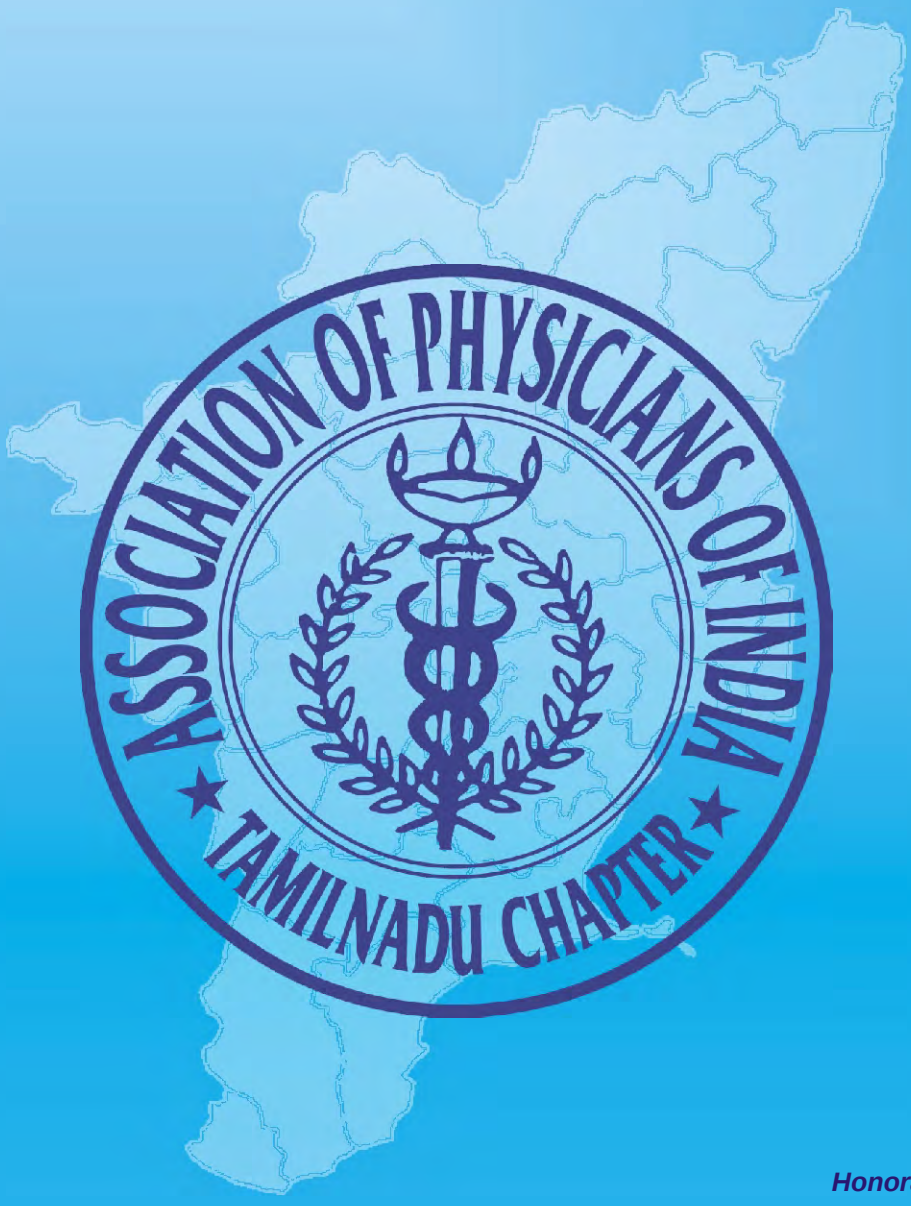
TAPIJ

The Journal of the Association of Physicians of India
(Tamil Nadu Chapter)

Vol.2 Issue : 2 May - August 2010



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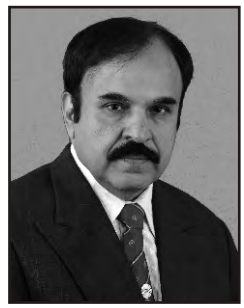

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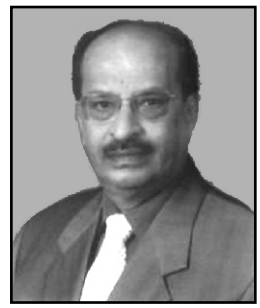

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Editor's Message

Dear colleagues,

I am happy to present you the 2nd issue of TAPIJ in the year 2010.

The API Chennai chapter had successfully organized the 6th Annual Conference of API-TNSC, TAPICON 2010 at Chennai on 3rd and 4th April. More than 500 delegates participated and all the scientific sessions were very interesting and appreciated by all the delegates.

This particular issue has some original articles on *'Microbial Prevalence and their antibiotic susceptibility pattern in Diabetic Infections'* by Dr.V.Mohan and colleagues, *'CNS Tuberculosis in Kerala - a continuing challenge with a changing face'* by Dr.S.R.Chandra and colleagues, and as in earlier issues, there are some useful review articles.

We are continuing with the series on Toxicology and Dermatology. We have introduced a new section called *"Dermatology Photo Feature"* where some interesting cases in Dermatology will be presented.

I hope you will find this issue useful and informative. I would appreciate your comments sent as "Letters to the Editor".

With warm personal regards,

Dr.Vijay Viswanathan

ASSOCIATION OF PHYSICIANS OF INDIA
TAMIL NADU CHAPTER

To
The Secretary
Association of Physicians of India – Tamil Nadu State Chapter
Chennai.

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Original Article

CNS Tuberculosis in Kerala – A Continuing Challenge with a Changing Face

Dr.S.R.Chandra and Dr.C.S.Vidhya Annapoorni

ABSTRACT

CNS tuberculosis is a global disease causing approximately 3 million deaths annually. In India, 3 million infectious cases, 12 million non-infectious cases and half million deaths occur annually. This is likely to increase with increasing HIV as 50 % of patients with extrapulmonary TB in USA have HIV making it a global health problem. Evaluation of patients with CNS tuberculosis admitted to government medical college, Trivandarum for one year shows an interesting picture. It seems to affect immunocompetent, high socio-economic group with a long indolent course and leaves significant complications. Hence we insist the need to initiate treatment on clinical suspicion only.

Keywords: CNS tuberculosis, immunocompetent adults.

INTRODUCTION

Tuberculosis is a bacterial disease caused by airborne droplets of Mycobacterium *tuberculosis, avis and africanum*. According to WHO one-third of world's population is infected and approximately nine million new cases and three million deaths occur worldwide.[1] In India, three million infectious cases, 12 million non-infectious cases and half million deaths occur annually.[2] Meningitis in patients with tuberculosis is 7 – 12 % [3]. Tuberculosis forms 20 – 30 % of all space occupying lesions. With the appearance of HIV, there is increased incidence in the developed countries as well. Extrapulmonary tuberculosis is considered as an AIDS defining condition. 5 – 9 % of world's AIDS patients have TB and 50% of patients with extrapulmonary TB are HIV positive in USA.

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PATHOGENESIS

Virtually all CNS lesions are produced by Mycobacterium tuberculosis.[4] It is an obligate aerobic bacillus, non-motile, non-capsulated, and non-sporing and resembles fungal organisms forming mould like pellicles in liquid culture.[5] Its genome is the largest among bacteria and has enzymes for synthesis of complex lipids, glycolipids, mycolic acid, wax, alcohols etc. These molecules form a physiological barrier to most drugs. It has a system for antigenic variation causing chronicity of disease. It spreads from person to person by aerosolized droplet nuclei. One to ten organisms are needed to cause infection. Severity of disease in the infecting individual determines severity of disease in the recipient. It multiplies in the alveoli or macrophages. Tuberculous exposure occurs in 100% of persons in endemic areas. Most of them are killed in 2 – 4 weeks. The surviving organisms hematogenously spread to extrapulmonary sites. This leads to PPD reactivity indicating asymptomatic TB infection. A small percentage of these patients progress to symptomatic infection. Attempts by mononuclear cells to control this causes caesation and necrosis, which breaks and release the organisms in lung parenchyma. During hematogenous spread lesions occur in CNS choroids plexus called Rich focus. They rupture into subarachnoid space causing meningitis and into parenchyma causing tuberculoma or abscess. Hypersensitivity reaction to this causes thick exudates in the basal cisterns

around vessels and nerves causing proliferative arachnoditis, vasculitis and hydrocephalus. Because of these devastating complications it is called white plague or captain of man's death. Damage to brain parenchyma adjacent to areas of exudates causes borderzone encephalitis and leucoencephalopathy at distant sites. Other then the Rich foci, CNS TB occur also from subependymal, subpial, vertebral, middle ear, nasopharyngeal and vertebral foci. Based on host resistances and number of bacilli, spectrum of clinical presentation varying from focal plaques, miliary lesions, proliferative meningitis or inflammatory caseous meningitis occurs.[6] Thick exudates are seen in interpenducular fossa, infundibulum, optic chiasma, sylvian fissure etc. Semifibrinous material in between the layers of leptomeninges, perivascular epitheloid cells, subintimal thickening of vessels and necrotizing vasculitis is seen. With introduction of treatment this becomes organized to fibrous endarteritis leading to infarctions in 37.5 – 55% of patients. Obstructive hydrocephalus occurs due to obliteration of prepontine cisterns whereas communicating hydrocephalus is due to leptomeningeal obstruction. Tuberculomas are commonly found infratentorially among children and supratentorially in adults[6]. Spinal involvement occurs as an extension of cranial involvement.

CLINICAL FEATURES

Most often illness starts with vague nonspecific symptoms and low-grade fever of several weeks. Past history of TB is present in 50% children and 10% adults.[6, 7] Cranial neuropathy is seen in 20-30%. Signs of meningeal irritation, hemiparesis, quadriparesis, raised intracranial tension, seizures, movement disorders followed by lethargy, confusion, stupor and coma sets in. Mild to moderate hyponatremia and syndrome of inappropriate ADH secretion are common. CNS picture is not much altered by HIV status. Udani and Dastur[8] have described tuberculous encephalopathy in children that resembles hemorrhagic leucoencephalopathy. British Medical Research council staging [9]

Stage I –	prodromal phase with no definite neurological symptoms
Stage II –	mild meningeal irritation and cranial neuropathy
Stage III –	severe clouding of sensorium, convulsions, focal neurological deficits

Advanced stage of disease, extremes of age, underlying multiple comorbidities, hydrocephalus, persistent CSF AFB and culture positivity are bad prognostic factors.

DIAGNOSIS

Early diagnosis is often difficult due to lack of specific signs and symptoms. Laboratory methods are also inadequate.[10] CSF shows lymphocytic pleocytosis with low sugar and raised proteins. Acute neutrophilic response that shifts to lymphocytes in 24 – 48 hours is also seen. Persistent neutrophilia is seen in multidrug resistant TB (MDR-TB) and mixed infections. A therapeutic paradox where the initial lymphocytic CSF shifts to polymorphonuclear after initiation of treatment is also reported due to massive release of tuberculoprotein which often ends in death. AFB stain is positive in 5 – 25 % and culture positive upto 60%. Approximately 10,000 organisms are required for culture to become positive which takes 4 – 8 weeks to yield results. Determination of CSF adenosine deaminase is seen in all disorders that induce cell mediated immune response and has 90% sensitivity and specificity in the diagnosis of tuberculous meningitis. Diagnostic sensitivity of PCR in CSF is variable. However evolution from positive to negative indicates treatment efficacy. TB – color cold staining is more sensitive method of microscopic examination of the mycobacterium. Solid phase enzyme immunoassay is used for the detection of TB IgG, A, and M; Fast plaque TB test with application of phage amplification technology is very sensitive but not easily available.

Neuroimaging shows enhancement of basal cistern and the complications like hydrocephalus, infarcts and tuberculoma.

OUR OBSERVATION

Patients admitted to Government medical college hospital, Trivandrum during 2004 March to 2005 March were evaluated and followed till 2008 December. Twenty-three patients comprised of nineteen males and four females. Age varied from eleven years to sixty-two years, 17.8% of these patients were businessman, 17.8% laborers, and 17.4% engineers. The rest 47% belonged to students, doctors and bank officials. The commonest symptom - fatigue and headache was seen in all patients. Recurrent superior orbital fissure (Fig. 1) was seen in two, nasopharyngeal (Fig. 2) lesion in one, extensive and cranio-spinal tuberculomas (Fig. 3 & 4) in one. Other features present were pyrexia of unknown origin, seizures, stupor etc. All of them were immunocompetent. Delay in initiating treatment varied from 3 weeks to 4 months. There was no mortality. However only five patients recovered without any major sequelae. The rest of the patients were left with varying degrees of cognitive decline, seizures and focal deficits. The larger the delay in starting the treatment greater was the sequelae.

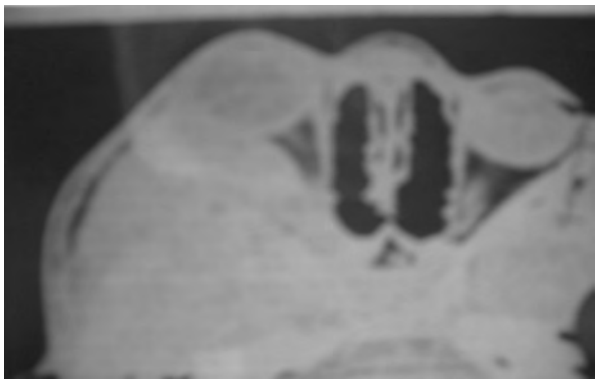

Fig 1. Right orbial granulmatous mass

TREATMENT

As confirmative diagnosis is not easy and delay is dangerous, decision to treat is clinical based on high index of suspicion. The centre for disease control recommends isoniazid 10-20 mg/kg/day, rifampicin 10-20 mg/kg/day,

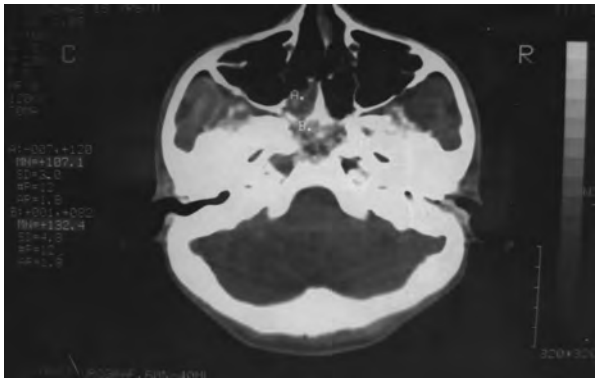

Fig. 2. Nasopharyngeal tuberculous granuloma

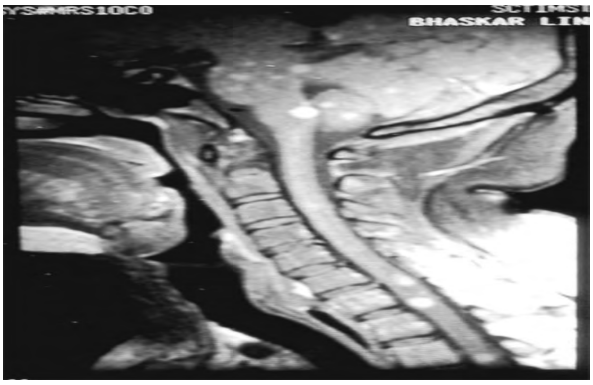

Fig. 3 Multiple tuberculomas in brainstem and spinal cord

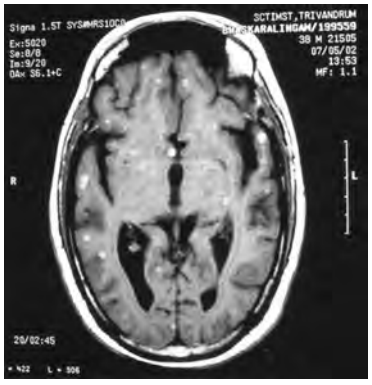

Fig 4. Multiple tuberculomas in brain

pyrazinamide 15-30 mg/kg/day, ethambutol or streptomycin can be added. Hepatotoxicity should be monitored every 2 weeks. Duration of treatment is 6 – 12 months. WHO puts CNS TB under category I with initial phase for 2 months with streptomycin, isoniazid, rifampicin and pyrizinamide followed by 7 months continuation phase with isoniazid and rifampicin. As complications in CNS TB are more disabling most neurologists believe in a conventional

18-month regimen. Indication for steroids are altered sensorium, focal neurological deficits, CSF pressure more than 300 mm of water, protein more than 400 mg/dl, basal exudates and tuberculomas. Prednisolone 1-3 mg / kg in children and 60 mg/ day in adults is recommended. It is reduced to 50% in second week and tapered gradually over 4 weeks. Surgery is indicated in the presence of hydrocephalus.

LESSONS LEARNT

CNS TB in Kerala now seems to be a disease of immunocompetent, higher socioeconomic group. Rare presentations like recurrent superior orbital fissure, nasopharyngeal and cranial spinal tuberculosis also occur in immunocompetent individuals. The factors involved could be stress induced defect in cell mediated immunity and also frequent use of quinolones for all kinds of infection leading to the suppression of symptoms and indolent course.

CONCLUSION

Central system tuberculosis is a potentially treatable but very dangerous form of CNS infection. Confirmation of diagnosis is not easy and clinical suspicion is the indication to start the treatment. It seems to be common among the affluent immunocompetent adults probably due to the effect of wide spread use of quinolones and life style related stress. It is better to treat for a longer period of time – 12 to 18 months, with daily drugs when the CNS is invaded. When resistance to any drug is suspected susceptibility studies mandate the drug use.

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Review Article

Newer Insulin and Insulin Pumps

Dr. Jothydev Kesavadev, Ms. Gopikakrishnan Gopalakrishnan, Ms. Sunitha Jothydev

ABSTRACT

Since the discovery of insulin in 1922 the ideal route and device for delivery of insulin have been experimented and studied in several trials. Although syringes are still popular, insulin pens have become more acceptable in the last 5 years. Delivery of insulin with the help of Insulin Pump described as Continuous Subcutaneous Insulin Infusion (CSII), though more than 3 decades old is recently gaining more attention and popularity because of its multitude of benefits over and above that of glucose reduction. Insulin Pumps are a time tested device for continuous subcutaneous insulin infusion.

Unlike the popular syringes and insulin pens, insulin pumps will have only regular human insulin or the rapid acting analogue insulin in it for both basal and bolus requirements. There are 4 basal options now available for the clinician - NPH, glargine, detemir and CSII. Intrasubject variability is minimal when rapid acting insulin is used as a basal with CSII. In India, now majority of pumpers are using rapid acting analogue insulin like aspart. When used in Insulin pump, insulin aspart has proven to produce minimal or no infusion set blockage compared to insulin lispro. When rapid acting analogue insulins like aspart, glulisine etc., are used in pumps, subjects feel more comfortable and convenient because of its ease of administration just before the main meals and snacks. In India, unlike the west, 80% of the pumpers are Type 2 Diabetes subjects. Studies published in India have thrown light into the new findings on dramatic improvement in peripheral neuropathic pain and improvement in sexual function when CSII is made use of in the treatment of Type 2 diabetes. Oral hypoglycemic agents like metformin and sulfonylureas are administered along with insulin in pumpers with type 2 diabetes so that the TDD (Total Daily Dose) of insulin can be drastically reduced and at the same time achieve intensive control of glycemia without the risk of hypoglycemia, by utilizing the multitude of advanced functions in pumps. More perfect control of sugars with minimal excursions is possible with intelligent use of extra functions like extended bolus, temporary basal, bolus wizard etc. Whether it is type 1or type 2 diabetes, periodic CGM (Continuous Glucose Monitoring) is mandatory to fine tune the multiple basal profiles and to decide on diet and exercise pattern. It is intriguing to realize that the same insulins used in syringes and pens when incorporated into CSII, subjects are reporting a profound improvement in QOL within 3 months of use provided the right candidate is selected and intensively followed up.

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HOW DOES THE PUMP WORK?

Continuous Subcutaneous Insulin Infusion (CSII) or Insulin Pump Therapy by itself is not a new therapy for Diabetes mellitus. It is an alternate delivery mechanism for administration of insulin and is found to be far superior to ordinary syringes and insulin pens. When insulin is administered sub-cutaneously via a properly programmed insulin pump, physiological delivery of insulin mimicking a normal healthy pancreas is achieved.

Modern insulin pumps consist of a small battery powered device (about the size of a small cell phone), a disposable reservoir filled with

insulin and an infusion set, one end of which is attached to the pump and the other end of which there is a cannula inserted under the skin, near the abdomen to deliver insulin to the body. The pump is programmed in such a way as to the deliver insulin continuously in tiny doses throughout the day and night (basal dose in the range of 0.1-3.0 u/h or more) by using a computer chip which controls insulin delivery.[2]

HOW THE PUMP EVOLVED?

The history of insulin pump dates back to 1960s when a Los Angeles doctor named Arnold Kadish introduced insulin pump, a model that had to be worn as a backpack due to its big size. Later, the model underwent several clinical tests before it finally gained recognition as a potential replacement to regular insulin delivery and in 1978 the first use of CSII was reported by John Pick up et al[10]. Serious side effects such as ketoacidosis, hypoglycemia, infections and subsequent mortality caused a setback to the use of CSII. Pump therapy breathed a new life with the proclamation of DCCT in 1993 pointing out CSII to be a significantly better method of maintaining strict glycemic control in comparison to other modes of intensified treatment[4].The importance of tight glycemic control was also demonstrated by the UKPDS.[8] Since then the use of CSII gained popularity and there appeared more user-friendly models with features like bolus calculators and compatibility with personal computers so that pumpers could have strict control on their insulin intake and monitor blood sugars more effectively.

In 2006 Minimed Medtronic, recognized as pioneers in insulin pump therapy once again made history, when they introduced real time insulin pumps where the glucose sensor and the pump were combined. Introduction of real time insulin pumps was a major steppingstone towards "closing the loop" of insulin delivery, very near to the dream of inventing fully automatic devices. Newer pumps are smaller and easier to operate making it an increasingly attractive option with added benefits like a reliable alarm system for malfunction to name a few.

BENEFITS OF NEW INSULINS

When pumps were introduced 2-3 decades back, only regular human insulins were in the scenario. More often buffered human insulins were used in CSII to make the insulin more stable for use in the pump. The inherent limitations of human insulins like crystal formation, slow onset and prolonged duration of action, inadequate concentration in the portal circulation and inappropriate 24 hour basal serum insulin concentrations leading to poor long term glycemic control, paved the way for analogue insulins to hit the pump market.

There exist no arguments on the use of rapid acting insulin analogs in insulin pump therapy. Studies have shown that absorption of soluble, short-acting insulins used in CSII varies by less than 3% daily [2] when compared to basal insulins which vary from 19% to 55% in the same individual, which accounts for blood glucose variability when syringes or pens are used as delivery devices. Rapid acting insulins can be administered just before or even soon after food resulting in improved compliance and better quality of life for subjects on CSII. Tiny doses can also be administered along with snacks without poking the skin. In our center we have never come across pump blockage in more than 110 subjects on insulin aspart in the pumps. Insulin aspart is the preferred insulin analogue for use in CSII due to improved glycemic control, lower post prandial peaks, lesser risk of hypoglycemia, decreased glycosylated hemoglobin, fewer pump-tubing occlusions and improved quality of life[13].

An added benefit of using aspart in CSII is that it causes no weight gain as opposed to the same insulin when used in MDI regimen [14]. Insulin glulisine is also found to be suitable for use in pumps. Insulin lispro have been reported to cause erratic and unpredictable glucose fluctuations because of precipitation in infusion catheters [11,12].

INSULIN STACKING AND BOLUS WIZARD

When new rapid acting analogue insulins are used in pump, 1800 rule is made use of in calculating the Insulin Sensitivity Factor. This takes into consideration the Total Daily Dose (TDD) of insulin, a sum of both basal and bolus. *Eg*.for a patient taking 40 units (TDD) of insulin aspart daily, ISF = 1800/40= 45 and therefore 1 unit of aspart in this subject will help reduce blood glucose by 45 mg%. Modern insulin pumps will help program the different ISFs at different times of day and night based on the diurnal changes in insulin sensitivity.

Smart insulin pumps take into consideration the phenomenon of "active insulin" which is the bolus insulin which is active from a previously administered bolus (Bolus on Board or BOB) so that when the subject is using the Wizard function for administering bolus, the active insulin is subtracted with total avoidance of hypoglycemia.

ADVANTAGES OF CSII

CSII provides opportunity for setting several basal rates thus allowing flexibility in dosing. Extra boluses can also be administered at the will of the patient before, after or during a meal[16]. Earlier studies have shown that most poorly controlled subjects on MDI achieved a significant improvement in control after changing over to insulin pump therapy [10]. The following improvements can be reasonably expected following initiation of pump therapy.

- Near normal achievement of glucose levels
- Minimizing glucose excursions (MAGE)
- Reduction in major and minor hypoglycemic episodes
- Improvement in neuropathic pain and sexual function
- Reduction in Total Daily Dose of insulin
- Improvement in Quality Of Life

As early as 1980s, the benefits of using an insulin pump in patients in a hospital setting were published from India.[15] Recent scientific evidence supporting the use of insulin pumps in T2DM points to not only significant reduction in glycated hemoglobin levels but also to improved quality of life. In a real life study conducted in our center, a total of 46 subjects with T2DM using MDI were switched over to CSII for 6 months. HbA1c, body weight and total daily dose of insulin were measured before initiation of CSII and compared with the values 6 months later. After 6 months of CSII, study subjects were asked about their satisfaction with the therapy; they were also asked to assess treatment flexibility, frequency of side effects and interference with regard to side effects. The mean HbA1c value 6 months after initiation of CSII was 7.6 ± 1.2%, compared to 8.1 ± 1.4% at baseline while using MDI. The difference in mean between the 2 groups (0.541) was statistically significant and subjects also expressed high overall satisfaction level with CSII after 6 months.[1]

Subjects were also asked to assess how CSII affected the sexual function and peripheral neuropathic pain. After 6 months of CSII 83% of subjects noted an improvement in sexual function as opposed to when they were using MDI. With respect to peripheral neuropathic pain, 87% of subjects reported that they experienced significant reduction in pain after initiation of CSII.[1]

In a retrospective analysis of the medical records of 43 patients who were initiated on Insulin pump therapy between 2002 and 2007 (Dr.V.Mohan et al), 33 patients, 17 with type1 diabetes and 16 with type 2 diabetes who were on CSII were followed up for a mean duration of 3.4 years. The study aimed at evaluating the safety and effectiveness of CSII among "Recalcitrant Diabetes" showed a statistically significant reduction in HbA1c after initiating CSII (prepump 10.7% vs.postpump 8.3%, $p<0.001$) and there also occurred a reduction in frequency of severe hypoglycemia after starting the CSII with no instances of diabetic ketoacidosis. The greatest reduction in HbA1c levels occurred in the first 6 months with a slight

deterioration thereafter possibly because some patients "relaxed" the control after the initial success with pumps was achieved.[3]

In insulin requiring T2DM, a judicious use of insulin pumps in selected candidates is not only beneficial in reducing glycated hemoglobin (HbA1c) levels, but also in minimizing glycemic excursions[5]. More recent studies with insulin pumps have shown excellent improvement in quality of life, sexual function and symptoms of peripheral neuropathy.

A case report was presented at the American Diabetes Association (ADA) meeting in 2007 of a 58 year old subject with T2DM of 20 years duration with bilateral peripheral painful neuropathy. Insulin pump therapy resulted in dramatic improvement in neuropathic symptoms. By the sixth day of pump deployment definite signs of improvement were revealed without any concomitant medications for neuropathy and by the tenth day the pain almost disappeared which had most responded to multiple daily insulin shots. The relief of pain remained consistent resulting in incredible improvement in the quality of life.[6]

INDICATIONS FOR INSULIN PUMP THERAPY

T1DM

Insulin Pump Therapy is a fully established insulin delivery option in T1DM. In the scenario where virtually no insulin is being produced from pancreas, pumps offer near physiological delivery of insulin and are a proven time tested therapeutic option in T1DM at all ages. Any subject with an established diagnosis of T1DM is a potential candidate for pump provided other inclusion criteria are fulfilled.

T2DM

T2DM is characterized by progressive beta cell dysfunction in the presence of insulin resistance. Eventually the insulin secretory defect predominates, resulting in an insulin-requiring state. As opposed to insulin resistance, which tends to plateau, beta cell dysfunction progresses over time. Thus people with T2DM eventually require insulin therapy to maintain glycemic control, in addition to their oral antidiabetic agents [9].

In insulin requiring T2DM, a judicious use of insulin pumps in selected candidates is not only beneficial in reducing glycated hemoglobin (HbA1c) levels, but also in minimizing glycemic excursions. More recent studies with insulin pumps in T2DM have shown excellent improvement in quality of life, sexual function and symptoms of peripheral neuropathy [5].

Other indications:

- Patients with serious symptomatic recurring hypoglycemic episodes
- High HbA1c (greater than 7%) despite MDI
- Brittle diabetes
- Dawn phenomenon
- Patients with insulin resistance
- Patients craving for flexibility in life style
- Chronic Kidney Disease (CKD) on dialysis or post renal transplant patients
- Pregnancy (where strict glycemic control is obligatory to prevent foetal anomalies)

POTENTIAL CONTRAINDICATIONS

- Unaffordability for pump/ consumables
- Psychiatric illness
- Lack of motivation/ who are not willing to perform SMBG
- Lack of responsible caregiver
- Patients who feel physically and emotionally uncomfortable wearing
- Insulin pump

INSULIN PUMPS IN BODY WEIGHT REDUCTION

Weight gain with insulin therapy is a major concern, during the course of diabetes treatment. This phenomenon is more of a consequence of treatment rather than property of insulin. When insulin pumps are used insulin delivery can be adjusted based on carbohydrate

content of the diet, exercise type and duration, time of the meal etc etc. Intelligent and timely use of pump functions like temporary basal, extended bolus etc prevents hypoglycemia and overeating. This invariably leads on to glycemic reduction without the associated hazard of weight gaining.

The property of the pump to deliver tiny boluses can be made use of snacks which precludes overuse of insulin resultant low sugars, overeating and weight gain. However studies have shown[1,14] weight reduction with use of insulin pumps only when subjects are judiciously using it, utilizing atleast the basic functions combined with a structured exercise pattern.

VALUE OF CONTINUOUS GLUCOSE MONITORING (CGM)

Continuous Glucose Monitoring system should be regarded as the next revolution in glucose monitoring and thereby in the day to day management of diabetes. CGM is advocated for monitoring blood glucose continuously over a period of three to six days or more whereby which 288 blood glucose readings are obtained in a single day over an interval of 5 minutes. CGM presents data on blood sugar pattern which can never be obtained with the help of blood sugar meters. CGM is similar to a video providing blood glucose pattern over several days whereas self monitoring of blood glucose can only provide values similar to that of a picture which is less descriptive. Continuous glucose monitoring devices are being marketed by several manufacturers nowadays. The Paradigm Real Time Insulin pumps from Minimed Medtronic are also available now along with Continuous Glucose Sensing technology and this is called Real Time Paradigm Insulin pump and it offers the added advantage of predictive alerts. The data that has been gathered from CGM has enabled us to learn more about the phenomenon of glycemic excursions, to redefine the so called normal sugars in entities like Gestational Diabetes Mellitus, to decide on the basal profiles in patients on Continuous Subcutaneous Insulin Infusion etc. The CGM data has also helped the scientific community to establish the intimate link between diabetes and cardiovascular illnesses from a different dimension. Excessive oxidative stress due to hyperglycemia and glycoxidation leads to increased production of F2-isoprostane and eventually 8-iso- PGF2 alpha. This in turn will lead on to higher platelet activation which is reflected upon by an increased urinary excretion of platelet derived TxB2 and this will result in the higher levels of plasminogen activator inhibitor (PAI-1) levels. The glucose trends as studied from CGM data offers one explanation for the higher cardiovascular events in diabetes.

In an on original study presented at ADA 2009, we proved CGM,an invaluable tool for fine tuning sugars in motivated subjects enabling them to restructure lifestyle based on glycemic pattern and without any modification in medications.[7] In our center, 10 highly motivated subjects on insulin pumps(Minimed Paradigm),who had training on diet and self management techniques and on regular DTMS(Diabetes Tele Management System)follow up underwent CGM for 3 days. Subjects were advised to learn by themselves glycemic pattern and possible cause for fluctuations like diet, exercise, stress etc. No significant modification in dosages was carried out afterwards; but reported their sugars & quality of life improved significantly in subsequent weeks. This generated profound interest and prompted us to go for a qualitative inquiry based on patient interview. A semi structured interview with open ended questions on lifestyle depicted their self modulated response to diet, exercise pattern, relaxation technique, appreciation of CGM during sleep & intimate activities. The qualitative analysis of interview excerpts generated 8 key themes and frequency of each theme in the group was captured. Unlike glucometer, CGM helped in-depth analysis of glycemic pattern which inspired them to go for diet and lifestyle modifications assisted with timely advice from DTMS team. Diabetics in general are scared of

hypoglycemia during sleep which again got benefited with CGM.Subjects could appreciate role of stress in glycemic excursions. A significant number opted for periodic CGM.These results strongly indicates utility of CGM in motivated subjects as a therapeutic tool enabling them to restructure lifestyles based on glycemic patterns.

CONCLUSION

The new generation insulin pumps and the newer evidences of benefits, over and above that of lowering glycated hemoglobin, promise its extensive use in revolutionizing treatment of diabetes.

Rapid acting analogue insulins with short duration of action combined with extra functions in an insulin pump, when used in the right candidate, results in profound improvement in quality of life, diminution of pain of neuropathy and remarkable improvement in sexual function.

The major disadvantages at present are the prohibitatively high cost, requirement of intensive education on a prolonged and continuous basis and selecting the ideal candidate who can use it with optimal efficacy.

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Dermatology

Psoriasis - A newly defined systemic disease

Jayakar Thomas, Ashok Kumar N, Manoharan D, Cynthia S, Selva Prabu SK, Ashwak Ahmed.

ABSTRACT

Objective: To study the association of psoriasis with various comorbid conditions.

Methods: One hundred and twenty consecutive patients with psoriasis were included in the study. Complete physical examination was done. Blood pressure monitoring was done in all patients. Blood sugar (fasting), fasting lipid profile and thyroid function test were done in all patients.

Results: Diabetes mellitus was seen in 11.6% of patients. Hypertension was present in 14.1%. Both diabetes and hypertension was seen in 12.5% of patients. 6.6% of patients were obese. Thyroid disorder and ischemic heart disease were seen in 3.3% of the patients. Lipid abnormalities were seen in 4.1% of patients. A total of 55.8% of patients had some comorbidity in our study.

Conclusion: All patients with psoriasis should be monitored for associated comorbid conditions. This study highlights the importance of psoriasis as a newly emerging systemic disease with associated co morbid conditions and the role of dermatologist and physicians in the effective management of psoriasis.

Key words: psoriasis, co morbid conditions

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INTRODUCTION:

Psoriasis is newly defined as a systemic disease. Common co-morbidities associated with psoriasis include diabetes, hypertension, and metabolic syndromes. Psoriasis can have a significant impact on a patient's quality of life and is associated with loss of productivity, depression, and an increased prevalence of malignancy[1]. Pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-alpha), and other factors like pro-inflammatory T- helper type I cytokines that are overproduced in patients with psoriasis likely contributes to the increased risk for development of metabolic syndrome[2]. In terms of the other diseases associated with psoriasis, Crohn's disease is another condition that is not common but its prevalence is certainly increased in patients with psoriasis[3]. Depression or anxiety is another common problem in patients with psoriasis as is genitourinary disease. 20 % of hospitalised patients with psoriasis have some genitourinary complaints. Patients should adopt a healthy lifestyle so as not to contribute any more to risk factors. Treating psoriasis and the associated co-morbid conditions aggressively from the beginning will definitely improve the quality of life of the patient.

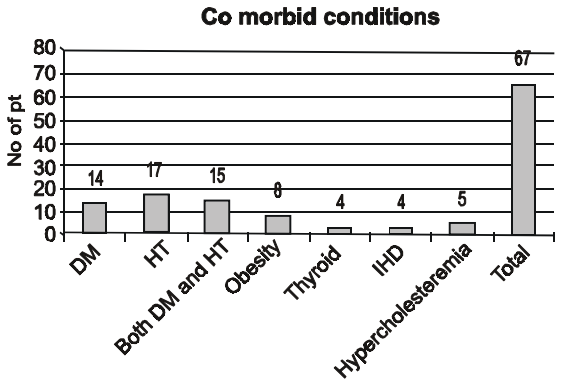
PATIENTS AND METHODS:

The study was conducted in the department of Skin and STD, Sree Balaji Medical

College from April 2009 to December 2009. One hundred and twenty consecutive patients with psoriasis were included in the study. All types of psoriasis patients were included. Complete physical examination was done. Blood pressure monitoring was done in all patients. Blood sugar (fasting), fasting lipid profile and thyroid function test were done in all patients. Patients with recent blood reports were not subjected to further investigation.

RESULTS:

Total of 120 patients were included in the study. Forty six patients (38.3%) had Palmo-plantar type followed by chronic plaque type psoriasis in 50% of patients. Most common age group was in the range of 41-50 yrs (29%) followed by 51-60 yrs (27%). 55 % of patients had the disease for a period ranging from 1-5 yrs. Diabetes mellitus was seen in11.6% of patients. Hypertension was present in 14.1%. Both diabetes and hypertension was seen in 12.5% of patients. 6.6% of patients were obese. Thyroid disorder and ischemic heart disease were seen in 3.3% of the patients. Lipid abnormalities were seen in 4.1% of patients. A total of 67 (55.8%) of patients had some co-morbidity in our study. [chart:1]



DISCUSSION:

Psoriasis is emerging as an important systemic disease associated with various co morbid conditions. Various co morbid conditions associated with psoriasis include diabetes, hypertension, thyroid abnormalities and abnormal lipid abnormalities. Co-morbid conditions linked with psoriasis are associated with increasing rates of morbidity and mortality.[4]Besides psoriatic arthritis, other diseases such as metabolic syndrome and cardiovascular diseases are becoming of major importance. The relationship between psoriasis and co morbidities such is likely linked to the underlying chronic inflammatory nature of psoriasis[5]. Tumour necrosis factor-alpha plays a central role in the pathogenesis of psoriasis. It plays a critical role in activation of innate and acquired immune responses leading to chronic inflammation, tissue damage and keratinocyte proliferation. TNF-a levels are markedly increased in skin lesions, synovium and serum of patients with psoriasis and these correlate with the severity of the disease. Decreased levels are associated with clinical resolution.[2]

In a survey on psoriasis patients hospitalized for treatment, Henseler T and Christophers E[6] investigated a list of concurrent disorders, both cutaneous and non-cutaneous and a significant proportion of these patients had obesity, cardiac disease, hypertension and/or diabetes. In a study by Sommer DM *et al* [7], psoriasis patients are likely to be at risk for the development of signs of obesity, hypertension and diabetes, as well as dyslipidaemia and chronic heart disease. Mallbris *et al*[8] compared rates of cardiovascular mortality in patients who were admitted one or more times for psoriasis treatment with an outpatient cohort and found that the mortality ratio was 50% higher in inpatients than in the outpatient cohort.

Although further data are needed it now seems mandatory to closely monitor psoriasis patients with a focus on risk factors, including body weight, hypertension and hyperlipidaemia, in addition to chronic heart disease. It also appears necessary to adopt treatment regimens that not only provide early clearing of the involved skin but also provide persistently low inflammatory activity. For effective management of psoriasis and related co-morbidities, an integrated approach targeting both cutaneous

and systemic inflammation may be beneficial, and strategies to improve overall management of the patient should be encouraged to reduce the disease burden.[9]

Genetic markers [10,11] in future will tell us who are at risk of developing co-morbidities and we will be able to intervene earlier and much more aggressively to prevent premature death.

This study highlights the importance of psoriasis as a newly emerging systemic disease with associated co morbid conditions, role of dermatologist and physicians in the effective management and drawing up an effective treatment plan.[12].

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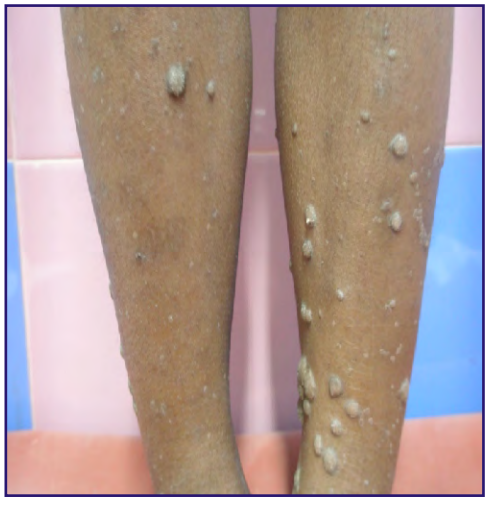
Dermatology

Dermatology Photo Feature

Prof. Jayakar Thomas



This 15-year-old boy was seen with multiple grayish-coloured papules and nodules over his legs. The lesions were asymptomatic and were present for the past four years (see image).

DIAGNOSIS

Viral Warts (verrucae vulgaris)

DEFINITION/ DESCRIPTION

These are common, contagious, epithelial tumors caused by at least 60 types of human papillomavirus (HPV).

CLINICAL PICTURE

Common viral warts (verrucae vulgaris) are almost universal in the population. They are sharply demarcated, rough-surfaced, round or irregular, firm, and light gray, yellow, brown, or gray-black nodules 2 to 10 mm in diameter. They appear most often on sites subject to trauma (e.g., fingers, elbows, knees, legs, face) but may spread elsewhere. Periungual warts (around the nail plate) are common, as are plantar warts (on the sole of the foot, which are flattened by pressure and surrounded by cornified epithelium. They may be exquisitely tender and can be distinguished from corns and calluses by their tendency to pinpoint bleeding when the surface is pared away.

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TREATMENT

Treatment depends on lesion location, type, extent, and duration and the patient's age, immune status, and desire to have the lesions treated. Most common warts disappear spontaneously within 2 yr or with simple nonscarring treatment (e.g., a flexible collodion solution containing 17% salicylic acid and 17% lactic acid applied daily, after gentle peeling, by the patient or parent), or the physician may freeze the wart (avoiding the surrounding skin) for 15 to 30 sec with liquid nitrogen. This procedure is often curative but may need to be repeated in 2 to 3 wk. Electrodesiccation with curettage is satisfactory for one or a few lesions, but it may cause scarring. Laser surgery may be useful but may cause scarring. Recurrent or new warts occur in about 35% of patients within 1 yr of treatment, so methods that scar should be avoided as much as possible.

Original Article

Microbial Prevalence and their Antibiotic Susceptibility Pattern in Diabetic Infections

V. Mohan., K. Saritha.,T. Palaniappan., R. Vasudevan

Diabetic individuals have decreased immunity levels and hence are highly susceptible to infections (1,2). The relation between diabetes and infection is synergistic and they form a vicious cycle by perpetuating each other. Infection in diabetes can be severe, prolonged and resistant to treatment and is marked by defective granulocyte, leukocyte and macrophage function (3 - 6). The presence of infection can cause worsening of hyperglycemia or even precipitate ketoacidosis in some cases.

Diabetic patients are prone to develop a wide range of infections which include respiratory, gastrointestinal, urinary tract (7) and skin and soft tissue infections (8). However, the most common reason for hospitalization among diabetic individuals, in India, which also accounts for a major economic burden (9) at both individual as well as community level, is diabetic foot infection. In this paper we report on a 'real life' experience of the pattern of infections in diabetic subjects as seen at a tertiary diabetic centre in Chennai.

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METHODS:

We conducted a 6-month retrospective analysis of 474 diabetic inpatients admitted at Dr. Mohan's Diabetes Specialties Centre, Gopalapuram during the period of January 2009 to June 2009. We studied the type of micro organisms causing infection in diabetic patients. The study population included 185 male and 289 female patients aged between 15-89 years with either type 1 or type 2 diabetes. A total of 551 samples were studied which included pus, urine, blood and tissue from diabetic wounds. Microorganisms were isolated from clinical specimens using standard culture methods. Isolation was done by plating samples on MacConkey agar & sheep blood agar. Isolated colonies were processed based on their Gram stain property.

RESULTS:

The results showed that E.coli was the commonest organism which accounted to 46.1% of the total isolates, followed by Enterococcus faecalis (19.24%) as shown below in Figure 1.

Looking at the pus cultures alone, the predominant microbe isolated turned out to be Staphylococcus aureus, which constituted 39 % of the total isolates followed by Enterococcus faecalis (19%), E.coli (13%) and Pseudomonas aerugenosa (9%) respectively as shown in Figure 2. There was not a single isolate of MRSA found during this study period.

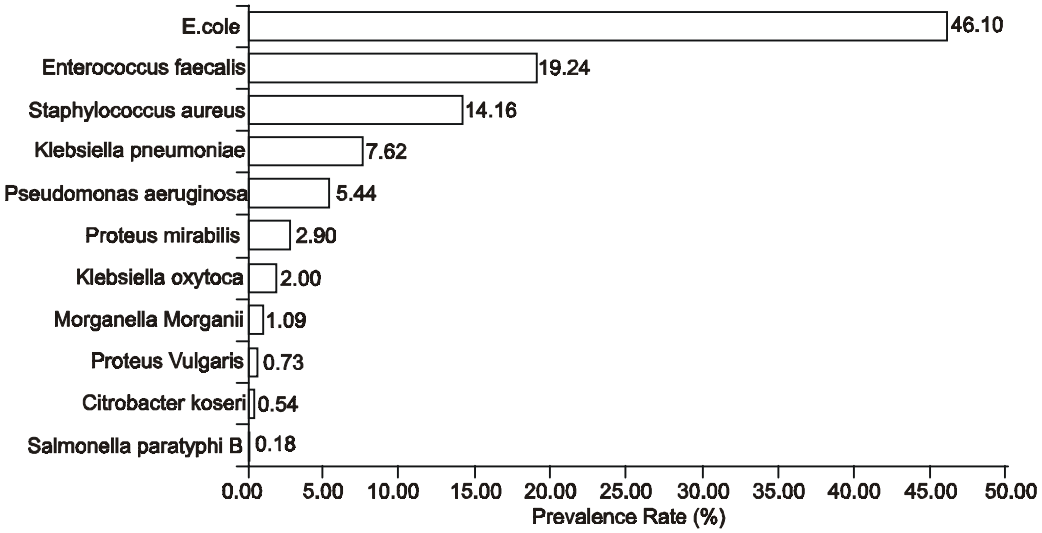

Figure 1 : Diagram showing the overall prevalence of microorganisms

We next looked at the microbial prevalence in relation to the glycated hemoglobin (HbA1c) levels. Figure 3 shows an increasing prevalence of staphylococcal infection as the HbA1c increases above 10%.

We also studied the sensitivity pattern of various antibiotics towards the different microorganisms isolated. Antibiotic susceptibility testing was done on Muller Hinton agar with antibiotic discs by Kirby-Bauer disc diffusion method. The resistance levels were correlated by determining the size of zone inhibition for each antibiotic tested. The sensitivity reports were analyzed and the results are depicted in Figure 4. The antibiotic sensitivity pattern of individual microorganism towards each antibiotic tested is shown as percentage values in Table 1.

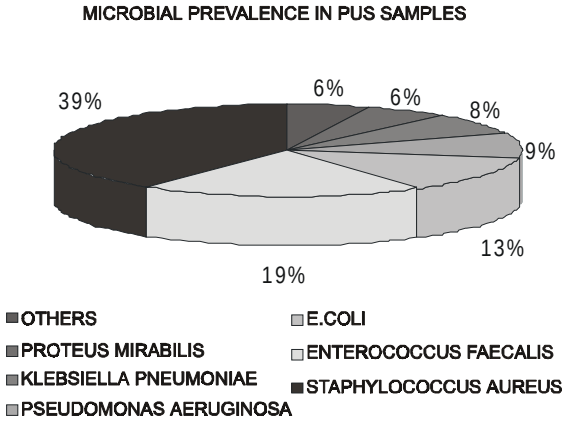

Figure 2 : Microbial prevalence in pus samples

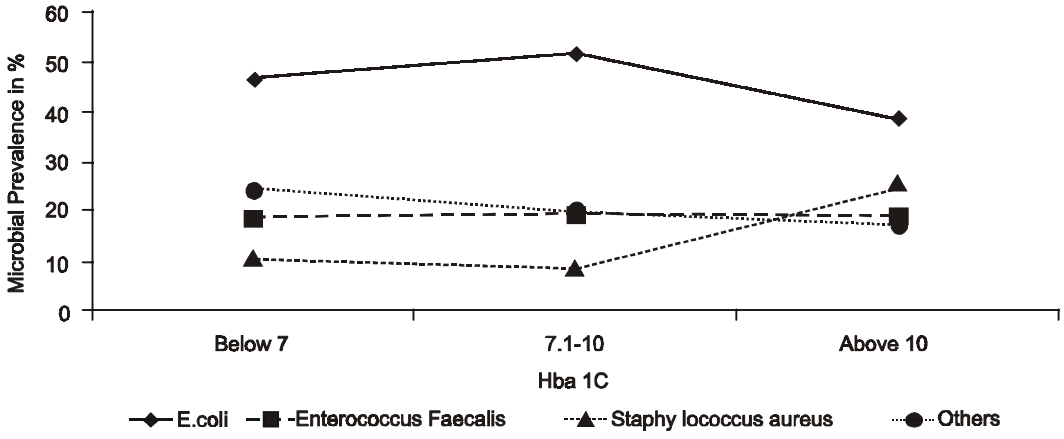

Figure 3 : Prevalence of staphylococcal infection in relation to HbA1c

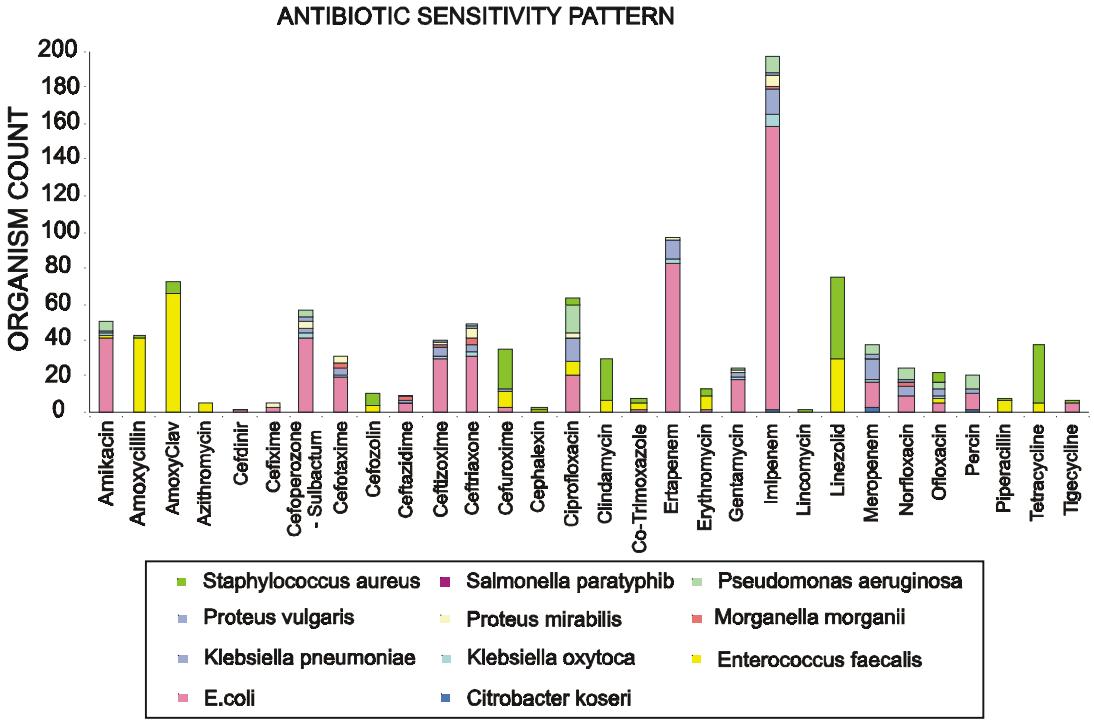

Figure 4 : Antibiotic sensitivity pattern

Table 1 : Percentage of each organism susceptible to a particular antibiotic

ANTIBIOTIC	Citrobacter Koseri	E.Coli	Enterococcus Faecalis	Klebsiella Oxytoca	Klebsiella Pneumoniae	Morganella Morganii	Proteus Mirabilis	Proteus Vulgaris	Pseudomonas Aeruginosa	Salmonella Paratyphi B	Staphylococcus Aureus
AMIKACIN		8.4	0.5	4.5	1.2				8.6		
AMOXYCILLIN			20.5								1.3
AMOXYCLAV			32.5								3.8
AZITHROMYCIN			2.9								
CEFDINIR		0.2	0.5								
CEFIXIME		0.6					6.3				
CEFOPEROZONE-SULBACTUM		8.2		13.6	3.6		12.5	25.0	6.9		
CEFOTAXIME		3.8		4.5	6.0	16.7	12.5				
CEFOZOLIN			1.9								4.5
CEFTAZIDIME		1.0		4.5	1.2	16.7			1.7		
CEFTIZOXIME		5.8		9.1	6.0	8.3	6.3	12.5			
CEFTRIAXONE		6.2		9.1	4.8	33.3	18.8	12.5	1.7		
CEFUROXIME		0.6	4.3		1.2						14.1
CEPHALEXIN			1.0								0.6
CIPROFLOXACIN		4.2	3.4		15.5	8.3	6.3		25.9	50.0	2.6
CLINDAMYCIN			3.4								14.7
CO-TRIMOXAZOLE		0.2	2.4								1.3

ANTIBIOTIC	Citrobacter Koseri	E.Coli	Enterococcus Faecalis	Klebsiella Oxytoca	Klebsiella Pneumoniae	Morganella Morganii	Proteus Mirabilis	Proteus Vulgaris	Pseudomonas Aeruginosa	Salmonella Paratyphi B	Staphylococcus Aureus
ERTAPENEM		16.6		9.1	11.9		6.3				
ERYTHROMYCIN		0.2	3.8								3.2
GENTAMYCIN		3.6		4.5	3.6		3.1		1.7		
IMIPENEM	33.3	31.5		27.3	16.7	8.3	21.9	12.5	15.5		
LINCOMYCIN											0.6
LINEZOLID			15.2								28.8
MEROPENEM	50.0	2.8		4.5	13.1		3.1	25.0	10.3		
NORFLOXACIN		1.8			7.1	8.3	3.1	12.5	12.1	,	
OFLOXACIN		1.0	1.4	9.1	4.8				3.4	50.0	3.2
PERCIN	16.7	2.0			3.6				12.1	,	
PIPERACILLIN			3.4								0.6
TETRACYCLINE			2.9								19.9
TIGECYCLINE		1.2									0.6

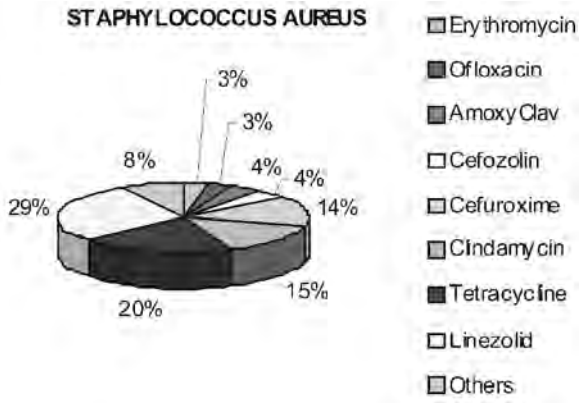

Figure 5 : Staphylococcus aureus

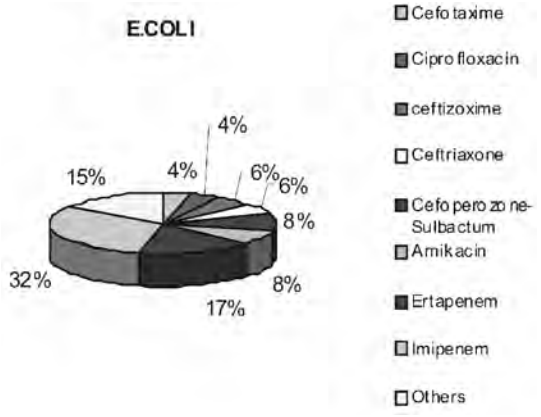

Figure 6 : E.Coli

Gram-positive organisms like Staphylococcus (Figure 5) and Enterococcus showed high sensitivity to drugs like linezolid, clindamycin, amoxicillin and tetracycline. Among the gram-negative organisms, majority of them showed high sensitivity to carbepenems, with E.coli (Figure 6) showing the highest sensitivity. Pseudomonas showed highest sensitivity rates to fluoroquinolone group followed by the carbepenem group.

DISCUSSION:

The results of the present study showed that E.coli was overall the commonest organism isolated while Staphylococcus aureus was the commonest organism isolated from pus samples. In an earlier study conducted at our centre in 2007 (10), the most frequent bacterial isolates from pus samples were Pseudomonas aeruginosa.

We also found that as the HbA1c (11) increases, the prevalence of Staphylococcal infection also increased. The positive correlation with higher HbA1c values shows that more severe infection is associated with staphylococcus aureus infection. Increased glycemic levels and

thereby increased HbA1c values are associated with a greater risk of foot infections in susceptible individuals. Staphylococcus aureus is commonly isolated from purulent discharge of diabetic foot ulcers and thus seems to be positively associated with higher HbA1c values. The exact reason behind this is to be further elucidated.

We also compared the antibiotic susceptibility patterns of different micro organisms studied against the previous results. Since MIC determination is not done on a routine basis at our center and in view of the increasing vancomycin creep (12) and hetero VISA (13) in the recent times we have not tested susceptibility to vancomycin. According to the earlier analysis conducted at our center (10), Cefoperazone-sulbactam, exhibited high sensitivity towards gram negative organisms like Proteus, E.coli and Klebsiella, but now it seemed to be moderately sensitive against them. Likewise, Pseudomonas exhibited high sensitivity to piperacillin, amikacin and imipenem according to the previous study results (10) but now the most sensitive was fluoroquinolone group followed by the carbepenems.

This shows that microbial sensitivity pattern to antibiotics keeps changing over time. Hence it is very important to form an antibiotic policy according to the prevalent organisms in each institution rather than strictly following the routine guidelines. Selection of the antibiotic should be empirical according to the existing sepsis guidelines and available gram stain or culture data in the first 24 hours. We can later alter the antibiotic regimen on the basis of the available data. Treatment plan should thus be tailored according to the clinical and microbiological profile of each patient.

This study also shows that both antibiotic therapy and good glycemic control are important in the treatment of infection in a patient with diabetes. It has been well documented that improper selection and inappropriate overuse of antibiotics is more often responsible for the emergence of resistance and thereby failure of antimicrobial therapy (14 -16). Hence it is recommended that the antibiotic choice should be made after taking into account factors like, pharmacoeconomics, Pk / Pd properties, prevalence of MDR strains and the antibiotic resistance patterns prevailing in that particular centre / region. Local susceptibility data should always be kept in mind. Indeed data from one centre in an area may be useful to other centres in that region.

Though there is ample clinical data supporting the role of hyperglycemia in increasing the risk of serious infections, a study done by Van den Berghe et al (17) demonstrated a significant decrease in mortality in patients, who received intensive insulin treatment (blood sugars between 80-110mg/dl), while in ICU. The role of good glycemic control in minimizing postoperative infections is also well supported (18,19).

To summarize, studies done at a three to six months interval, to analyze the pattern of microbial infections and change in their antibiotic susceptibility should be considered at an institutional level and this along with optimized antibiotic usage and good diabetes control certainly helps in achieving better outcomes in the management of diabetic infections. Every institution must have an antibiotic policy and stewardship (20,21). Patients with certain infections must be quarantined. The use of certain higher antibiotics on a routine basis in the general wards must be curtailed and they should be used only by the concurrence of two treating physicians in order to prevent the emergence of antibiotic resistance.

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Epidemiology

Intra Urban differences and Double Burden of Under Weight and Over Weight in Developing World

Dr. Vijay Viswanathan., Dr. Shabana Tharkar

Urbanization is on rise and so is urban poverty in the developing nations. Even though there is evidence of 21st century epidemiologic transition, the constant fear of malnourishment cannot be evaded. The paradox of overweight and underweight is continuing to haunt the public health professionals and policy makers.

The double burden of underweight and overweight in a developing country is an issue which is being addressed lopsidedly. The WHO Collaborating centre for research, education and training in diabetes has generated substantial evidence on growing disparities of weight among the two populations – slums and the higher elite group within the same geographic region in city of Chennai. The survey conducted in 2008, showed huge intra urban differences in the age-wise mean weight between the two groups

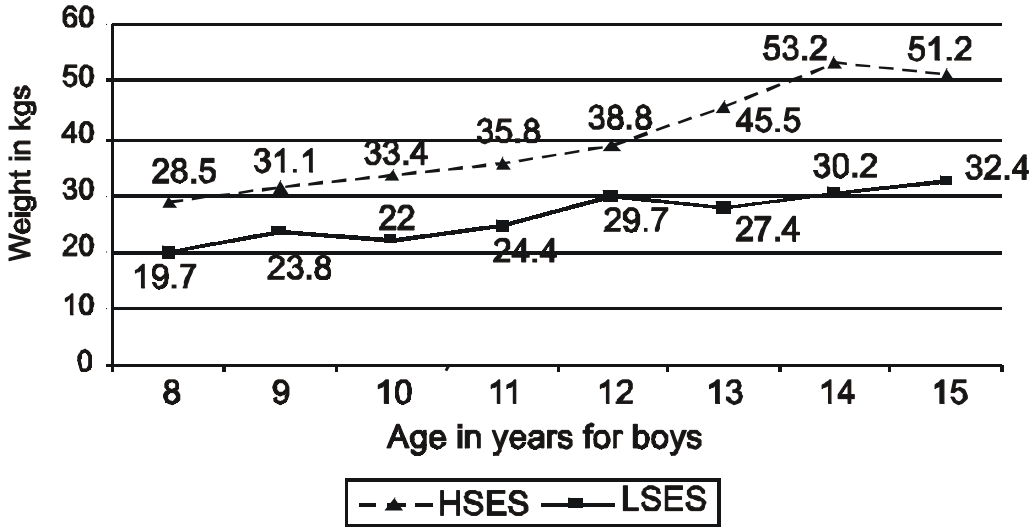

Figure – 1 Comparison of age-wise mean weight in kgs for boys between high socio economic (HSES) status and slum dwellers (LSES)

On comparison with WHO standards- Weight for Age Boys:

Z Scores (8 to 10 years)

(Age in years –Weight in Kgs)

8 - 25.4; 9 - 28.1; 10 - 31.2

of populations as shown in figure 1 and 2 for boys and girls respectively. Data on mean weight is available for the general population upto 80 years and the disparity between the two groups exists at all ages and the gap between under nutrition and over nutrition continues to widen. Economic growth, affordability and easy

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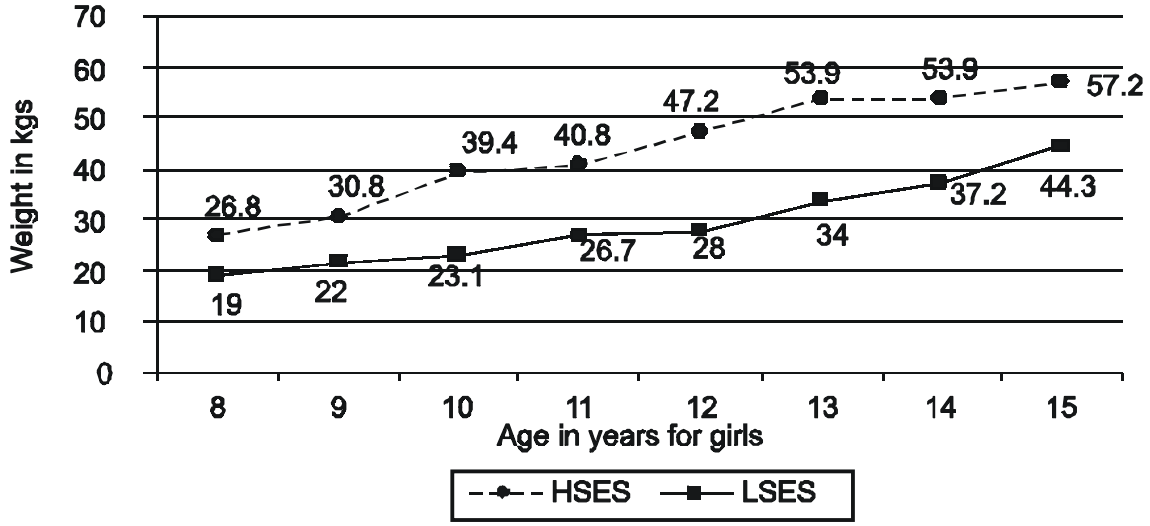

Figure – 2 Comparison of age-wise mean weight in kgs for girls between high socio economic status and slum dwellers

On comparison with WHO standards- Weight for Age Girls:

Z Scores (8 to 10 years)

(Age in years –Weight in Kgs)

8 - 25.0; 9 - 28.2; 10 - 31.9

availability of calorie rich food are the causes of over nutrition among higher socio economic group while poverty, unemployment and unaffordability are the causes for underweight and under nourishment among slum dwellers. Hence, both non communicable diseases and obesity related conditions like heart disease, stroke, diabetes and cancer which are lifestyle disorders and communicable diseases, infections are on a parallel rise in low and middle income countries.

Despite the WHO Global strategies on health promotion and chronic disease prevention, an increasing trend exists among the non communicable diseases. Hence the healthcare system must fight from two different fronts. Strategies must be developed with comprehensive planning and multi - sectoral approach to optimize the malnutrition and weight – reduction of obesity (over nutrition) among high socioeconomic status and improvement of under nutrition among the under privileged society. A framework of guidelines must be formed exclusively for developing countries to combat the nutrition related diseases and disorders. In countries like India, where the public health system is not very well developed, a public-private partnership is solicited to work towards the common goal of health promotion, disease prevention and the right for health for every human.

Views and suggestions are welcomed by leading physicians, researchers and policy makers from developing world to plan strategies to confront this issue of double burden.

Toxicology

Toxicology clinics – bench to bed side: Oximes in OP poisoning - Absolute or Obsolete?

Dr.S.SenthilKumaran, Dr.N.Balamurgan, Dr.V.Karthikeyan

Organophosphate (OP) poisoning is prevalent in agricultural communities and has reached an epidemic proportion in the developing world. Clinical features of acute poisoning can be rapid or delayed depending on the nature of the compound and the route of exposure. OP pesticides inhibit acetyl cholinesterase (AChE) at the muscarinic and nicotinic synapses by depositing a phosphoryl group at the enzyme's active site, thus resulting in accumulation of acetylcholine and uncontrolled activation of cholinergic synapses. Standard therapy attempts to reduce absorption by gastric lavage and oral administration of activated charcoal, as well as administration of atropine and oximes to counter the effects of absorbed pesticide. Though the use of atropine is well established, ***the use of oxime is debatable.***

What are the available oximes?

Pralidoxime, Obidoxime, Hl6, and Hlo7 are the available oximes across the globe. Among all oximes obidoxime is the most potent. Pralidoxime is the commonly available oxime in India. It is very expensive, but less potent.

What is P_2AM?

It is nothing but pralidoxime chloride. Pralidoxime occurs in three forms - chloride, iodide and sulphate. Among all three, chloride form, is about 1.5 times more potent than the iodide salt. It mainly acts on the peripheral nervous system because of its poor lipid solubility and restricted entry into the CNS. The main therapeutic effect of pralidoxime is expected to be recovery of neuromuscular transmission at nicotinic synapses.

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How do oximes work?

These oximes cleave covalently bound OP off the OP-acetyl cholinesterase (AChE) complex; thereby reactivate acetyl cholinesterase by removing the phosphoryl group. *In vitro* experiments have shown that oximes are effective reactivators of human AChE inhibited by OP compounds. This pharmacological effect of oximes has not translated, in oxime trials in human OP poisoning, to improvements in clinical outcomes.

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Why oximes are ineffective in human?

I Poor affinity for the particular OP-AChE complex

Most OP pesticides can be classified as compounds that form either a dimethylphosphoryl or a dimethylphosphoryl-AChE complex. Diethyl compounds both reactivate and age significantly slower than dimethyl compounds.

II Persistence of the OP within the patient and therefore rapid re inhibition of newly reactivated enzyme,

III Ageing of the inhibited AChE

In the inactive state, AChE is prone to "aging," a process by which one alkyl side chain of the phosphoryl moiety is removed

nonenzymatically, leaving a hydroxyl group in its place. Once AChE is "aged," regeneration is not possible. The therapeutic window for oximes is, therefore, very much determined by the rate of ageing.

What are the complications of oximes?

Complications of oximes reported in literature include hypertension, dysrhythmias, cardiac asystole, headache, blurred vision, dizziness, methemoglobin and muscle weakness.

Why there are controversies?

In the current scientific milieu, practice in medicine is largely evidence based. When we look at the issue of oxime therapy in humans, the recommendations are largely based on animal data. *In vitro* studies in animals and on human erythrocytes have suggested beneficial effects of oximes on reactivating AChE. However, clinical experience in the developing world has questioned the relevance of oximes for any form of OP poisoning. Senanayake's group[1] from Sri Lanka reported that pralidoxime was of no clinical benefit and should not be used.

Trials against oximes:

Vellore RCT 1: low dose Vs high dose[2]:

The authors argued that 'high-dose' pralidoxime was "associated with a worse outcome" and stated that pralidoxime has "no role in the routine management of patients with OP poisoning".

Limitation: There was no untreated control group. This study was criticized for the methodology.

Vellore RCT 2: high dose Vs placebo[3]:

The authors concluded that PAM "has no role in the management of patients with organophosphrous poisoning and that it "Does more harm than good".

Limitation: the studies did not evaluate the current WHO-sponsored recommendations for pralidoxime therapy

Iran trial[4]:

The authors concluded that atropine alone should be used in the treatment of acute OP poisoning.

Limitation: it was not a randomized trial

Eddleston RCT: high dose Vs saline [5]:

There is no benefit from the administration of the WHO's recommended regimen of pralidoxime chloride to patients with symptomatic OP insecticide poisoning.

Trials for oximes:

Prof. Shiva Kumar trial [6]:

The author concluded that patients on high dose P2AM had better survival compared to those on low dose P2AM. Limitation: There was no untreated control group.

Kirti S Pawar trial [7]:

Patient received high-dose regimen of pralidoxime (infusion of 1 g/h for 48 h) after a 2 g loading dose to reduce the morbidity and mortality in moderately severe cases of acute OP poisoning.

Reasons for the discrepancy

- Bias in the selection of cases (Included only early presentation)
- Confined to moderately severe cases
- Extent of supportive care (treated in ICU & 66% were incubated at baseline)
- Not incorporated the dimethylphosphoryl group of OP compounds
- This trial did not address the role of oximes in severe intoxications or late presentations of OP poisoning.

What current evidence says?

Thus, use of oximes in OP poisoning remains conflicting and controversial. From the randomized controlled trials, it appears that Oximes have no effect in moderate and severe poisoning, and do more harm than good. The treatment options are anticholinergic drugs and assisted ventilation, which is often required.

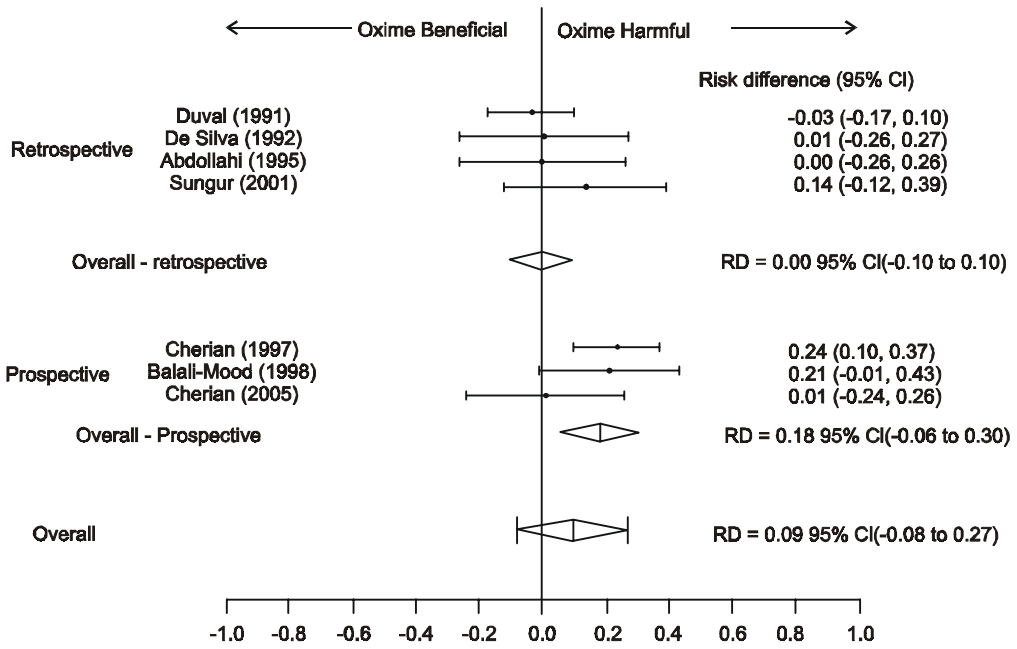

Figure 1. Association between oxime therapy and mortality; forest plot representation random effects model. The vertical straight line denotes null effect. The individual points denote the risk difference (*RD*) of each study and the lines on either side the 95% confidence intervals (*CI*).

Our experiences:

We have gone through several phases in our hospital from aggressive high dose oxime therapy to nothing at all. We couldn't see any difference that was worth noticing. We have stopped using oximes for the treatment of acute poisoning with organophosphrous pesticides. With improved standard of care in the medical intensive care unit, we are able to decline the mortality to less than two percent.

Acknowledgments:

We thank Dr. J. V. Peter for the guidance & literature support including the meta-analytic techniques. Dr. Michael Eddleston information on the recent srilankan RCTs .Prof. P. Thirumalaikolundusubramanian for the critical review

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Review Article

Hypertension in Diabetes Is Blood Pressure Control more important than Glycemic Control?

K.Raghavan

It is a well known and well established fact that the incidence of hypertension is upto twice as common in the diabetic as in the general population. About a third of Type I and almost half the Type II diabetes patients would need antihypertensive medication; even more significant is the fact that hypertension is present in 20 – 40% of patients with IGT. "Risk reduction by optional BP control is greater in diabetic than in non-diabetic individuals". From the MRFIT trial it is evident that the desirable BP in diabetics is < 130/85 mm Hg. And <125/80 mm Hg in those with Nephropathy. Both microvascular and macrovascular complications can be prevented if the target BP is consistently maintained.

THE EFFECTIVENESS OF BLOOD PRESSURE – LOWERING IN DIABETES:

Lessons from recent trials: "The Hypertension optional treatment (HOT) study": In all 18790 patients were randomly assigned to one of three blood pressure targets (<90, <85 and <80 mm Hg.) Within the HOT study there was a large cohort (8%, 1501) of people with diabetes, almost all Type 2 diabetes. In this population there was a significant trend towards greater benefit, the lower the target (and achieved) blood pressure. The risk of CV event was halved when the target diastolic BP was <80 mm Hg.

In the Systolic Hypertension – Europe study (Syst – Eur) key data emerged about the safety and efficacy of treating Isolated Systolic hypertention in elderly people with Type 2 diabetes. Of the 4203 patients in the Syst Eur study there were 492 hypertensive patients (8.6%) with diabetes. In this diabetic cohort treatment of hypertension was associated with an astounding benefit in terms of cardiovasular risk reduction and reduced mortality, much greater than that observed in non-diabetic patients.

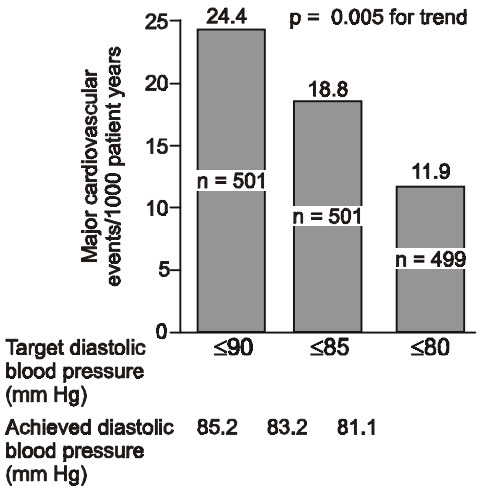

Fig 1: The reduction in cardiovascular events in patients with diabetes in the HOT study according to the target blood pressure, The actual number of events and achieved diastolic blood pressures are shown below each column.

In the UKPDS, the impact of improved blood pressure control on all diabetes – related and points, macrovasular and microvasular, was remarkable. The reduction in diabetes related end points was 24% which was twice as effective as that achieved by efforts to improve glycemic control. "Primary hypertension is an insulin resistance state"

The blood vessels of a diabetic function as though they are 10 years older than the patient. Hence Isolated Systolic hypertension is more common in the diabetic.

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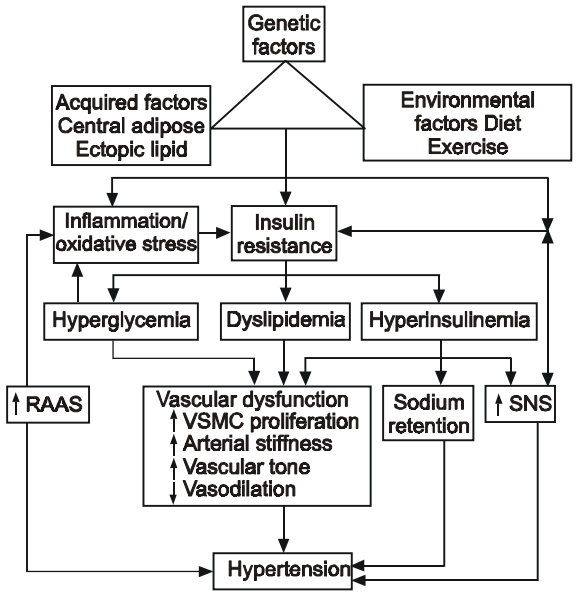
POSSIBLE MECHANISMS OF HYPERTENSION IN CONDITIONS OF INSULIN RESISTANCE.

Insulin has two diametrically opposing actions on the vascular system. It has a vasodilator influence mediated by release of Nitric oxide from the endothelium. It can also "induce hypertension" by facilitating Na+ and water reabsorption at distal renal tubule and by stimulation of Na+ K+ ATPase which increases intracellular Na+ Ca+ in the vascular smooth membrane. Cytokine induced acute phase (inflammatory) response associated with Type 2 diabetes may cause hypertension including cytokine stimulation of ACTH and glucocorticoid secretion and activation of sympathetic nervous system.

"Insulin resistance is linked to hypertension". Approximately 50% of patients with hypertension can be considered to have insulin resistance and hyperinsulinemia.

How does insulin resistance cause hypertension ?



RAAS - Renin Angiotensin-Aldosterone system.

SNS - Sympathetic Nervous System

VSMC - Vascular Smooth Muscle Cell

Fig. 2. Summary of putative pathophysiologic mechanisms in the development of hypertension

Specifically there exists a defect in the ability of insulin to stimulate glucose disposal by muscle in an individual without any abnormally in the ability of insulin to either stimulate renal Na+ retention or enhance CNS activity. Hence normal tissue response to insulin by the kidneys and SNS (in individuals whose muscle and adipose tissue are insulin resistant) helps to explain why such individuals are at increased risk for developing hypertension.

"Microalbuminuria, which heralds the onset of nephropathy is defined as albaminuria detected in the urine at levels of 30-299 mg/day".

In Type I diabetes hypertension is most obviously associated with diabetic nephropathy.

Blood pressure begins to rise when the albumin excretion rate enters the microalbuminuric range (>30 mg in 24 hrs.). Hypertension affects virtually all patients with persistent proteinuria. A corollary of this is that a diabetic patient with microalbuminuria or proteinuria cannot be labelled normotensive.

Once type 1 a type 2 diabetes patients develop overt proteinuria (ie., nephropathy – urinary albumin excretion > 300 mg 24 hrs) BP increases further and the 24 hrs BP profile is in markedly disturbed.

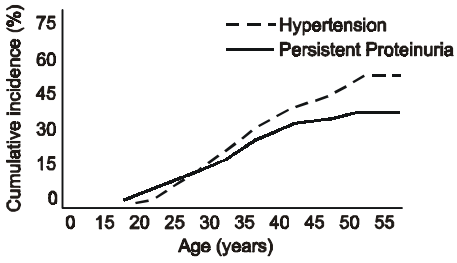


Fig. 3. Hypertension rises in parallel with proteinuria in Type 1 Diabetes patients of various ages.

In the UKPDS tight BP control (mean 144/82 mm Hg) resulted in a 29% reduction in the risk of microalbuminuria developing. Hypertention results in progression of microalbuminuria to overt proteinuria. Albumin excretion can be reduced by above 50% by 2 years treatment with ACE inhibitors. Microalbuminuria represents an increased

permeability of the glomerulus and parallels vascular endothelial dysfunction and predicts development of CVD and stroke as well as progression to diabetic nephropathy.

GENETIC PREDISPOSITION INFLUENCES THE DEVELOPMENT OF NEPHROPATHY.

The risk of developing nephropathy is increased three fold if at least one parent has hypertension – several candidate genes display polymorphism associated with diabetic nephropathy.

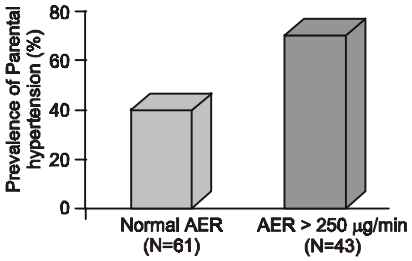
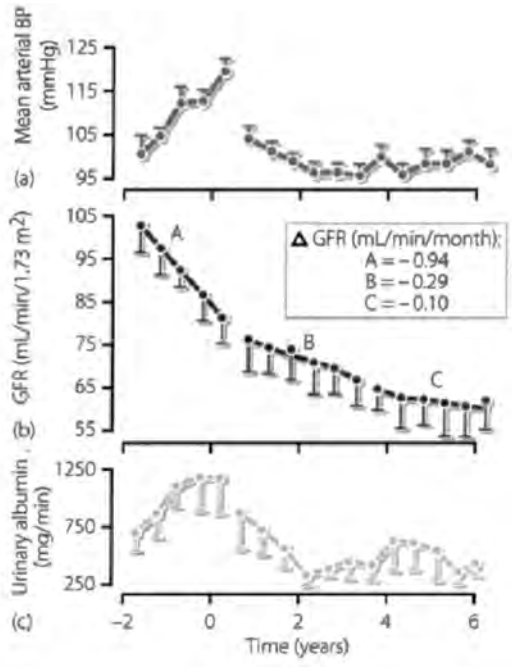


Fig. 4. The prevalence of Hypertension is increased in parents of those with proteinuria, which suggests that genetic position may influence the development of nephropathy



Early, effective BP control is again important in overt proteinuria and typically reduces the rate of decline in GFR from above 12 -<5 ml/min/yr

Fig. 5. Antihypertensive treatment

The RENAAL (reduction of end points in NIDDM with Angiotensin II antagonist Losartan, the IDNT (Irbesartan Diab Nephropathy trial), IRMA 2 (Irbesartan microalbuminuria for Type 2 DM) have all shown reduction in proteinuria and slowed the progression of renal disease. The beneficial effects of ARB's on nephropathy were independent of the changes in BP.

HYPERTENSION / DIABETES & (CAD)

Effect of BP on risk of fatal coronary artery disease is 2 to 5 times greater in diabetic than in non-diabetic population. Hypertension also worsens LV function. Lowering of systolic BP by 10 – 12 mm. Hg. and diastolic BP by 5-6 mm. Hg. confers risk reduction of 35 – 40% for stroke, 12 – 16% for CHD, within 5 years of initiating treatment. "Appropriate combination of drugs at lower doses has additive effects on control with less side effects"

To achieve recommended BP goals the majority of individuals with require treatment with more than one drug. ≥ 3 drugs are required in patients with diabetes and renal insufficiency. Diabetes tends to eliminate the female advantage women have over men as candidates for all CVD.

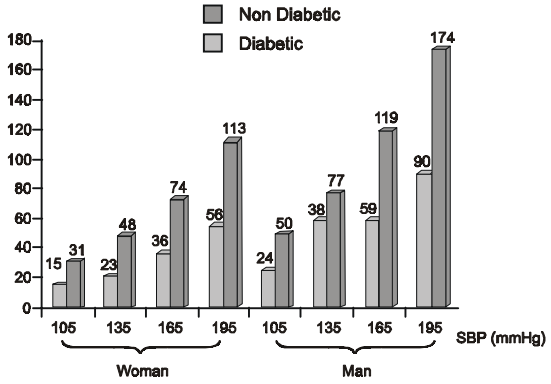


Fig. 6. Risk of Cardiovascular events according to SBP & Diabetic status. Framingham Study

In both DCCT (Type 1) & UKPDS (Type 2) improved glycemic control had no significant effect on cardiovascular outcomes. However in UKPDS tight BP control over 9 years showed a large reduction in risk of strokes (44%) and in microvascular end points (retinopathy, microalbuminuria)

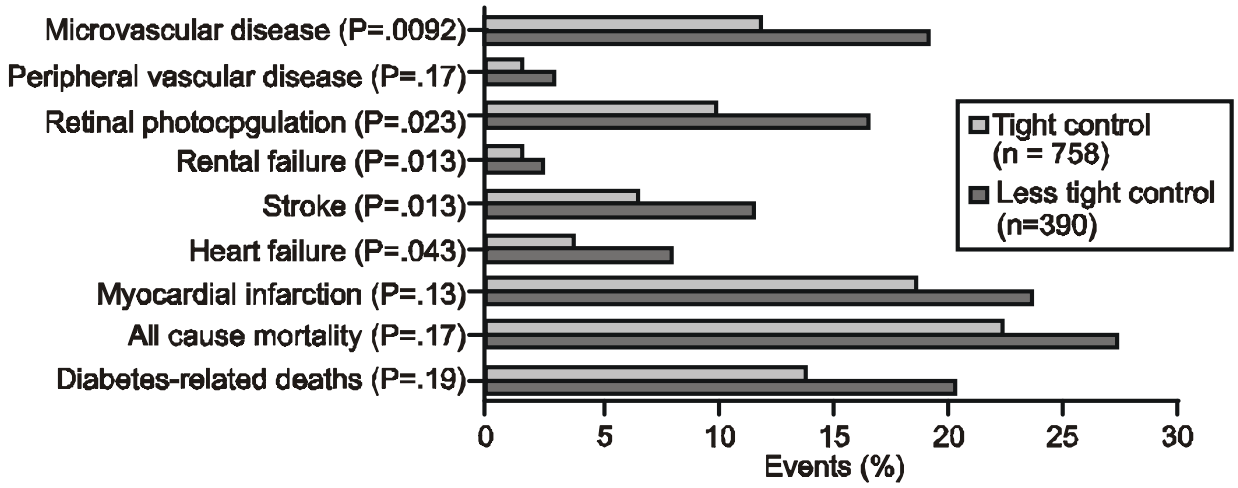


Fig. 7. Effects of Blood Pressure Control on Mortality & Vascular events in patients with Type 2 DM.

In the 10 year follow up study of patients in the UKPDS (NEJM 2008, 369 : 565-76) the benefits of previously improved BP control was not sustained when between group difference the BP were lost – it appears that good BP control must be continued if the benefits are to be maintained. Interestingly in case of blood sugar control in the same study a "legacy effect" was observe more than 10 years after the study period; in other words individuals whose glycemic control was strictly maintained continued to have sustained benefits long after study period. The benefits shown in UKPDS were corroborated in subsequent trials such as the "Hot study" Syst-Eur and SHEP. In the 'Micro-Hope" study 3577 patients with Type 2 DM who were treated with Ramipril showed a reduction of primary combined end point of MI, Stroke and CVD mortality by 25% and of stroke alone by 33%.

The ALLHAT, LIFE & the recent ADVNCE have all shown similar benefits. "Reduced Nocturnal dip"

The characteristic disturbance in 24 hours BP regulation in Type I and Type 2 diabetes is a reduction in the normal nocturnal dip in BP usually associated at higher nocturnal heat rate. The night – day BP ratio is particularly disturbed in patients with microalbuminuria (incipient nephropathy) and diabetes. "Target the associated deceases like recent MI, CCF, kidney deceases".

Treatment strategy : What is the initial drug choice ?

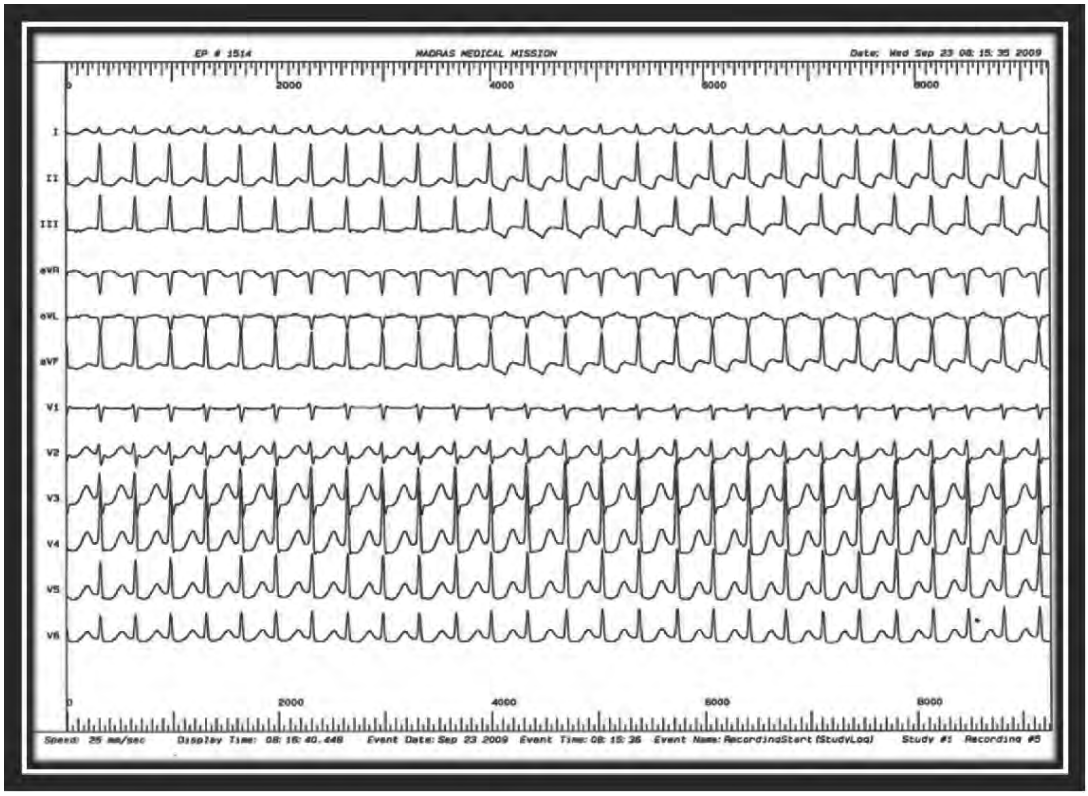
Answer : It doesn't matter. Because multiple medications will be required to achieve blood pressure goals.

Although an ACE – I is reasonable. *(Robert C Stanton , Joslin Diabetes Centre)*

ECG - Section

Diagnose the ECG Abnormalities

Dr. Ulhas M. Pandurangi MD, DM



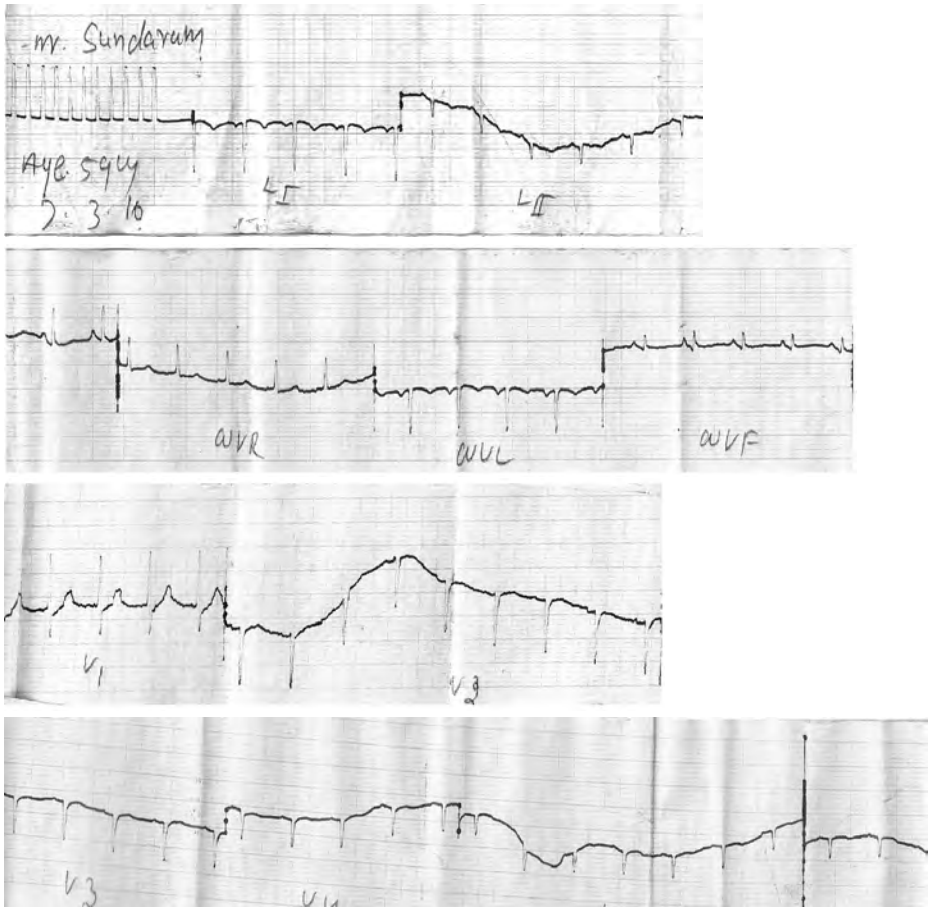
What is the diagnosis of tachycardia in the ECG?

The answer for the previous issue (Volume 2, Issue 1, January -April 2010) is "intermittent pre excitation with "T" wave memory sign"

Dr. Ulhas M. Pandurangi MD, DM
Cardiac Electrophysiologist and Interventional Cardiologist, Madras Medical Mission, Chennai, Tamilnadu

QUIZ

QUIZ: E.C.G. (non progression of R wave)



(a) What is this condition which led to Non-progression of R waves in precordial leads?

(b) What other special leads would help to confirm it?

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Review Article

Saxagliptin: A New DPP- 4 Inhibitor in Type 2 Diabetes

DR. Vijay Viswanathan., MD., Ph.D., FRCP (London), FRCP (Glasgow)

Summary

- Saxagliptin, an incretin enhancer, is the recent addition to incretin-based therapies in the management of type 2 diabetes. The oral selective dipeptidyl peptidase 4 (DPP-4) inhibitor is just the second in its class to be approved in the U.S. and third in India.
- Saxagliptin and its active metabolite M2 are dipeptidyl peptidase-4 inhibitors that improve glycemic control by preventing the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. This increases GLP-1 levels, stimulates insulin secretion and reduces postprandial glucagon and glucose levels.
- Saxagliptin is approved in India as an adjunct therapy to diet and exercise to improve glycemic control. Published clinical trial data indicate that saxagliptin as monotherapy or add-on therapy to metformin, sulfonylureas and thiazolidinediones is effective in improving glycemic control (as measured by hemoglobin A1C [HbA1C] levels), fasting and post-prandial glucose levels and percentage of patients achieving glycemic targets (<7% HbA1C).
- Saxagliptin as monotherapy or in combination with other oral antihyperglycaemics was generally well tolerated, with most adverse events being of mild to moderate severity. In clinical trials, the incidence of hypoglycaemic events in patients receiving saxagliptin was generally similar to that in patients receiving placebo or other oral antihyperglycaemic agents.
- Saxagliptin therapy was not associated with an increased risk of cardiovascular events according to pooled data from eight clinical trials. Saxagliptin generally had a weight-neutral effect. These added benefits are expected to improve therapy adherence.

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Introduction

Diabetes mellitus is a group of chronic metabolic diseases characterized by hyperglycaemia [1]. Approximately 90% of these cases are type 2 diabetes[2] which is the result of underlying insulin resistance and a progressive insulin secretory defect[1]. There is a wide range of antidiabetic drugs currently available in the market, but the success of many of these agents is undermined by safety and tolerability issues, barriers to adherence and waning efficacy as the disease progresses. The newest line of treatments against type 2 diabetes, the so-called incretin-based therapies, including the dipeptidyl peptidase 4 (DPP-4) inhibitors was designed to address these issues.

Saxagliptin (Onglyza) is one such DPP-4 inhibitor that has recently been approved for use in patients with type 2 diabetes[3]. Saxagliptin is approved in India, as monotherapy and combination therapy, as "an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes"[3]. It has not been evaluated as an adjunct to insulin[3]) and is not indicated for type 1 diabetes nor diabetic ketoacidosis[3]. This article reviews the pharmacological properties, clinical efficacy and tolerability of oral saxagliptin in adult patients with type 2 diabetes.

Pharmacodynamic Profile

The incretin pathway plays a key role in the pathogenesis of type 2 diabetes. Incretin hormones are produced in the gastrointestinal tract following food intake to exert glucoregulatory actions, the so-called incretin effect[6,7]). The incretin effect works through the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) which stimulate insulin secretion regulate gastric clearance and inhibit glucose production by the liver. These hormones are normally degraded and inactivated by the serine protease enzyme DPP-4.

In patients with type 2 diabetes, the incretin effect is significantly diminished due to dysfunction in the secretion, metabolism and responsiveness of the incretin hormones [7]. The class of drugs called DPP-4 inhibitors is designed to counteract DPP-4's degradation effects. One of these drugs is saxagliptin, a selective potent inhibitor of the DPP-4 enzyme system. Its mechanism of action is to exert long-lasting yet reversible inhibition of the DPP-4, thereby slowing down the inactivation of the incretin hormones and enhancing the incretin effect. The chemical structure of saxagliptin is shown in Figure 1 and its chemical development has been described in several papers[8-10].

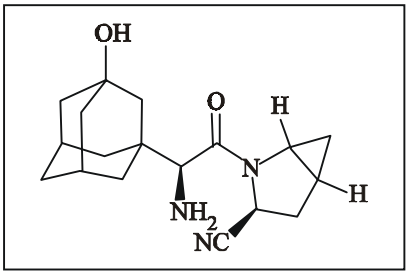

Fig 1. Chemical Structure of Saxagliptin

Saxagliptin is a potent, selective, reversible inhibitor of the DPP-4 enzyme.[5] It is 10-fold more potent than vildagliptin or sitagliptin, with an inhibitory constant (Ki) of 1.3 nmol/L for DPP-4 at 37°C (Ki = 13 and 18 nmol/L for vildagliptin and sitagliptin).[13]. The active metabolite of saxagliptin, M2 (BMS-510849), is 2-fold less potent than saxagliptin, with a Ki of 2.6 nmol/L. [5]

Saxagliptin dosages of 2.5–400 mg once daily for 14 days inhibited DPP-4 enzymatic activity in a dose-dependant manner in patients with type 2 diabetes and in healthy volunteers, with the inhibition profile at these dosages being consistent with once-daily administration [4]. Saxagliptin and its active metabolite are more selective for the inhibition of DPP-4 than DPP-8 (400- and 950- fold) or DPP-9 (75- and 160-fold) enzymes or a large panel of other proteases (>4000-fold) [5]. It has been suggested that once bound, saxagliptin and its active metabolite would continue to inhibit DPP-4 during rapid increases of substrate in vivo, owing to their slow dissociation from the enzyme[5]. Saxagliptin 2.5–400 mg once daily increased postprandial plasma intact GLP-1 levels by 1.5- to 3-fold after breakfast, lunch and dinner on day 13 (in patients with type 2 diabetes) or day 14 (in healthy volunteers) compared with placebo, with no apparent dose-relationship being observed[4]. Saxagliptin as monotherapy or in combination with other antihyperglycaemic agents improved glycaemic control and generally improved β-cell function in large clinical trials of up to 24 weeks' duration in patients with type 2 diabetes. Saxagliptin (2.5–400 mg/day for 14 days) or its active metabolite did not prolong the corrected QT interval in patients with type 2 diabetes or healthy volunteers [4].

Pharmacokinetic Profile

Special Populations

In patients with mild renal impairment (creatinine clearance [CLCR] 50–80 mL/min [3–4.8 L/h]), the AUC from time zero to infinity (AUC∞) of saxagliptin and M2 were 1.2- and 1.7-fold higher than in patients with normal renal function (CLCR > 80mL/min [>4.8 L/h]); however, this increase was not considered clinically relevant and no dosage adjustment is recommended [3,15]. In patients with moderate (CLCR 30–50 mL/min [1.8–3.0 L/h]) or severe

(CLCR <30mL/min [<1.8 L/h]) renal impairment, the AUC∞ of saxagliptin and M2 were up to 2.1- and 4.5-fold higher than in patients with normal renal function; therefore, dosage reduction is recommended in these patients. In eight patients with end-stage renal disease, 23% of the saxagliptin dose was eliminated during a 4-hour haemodialysis session[3,15]. No dosage adjustments are required in patients with hepatic impairment (Child-Pugh classes A, B or C) as, overall, the pharmacokinetics of saxagliptin differed by less than 2-fold between individuals with mild to severe hepatic impairment and healthy volunteers, and were not considered clinically relevant[3,17]. The pharmacokinetics of saxagliptin are generally not affected by sex or age in healthy volunteers and no dosage adjustments are considered necessary[3,18]. As the metabolism of saxagliptin is mediated by CYP3A4 and CYP3A5 isoenzymes, strong inhibitors and inducers of these isoenzymes will alter the pharmacokinetics of saxagliptin[3]. Studies have investigated potential drug-drug interactions of saxagliptin in healthy subjects and came to the conclusion that the potential for clinically meaningful interactions between saxagliptin and metformin[12], glibenclamide [13], pioglitazone[14], digoxin[15], omeprazole [16] or famotidine [16] is low.

Monotherapy

Saxagliptin has been approved by the U.S. Food and Drug Administration (FDA) and Drug Controller General of India (DCGI) as an adjunct to exercise and diet in the treatment of type 2 diabetes. It is administered orally once daily with or without food [3]. Several studies reported on the efficacy and safety of saxagliptin monotherapy. Rosenstock et al evaluated saxagliptin as monotherapy for type 2 diabetes drug naive patients in several studies, two of which have been published in peer-reviewed journals [19,20]. In one study, following administration of saxagliptin at 2.5, 5 and 10 mg once daily for 24 weeks, significant and clinically meaningful reductions in HbA1C (–0.43, – 0.46 and –0.54%, respectively) and FPG-AUC from baseline were observed [19]. No weight gain or increased incidence of hypoglycemia was reported. The number of patients that achieved glycemic goals was higher in groups administered with saxagliptin (35, 38, 41%, for 2.5, 5 and 10 mg, respectively), compared to placebo (24%). In another similar study with higher saxagliptin doses (2.5-40 mg), a similar trend in improvements in glycemic parameters was observed [20].

Add-on therapy

Several clinical studies have investigated the efficacy of saxagliptin as add-on therapy to some of the most commonly used antidiabetic drugs. The changes from baseline in HbA1C levels and the proportion of patients reaching glycemic targets in these comparative studies are shown in Table I [21-25]. These studies demonstrated the efficiency of saxagliptin as add-on therapy. Thus, it has been approved by the European Medicines Agency as an add-on combination therapy to one of existing glucoregulatory drugs (metformin, a sulfonylurea, and a thiazolidinedione) in patients who are not able to achieve glycemic goals with their existing therapy plus diet and exercise [3]. In Canada, saxagliptin has been approved as adjunct to metformin or a sulfonylurea when these drugs alone, with diet and exercise do not provide adequate glycemic control [3].

Saxagliptin and metformin

Metformin is the most commonly prescribed drug for first line treatment of type 2 diabetes. However, with the progression of the disease, increasing insulin resistance and β-cell dysfunction, metformin becomes inadequate in controlling glucose levels. It is also associated with adverse events that include hypoglycemia, weight gain and gastrointestinal intolerance [26]. Several studies observed improved glycemic control when saxagliptin is used in combination with metformin, either as add-on initial therapy or as add-on to ongoing metformin therapy

[21,22,24,27-28]. Two of these studies have been published in peer-reviewed journals. The efficacy and safety of saxagliptin plus metformin as initial combination therapy vs. monotherapy of either drug was investigated by Jadzinsky et al[21]. The results showed that the combination therapy was significantly better in lowering HbA1C levels compared to either saxagliptin or metformin as stand-alone agents. Other glycemic parameters (FPG and PPG-AUC) also significantly improved with the combination therapy (Table I). In another study, the efficacy of add-on saxagliptin (2.5, 5 and 10 mg) plus metformin combination therapy vs. metformin monotherapy was compared[22]. The results showed that a once-daily saxagliptin as add-on to ongoing metformin therapy significantly improved glycemic control (Table I).

Hypoglycemia

The occurrence of hypoglycemic events is a major hindrance to type 2 diabetes therapy adherence. Many of the existing antidiabetic agents are associated with increased incidence of hypoglycemia. As part of safety evaluation of saxagliptin, clinical studies reported the frequency of hypoglycemic events. Six published papers reported low incidence of hypoglycemia associated with saxagliptin as mono- or add-on therapy [19-23,25]. Rosenstock et al[20] reported hypoglycemia incidences to be similar between saxagliptin and placebo.

Table 2: Adverse events reported in studies

Reported in published studies on saxagliptin (frequency of = 5)	
Reported adverse event	Reported by
Dyspepsia	[22]
Headache	[21,22,23,25]
Influenza	[22,23]
Nasopharyngitis	[21,22,23,25]
Pain in extremity	[22,23]
Peripheral edema	[25]
Upper respiratory tract infection	[22,23,25]
Urinary tract infection	[22,23,25]

Incidences of hypoglycemia in studies on saxagliptin as add-on therapy are shown in Table I. In an abstract, Chen et al[30] presented hypoglycemic incidence data from six double-blind randomized trials comparing saxagliptin as monotherapy vs. as add-on therapy to metformin, TZD or a sulfonylurea. Results showed that hypoglycemic events were infrequent, with similar incidence rates in all groups.

Weight gain

Some antidiabetic drugs are associated with weight increase. Published data indicate that saxagliptin is generally weight-neutral, i.e. its use does not result in weight increase or reduction. Two published studies reported slight weight increases[23,25] and another 2 reported weight losses [21,22] but these changes in weight from baseline were not considered to be clinically significant.

Cardiovascular Events

Saxagliptin as monotherapy or in combination with other oral antihyperglycaemic agents was not associated with an increased risk of cardiovascular events, according to pooled data from eight clinical trials[31]. In these trials, the overall exposure to saxagliptin was 3758 patient-years and to the comparators (placebo, metformin or glibenclamide) was 1293 patient-years; 81% of patients had at least one cardiovascular risk factor in addition to diabetes (including hypertension [52%], dyslipidaemia [44%] or history of smoking [39%]) and 12% had prior history of cardiovascular disease[31]. In this analysis, acute cardiovascular events occurred in 1.1% of patients in the saxagliptin group compared with 1.8% of patients in the comparator group (hazard ratio [HR] 0.59 [95% CI 0.35, 1.0]; n = 3356 and 1251); few patients receiving saxagliptin had major adverse cardiovascular events (0.7% vs 1.4% in the comparator group; HR 0.44 [95% CI 0.24, 0.82]) [31]. The incidences of all-cause death (0.3% vs 1.0% comparators) and cardiovascular death (0.2% vs 0.8%) were also low in patients receiving saxagliptin therapy (Table 3) [31].

β-Cell function

As type 2 diabetes progresses, the functioning of the β-cells of the pancreas responsible for insulin secretion also progressively declines, undermining the efficacy of antidiabetic drugs. One hypothesis regarding the mechanism of action of saxagliptin is the improvement of β-cell response. A randomized double-blind placebo controlled study investigated the effect of saxagliptin monotherapy on β-cell function in drug-naive patients[32]. Saxagliptin was administered through an intravenous hyperglycemic clamp. The primary endpoint was the change in total insulin secretion from baseline in the fasting state; secondary end point the change in postprandial insulin secretion. Following a 12-week saxagliptin treatment, fasting and postprandial insulin levels relative to baseline were significantly improved and postprandial glucagon concentration lower compared to those who received placebo. The results suggest a positive effect of saxagliptin on the pancreatic β-cells. Hollander et al[25] evaluated β-cell functioning in a randomized, placebo-controlled study using HOMA-2β measurements. Following 24 weeks of saxagliptin plus TZD treatment, increases in HOMA-2β were observed, indicative of improved β-cell function. Two other published studies reported significant increases in HOMA-2β (Table I) following saxagliptin treatment[23,24]. In addition, significant improvements in insulinogenic index, which is a measure of early insulin response to a glucose load, were also observed.

Dosage and Administration

In patients with type 2 diabetes, the recommended dosage of saxagliptin is 2.5 mg or 5 mg once daily administered orally without regard for food[3]. In patients with moderate or severe renal impairment (CLCR ≤ 50mL/min [≤ 3L/h]), and in patients with end-stage renal disease requiring haemodialysis, the dosage of saxagliptin should be adjusted to 2.5 mg/day to achieve plasma exposures of saxagliptin and M2 that are similar to those in patients with normal renal function; no dosage adjustment is required in patients with mild renal impairment[3]. Saxagliptin dosage should also be adjusted to 2.5 mg/day when the drug is co-administered with strong CYP3A4/5 inhibitors (e.g. ketoconazole, atazanavir or clarithromycin). Saxagliptin should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis and the drug has not been studied in combination with insulin[3]. Local prescribing information should be consulted for comprehensive dosage and administration guidelines, contraindications, precautions and drug interactions.

Conclusion

Most of the clinical studies on saxagliptin reported a positive efficacy profile as mono- or add-on therapy in improving key glycemic parameters and in attaining glycemic targets. These studies also reported a good saxagliptin tolerability profile, with little indication of CV effects, and with the additional benefit of having no significant effect on weight or incidence of hypoglycemia. These improvements are expected to improve adherence to therapies and help achieve long-lasting glycemic control in patients with type 2 diabetes. Saxagliptin, therefore, is a welcome addition to the wide range of antidiabetic drugs currently available and may be a potent weapon in the fight against the type 2 diabetes epidemic. However, like all new drugs, the long-term safety and efficacy of saxagliptin needs to be established by post-marketing data.

Saxagliptin: Current Status

In India, saxagliptin is indicated as an adjunct to diet and exercise (monotherapy and combination therapy) to improve glycaemic control in patients with type 2 diabetes. Oral saxagliptin as monotherapy or in combination with other antihyperglycaemic agents improved glycaemic control and was generally well tolerated in several large, well designed trials of up to 24 weeks duration and in a long-term extension study in adult patients with type 2 diabetes.

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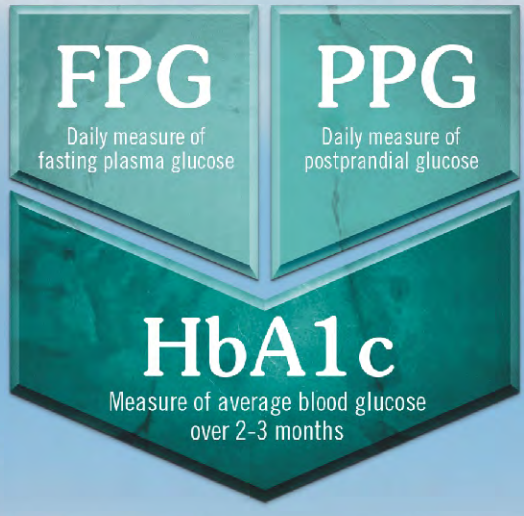

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1) DeFronzo R A et. al., Diabetes Care, 2009;32: 1649-55. 2) Chacra AR, et al. Int J Clin Pract. 2009;63(9):1306-406 3) Allen E, et al. Diabetologia. 2009; 51 (Suppl 1): S342-S343, Abstract 859.
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