Prevalence of Tuberculosis in Patients of Diabetes Mellitus: a Review

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Abstract:- **This review focuses the prevalence of Tuberculosis in patients of diabetes. Tuberculosis & Diabetes are very joint infections & both are showing an increasing trend. Tuberculosis is a infection and the pathogen responsible for this is Mycobacterium *tuberculosis*. The Mycobacterium is the bacteria primarily responsible for lung infection and this infection some times might be spread in other organ system beyond the lungs. Diabetes mellitus is a category of a typical metabolic disorder responsible for increased blood sugar level in a person . In diabetes the body is not having ability to produce sufficient insulin or the cells of the body do not respond in a proper way to the insulin that is produced inside body. Most of the time patients of diabetes are very much susceptible against different types of infections & tuberculosis is one of most important amongst them. Prevalence of tuberculosis is three to five times more in patients of diabetes than the non-diabetic people. There is more difficulty in the management of patients of tuberculosis who are having diabetes due to postponement in diagnosis as these both the disease have some common symptoms such as lethargy, weight loss & anorexia etc. The risk of diabetes in patients of tuberculosis should be considered because patient have very poor clinical response to Anti tubercular drugs (ATT) & correspondingly the doubt of accompanying tuberculosis infection should be measured in patient with uncontrolled diabetes. Recent different systematic reviews showed that diabetes is connected with a bigger risk of Tuberculosis. The main aim of the present review is to appraise the epidemiology of diabetes mellitus and tuberculosis , the effect of diabetes on tuberculosis and vice versa and to explore the critical and urgent need of the good-quality experimental application of research which may be responsible for creating vigorous action plans to address this double burden.**

Keywords:- Tuberculosis; Mycobacterium tuberculosis Diabetes, Insulin; Glucose intolerance; Blood sugar level clinical implementation research.

I. INTRODUCTION

Diabetes mellitus and Tuberculosis are two main persistent diseases are very much common and have foremost effect on the healthiness of individuals in developing and low income countries. Diabetes mellitus and tuberculosis are two main and susceptible chronic diseases which have a chief influence on the mortality of the population. About 5 million deaths triggered by Diabetes Mellitus [1] and about 1.4 million deaths instigated by tuberculosis [2], being recorded each year. Globally , it is reported that there are 415 million individuals with Diabetes mellitus and this quantity may be increased up to 642 million by the year 2040 [3]. Diabetes is a sustained, non-communicable disease, characterised by hyperglycaemia, triggered by insulin-resistance, and inadequate secretion of insulin or both of them. Tuberculosis is a disease is an airbone disease and the bacteria responsible as the pathogen is *Mycobacterium tuberculosis*, an airborne bacteria. Diabetes Mellitus represents a three times more risk in progress of tuberculosis and their relationship of both the diseases can be measured as one of the most important responsibilities as for alarm with different control programme of tuberculosis Tuberculosis some times may be the purpose of momentary reduction in glucose tolerance, which may be some times the risk factor for development of diabetes mellitus. There are more projections of reversion or death of a patient having tuberculosis is meaningfully more higher when the patient also suffering from diabetes. The Diabetes–Tuberculosis association characterises a significant risk to the population and needs the operation of acceptable agendas in order to reduce the prevalence and incidence of these two diseases. The double load of tuberculosis and diabetes has become a main world-wide communal health issues. Diabetes has long been known to be a risk factor for active tuberculosis and reactivation of latent tuberculosis. It is also associated with worse tuberculosis treatment outcomes. In addition, tuberculosis infection in itself can worsen glycaemic control. Drug–drug interfaces can further confuse the picture, leading to a decrease in the efficacy of both Tuberculosis and diabetes treatments, and probable deteriorating of drug side effects. Diabetes and Tuberculosis frequently exist together and complicate each other at various levels. A joint structure for carefulness and control of diabetes and tuberculosis established by World Health Organisation and International Union against Tuberculosis and Lung Diseases emphasizes routine bi-directional screening for the two. About 95% tuberculosis patients and about 70% of with diabetes patients live in the low and middle income countries [3, 4].The epidemic growth of diabetes mellitus has occurred in developing countries where Tuberculosis is highly endemic. As a result, diabetes and Tuberculosis are increasingly present together, and this calls for renewed interest in this topic [5]. India is fronting the double problem of being the maximum tuberculosis burden country taking a large figure of people with diabetes posturing a serious task for the health system [6, 7]. Among those who are with active

tuberculosis, diabetes may be responsible for deleterious effect of tuberculosis treatment results by suspending the time for microbiological response, reducing the probability of encouraging outcome and increasing the threat of setback, death and drug resistance

II.   DIABETES AS A RISK FACTOR FOR TUBERCULOSIS

It is evident of different studies that the frequency of diabetes mellitus is developing globally, predominantly in low income and developing countries where there is more prevalence of tuberculosis [8]. Diabetes mellitus is an independent threat for all types of lower respiratory tract infections [9].Tuberculosis is the disease which is more powerfully accompanying with other types of immune deficiency diseases for example HIV, as many of the people with diabetes mellitus are more than that of patients who are having other immunocompromised states, however it will make the diabetes mellitus a additional important threat for the population level having tuberculosis [10]. However type 2 diabetes is having more prevalence but sometimes type 1 diabetes may have stronger risk of contracting tuberculosis [11]. Some studies reported a upper, while others reported a lower, occurrence of cavities in the lungs of patients who are having diabetes as equated to non-diabetic patients who are having tuberculosis. [12].Tuberculosis have a high occurrence in diabetics or patients suffering with diabetes and will be responsible for significantly greater mortality [13]. Tubercular lesions with increased amounts has also been documented in diabetics. At the same time, it is also reported in several studies that tuberculosis will be responsible for worsening of patients who are requiring higher doses of insulin than before [14]. As linked with the general population, the existence of diabetes mellitus appears to be more amongst the patients of tuberculosis in comparison to the normal and general population who are not having tuberculosis [15].

III.   TUBERCULOSIS AS A RISK FACTOR FOR DIABETES

The association between these two diseases as diabetes mellitus and tuberculosis is always bi-directional. Some times tuberculosis may be responsible as the main source for the development of new diabetes cases [16,

17].The development of tuberculosis occurs ten times more recurrently in juvenile diabetics. In most of the cases, progression of tuberculosis occurs after the commencement of diabetes. Occurrence of the pulmonary tuberculosis some times increases with the period of diabetes. It is clear that diabetic patients have a habit of being having a contract with tuberculosis but the reverse would be rare. The important threat for developing diabetes mellitus is the compromised glucose acceptance. In maximum number of the cases with compromised glucose acceptance returns back to normal value after having positive treatment for tuberculosis, however the increased risk of developing diabetes may some times persists [18].

IV.   GLUCOSE INTOLERANCE IN TUBERCULOSIS

Many of the Studies were of the opinion that a high prevalence of diabetes, as well as impaired glucose tolerance, will be present in patients of tuberculosis [19]. Impaired glucose tolerance (IGT) in tuberculosis is found much more than obvious diabetes [20]. Acute severe stress may be the important cause of the development of impaired glucose tolerance. Some of the stress hormones such as epinephrine, glucagon, cortisol and growth hormone are stimulated by fever, protracted inactivity and malnutrition which are responsible for the increase of the blood sugar level in surplus quantities [21].Enlargement of pancreas should be a differential diagnosis in patients with active tuberculosis In severe cases of tuberculosis, endocrine function of Pancreas has also been found to be affected adversely In patients of diabetes and tuberculosis, association a occurrence of long-lasting calcify pancreatitis is complex, will have comprehensive or comparative deficiency state of insulin [22].Tuberculosis is a recognised and chief source of pancreatitis [23] and tuberculous pancreatitis may have capability to represent itself solitary after the progression of diabetes mellitus. Even nevertheless a part of the hyperglycaemia linked with tuberculosis may be recognised as the severe stress associated with the contamination itself, however the main feature in this development is hypo function of the pancreas [18, 23].

V.   ROLE OF ANTI-TUBERCULOSIS DRUGS ON BLOOD SUGAR LEVEL

Rifampicin is a drug that is considered as the significant inducer of the hepatic microsomal enzyme which is responsible for lowering of the serum levels of sulphonylurea and biguanides [6].Rifabutin, is a drug that acts as another inducer which induces hepatic metabolism but is not as effective as Rifampicin. Other drugs which have anti-tuberculor activity, very rarely inhibits the blood sugar level [24].Some times an additional dose of Isoniazid or Isonicotinyl hydrazine (INH) may be responsible for hyperglycaemia [25] ,while in some cases or situations it is very challenging to control diabetes in patients who are taking Pyrazinamide [26].Tuberculosis can lead to an hyperglycaemia which is infection-related that may be responsible for developing Diabetes mellitus. The hyperglycemia in diabetic patients accompanying with tuberculosis normally will be responsible for deteriorating the glycaemic control in patients of diabetics and therefore this will be responsible for adjustment in the dose of insulin [18]. The adjustment of dose should be continued after the successful treatment of patients of tuberculosis. On the other hand, it has been clear that testing is essential for the patients of diabetes mellitus in formerly undiagnosed patients before the suitable treatment for tuberculosis , it may lead to an over-diagnosis of diabetes [23]. Some studies have also reported a adverse effect of diabetes on the treatment efficacy and prognosis of tuberculosis [12]. Since the efficacy of most anti-tuberculosis drugs will depend on concentration of their plasma, it may clarify the adverse effect of diabetes mellitus on the treatment of tuberculosis [8].The transformed plasma levels may be due to alterations

in absorption, distribution, metabolism and/or excretion in diabetics. Lower plasma levels of anti-tuberculosis drugs are linked with resistance to these drugs which may be responsible for the complication of the course of treatment of tuberculosis in patients with diabetes [27].

VI. ETIOLOGY OF THE TUBERCULOSIS AND DIABETES MELLITUS ASSOCIATION

Diabetes mellitus is associated with a decrease in immunity of body cellular system. A reduced T-helper1 (Th1) cytokine response level, TNF alpha production, and IL-1 beta and IL-6 production is also seen amongst people with concomitant diabetes and tuberculosis association as compared to non-diabetic patients [28, 29, 30]. Th1 cytokines have vital role in the control and inhibition of *Mycobacterium tuberculosis* bacteria. Is Hyperglycaemia is responsible for a direct depressive effect on the respiratory burst. A combination of these different types of dysfunctional processes donates to an increased risk of tuberculosis in patients of diabetes [28, 29] , is meaningful to the indication that both of these diseases may be responsible for simulation of the symptoms of the other. Such most common symptoms that are important to both include lethargy, fatigue, weight loss, fever and loss of appetite.

VII. THE DIABETES MELLITUS-TUBERCULOSIS ASSOCIATION: RISK FACTORS

A. Age and Gender

Although it is evident that Diabetes-Tuberculosis association has a higher prevalence regardless of age, most of the majority patients who has this association of diabetes and tuberculosis are having age over 40 years and are meaningfully old aged as compared to patients having no diabetes [31] The prevalence of type 2 diabetes is greater in old aged patients [6].Age more than 40 will be responsible for developing diabetes and tuberculosis co-epidemic in patients of both the diseases. However, maximum number of studies are in favour of co-occurrence of tuberculosis and diabetes association belonged to the age group of >57 years with occurrence of 35.13%. Some of the studies stated that 77.7% diabetes patients are positive for tuberculosis diagnosis were from age groups of 30–49 years[32], however other studies were in favour of greater frequency of diabetes in patients of old age [33].Many studies have reported, the majority of the males in the group of patients with diabetes-tuberculosis association [34].Analysis of the gender-based distribution of different studies revealed that males were more affected by both of the diabetes and tuberculosis association as equated to females .Several other studies conducted in Indian population showed that most of the patients of tuberculosis-diabetes combination were male (73.68%) while female were in the minority (26.32%)[35].This fact can be acceptable by smoking and alcohol consumption, as risk factors, through their collective outcome [36]. The prevalence of greater percentage of tuberculosis-diabetes association may be due to the reason that males are bare to the external atmosphere more in comparison to females and they are encountered by multiple types of infections. However, there are several other studies which were of opinion of an increased risk of diabetes-tuberculosis association in the case of females [37].The reason for this is ethnic differences of tribal communities, with matriarchal families, in which females have most of the activities which are similar to males. In addition to these truths, other reasons for increased prevalence of diabetes-tuberculosis association in females from these tribal civilizations may be smoking and disproportionate alcohol intake by females [38].

B. Body mass index and waist circumference.

Many of the Studies reported the expressively greater medium BMI in those who have diabetes and tuberculosis association [39].Maximum number of tuberculosis-diabetes patients have the BMI between 18.50 and 22.99 kg/m2, consequently, the risk of tuberculosis and diabetes association increases with the increase of BMI, this may be one of the important risk factor of diabetes – tuberculosis co-epidemic [40] .Other studies were of opinion that patients with diabetes and tuberculosis have lower BMI in comparison to those without tuberculosis [41],this fact is due to the weight loss determined both by poor control of diabetes and due to active tuberculosis [42].Many other studies, however, not showed any significant alteration of BMI in tuberculosis-diabetes patients and those with tuberculosis and normoglycemia [43]. Most of the studies showed an insignificant association between BMI or waist circumference and diabetes. A small number of studies were in favour of the patients with tuberculosis and diabetes are significantly malnourished and have more weight loss [[29, 30]. It is evident from some studies that tuberculosis-diabetes patients have asignificantly higher median BMI in comparison to non-diabetic tuberculosis patients. [18].A waist circumference more than 90 cm both in women and in men has been connected with diabetes mellitus in patients of tuberculosis, having a significant higher medium value of BMI as compared to patients with tuberculosis and normoglycemia [44].Contrary to these studies, some researchers were not able to show a important relationship between waist circumference and diabetes progress in patients of tuberculosis [45].

C. Life Style

Life style including smoking habits and alcohol consumption and also drug intake are the common risk factors considerably connected with diabetes mellitus – Tuberculosis co-epidemic [46].Patients have smoking habit on daily basis were more prone to the tuberculosis for an extended period [47]. On the other hand, there are several studies that showed a more number of people with smoking habits in the diabetes-tuberculosis group, but a noteworthy difference as compared with the patients of diabetes without tuberculosis may not be reported [48].Alcohol intake is also a threat significantly associated with diabetes-tuberculosis co-epdemic [49]. However, many of the other studies did not settle any of the important relationship in between drinking of alcohol and progress of tuberculosis [50]. Drug consumption is also an important risk factor related with tuberculosis, as the researchers are in favour of a study reporting more drug consuming patients in the tuberculosis normoglycemia group [51], but other studies did not confirm

a significant difference between these two groups of patients [52]. An important limitation found in the conducted studies is the frequent under-appreciation of drug and alcohol consumption in the case of self-reporting [53]. The tuberculosis-diabetes co - epidemic is always associated with the diet rich in calories, having high percentage of fat and salt and also reduced fibres [54] and connected with the increase of morbidity and mortality rates determined by different diseases which are caused by an unhealthy diet [55]. Different activities of different life style increase the risk of diabetes mellitus development among patients of tuberculosis [56].Along with a unhealthy diet, in activeness in different physical activities always increases the risk of increasing obesity, therefore rising resistance against insulin, one of the most determinant factors of Diabetes mellitus [48].

D. Family History

Family history is an important factor for determining the diabetes and tuberculosis association. The presence of tuberculosis in family history among the patients of diabetes gives them a statistically higher risk of developing active Tuberculosis [57].Some studies did not find any major differences between the groups of patients with family history of diabetes, associating with tuberculosis [39]. Family history of obesity is very important and significant risk factor concerned with diabetes in patients of tuberculosis, therefore increasing the risk of the diabetes-tuberculosis co-epidemic [56].However the family history of hypertension revealed more percentage of tuberculosis-diabetes patients equated to those having tuberculosis and not having Diabetes [56].

VIII. TYPE OF DIABETES MELLITUS AND TUBERCULOSIS

Though both types of diabetes as type 1 and 2 will be responsible for an increase in the risk of developing tuberculosis , but the most of the people with diabetes-tuberculosis co-epidemic have type 2 diabetes [58], the reason for this is greater prevalence of type 2 diabetes in comparison to type 1 diabetes. However, sometimes patients belong to type 1 diabetes are more prone to *Mycobacterium tuberculosis* infection [6] ,because of longer period of diabetes or a challenging control of hyperglycaemia in patients of type 1 diabetes [59].Beside all this the threat of development of tuberculosis always rises in the patients who are taking insulin [60] and also with disease duration which is longer than 5 years [61].Glycated haemoglobin (HbA1c) is increased in the patients of diabetes-tuberculosis co-epidemic [40].It is evident from several studies that the majority of patients who are having diabetes and tuberculosis association have pulmonary tuberculosis, this being expressively connected with diabetes [62] .On the other hand, extra-pulmonary tuberculosis is more common in patients with normoglycemia [63]. History of tuberculosis in patients is considered as significant factor, this is the reason that the patients having diabetes and also have history of tuberculosis were 13 times more prone in developing pulmonary tuberculosis in comparison to those not having any history of tuberculosis [48].

IX. THE DIABETES MELLITUS-TUBERCULOSIS ASSOCIATION AND SOCIETY

Social status and society itself is a very important factor for the diabetes and tuberculosis association .Educational position of every society have a significant percentage of patients with diabetes and tuberculosis association this showed a low educational level, however sometimes tuberculosis being negatively associated with schooling of patients [64]. Occupation of people is also very important risk factor due to the reason that diabetes mellitus is one of the most frequent disease connected with sedentarism in patients of tuberculosis. Most of the people having diabetes and tuberculosis association are known to be unemployed [65].Some time the low income is associated with active tuberculosis in patients of diabetes [66]. Moreover, it is projected that there will be an increase in number of diabetes patients in the coming next decades in low and middle income countries, which are having already higher occurrence of tuberculosis [55].Several studies are in opinion that up to 80% of patients of diabetes are the habitants of low income and developing countries .Asia is considered as the epicentre of the increasing load of diabetes mellitus [10] and also the largest contribution is known from India and China [11].The diabetes and tuberculosis co-epidemic being a chief problem related to the health in these areas where poverty level prevails. The consequences of low economic status are that an significant percentage of persons with diabetes live or work in congested or incompetently ventilated spaces, therefore resulting an increasing threat in the development of tuberculosis [66]. The majority number of patients having diabetes and tuberculosis association are with married status [48], this factor significantly may be responsible to the risk of development diabetes tuberculosis co-epidemic [39]. People having tuberculosis and are married are two times susceptible to the risk of developing diabetes mellitus in comparison to those who are unmarried [46]. This is very common thing that the sedentary lifestyle, unhealthy diet, overcrowding are the important factors which are commonly found in the people who live in an urban environment. Therefore it is evident that the diabetes and tuberculosis co-epidemic has a significantly higher prevalence about six times in urban inhabitants, in comparison to the rural environment [48]. However studies of some researchers reported a higher number of diabetes and tuberculosis association will be present in the rural environment [46]. Moreover, speedy urbanization represents an significant problem regarding control of tuberculosis [63].

X. CONCLUSION

This present review showed a significant relation between diabetes and tuberculosis. Prevalence of diabetes among tuberculosis was significantly depend upon age, gender, life style, socioeconomic status, family history, smoking and drinking. These factors have augmenting on the co-occurrence of tuberculosis and diabetes. Diabetic patients face a higher risk of tuberculosis than non-diabetics. Clinicians diagnose diabetes in people with tuberculosis and

also tuberculosis in diabetic patients. Diabetes depresses or let down the immune response, which in turn facilitates infection with *Mycobacterium tuberculosis* and/or progression to symptomatic disease Diabetes mellitus is associated with a modest increase in the risk of developing tuberculosis. The risk is greater among those treated with insulin for diabetes. Diabetes is a common co-morbidity in people with tuberculosis. Screening patients with tuberculosis with fasting blood sugar estimation will help in early detection of diabetes. Strategies are needed to ensure that optimal care is provided to patients with both diseases. Therefore it is recommended that diabetes screening should be incorporated into the routine assessment of all patients with tuberculosis in our environment. In this review we found the high prevalence of diabetes among the tuberculosis patients compare to general population suggest that screening of diabetes among tuberculosis is necessary and should be performed during the diagnosis of tuberculosis. Several studies are in favour that this association is found in males as well as in females having higher weight found compare to males. According to some studies age of the patients having diabetes was found to be significantly high compare to patients of tuberculosis. Some of them revealed that central obesity was found almost thrice among diabetes with tuberculosis as compared to only in tubercular patients. Some of them are in opinion that smoking as a risk factor among diabetes with tuberculosis compare to smoking in only tuberculosis was found to insignificant, beside that drinking habit as a risk factor for diabetes with tuberculosis patients compare to drinking among only tubercular patients, it was found to be significant. There is need of awareness and education among common people to avoid such unhealthy habits. The diabetic epidemic encounters the global tuberculosis control, particularly because most of the countries with higher tuberculosis burden bear the higher burden of diabetes too. There are several questions, such as the relationship of tuberculosis treatment outcome and the glycaemic control, whether frequently recommended DOTS is acceptable for patients with both the situations, and whether chemoprophylaxis should be made compulsory for the diabetic patients with latent tuberculosis infection. All these problems have to be addressed by directing well-designed forthcoming trainings. Incorporation of nation-wide tuberculosis and diabetes programs is also necessary to tackle the situation in India. As per report of some studies in tuberculosis -HIV, we must adapt similar methods to prevent, screen and manage the two diseases diabetes and tuberculosis together and it is also vital to ensure the availability of medicines for proper management of the two diseases (Harries et al.)[3]. The advantage of tuberculosis treatment observance through current DOTS programme can be exploited for the acquiescence to diabetic drugs and lifestyle amendments also, which will have benefit in the long run for the management of diabetes among those affected with both diseases. The link between tuberculosis and diabetes mellitus has been documented, now good-quality implementation investigation to screen out, to care off, and to monitor this dual load of diseases.

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