PERSONS WITH TYPE 2 DIABETES AND CO-MORBID ACTIVE TUBERCULOSIS SHOULD BE TREATED WITH INSULIN

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ABSTRACT

Tuberculosis remains a significant cause of morbidity and mortality in diabetes in developing countries. The magnitude of the problem should be considered with serious concern as overwhelmingly larger number of people in our country have type 2 diabetes and they are more likely to suffer from reactivation of old foci and contracting fresh infection. Tuberculosis is a chronic and serious infection which also affects endocrine function of pancreas, adrenal, thyroid and pituitary, warranting exogenous insulin and other hormone replacements. Oral antidiabetic therapy is definitely contraindicated in tuberculosis, as marked weight loss, adversity of aging, longer duration of diabetes, higher insulin and calorie needs, and likely hepatotoxicity of ATT are the hallmarks of tuberculosis infection. Better glycemic control can only be achieved with intensive insulin treatment regimens.

KEY WORDS : DIABETES, TUBERCULOSIS, INDIANS, PREVALENCE, RISK, AGE, ENDOCRINE (DEFICIENCY), INSULIN, CACHEXIA

INTRODUCTION

Diabetic patients are not only more susceptible to infection but when infections do occur they are more severe, as the diabetic is a comprised host [1]. Tuberculous infection in diabetes is usually due to reactivation of an old focus rather than through fresh contact [2]. Patients with diabetes and tuberculosis present with more advanced disease and have more changes in the lower lobes. For these reasons, Kelly West aptly described tuberculosis as a complication of diabetes, as it was a specific morbid effect of diabetes [3].

In populations of developing countries, tuberculosis remains a significant cause of morbidity and mortality in both types of diabetes. In Birmingham, UK Asians with diabetes have more lung cavitation and higher incidence of smear and culture positive disease (71 and 86%) than non-diabetic Asians (32 and 45%) [1].

In Dar es Salaam, Tanzania 5.4 per cent of 1250 diabetic patients were known to have developed pulmonary tuberculosis (PTB) and 0.2 per cent spinal tuberculosis [6]. Tuberculosis prevalence in these Africans was greater in the young, in those with a low body mass index (BMI), in patients with insulin-dependent diabetes mellitus (IDDs) compared to those with non-insulin-dependent diabetes mellitus (NIDDs) (9.0% vs 2.7%) [6].

Vulnerability of IDDs to tuberculosis is amply evidenced in many reports from many parts of the world. The ten year actuarial risk of acquiring tuberculosis was 24.2 per cent for 116 IDDs and 4.8 per cent for the rest (p<0.001), out of 1529 diabetic patients, at a teaching hospital in Concepcion, Chile [7]. In South Africa, tuberculosis was reported in 6.1 per cent of 66 blank IDDs the age of 30 years [8]. Tuberculosis was the most common complicating illness of young diabetics in Addis Ababa, Ethiopia, as it occurred at some time in 16.5 per cent of 431 consecutively registered Ethiopian type 1 (IDDs) patients [9]. In these young diabetics, failure to gain weight with treatment was related to tuberculosis [10]. It was also reported that 30 per cent of these young, undernourished, insulin-requiring and ketosis-resistant diabetics, had large insulin requirements of 1.0 to 1.5 U/kg and they have has tuberculosis in the past [11].

Tuberculosis in NIDDs is not uncommon either, as unfortunately even in this modern era, almost 5-10 per cent of type a diabetics (NIDDs) in developing countries have PTB. Tuberculosis was diagnosed in 509 per cent of 8793 hospitalized type 2 diabetics in Bombay [12]. In Port Moresby, Papua New Guinea, of 88 newly diagnosed Melanesian NIDDs, 5.7 percent were suffering from PTB [13]. In Concepcion, Chile, the 10 year actuarial risk of acquiring tuberculosis was 4.8 per cent for 1413 NIDDs [7].

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Though tuberculosis is more prevalent in type 1 diabetes, the magnitude of the problem in type 2 diabetes should be considered with no less concern in purview of type 2 diabetes affecting overwhelmingly larger number of people and also emerging as a serious public health problem in developing countries [14].

Lack of prospective controlled studies and selective indifference of the Western authors to this subject, prompted ensuing review of available Medline abstracts to highlight the chronic and serious nature of tuberculous infection in type 2 diabetes, and the definitive contraindications for oral antidiabetic therapy and essential need for intensive insulin treatment regimens for diabetes control in tuberculosis. Indications for exogenous insulin therapy in type 2 diabetes with active tuberculosis are annotated in table 1 and elaborated below.

Table 1 : Indications for insulin in type 2 diabetes with tuberculosis

1) Chronic and severe tuberculosis infection
   a) increased susceptibility in diabetes
   b) reactivation of old focus of infection
   c) more cavitation, smear or culture positivity
   d) deceptively mild or absent toxic symptoms and signs
   e) ineffective chemotherapy in hyperglycemia

2) Loss of tissue and function of pancreas
   a) pancreatic endocrine deficiency
   b) tuberculous pancreatitis
   c) tuberculin toxicity on pancreas

3) Requirement of high calorie, high protein diet
   a) counter negative nitrogen balance
   b) facilitate tuberculosis therapy
   c) prevent further infection, reactivation

4) Interactions and adverse effects of antituberculosis drugs
   a) rifampicin accelerates the metabolism of antidiabetic drugs
   b) rifampicin per se may increase insulin requirements
   c) isoniazid antagonizes sulphonylureas
   d) isoniazid may rarely cause pancreatitis
   e) interference with intestinal absorption of carbohydrates

5) Associated hepatic disease
   a) with tuberculosis and/or diabetes
   b) induced by antituberculosis therapy

6) Contraindications for oral antidiabetic drugs
   a) for sulphonylureas
      i) tuberculosis, a serious intercurrent illness
      ii) pancreatic disease
      iii) hepatic disease
   b) for biguanides
      i) loss of appetite
      ii) loss of weight
      iii) glucose malabsorption

7) Aging
   a) augments susceptibility to tuberculosis
   b) masks tuberculous infection
   c) more severe b-cell dysfunction
   d) long duration of diabetes
   e) labile diabetic control

8) Other factors in diabetes-tuberculosis association
   a) anti-insulin stress hormones induced by infection
   b) requirement for thyroid of glucocorticoid supplementation
   c) supranormal concentrations of insulin antagonists
   d) possible improvement of immune deficits by insulin
   e) defective lung defence mechanisms, laryngeal injury
   f) rarer forms of tuberculosis common

PANCREATIC ENDOCRINE DEFICIENCY

A high proportion of chronic respiratory failure patients might have an intolerance for glucose loading, but a normal insulin secretion pattern [15]. However in active PTB, immunoreactive insulin, C-peptide and glucose levels before and after glucagon stimulation demonstrated absolute insulin deficiency and more frequent development of severe diabetes mellitus. Hyperglycemia, in a study of 51 patients with PTB, was at first due to relative insulin deficiency coupled with higher pancreatic secretory function, but it rapidly worsened due to decreased pancreatic functional reserve as tuberculosis progressed [16].

The functional disorders of the insular system of the pancreas were more evident in middle-aged and elderly patients with PTB [17]. Further, antituberculosis therapy (ATT) was also reported to be detrimental to serum C-peptide secretion as well as to the insulin sensitivity, in a study of 88 diabetic patients. These negative effects on the inherent insulin resistance and rapid loss of pancreatic residual
function in chronic tuberculosis warranted exogenous insulin administration in these diabetics [18].

One of the 10,513 school students between 3 and 20 years of age examined in Chennai, had transient glycosuria attributed to ATT, nevertheless he did not develop diabetes [19]. Such reports exemplify that even in a previously not ascertained diabetic, ATT may affect b-cell function and unmask the diabetic state.

**TUBERCULOUS PANCREATITIS**

Active tuberculosis should be a leading differential diagnosis in patients with enlarged pancreas when the usual diagnostic reasoning does not yield conclusive results [20], as in a 65-year old women, isolated tuberculous pancreatitis associated with lobular panniculitis and laboratory features was consistent with a tumor of the endocrine pancreas [21]. Even a clinical diagnosis of insulinoma was no exception for subsequent detection of active abdominal tuberculosis on exploratory laparotomy [22].

Tuberculosis is one of the rarer causes of pancreatitis [23], and only with the development of diabetes mellitus, a chronic pancreatitis of probably tuberculous origin might reveal itself [24]. Interestingly, PTB had a higher prevalence in 40 patients with diabetes secondary to chronic pancreatitis than in IDDs (22.5 vs 5% p<0.01) matched for the disease duration [25]. Perhaps in most, tuberculous infection in pancreas is dormant, even preceding diabetes!

**PANCREATIC TOXICITY OF TUBERCULIN**

Purified protein derivative (PPD) of tuberculin is widely used for induction and study of autoimmunity in vitro or in vivo in animals and humans and many available reports have described its direct toxic effects on pancreas. Glucose stimulated insulin-release, and contents of insulin and glucagon were reported as markedly reduced in isolated human islets incubated with cytokine-rich supernatants of blood mononuclear cells stimulated with PPD of tuberculin [26]. Such supernatants of mononuclear cells stimulated with purified PPD of tuberculin were more potently cytotoxic to human islets in inhibiting insulin release than any other known media [27]. At the 12th International Immunology of Diabetes Workshop, held during April 1993 in Orlando, Florida, one of the reviews was on the insulitis in the NOD mouse induced by tuberculin antigen in which diabetes onset was delayed by insulin administration [28]. Thioredoxin is a more specific mycobacterium tuberculosis protein recently identified with functional activity and enzymatic ability to reduce insulin [29].

**PITUITARY, THYROID AND ADRENAL DEFICIENCIES**

Glucose, ACTH, cortisol, growth hormone (GH), and prolactin (PRL) in fasting and following insulin-induced hypoglycemia were reported as high in 96 pulmonary and 15 hematogenous tuberculosis patients due to stress induced by infection [30]. Higher levels of anti-insulin hormones exhausted eventually due to supramaximal stimulation, as measurements of C-peptide as well as T3, T4, TSH, ACTH and the circadian excretion of 17-OCS, revealed high frequency of absolute and relative insufficiencies of pituitary, thyroid and adrenal glucocorticoid functions in PTB. Cocomitant thyroid treatment benefited in 92.8 percent of such 111 patients with PTB suffering from diabetes mellitus [31].

In adolescents with PTB, the reduced levels of somatotrophic hormone, immunoreactive insulin and 17-keto-steroids were related to impaired physical development, evaluated by using the main anthropometric tests (weight, height, chest circumference) [32,33,34]. As endocrine insufficiencies in PTB were pronounced, blood plasma cortisol/insulin ratio was recommended as a diagnostic marker for dissemination in PTB [35].

Supranormal concentrations of substances cross-reactive with insulin (SICRI), were also frequently associated with nonmalignant pulmonary tissue proliferation, as in tuberculosis [36], which might also contribute to insulin resistance. In all these situations, exogenous insulin not only offsets the possible insulin resistance induced by hormone supplements, but insulin administration was also known to improve immune responses as demonstrated in alloxan rats [37].

**WEIGHT LOSS**

The association between marked weight loss and diabetes and/or tuberculosis is uncontested. Cachexia may not always be the effect of diabetes or tuberculosis, but it also has a formidable causative role in tuberculous infection and its therapy. To this effect, the clinical evidence are abounding. In consonance, animal experiments demonstrated that loss of weight was detrimental, and high protein diet protected from Mycobacterium [38].
In diabetes with tuberculosis, Ahuja’s recommendation is to allow calories as for standard weight, or at least 2000-2400 kcal per day irrespective of their absolute weight, to ensure that patients is not in negative nitrogen balance, and also to adequately cover the insulin doses prescribed [39].

**ADVERSE EFFECTS AND DRUG INTERACTIONS OF ANTITUBERCULOSIS THERAPY**

Rifampicin accelerates the metabolism of oral hypoglycemic agents, as it is a potent hepatic enzyme-including agent. It was also known to cause early hyperglycemia in non-diabetic patients with or without PTB, and also to augment intestinal absorption of glucose [40].

Some of the adverse effects of rifampicin in type 1 diabetes as detailed below may well be applicable to the altered glycemic control in type 2 diabetes as well. Rifampicin per se, and not tuberculous infection, INH or prazinamide, was attributed to be the cause of increased insulin requirements in a 54-year old woman with type 1 diabetes [40]. Chronic rifampicin treatment manifesting as hypercortisolism and unstable glycemic control led to a misdiagnosis of Cushing’s syndrome due to occult ectopic ACTH secretion in a man with long-standing IDDM and active tuberculosis. However after withdrawal of rifampicin, his urinary free cortisol excretion returned to normal within two weeks, as did the 24-h cortisol profile and dynamic tests [41]. Malabsorption of rifampcin was also reported in poorly controlled diabetes mellitus, as reported in a 14 year-old boy with INH resistance [42].

Apart from causing pancreatic hypofunction and peripheral insulin insensitivity, long-term administration of ATT interfered with hydrolysis and absorption of carbohydrates in the small intestine of 106 newly-diagnosed persons with PTB. A chemotherapeutic regimen supplemented with insulin, glucocorticoids, and folic acid (in particular), improved intestinal carbohydrate absorption in them [43].

The epidemiologic, paraclinical and therapeutic view points in 68 diabetic patients, clearly established the efficiency of ATT in annulling the negative influence of diabetes-tuberculosis morbid association. Unfortunately, the lability of these diabetic patients persisted in spite of the best control of tuberculosis by tuberculostatics [44].

Isoniazid antagonizes sulphonylureas and impairs insulin release and action and rifampicin shortens plasma half-life of sulphonylureas [45]. Isoniazid, rifampicin, pyrazinamide and ethambutol may cause hepatitis, and streptomycin may rarely cause renal damage [46]. Isoniazid was also reported as causative of pancreatitis in rare reports [23].

**HEPATIC DISEASE**

In addition to the hepatotoxicity of isoniazid, rifampicin, pyrazinamide and ethambutol, the association of hepatic disease with PTB and diabetes mellitus is ubiquitous. Comprehensive examination of 50 patients with PTB and diabetes mellitus, confirmed chronic active hepatitis in three, chronic persistent hepatitis in eight, non-specific reactive hepatitis in four, liver cirrhosis in three, fatty degeneration in ten and fibrosis of the liver in 22 patients [47].

**CONTRAINDICATIONS FOR ORAL ANTIDIABETIC DRUGS**

Sulphonylureas are not indicated in tuberculosis, as it is most chronic and serious of all infections in diabetes. They are not indicated in diabetes associated with destruction of pancreas either, which is the extra-pulmonary manifestation of active tuberculosis in many instances.

Biguanides are contraindicated, as metformin in specific, produces weight loss due to induction of malabsorption, particularly in high doses, and it is also an anorectic. Biguanides as well as sulphonylureas are contraindicated in hepatic disease, which is a common adverse effect of ATT.

Marked weight loss, increasing age, longer duration of diabetes, higher insulin and calorie needs in tuberculosis are other important indications for with holding oral antidiabetic therapy in diabetes.

**AGING**

Usual signs and symptoms in tuberculosis may be absent or show only a mild toxic reaction, with absence of cough or fever. Thus masking of serious infection is likely in diabetes, and autonomic neuropathy and aging also facilitate it. As non-respiratory tuberculous presentations are atypical or relatively insidious, delayed diagnosis is crippling or even potentially life threatening.
Less favourable course and outcomes of the disease related to older age and late diagnosis of PTB were registered in 40 NIDDs as compared to 110 IDDs. PTB in NIDDs runs often asymptomatically and torpidly, specific changes in the lungs seem limited, and foci of destruction are solitary and large [48,49].

Adverse reactions to respiratory drugs such as isoniazid were also known to increase with age [50]. The prevalence of tuberculous infection was 11.5 per cent in 228 type 2 diabetics at a Spanish Health Centre, and the average age of the patients was 62.6 ± 11.4 years. As the risk of tuberculous infection did increase with age and years of evolution of the disease, protocol use of PPD test in diabetics and chemoprophylaxis if necessary, was recommended [51]. Elderly individuals aged 60 and older have four to five times the case rate of tuberculosis, and some of their immune deficits of aging could be reversed by GH and/or IGF-1 treatment as demonstrated in humans and primates [52].

DEFECTIVE LUNG DEFENCE

The lungs of diabetic patients with tuberculosis show defective defence mechanisms in the form of dystrophy of alveolar macrophages, type II alveolocytes and fibroblasts, generalized affection of pulmonary vessels, intensive fibrosis and disorganization of the forming connective tissue, which have a bearing on the development of the pathological process [53]. Diabetes mellitus and tuberculosis also increase the likelihood of severe laryngeal injury [54].

RERER MANIFESTATIONS OF TUBERCULOSIS

Populonecrotic tuberculid [55], tuberculosis of maxilla, zygoma and sinus [56], spindle cell pseudotumors in the lungs [57], visceral neuropathy [58], hypercalcemia [59], primary left lower lobe tuberculosis [60], hyperosmolar hyperglycemic nonketotic coma [61], and ketoacidosis [62] are some of the rare presentations of tuberculosis recored in compromised diabetic hosts.

Cutaneous infection caused by Mycobacterium chelonae after self-injection of insulin using a jet injector was another rare report of mycobacterium related complication in diabetes [63]. The lesions are painful, indurated, purplish, multiple at the injection sites, and the culture of pus eventually grows the atypical mycobacterium resistant to usual ATT [64].

In diabetes, a superinfection is rarely missed or a misdiagnosis of tuberculosis is not uncommonly made for silicosis [65], adrenal [66] or disseminated histoplasmosis [67], melioidosis [68], aspergillosis [69], or coccidiodomycosis [70]. Such overzealous diagnosis of tuberculosis is most certainly justified in the Indian context. The dictum that if diabetes is not controlled look for tuberculosis and if tuberculosis is not controlled look for diabetes, still holds good.

CONCLUSIONS

The recommendations are that diabetes and tuberculosis should be treated with insulin injections [71], or in case a diabetic with tuberculosis is on oral hypoglycemic agents, it is necessary to switch to insulin [39].

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