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

P.V. RAO *

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 UK, tuberculosis is quoted first among common infections in diabetes, although the last UK publication on increased frequency of tuberculosis in diabetics appeared in 1948 [1]. In spite of successfully eradicating tuberculosis in there communities, American Thoracic Society and Centers for Disease Control cautiously list diabetes as a special clinical situation, and prescribe chemoprophylaxis with isoniazid in those with diabetes and positive Heaf test [4,5].

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 position 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 evidanced 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, inseulin-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].

** Professor and Head, Department of Endocrinology and Metabolism, Nizam's Institute of Medical Sciences, Hyderabad 500 082 AP.*

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) tuberculolsis, 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 repidly 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 cytotoxis 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 therapeutical 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 injure [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 compromized 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], meliodosis [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].

REFERENCES :

1. Tattersall RB, Gale EAM. Infections. In : Tattersall RB, Gale EAM, eds. Diabetes, clinical management. Edinburgh : Churchill Livingstone, 1990; 358 –64.

2. Wilson R.M. Infection and diabetes mellitus. In : Pickup JC, Williams G, eds. Text book of diabetes. Oxford : Blackwell Scientific Publications, 1991; 813-9.

3. West KM. Epidemiology of diabetes and its vascular lesions. New York : Elsevier, 1978; 351.

4. American Thoracic Society/Centers for Disease Control, Treatment of tuberculosis infection in adults and children. Am Rev Respir Dis 1986;134: 355-63.

5. Centers for Disease Control. Screening for tuberculosis and tuberculosis infection in high-risk populations, and the use of preventive therapy for tuberculous infection in the United States: Recommendations of the Advisory Committee for Elimination of Tuberculosis. MMWR 1990; 39: 1-12.

6. Swai AB, McLarty DG, Mugusi F. Tuberculosis in diabetic patients in Tanzania. Trop Doct 1990; 20: 147-50.

7. Olmos P, Donoso J, Rojas N, Landeros P, Schurmann R, Retamal G, Meza M, Martinez C. Tuberculosis y diabetes mellitus : estudio longitudinal-restropectivo en un hospital docente [Tuberculosis and diabetes mellitus: a longitudinal-retrospective study in a teaching hospital]. Rev Med Chil 1989; 117: 979-83.

8. Gill GV, Huddle KR, Krige LP. Intensive health screening of young black diabetics. S Afr Med J 1984; 65: 815-6.

9. Lester FT. Clinical features, complications and mortality in type 1 (insulin-dependent) diabetic patients in Addis Ababa, Ethiopia, 1976-1990. Q J Med 1992; 83: 389-99.

10. Lester FT, A search for malnutrition-related diabetes mellitus among Ethiopian patients. Diabetes Care 1993; 16: 187-92.

11. Lester FT. Nutritional status of yound adult Ethipians before onset and after treatment of diabetes mellitus. Ethiop Med J. 1990; 28: 1-7

12. Patel JC. Complications in 8793 cases of diabetes mellitus 14 years study in Bombay Hospital, Bombay, India. Indian J Med Sci 1989; 43: 177-83.

13. Patel MS. Bacterial infections among patients with diabetes in Papua New Guinea. Med J Aust 1989; 150: 25-8.

14. Ahuja MMS. Diabetes mellitus in India in the context of social change. Bombay: Health Care Communications, 1996.

15. Umeki S. Glucose intolerance in chronic respiratory failure. Angiology 1994; 45: 937-42.

16. Karachunskii MA, Beglarian NR. Izmeneniia uglevodnogo obmena u bol'nykh tuberkulezom [Changes in carbonhydrate metabolism in patients with tuberculosis]. Vestn Ross Akad Med Nauk 1995; 7 : 18-21.

17. Iashchenko BP, Epshtein EV, Voloshin AA. Narushenie funktsii insuliarnogo apparata podzheludochnoi zhelezy u bol'nykh tuberkulezom legkikh pozhilogo I starcheskogo vozrasta [Functional disorders of the insular system of the pancreas in middle-aged and elderly patients with pulmonary tuberculosis]. Vrach Delo 1987; 12: 49-52.

18. Egorova IL. Inkretornaia funktsiia podzheludochnoi zhelezy u bol'nykh tuberkulezom legkikh I sakharnym diabetom [The incretory function of the pancreas in patients with pulmonary tuberculosis and diabetes mellitus]. Probl Tuberk 1991; 9: 36-8.

19. Bai PV, Krishnaswami CV, Chellamariappan M, Kumar GV, Subramaniam JR. Glycosuria and diabetes mellitus in children and adolescents in south India. Diabetes Res Clin Pract 1991; 13 : 131-5.

20. 'Neufang KF, Moddar U, Heuser L. Differential diagnose raumfordernder Prozesse in der Pankraskopfregion [Differential diagnosis of masses in the head of the pancreas area]. ROFO Foprtschr Geb Rontgenstr Nuklearmed 1985; 142: 679-84.

21. Fischer G, Spengler U, Neubrand M, Sauerbruch T. Isolated tuberculosis of the pancreas masquerading as a pancreatic mass. Am J Gastroenterol 1995; 90: 2227-30.

22. Brooks M. Insulinoma and abdominal tuberculosis. Scott Med J. 1988; 33: 207-8.

23. Geevarghese PJ. Pancreatic Diabetes. Bombay: Popular Prakashan, 1967; 26-68.

24. Benfiguig K, Anciaux ML, Eugene C, Mauguy B, Hillion Y, Bergue A, Etienne JC, Diabete revelant une pancreatite chronique d'origine vraisemblablement tuberculeuse [Diabetes mellitus revealing chronic pancreatitis of probably tuberculous origin (letter)]. Gastroenterol Clin Biol 1003; 17: 150-2.

25. Garcia H, Tapia JC. Diabetes post pancreatitis: experiencia clinica en 40 casos [Post-pancreatitis diabetes: clinical experience in 40 cases]. Rev Med Chil 1994; 122: 1163-8.

26. Mandrup-Poulsen T, Bendtzen K, Nielsen JH, Bendixen G, Nerup J. Cytokines cause functional and structural damage to isolated islets of Langerhans. Allergy 1985; 40: 424-9.

27. Mandrup-Poulsen T, Bendtzen K, Nerup J, Egeberg J, Nielsen JH, Mechanisms of pancreatic islet cell destruction. Dose-dependent cytotoxic effect of soluble blood monouclear cell mediators on isolated islets of Langerhans. Allergy 1986; 41: 250-9.

28. Maclaren N, Lafferty K, The 12th International Immunology and Diabetes Workshop. Orlando, Florida. Diabetes 1993; 42: 1099-104.

29. Wieles B, Nagai S, Wiker HG, Harboe M, Ottenhoff Th. Identification and functional characterization of thioredoxin of Mycobacterium tuberculosis. Infect Immun 1995; 63: 4946-8.

30. Hafiez AR, el-Kamma B, Abdel-Hafez MA, el-Nady E, Abdou MA, Abdel-Hakim AH, Ramadan SM. Adenohypophyseal activity in relation to suprarenal function in tuberculosis. Kekkaku 1992; 67: 363-7.

31. Smurova TF, Egorova IL, Endokrinnye narusheniia i printsipy ikh korrektsii u bol'nykh tuberkulezom legkikh, stradauyshchikh sacharnym diabetom [Endocrine disorders and principles of their correction in patients with pulmonary tuberculosis and concomitant diabetes mellitus]. Klin Med Mosk 1993; 71: 58-62.

32. II'nyts'kyi IH, Hud' MV , Stebletsov DV, Panasiuk VO, Kozubs'kyi IuO, Kolishyts'ka Ol. Osoblyvosti anatomofiziolohichnoho rozvytku ta hormonal' noi aktyvnosti u pidlitkiv, khvorykh na tuberkul'oz orhaniv dykhannia [The characteristics of the anatomicrophysiological development and hormonal activity in adolescents with tuberculosis of the respiratory organs]. Lik Sprava 1994; 2: 33-5.

33. Firsova VA, Zalesskaia luM, Ovsiankina ES, Melikova VM, Snegireva Rla. O fizicheskom razvitii I sostoianii gormonal'noi sistemy u podrostkov s razlichnymi klinicheskimi formami tuberkuleza [Physical development and the status of the hormonal system in adolescents with various clinical forms of tuberculosis]. Probl Tuberk 1986; 7: 13-7.

34. Ovsiankina ES. Nekotorye pokazateli gormonal'nogo profilia i fizicheskogo razvitiia podrostkov, bol'nykh tuberkulezom. [Various indicators of the hormonal profile and the physical development of adolescents with tuberculosis]. Probl Tuberk 1984; 4: 36-41.

35. Lomako MN, Abramovskaia AK, Grozovskaia MS, Gurevich GL, Kazakov AF, Lavor ZV, Lapteva IM, Skriagina EM, Surkova LK, Shpakolvskaia NS. Kompleksnye metody issledovaniia v diagnostike disseminirovannykh protsessov organov dykhaniia [Complex methods of examination in the diagnosis of disseminated processes in the respiratory organs]. Probl Tuberk 1991; 3: 9-13.

36. Baltic V, Levanat S Petek M, Bratic-Mikes V, Pavelic K, Vuk-Pavlovic S. Elevated levels of substances immunologically cross-reactive with insulin in blood of patients with malignant and nonmalignant pulmonary tissue proliferation, Oncology 1985; 42: 174-8.

37. Dimitrov V, Kosturkov G, Dimitrova A. Vliianie na aloksanoviia diabet i ekzogenniia insulin vurkhu imunniia otgovor na plukhove ot poroda Wistar [Effect of alloxan diabetes and exogenous insulin on the immune response of Wistar rats]. Eksp Med Morfol 1986; 25: 6-10.

38. Cohen MK, Bartow RA, Mintzer CL, McMurray DN. Effects of diet and genetics on Mycobacterium bovis BCG vaccine efficacy in inbred guinea pigs. Infect Immun 1987; 55: 314-9.

39. Ahuja MMS, Diabetes care in clinical practice New Delhi: Japee, 1996; 125.

40. Atkin SL, Masson EA, Bodmer CW, Walker BA, White MC. Increased insulin requirement in a patient with type 1 diabetes on rifampicin [letter]. Diabet Med 1993; 10: 392.

41. Terzolo M, Borretta G, Ali A, Cesario F, Magro G, Boccuzzi A, Reimondo G, Angeli A. Misdiagnosis of Cushing's syndrome in a patient receiving rifampicin therapy for tuberculosis. Horm Metab Res 1995; 27: 148-50. [published erratum appears in Horm Metab Res 1995; 27: 261].

42. Dieterlen P, Cassereau H, Lestrade H. Malabsorption permanente de la rifampicine chez un diabetique atteint d'une maladie coeliaque [Permanent malabsorption of rifampicin in a diabetic with celiac disease]. Arch Fr Pediatr 1986; 43:421-2.

43. Grishchuk LA. Gidroliz, vsasyvanie uglovodov i korrektsiia ikh narushenii u bol'nykh tuberkulezom legkikh [Hydrolysis and absorption of carbohydrate and correction of their disorders in patients with pulmonary tuberculosis]. Probl Tuberk 1990; 3: 22-5.

44. Ghinescu V, Mihaltan F, Chiotan D. Aspecte actuale ale chimioterapiei antituberculoase la bolnavoi noi cu tuberculoza si diabet zaharat [Current aspects of the antirubercular chemotherapy of new patients with tuberculosis and diabetes mellitus]. Rev lg Bacteriol Virusol Parazitol Epidemiol Pneumoftiziol Pneumoftiziol 1989; 38: 115-26.

45. Lebovitz HE. Oral hypoglycemic agents In: Rifkin H, Porte Jr D, eds. Ellenberg and Rifkins's diabetes mellitus, theory and practice. Fourth Edition. New York : Elsevier, 1990; 554-574.

46. Chan SL. Chemotherapy of tuberculosis. In: Davies PDO, ed. Clinical Tuberculosis. London: Chapman & Hall, 1994; 141-156.

47. Abdullaev A, Matsulevich TV, Panasek IA, Ergeshov A. Kliniko-morfologicheskie i ekhograficheskie sopostavleniia pri issledovanii pecheni u bol'nykh tuberkulezom legkikh i sakharym diabetom' [Clinico-morphologic and echographic comparisons during the study of the liver in patients with pulmonary tuberculosis and diabetes mellitus]. Probl Tuberk 1990; 8:24-7.

48. Karachunskii MA, Kossii IuE, Lajivkeva OB. Osibennosti klinicheskoi simptomatiki i techeniia tuberculeza legkiikh u bolnykh s raznymi tipami sakharnogo diabeta [Clinical symptoms and course of pulmonary tuberculosis in patients with various types of diabetes mellitus]. Probl Tuberk 1993; 4: 20-1.

49. Voloshin AA. Techenie tuberkuleza legkikh pri sochetanii s sakharnym diabetom u lits pozhilogo i starcheskogo vozrasta [The course of pulmonary tuberculosis associated with diabetes mellitus in middle-aged and elderly patients]. Probl Tuberk 1990; 4: 65-7.

50. Morris JF. Physiological changes due to age. Implications for respiratory drug therapy. Druga Aging 1994; 4: 207-20.

51. Hernandez-Garcia P, Martinez-Cruz F, Cayuelas-Martinez T. PPD y quimioprofilaxis en la diabetes mellitus [PPD and chemoprophylaxis in diabetes mellitus (see comments)] Aten Primaria 1993; 11: 204.

52. Gerlato MC. Aging and immune function: a possible role for growth hormone. Horm Res 1996; 45: 46-9.

53. Erokhin VV, Gedymin LE. Funktsional'na morfologiia legkikh u bol'nykh I sakharnym diabetom [Functional morphology of the lungs in patients with tuberculosis and diabetes mellitus]. Probl Tuberk 1992; 5-6: 37-41.

54. Volpi D, Lin PT, Kuriloff DB, Kimmelman CP. Risk factors for intubation injury of the larynx. Ann Otol Rhinol Laryngol. 1987; 96: 684-6.

55. Held JL, Kohn SR, Silvers DN, Grossman ME. Populonecrotic tuberculid. N Y State J Med 1988; 88: 499-501.

56. Klaudel A, Gawlicka G, Spyra W, Wiewiora A. Rzadki przypadek gruzlicy szczeki, okolicy jarzmowej, zatoki szczekowej I skory twarzy u chorej na cukrzyce. [A rare case of tuberculosis of the maxilla, zygomatic region, maxillary sinus and facial skin in a patient with diabetes mellitus]. Wiad Lek 1992; 45: 317-9.

57. Sekosan M, Cleto M, Senseng C, Farolan M, Sekosan J. Spindle cell pseudotumors in the lungs due to Mycobacterium tuberculosis in a transplant patient. Am J Surg Pathol 1994; 18: 1065-8.

58. Sosnowski W, Babicz D. Cukrzycowa neuropatia trzewna u chorej na gruzlice pluc [Diabetic visceral neuropathy in a patient with pulmonary tuberculosis]. Pneumonol Pol 1985; 53: 251-5.

59. Peces R, Alvarez J. Hypercalcemia and elevated 1,25 $(OH)_2$ D3 levels in a dialysis a patient with disseminated tuberculosis. Nephron 1987; 46: 377-9.

60. Heinrich I, Peleg H. [Primary left lower lobe tuberculosis and diabetes mellitus]. Harefuah 1989; 116: 354-5.

61. Cirasino L, Thiella G, Invernizzi R, Silvani A, Ragini S. Hyperosmolar hyperglycemic nonketotic coma in Waldenstrom's macroglobulinemia associated with type II diabetes and complicated by pulmonary tuberculosis. Recenti Prog Med 1992; 83: 194-6.

62. Lakhdar AA, Elhabroush S. Diabetic ketoacidosis in Tripoli. The causes and outcome of 100 consecutive cases. Diabetologia 1997; 40 (suppl1): 2345A.

63. Escobedo JA, Gil D, Pascual A, Aguirre JJM. Infeccion cutanea por Mycobacterium chelonae tras autoinyeccion de insulina con pluma [Cutaneous infection caused by Mycobacterium chelonae after self-injection of insulin using a jet injector (letter)]. Enferm Infecc Microbiol Clin 1994; 12: 274-5.

64. Jackson PG, Keen H, Noble CJ, Simmons NA. Injection abscesses in a diabetic due to Mycobacterium cheloni va absecessus. Br Med J 1980; 281: 1106-1106.

65. Rogler G, Balle C, Antoniou E, Heinisch A, Bocker T, Denner B, Scholmerich J. Millar-Silikotuberkulose mit vorwiegend zerebraler Symptomatik [Miliary tuberculosis and silicosis with predominantly cerebral symptoms]. Dtsch Med Wochenschr 1996; 121: 588-92.

66. Sert C, Achrafi H, Jacqueminet S, Hoang C, Bosquet F, Affres H, Chigot JP, Thervet F. Histoplasmose surrenalienne chez un sujet idabetique non insulinodependant [Adrenal histoplasmosis in a non-insulin-dependent diabetic patient]. Rev Med Interne 1995; 16:771-4.

67. Chan KS, Looi LM, Chan SP. Disseminated histoplasmosis mimicking miliary tuberculosis: a case report. Malays JJ Pathol 1993; 15: 155-8.

68. Turner MO, Lee VT, FitzGerald JM. Melioidosis in a diabetic sailor. Chest 1994; 106: 952-4.

69. Caulet S, Capron F, Laaban JP, Prudent J, Rochemaure J, Diebold J. Hemoptysie fatale au cours d'une aspergillose bronchique par anevrysmes arteriels pulmonaires multiples [Fatal hemoptysis during bronchial aspergillosis with multiple pulmonary artery aneurysms]. Ann Pathol 1990; 10: 177-80.

70. Forbach-Sanchez G, Fuentes-Pensamiento R-Coccidioidomicosis pulmonar cronica progresiva en una paciente con diabetes mellitus tipo II [Progressive chronic pulmonary coccidioidomycosis in a patient with diabetes mellitus type II]. Rev Invest Clin 1985; 37: 49-51.

71. Pendsey S. Practical management of diabetes. New Delhi: Jaypee, 1997; 91.