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Co-Management of Active Tuberculosis and Diabetes Mellitus Under Supervised DOTS Strategy—A Saudi Perspective

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Abstract: Tuberculosis (TB) is a global public health concern, specifically in countries which have high prevalence of HIV/AIDS, malnutrition, unhygienic conditions, etc. Some evidence has been presented that diabetes mellitus (DM) is a risk factor for TB. On the other hand, among those who have DM, TB infection enhances glucose intolerance and worsens glycemic control. The combination of TB and DM, due to immuno-compromised status of DM, can delay the healing process of TB. The focus of this paper is the World Health Organization directly observed treatment, short course (DOTS) program implemented in Gazan province, Saudi Arabia, to treat TB. The data included some patients with both TB and DM. The data has been analyzed to assess how effective the DOTS program was in managing TB. It was found that DM was not a significant factor in the outcome of TB treatment. We used the same data and observed that the non-significance of DM is due to heterogeneity of patient population, Saudis and Non-Saudis. The prevalence of DM was very high among Saudis. This is understandable in view of different lifestyles. Non-Saudis are predominantly Yemenis. For Saudis, DM was indeed found to play a role in the treatment outcome of TB, after an application of a classification tree methodology on the data. This is the main focus of the paper.

Keywords: diabetes; tuberculosis; DOTS

1. Introduction

Tuberculosis is an infectious disease and is a significant public health and medical concern globally. Its epidemiological mode of transmission is also of great concern, specifically with the co-morbidities of diabetes, HIV/AIDS, malnutrition [1], tobacco smoking [2], and harmful alcohol use [3]. In 2016, 10.4 million people contracted tuberculosis (TB) and 1.7 million died from the disease around the world, which translates into a global incidence of 130 per 100,000. TB occurs to some degree in every part of the world. In some countries it is very common and it can affect all ages. Over 95% of TB deaths occur in low–income, developing countries. Eighty seven percent of new TB cases occurred in the 30 most highly TB burdened countries [4]. TB is 100% curable and preventable [5]. The key to success is to find active cases in the early stages of TB and treat using directly observed treatment, short course (DOTS). Incidence of TB is higher among HIV patients, diabetics, excessive alcohol drinkers, and those who are immunocompromised than in the general population [4]. The definition of duration of symptoms is from the time of onset of classical symptoms of TB to the date of confirmation of its diagnosis.

1.1. What Is DOTS (Directly Observed Treatment, Short Course)

DOTS is the directly observed treatment, short course of tuberculosis, a guideline from the World Health Organization (WHO), which is a proven strategy in the eradication of TB. The eradication of TB is delayed by two factors—irregular and insufficient treatment using other than the standard first-line drugs sensitive to TB bacteria. To attain a complete cure and to avoid drug resistance, patients are required to go for treatment for at least six to eight months with multiple drugs. It is difficult for many patients to comply with their prescribed course (six to eight months) of standard medications. Thus, the irregularity and non-adherence to treatment results in prolonged infectiousness, relapse of TB, development of drug resistance, or even death. When resistance to TB drugs occurs, it is difficult to treat the disease and is very expensive with second-line drugs. The price may be as high as a thousand times the cost of initially treating the drug-sensitive infection [4]. Hence, the WHO developed a strategy known as DOTS, which is patient-centered, community-based, and cost-effective. DOTS is simple to implement, improves patient compliance, prevents transmission of the disease, and decreases multi-drug resistance [6]. Before implementation of DOTS, the cure rate used to be between 31% and 37%. TB was out of control in many parts of the world where treatment regimens were not consistent among physicians and varied from center to center [7].

1.2. Overview of Diabetes Mellitus

There is a worldwide increased prevalence of diabetes mellitus (DM), which is a growing burden and global concern, particularly in developing countries. DM is a metabolic disease commonly associated with multiple chronic diseases, have multiple etiologies (genetic, race, obesity, inactivity, high blood sugar, abnormal cholesterol, triglyceride levels, etc.), resulting in serious complications like stroke, blindness, heart attack, kidney failure, and amputation of limbs. Rising obesity rate and speedy change in socioeconomic development in Saudi Arabia are contributing factors to the high incidence in the region. Saudi Arabia (23.9% adults have DM) is among the top-ten countries of the world for DM prevalence. Other contributing factors are excessive nutrition, faulty eating habits, sedentary lifestyle, etc. [8].

1.3. Diabetes and TB (Tuberculosis) Coexistence

Diabetes is known to decrease the effectiveness of the immune system and TB is prone to infect persons with weaker immune systems. Studies have suggested that DM increases the risk of active tuberculosis. The escalating prevalence of DM in TB-endemic areas may critically affect TB control. DM is associated with an increased risk of TB, regardless of study design and population. People with DM may be important targets for interventions such as active case finding and treatment of latent TB. Efforts to promptly detect, diagnose, and treat DM may have a positive impact on TB control. Considering these associations, and how DM and TB are known to occur together more often globally, every so often both conditions together pose a challenge [9]. The occurrence of DM amongst TB patients is approximately 45%. Similarly, the prevalence of TB among DM patients is around 14%. It is observed that the highest prevalence of DM among TB patients is in Asian countries. An estimated 15% of all TB cases are attributable to DM, one third of which are in Asian countries [10].

1.4. Goals and Aims

The aim of this study was to identify risk factors for the combined management of DM and cure of TB. We also aimed to identify pockets of data in which one outcome is prominent and assess the cure rate of TB with patients who have DM.

1.5. Study Design

The study was a retrospective review of all registered cases of tuberculosis in one year (2014) that were treated in Gazan. Gazan is also known as Jizan and is a province in southern Saudi Arabia

bordering Yemen. Data were obtained from the Department of Primary Care, Regional Directorate of Health, Gazan, Saudi Arabia. In this paper we focus on Saudi citizens only. In an earlier study of tuberculosis and immigration [11], it was asserted that DM has a less significant outcome among TB patients who had diabetes compared to those who did not have diabetes.

2. Methods

Diabetes was present among some of the participants of the DOTS program during the year 2014 in the province Gazan, Saudi Arabia. We used a classification tree methodology to identify pockets of data in which one of the outcomes "cured" or "failure" were predominant. A logistic regression model was run. The subjects included both Saudi and non-Saudi to begin with. We observed a very high degree of heterogeneity among Saudi and non-Saudi patients, since diabetes is a life-style disease. The extent of missing data in non-Saudi patients was much more than in Saudi patients. We expected the prevalence of DM to be significantly higher in Saudi patients than in non-Saudi patients, contributing to heterogeneity. In view of these factors, we decided to focus only on Saudi nationals in this report.

3. Results

Table 1 is extracted from the survey data. At the outset, it looked as though DM with TB can lead to a TB cure (32 out of 33 (97%) were cured for patients with DM versus 107 out of 122 (88%) who were cured with no DM). The Fisher test (p-value 0.1955), however, signifies that the difference—97% versus 88%—is not significant.

Table 1. Diabetes versus cure.

	Cured	**Not Cured**
DM−	107	15
DM+	32	1

As practicing physicians in treating TB in the region at the time of data collection, two of the current authors treated DM and TB for patients with dual conditions by controlling glycemia and imposing strict diet regimes. This strategy may have impacted the cure rate of TB (32 were cured out of 33) (Table 2).

Table 2. Nationality versus diabetes.

	DM	**No DM**
Saudi	33	136
Non-Saudi	15	178

The Pearson's Chi-squared test with Yates' continuity correction showed: X-squared = 9.8264, df = 1, p-value = 0.00172. Therefore, the incidence of diabetes is significantly higher among Saudis than non-Saudis—19.5% versus 7.5%.

In the following, we focus on Saudis only. We fitted a logistic regression model to the data with response variable "outcome of DOTS program".

3.1. Output

Coefficients:

Estimate Standard Error z value Pr (> | z |)

(Intercept)	−1.16943	1.30617	−0.895	0.371
Age	0.01795	0.01795	1.000	0.317
Sex	−1.09099	0.68651	−1.589	0.112
BCG	−0.09706	0.72209	−0.134	0.893
Symptoms	0.02843	0.01980	1.436	0.151
Smear POS	−0.64692	0.57619	−1.123	0.262
Diabetes	1.67945	1.07182	−1.567	0.117

We employed a model selection procedure with a backwards elimination algorithm to identify risk factors of the outcome. They are sex, duration of symptoms, and presence of diabetes. The logistic model is fitted with these factors.

Coefficients:

Estimate Standard Error z value Pr ($>|z|$)

(Intercept)	−0.90937	0.91153	−0.998	0.318
Sex	−1.07514	0.67110	−1.602	0.109
Symptoms	0.02890	0.01938	1.491	0.136
Diabetes	−1.61452	1.06537	−1.515	0.130

The fit is good as the residual deviance/degree of freedom is 94.28/151, which is <1. The model used was:

$$ln\left(\frac{\Pr(Failure)}{\Pr(Cured)}\right) = -909 - 1.075^{*} \text{ sex} + 0.029^{*} \text{ symptoms} - 1.615^{*} \text{ diabetes}$$

3.2. Interpretation

1. As the coefficient of sex in the model was negative, males were codified as one and female as two, the chances of failure are lower for females than males (odds ratio = 0.34).
2. As the coefficient of diabetes in the model was negative, diabetics were codified by one and non-diabetics by zero, the chances of failure were lower for non-diabetics than for diabetics (odds ratio 0.199).
3. As the coefficient of symptoms was positive, the higher the duration of symptoms, the higher the chances of failure (odds ratio 1.029).
4. Individually, the factors are not significant, but overall the model is a good fit.

3.3. Data Mining

Following the lead model, we used the classification methodology of Breiman et al. [12] to identify two pockets of data in the prediction space of symptoms, sex, and diabetes (Table 3).

Table 3. Data in the prediction space of symptoms, sex, and diabetes.

	Duration of Symptoms	Diabetes	Gender	Number of Cases	Number of Cured	Percentage Cured
Pocket 1	<35 weeks	No	Female	48	46	96
Pocket 2	<25 weeks	No	Male	66	56	85

A pocket is a special subset of the prediction space of symptoms, sex, and diabetes. For example, the set of all patients with duration of symptoms <35 weeks, sex = Female, and Diabetes = is a pocket. The package "r part" in the computing software R identifies pockets in which the patients are either "cured" or "not cured". Using this package, we identified two large pockets, in which most of the patients are "cured".

In our study, diabetes mellitus did not have significant impact ($p = 0.12$) on treatment outcome. We reckon that the DOTS regimen, when patients are observed directly for a period of time until the completion of the TB treatment, also facilitated diabetics to keep their diabetes under control by

strict monitoring of blood sugar and diet until the treatment of TB was complete (OR = 0.23; 95% CI (0.3–1.74); p = 0.12; RR = 0.88) [11].

4. Discussion

We examined the impact of diabetes associated with TB infection on the overall outcome of the DOTS program. In this study, we discovered that DM, sex, and symptoms collectively impact TB cure. Simultaneous treatment of TB and DM gave a 97% cure rate of TB among the patients we treated. In addition, 107 out of 122 (88%) with no DM were cured. The Fisher test (p-value 0.1955) signified that the difference 97% versus 88% was not significant. We do not know what the cure rate among TB patients with DM would have been if we had not treated their DM condition as in-patients at hospital. We assumed that while patients were in hospital for the initial period of treatment for active TB, glycemic level and diet were strictly monitored, which led to a good outcome of treatment without altering the regime either for TB or for DM.

We suggest more studies should be designed to address satisfactory screening techniques in order to identify at-risk patients and to define an adequate treatment of dual disease are needed. We also urge clinicians to follow the DOTS strategy strictly and admit TB patients with uncontrolled diabetes for at least two months initially, or until sputum conversion goes from positive to negative; this will help to achieve a good outcome for TB and glycemic control. Further research is warranted to more efficiently study the implementation of the DOTS in the group with coexisting of TB and DM to prevent and stop TB.

5. Limitations

This observational study is based on a convenient sample—all the patients are self-reported or have been brought by their sponsors for treatment at the centers. The conclusions made cannot be generalized to other populations. A nationwide cluster sample is suggested for future study.

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