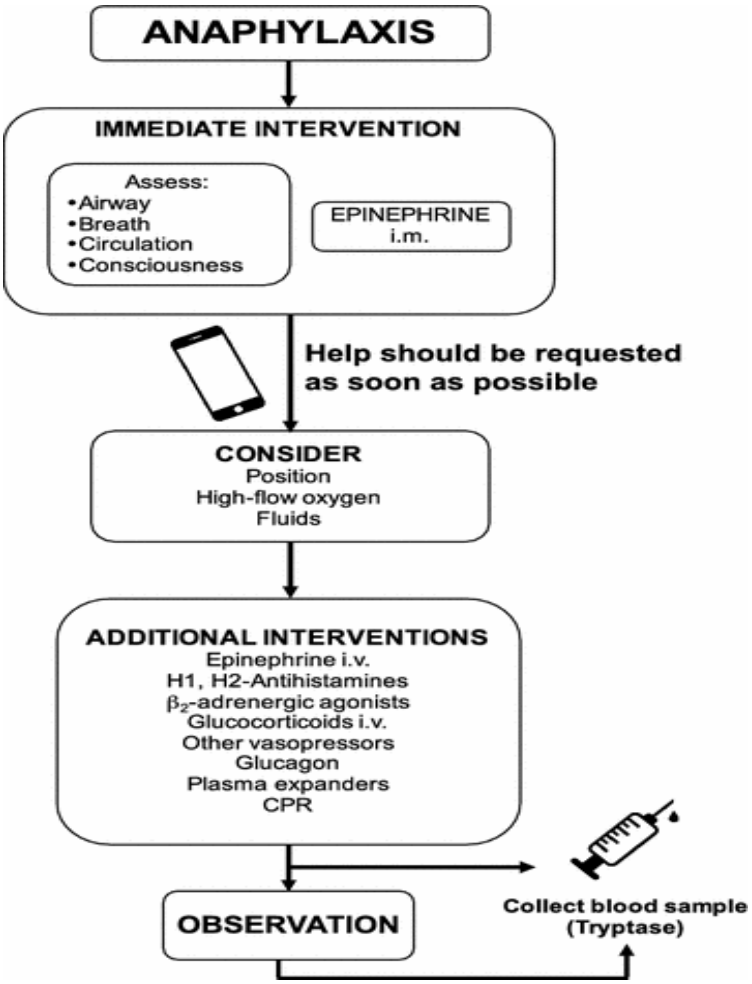
4. Lowe G, Kirkwood E, Harkness S. Survey of anaphylaxis management by general practitioners in Scotland. Scott Med J. 2010;55:11–4.

Acknowledgments:

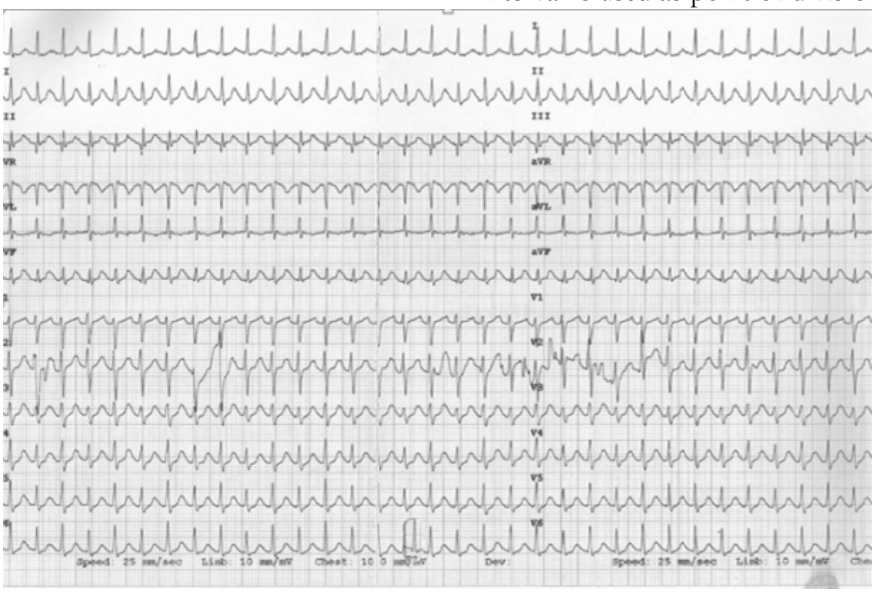
We thank Prof. P. Thirumalaikolandusubramanian, M.D for the critical review.



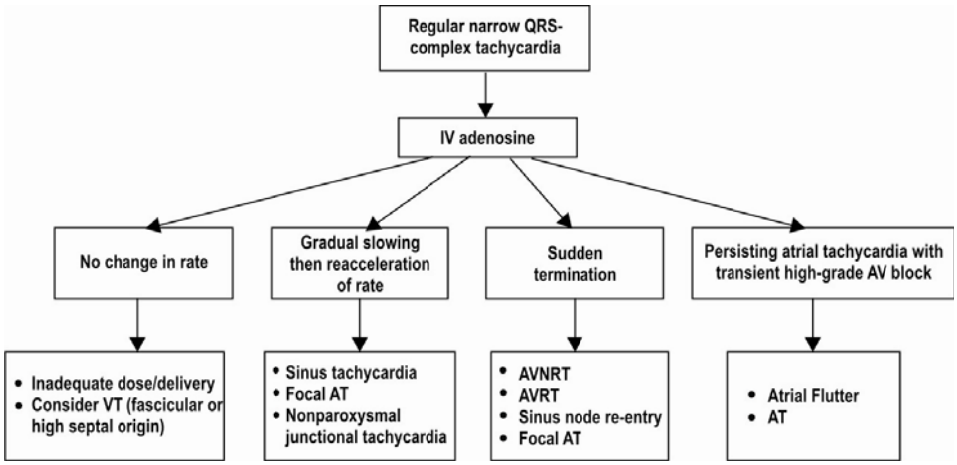
Answer and Explanations – ECG Section

Answer: Atrial tachycardia

Approach to narrow complex tachycardia is as follows. Narrow complex is as defined as QRS width of less than 120 msec. Presence of a narrow QRS indicated depolarization of the ventrices through the His-Purkinje system. Thus the rhythm has to arise either at or above the AV node.



Initial approach is to identify regularity of rhythm. Presence of an irregular rhythm is suggestive of atrial fibrillation or atrial tachycardia (AT) or flutter with variable AV conduction or multifocal atrial tachycardia (MAT). If a regular tachycardia is noted, it has to be further delineated as by presence of P waves. If no P waves are noted it is probably AVNRT. If P waves are noted, atrial rate and ventricular rate have to be calculated. If atrial rate is greater than ventricular rate, possibilities are of atrial flutter or atrial tachycardia. If it is not so, next step of observation is to analyse the RP interval. RP interval is used as point of differentiation as either short RP or long RP based on comparison of RP to the PR interval. The RP interval indicates the retrograde conduction property of AV tissue. If it is slow, the P wave will be far from QRS – wide RP and vice-versa. Long RP tachycardias are



usually atrial tachycardias, atypical AVNRT and permanent junctional reciprocating tachycardia (PJRT). Short RP tachycardias are again differentiated based on the RP cut off of 70 msec. If RP is shorter than 70 msec it is AVNRT, and if longer than 70 msec it is considered as either AVRT or Atrial tachycardia or AVNRT. Termination of rhythm is also important to assess the electrophysiology, as termination with a P wave indicates that AV block terminated the arrhythmia suggesting that AV blockade terminates the arrhythmia, which is suggestive of a re-entrant tachyarrhythmia.

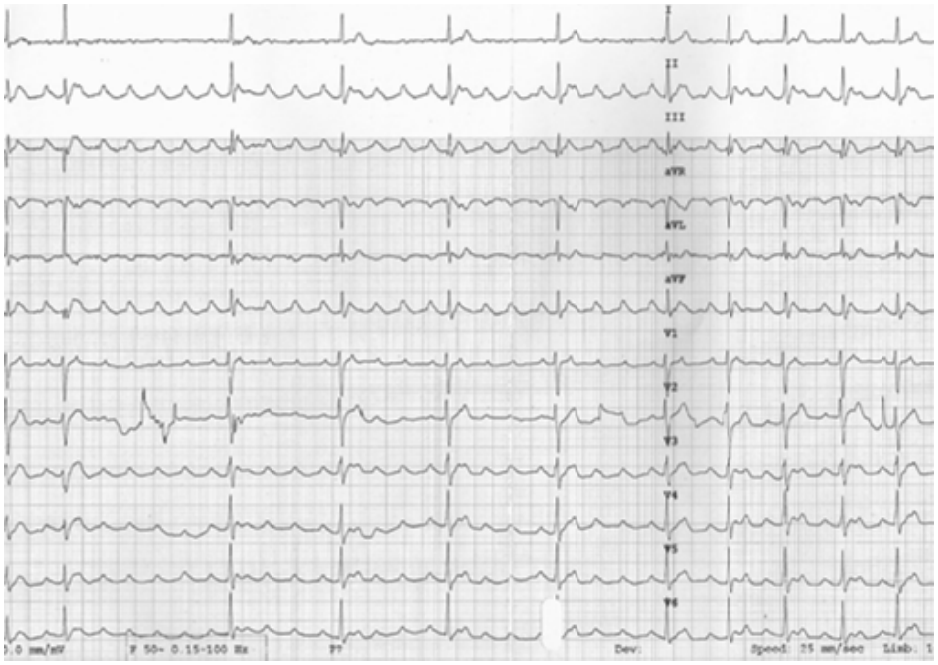
The response to transient AV block either by carotid sinus massage or by IV Adenosine is highly useful in differentiating various types of PSVT. If the arrhythmia persists despite AV bloc, then it is considered as an arrhythmia not involving the AV node (AV node independent SVT), whereas arrhythmias such as AVRT, AVNRT are readily terminated as they need normal AV nodal conduction as an integral part of the arrhythmia.

Response to adenosine:

In our patient the following response was noted when we gave Adenosine.

After administration of adenosine, transient AV nodal blockade was induced. Regularly occurring "P" waves seen at a rate of 160/min with variable conduction to ventricle seen, suggestive of AV-node-independent tachycardia.

The possibility of atrial flutter or atrial tachycardia was considered. However the atrial rate is 160/min only. Hence a diagnosis of atrial tachycardia was made. The morphology of P waves, (due to presence of upright P waves in leads II, III and aVF, with an isoelectric P wave in lead I with negative P wave in lead aVL and positive P wave in lead V1) is suggestive of origin of ectopic atrial tachycardia from posterior part of LA, probably of left superior pulmonary vein. The management of this condition involves Electrophysiology study with Radiofrequency ablation after ruling out all reversible and medically treatable causes.



T A P I J

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Honorary Editor:

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Introduction: This should comprise of; (1) purpose of the study/article (2) brief references to pertinent literature only. The introduction should not be an extensive review of the subject.

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Article from a Journal: List the first 3 authors with initials. The remaining authors may be given et al., e.g. Glogar D. H., Konar R. A., Muller J., et al; Fluorocarbons reduce myocardial ischaemic damage after coronary occlusion, Science. 1981; 211: 1439-41. (Note Punctuations)

Articles from a Book: Yokoyana K, Suyama T, Naito R Development of Fluosol D. A., And its perspective as a blood substitute. In: Oxygen and life, proceeding of the second Pristley conference. Royal Society of Chemistry, London, 1908; 142-52. (Note punctuations)

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Kindly enroll me as a Member of API – Tamil Nadu State Chapter. My details are as follows

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- I hereby state that the above information given is true and correct.

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Name

Membership No.

Subject to the approval of the Governing Body in an ordinary or a special meeting, I agree to become a member and if admitted, to abide by the Rules and Regulations of the Association.

Signature of Candidate

Note by Secretary

Xerox copies of registration with Medical Council and Postgraduation Certificate by a recognised university should accompany the application form

N.B. Kindly read carefully the rules and regulations printed overleaf before filling this form.

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LIFE MEMBERS : Life Members are required to posses a post-graduate degree such as MD/DNB, DM, or equivalent in internal medicine from any institution or university recognised by the Medical Council of India and/or approved by the Governing Body of the Association. MD General Medicine / Internal medicine includes specialities such as Cardiology, Gastroenterology, Diabetology, Nephrology, Neurology, Clinical Haematology, Chest & Tuberculosis, Endocrinology, Gerontology, Infectious Diseases, Allergy, Immunology, Rheumatology, Medical Oncology and others approved by the Governing Body notified by the General Body. Life membership shall be open to citizens of India only.

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5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.

5.2.1.3 Should have made a significant contribution to research / teaching / development in the field of medicine.

1.1.1.4 Should have contributed to API by way of scientific or Organizational works.

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  - ❖ The Nominee has completed 10 years after post-graduation
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- Proof of qualifications, publications, honours, awards, must be submitted as supporting data. The supporting data should be numbered parawise (eg 1., 2., 3. , etc), For more than one supporting documents, the numbering should be in alphabets (eg 1 (a), (b), (c), etc).
- No hand written applications will be accepted.
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- Last date for receiving application form is **31st May** of the year.

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Hon. General Secretary

Dr. B. R. Bansode
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3.	Date of Birth			
	Address Residence		Address Office	
4.	Tel.:	Fax : Mobile	E-mail:	
5.	Postgraduate degree in Medicine	Year of passing	Institute	University
	Other Professional Qualifications	Year	Speciality / Subjects	University / Institute
a.				
b.				
c.				
d.				
	Certificates Attached			
6.	Experience in Medical Profession after Postgraduation in Medicine			

Name of Hospital / Clinic / Organisation & Location	Number of Beds (if applicable)	Period Served year wise (From-To)

7.	Publications: List below. (If number of publications in Journals exceeds 8, publications which can qualify as research papers may be listed under Research section 9.)

a) Number of Publications in Indexed National / International Journals.	Attach title page / Abstract as Appendix
b) Number of Chapter in Books / monograms	
c) Editorship of National level or State level: Book /Monogram/Update Series	

8.	Honours And Awards (list below with photocopy of proof)

(a) Oration in National / State Association Meeting

Title of Oration	Organisation	Year

8 (b) Award National / International / or State level		
Title of Award	Organisation	Year

9.	Research work (list below)	
(a) Research sanctioned & funded by Research Agency		Attach Letter of sanction.
(b) Departmental Research. (To qualify, the findings should be published in National/International Journal) Do not include papers already listed under Publications		Attach title page / Abstract

10.	Contribution to API (list below and attach proof)		
Post held in Organisation / Meeting	Name of Organisation / Meeting / CME	National / Zonal / Under API/ICP	Year

11.	Participation in CME or Scientific Sessions of API or ICP as Faculty		
Speaker / Chairperson / Other	Title of Talk / Session	Name of Meeting	Year

12.	Social welfare / Community service. (Include under the headings given below, with documentary evidence) (a) Emergency services during National calamities (Quakes/ Floods/Cyclones, etc) (b) Public education Programme (Radio), TV talk/ writing in news papers . (c) Service in Rural Areas	
Service		Evidence

N.B : No handwritten application will be accepted. * To be typed on separate page
*One original and seven Xerox copies of sets to be submitted
Last date for receiving the application form is 31st May 2011.
Address : Turf Estate, No. 006 & 007, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai – 400 011.

Indian College of Physicians

Citation

The Fellows proposing and seconding the nomination for Fellowship of Indian College of Physicians should highlight the professional / scientific achievements of the candidate and the contribution to A. P. I. from personal knowledge in 200 words, in the format given below :

Name _____ Name _____

Membership No._____ Membership No. _____

Signature Proposer _____ Signature Seconder _____

Note:- The Fellowship form should be proposed and seconded by Founder Fellow / Fellow of ICP only. In case there are more than 3 nominations by any proposer/seconder, the first three nominations in order of receipt in API Office and complete in all respects will be considered for award of Fellowship of ICP and the others rejected for consideration.

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(2) Benbow M., Lossen G., A clinical evaluation of UrgoTul to treat acute and chronic wounds. British Journal of Nursing 2004: 13(2): 105-109.
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(4) M. Le Berre, Y. Lurton et al., Pansements imprégnés : tulles/interfaces. Oral communication, CPC 2005, Paris.
(5) Bernard FX. et al. Stimulation of the proliferation of human dermal fibroblasts in vitro by a lipidocolloid dressing. Journal of Wound Care, May 2005; 14(5): 215-220.
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