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DIABETES MELLITUS AND LUNG

Diabetes mellitus is a common disease but its effects on the structure and the function of the lung are less well studied. Whether the structural and functional changes are of clinical relevance is also not known. Diabetes mellitus also alters the various components of pulmonary defense mechanisms and may predispose to pulmonary infections.

A. Structural changes in the lung :

In experimental animal models of diabetes mellitus, ultra-structural changes have been described in type 2 pneumocytes and non-ciliated bronchiolar epithelial cells (clara cells). Studies in humans are difficult and most of the studies are based on postmortem specimens. The following changes have been described :

1. Thickened alveolar epithelial and pulmonary capillary basal laminae: This is the most consistent change described in the lungs of patients with diabetes mellitus. The degree of basal laminae thickening is either less or comparable to the basal laminae thickening found in kidney. There is no significant correlation between the thickening of pulmonary basal laminae and duration of diabetes mellitus. Increased synthesis of collagen, elastin and other extracellular proteins, the nonenzymatic glycosylation of protein and their decreased turnover are the causes for the thickening of basal laminae.
2. Microembolization of pulmonary arteries.
3. Some degree of centrilobular emphysema is also found in some studies in the lungs of diabetes subjects.

B. Diabetes mellitus and changes in pulmonary physiology :

1. Diabetes mellitus & pulmonary mechanics:

- a. The most consistent abnormality of reduced lung volumes is shown to be more in children and adolescents and in the patients who have limited joint mobility. This is attributed to impaired growth of lungs and chest wall, decreased mobility of chest wall joints and decreased

compliance of chest wall as a whole.

- b. Reduced pulmonary elastic recoil has been described in both young and adult diabetic subjects. This is manifested by an increased value of the exponential shape constants of pressure volume curve.

2. Diabetes mellitus and pulmonary diffusion :

In young insulin dependent diabetic subjects, there is reduced transfer factor expressed per unit alveolar volume (D^2CO/VA), possibly due to a diminished pulmonary capillary blood volume and secondary to pulmonary microangiopathy. The value of membrane diffusing capacity does not change from that of reference subjects.

3. Diabetes mellitus and ventilatory control :

The ventilatory increase in response to transient hypoxia is less in diabetics without autonomic neuropathy than in controls, but even weaker in diabetics with autonomic neuropathy. The same pattern is seen in the ventilatory response to hypercapnia. No correlation has been found between the presence of abnormal ventilatory responses and the duration of diabetes mellitus. There are attributed to the altered function of both the peripheral and the central chemoreceptors.

C. Diabetes mellitus and pulmonary infections :

The different factors which can predispose to pulmonary infections include.

1. Changes in polymorphonuclear leucocytes i.e. decreased mobilization

and chemotaxis, decreased phagocytosis, decreased adherence to endothelium and decreased bactericidal activity.

2. Changes in monocytes - decrease in total number, decreased lectin receptors and decreased phagocytosis of certain organisms.
3. Changes in cell mediated immunity.
4. Microvascular changes causing decreased tissue perfusion.
5. Diabetic nephropathy leading to renal failure.
6. Gastrointestinal disease like gastroparesis - increase the risk of aspiration.
7. Increased nasal carriage of *Staphylococcus aureus* and increased oropharyngeal colonization by gram negative bacilli.

a. Diabetes mellitus and pneumonia:

Whether diabetes mellitus is an independent risk factor for pneumonia or not is still inconclusive. Diabetes does not increase susceptibility to pneumococcal pneumonia. However, in diabetic patients with pneumococcal pneumonia, there are increased risks of bacteremia and mortality. *S. aureus* and gram negative (e.g. *Klebsiella*) infections are more common in diabetes mellitus and most patients with *E.coli* pneumonia are diabetics. There is also an increased mortality and increased incidence of bacterial pneumonias and diabetic ketoacidosis among diabetic patients during influenza epidemic. Pneumococcal and influenza

vaccinations are recommended in diabetes patients.

b. Diabetes mellitus and tuberculosis :

In endemic areas, a higher than expected proportion of tuberculosis patients have got diabetes. In different studies from India, prevalence of diabetes has varied from 6.6 to 20% in patients with tuberculosis. However, most of the tuberculosis patients who were found to be diabetic were asymptomatic. On the other hand, tuberculosis is a frequent complication in patients with established diabetes mellitus. Diabetes have 3-4 times higher prevalence of tuberculosis and severe forms of tuberculosis seem to develop more frequently among diabetes than nondiabetic controls.

Asymptomatic diabetes patients may develop symptomatic deterioration if they develop tuberculosis. Pulmonary TB was a common cause of brittle diabetes in 1950s.

The same regimen of antitubercular treatment is recommended in TB patients with diabetes mellitus. Compliance and clinical response need to be carefully monitored. If reactivation occurs, the tubercle bacilli are more likely to be drug resistant. The control of blood sugars need to be optimised. Rifampicin increases the metabolism of sulphonylurens and can worsen the metabolic control in patients receiving those drugs.

c. Diabetes mellitus and pulmonary mucormycosis

Mucor grows best in acidic, high-glucose medium. More than 50% of patients with pulmonary mucormycosis are diabetic and in 27-50% of these patients, the need for hospitalisation is diabetic ketoacidosis. Clinical and radiological pictures are indistinguishable from those of bacterial pneumonias. Diagnosis depends on high degree of clinical suspicion and microbiological work up. Fiberoptic bronchoscopy and appropriate specimen collection provide the diagnosis in many cases. The hyphae of mucor can penetrate bronchial and vessel walls and can produce distal embolization. Pulmonary mucormycosis has a high mortality of about 65% with isolated pulmonary disease and upto 96% with disseminated disease. The causes of death include fungal sepsis, respiratory failure, fatal hemoptysis and bacterial sepsis. Treatment includes Amphotericin B and correction of underlying metabolic abnormalities and supportive measures. Isolated pulmonary mucormycosis patients who are acceptable surgical risks and show no improvement after 48-72 hours of antifungal treatment should be considered for surgery.

D. Diabetic ketoacidosis and noncardiogenic pulmonary oedema :

It is a rare but well documented complication of diabetic ketoacidosis (DKA) having high mortality. The proposed causes include rapidly decreasing oncotic pressure following

resuscitation with large volume of hypotonic fluid and a specific alveolocapillary permeability defect induced by acidosis and hyperventilation. Hypotension, hypothermia and coma are additional risk factors for this condition. There is no specific treatment but for supportive measures and mechanical ventilation.

E. Diabetic mothers and infant respiratory distress syndrome :

At less than 38 weeks for any gestational age, risk of hyaline membrane disease is 5-6 times higher in infants born of a diabetic mother. Hyperglycemia with or without hyperinsulinemia causes morphologic immaturity of lung and delay in surfactant

production. Steroid induced enhancement of lecithin synthesis is also suppressed. With improvement of antenatal care and better control of diabetes in the antenatal period, the incidence of infant respiratory distress syndrome has decreased. Foetal lung maturity should be assessed before delivery and presence of phosphatidylglycerol in amniotic fluid is a better indicator of lung maturity in case of pregnancy in a diabetic mother.

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W.H.O. CATEGORY II RETREATMENT REGIMEN FOR TREATMENT FAILURE AND RELAPSE CASES OF TUBERCULOSIS : IS IT JUSTIFIED IN INDIA ?

INTRODUCTION :

“It is a sad reflection on society’s incompetence that, more than 30 years after the methods for cure and prevention were evolved and before the advent of HIV epidemic, there were already more patient with active tuberculosis in the world than there had been in the 1950’s”. This is how Sir John Crofton started his foreword of the book “Clinical Tuberculosis”.

In 1993, W.H.O. declared TB to be a global emergency. 30% of world’s TB patient are in India. Prevalence rate of tubercular disease in India is 1.5% of total population. The number of new cases have been growing steadily due to population growth. Population of India is estimated to increase by 75% in the next 30 years. 2 million cases of fresh TB cases occur every year, half of which are smear positive. A single sputum positive patient can infect 15 to 20 normal healthy individuals in a

year time. In India the disease is estimated to kill 5 lakhs per year, one thousands per day and one per minute.

While a case of sensitive TB can get cured, the drug resistant case will keep propagating the infection for many years untill the death of the patient. This sets in a vicious cycle, which increase an already existing pool of TB cases with an increase of polyresistant/MDR variants.

Cause of poor TB control & emergence of Drug resistance

1. Poor N.T.C.P. implementation
 - * Inadequate case finding
 - * Erratic supply of drugs
 - * Poor follow up
 - * Poor supervision
2. Failure to identify initial poly resistance or MDR in a patient.

3. Irregular intake of drugs.
4. Improper regimen.
5. Allopathic treatment by quacks & alternative systems of medicine.
6. Adding single drugs to a failing regimen.
7. Adding reserve drugs to a failing regimen.
8. No supervision.
9. Partial medication/selective medication.
10. Early termination of treatment course.
11. Poor management of adverse effects leading to
 - a) Elimination of Rifampicin & / or INH ; most potent drugs from the regimen.
 - b) Increase in drop out rate as patient thinks that he is getting wrong treatment.
 - c) Improper regimen & duration of treatment after elimination of Rifampicin &/or INH.
12. Reluctant/ half hearted treatment.
Not sure treatment. Adding 2ATDs to antibiotics
13. Poor quality of drugs/fake drugs in the market.
14. HIV epidemic.
15. Poverty, illiteracy, ignorance.
16. Overcrowding/slums.
17. Malnutrition.

Which country other than India can represent the best of all these factors playing its role to its optimal effect ?

In India 70% of TB patients are treated by private practitioners, significant number is also being treated by quacks. In private practice, large variations in the use of different regimens have been reported. In a study conducted in India, about 30 types of regimen are being used for treating tuberculosis.

Impact of HIV on TB control & emergence of resistant TB organism in India

HIV positive population in India is estimated to be 8 million to 10 million & doubling time of the

epidemic in India is around 2 years.

HIV seropositivity in tuberculosis patients as reported in various studies published from India is 0.4% to 20.1%.

It is estimated that 2,50,000 HIV related TB in India was seen in the year 2000.

Life time risk of developing active TB in HIV negative infected patients is 5% to 10%. Life time risk of developing active TB in HIV positive infected patients is 50%. In Tanzania the case rate nearly doubled in the early 90's and nearly 2/3rd of the increase in the population rate of smear positive cases was thought to be directly attributable to HIV infection. India is predicted to witness a massive lethal co-pandemic of these 2 infections, over the next 2 decades. It will lead to increase in the burden of illness 3-4 times compounding the existing problem of TB. WHO has estimated that by the year 2006, 25% of smear positive TB patients will be HIV positive in India.

Both diseases share the need to administer multiple drugs for a long time, which decreases the chances for complete adherence. With poor adherence, not only is continued progression and spread of the disease probable, but also the development of resistance to the drugs being used. The United States faced this dilemma in the early 1990's. In certain areas of the country, rates of resistance were rapidly rising, with some cities reporting as much as 19% of their strains to be MDR. It is unlikely that the DOT strategy with the currently available medications will be sufficient to control, much less eradicate, TB. This fact is illustrated by the surge of MDR cases throughout the world. For this reason, new therapies that will improve current regimens are being vigorously investigated. Emergence, transmission & outbreak of MDR TB are much commoner in HIV & AIDS patients.

Coinfection with HIV increases mortality rate to

10% due to TB as compared to 1.6% in HIV negative individuals.

Category II retreatment regimen not tested prior to 1993 WHO recommendation

The only regimen that should be prescribed for treatment are those that are tried out successfully in controlled clinical study. Unfortunately, no controlled clinical trial was conducted before 1993 to recommend Cat II retreatment regimen.

The results of RNTCP in India from October 1993 through mid 1999 has been reviewed by Khatri and Frieden (International Journal of Tuberculosis and Lung Diseases, 2000).

The cure rate of 79.4% is less than the goal of RNTCP to ensure that at least 85% of all newly detected sputum smear positive cases are cured and thus transmission of TB is interrupted. Similar aim should also be kept in mind while treating category II patients as it is important to prevent emergence of MDR TB patients.

Comparison of outcome of treatment of category I & II shows that outcome of category II is much inferior. There is 25% decrease in cure rate, and 100% increase each in death rate, failure rate and default rate. How such a regimen should be acceptable ?

Among the 1458 patients who had remained smear positive after category I treatment, category II regimen cured only 63%. This is much less than the desired goal of cure rate. In India, at least 30% have acquired resistance to both Rifampicin and INH. It is also documented that only 33% patients of MDR TB become smear negative on category II regimen. This is similar to the historic outcomes when no chemotherapy for TB was given. Thus 63% cure rate includes 1/3rd of MDR-TB patients (30%) becoming smear negative majority of whom will relapse later. Hence actually cure rate is only 52%. Unfortunately, relapse-patients of MDR TB

will again be subjected to category II regimen.

Authors concluded that although the category II regimen was controversial, even among patients who remained sputum smear positive after 5 months of category I treatment and who were placed on category II regimen, 2/3rd was successfully treated and only 8% remained smear positive. On critical analysis this conclusion appears an over simplicity. Those who died were sputum positive (8%). Those who interrupted treatment will continue to remain sputum positive (15%). Those who are not cured but completed treatment will eventually relapse (3%). This outcome by no means should be acceptable.

Prevention of emergence and transmission of MDR-TB is at least as important as prevention of transmission of TB bacilli susceptible to all drugs. In one year, one MDR-TB case will infect 20 patients. MDR-TB patients treated by category I and II regimen will be sputum positive for at least 18 months & may be much more as 50% of them will not be cured. Hence on an average one MDR-TB patient will infect 40 patients in two years. Out of 40 patients at least 4 patients will develop active pulmonary TB with primary MDR-TB strain. HIV co infection is likely to increase it by 50% to 75%. Thus approximately 1 MDR-TB patient will give rise to 6 MDR-TB patients. Impact of treating these 6 primary MDR-TB cases can be understood by the simple fact that as per WHO guidelines, they will be treated with category I and II regimen with no significant response leading to increased mortality, wastage of drugs, economic burden, increased transmission of MDR-TB strains & later 6 lakhs will be spent over a period of 2 years to achieve a cure rate of 50%. This economic burden is about 50 times for each MDR-TB patients in comparison to susceptible TB patients. 3 uncured MDR-TB patients of this group will further, create 18 more active pulmonary TB with primary MDR-TB strain.

It is apparent that RNTCP retreatment regimen is more suitable for patients harbouring bacilli resistant to INH or INH and streptomycin. In country like India, where primary drug resistance to INH and or Streptomycin is about 20%, nearly 1/5th of the category I patients are not getting the most appropriate and highly effective regimen. Such patients are likely to fail treatment and develop MDR-TB. Initial MDR is 3% to 13%. Such patients constitute the majority of the category I regimen failed patients (30% to 60% MDR).

WHO makes no distinction between relapse, default or treatment failure cases while recommending category II regimen. WHO believes that for all these 3 conditions, default and irregularity is the underlying cause. However most of the available data totally shatters this myth. Prevalence of poly resistance and MDR-TB strains is as important as irregular medication for causing failed category I and category II regimen. In category II regimen, continuation of 5RHE despite smear positivity at the end of 3 to 4 months of intensive 5 months regimen has no logic. No study has been done to prove the favourable outcome of this recommendation.

Whether developed countries are implementing WHO guidelines.

In United Kingdom, the initial resistance is very low. However their National guidelines are more strict and reflect their will to control and eliminate TB. A comparison between their guidelines & RNTCP of India will highlight the glaring facts.

Joint TB committee of the British thoracic society	RNTCP in India guidelines
Status : Initial durg resistance is <2% and initial MDR<0.2%	Status : initial durg resistance is >15-20% & initial MDR>3-13%
Drug sensitivity to be sought whenever	Not Sought even for treating treatment failure patients.
6 month SSC, with 4 drug in initial phase, should be used for all forms	Bindly follows category III, category I & category II

of TB, except meningitis, in both adults and children. Advice is given on	regimens of WHO.
a. Management in special situations & patient groups	a. Practiced
b. Drug interactions and special precautions & pretreatment screening.	b. Not Practiced
c. Management of single and multiple drug resistance	c. Not Practiced
5. Management of resistant TB as advised by WHO is further modified locally for each pattern of resistance.	No consideration given

CONCLUSION : Primary drug resistance in India is high & initial MDR-TB is alarming 3% to 13%. In India, patients who fail category I regimen have MDR strains in 30% to 60% cases. Results of category II retreatment regimen are far from satisfactory. Patients of polyresistance & MDR are as important as of irregular medication and defaults for failure of retreatment regimen and category I regimen. Unscientific implementation of category II retreatment regimen will further lead to emergence of MDR-TB; as well it will increase resistance rate against Streptomycin and Ethambutol. HIV pandemic is worsening the situation. It will further accelerate emergence of MDR-TB. Identification of resistant cases & prevention of emergence & transmission of MDR-TB strains is as important as treating a new smear + ve case with sensitive strains. Physicians will be highly susceptible to succumb to such pressures. Therefore we should act and develop our National guidelines rather than follow whatever has been given to us.

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PATHOGENESIS OF CLUBBING AND HYPER TROPHIC OSTEO ARTHROPATHY-A HYPOTHESIS

Although digital clubbing and hypertrophic osteoarthropathy (HOA) have fascinated physicians for long, their exact pathogenesis is unknown. A number of theories based on neurogenic, humoral, genetic and other mechanism such as the presence of circulating vasodilators, hypoxia and arteriovenous shunts have been proposed. None of these mechanism have satisfactorily explained the genesis of clubbing and HOA. Recently, a role for 'endothelium / platelet' unit has been proposed in the genesis of HOA.

Bone marrow normally releases larger sized than normal platelets, which are fragmented as they traverse the pulmonary circulation. It is postulated that macro-thrombocytes escape fragmentation in the pulmonary capillary bed because of right to left shunt. These large platelets show more rapid and complete aggregation and are believed to get trapped in the distal parts of systemic circulation and lead to endothelial cell activation through the release of platelet derived growth factor (PDGF), whose known effects could explain all the pathological changes in clubbing.

Evidence for the endothelium/platelet hypothesis is provided by the presence of thrombocytopenia and elevated levels of PDGF in patients with cardiogenic HOA and a histological report of platelet clumps seen at necropsy in the nail bed capillaries in patients with clubbing. Further, in case of patent ductus arteriosus with a right to left shunt, HOA is evident only in those limbs which receive blood which has bypassed the

lung, and reverses dramatically after surgical closure of the ductus. This hypothesis also explains HOA seen in infective endocarditis, aneurysms and infected arterial grafts, Presumably, the platelet clumps break off from valves or arterial walls and pass distally.

In bronchogenic carcinoma, and other malignancies, the genesis of HOA can be explained by abnormal circulation through the tumor that enables megathrombocytes to bypass pulmonary vasculature.

Cirrhosis liver, chronic active hepatitis and polyposis colon are shown to be associated with pulmonary arteriovenous fistulas that might allow the passages of large platelets, which would explain clubbing/HOA seen in these disorders. Furthermore, conditions such as inflammatory bowel disease, where there is chronic platelet excess, megakaryocytes or their fragments may reach the finger tips in axial vascular stream, which could explain the associated HOA.

Whether the present hypothesis stands the best of time is difficult to comment.

Further Reading :

1. Martinez - Lavin M. Hypertrophic osteoarthropathy Curr Opin Rheumatol 1979; 9: 83-6

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