PREVALENCE OF LATENT TUBERCULOSIS INFECTION AND ITS ASSOCIATED FACTORS AMONG PATIENTS WITH DIABETES IN HOSPITAL UNIVERSITI SAINS MALAYSIA

by

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DISCLAIMER

I hereby certify that the work in this dissertation is my own except for quotation and summaries which have been duly acknowledged.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Page

ABBREVIATIONS

AIDS – acquired immune deficiency syndrome

BCG – Bacille Calmette-Guérin

CPG – clinical practice guidelines

CRF - case report form

CXR – chest x-ray

DM – diabetes mellitus

HCW - healthcare worker

HUSM - Hospital Universiti Sains Malaysia

HIV – human immunodeficiency virus

IGRAs - Interferon-gamma release assays

KPP - Klinik Pakar Perubatan

KRK - Klinik Rawatan Keluarga

LTBI – latent tuberculosis infection

M. tuberculosis – Mycobacterium tuberculosis

NPV – negative predictive value

NTM - nontuberculous mycobacteria

PPD – purified protein derivative

PPV – positive predictive value

PTB – pulmonary tuberculosis

TB – tuberculosis

TST - tuberculin skin test

WHO – world health organization

ABSTRAK

Tajuk: Prevalen “latent tuberculosis infection” dan faktor-faktor yang berkaitan tentangnya di kalangan pesakit diabetik di Hospital Universiti Sains Malaysia.

Pengenalan: Hubungkait di antara penyakit tuberkulosis dan penyakit diabetik adalah lebih penting dan menonjol di negara sedang membangun seperti Malaysia, di mana penyakit tuberkulosis adalah endemik dan beban penyakit diabetik semakin meningkat.

Objektif: Untuk menentukan prevalen “latent tuberculosis infection” di kalangan pesakit diabetik di Hospital Universiti Sains Malaysia faktor-faktor yang berkaitan tentangnya.

Metodologi: Kajian berbentuk “cross sectional” (dijalankan di antara Oktober 2013 hingga Januari 2015). “Mantoux test”dilakukan terhadap pesakit yang berkelayakan dan memberi persetujuan untuk mengambil bahagian di dalam kajian ini, dan bacaan ujian dilakukan selepas 72 jam. Peserta yang mempunyai bacaan Mantoux sebanyak 10mm ataupun lebih bersama dengan X ray dada yang normal didiagnosa sebagai LTBI.

Keputusan: Kadar respons kajian ini adalah 93.7%, di mana 319 peserta diuji dengan “tuberculin skin test”. Prevalen “latent tuberculosis infection” di kalangan pesakit diabetik adalah 11.4%. Tahap pendidikan didapati mempunyai hubungkait yang signifikan dengan LTBI; sementara faktor-faktor berkaitan lain yang diuji (umur, jantina, status merokok, ko-morbid lain, tempoh penyakit diabetik, keputusan HbA1c dan rawatan insulin) tidak menunjukkan hubungkait yang signifikan dengan “latent tuberculosis infection” di kalangan pesakit diabetik.

Konklusi: Prevalen “latent tuberculosis infection” di kalangan pesakit diabetik di Malaysia adalah rendah secara relatif memandangkan negara kita mempunyai beban penyakit tuberkulosis yang intermediate. Walau bagaimana pun, hasil kajian preliminari ini memberi “baseline data” bagi reservoir “latent tuberculosis infection” di kalangan pesakit diabetik di populasi kita, yang amat penting bagi isu “tuberculosis chemoprophylaxis” untuk golongan ini.

ABSTRACT

Title: Prevalence of latent tuberculosis infection and its associated factors among patients with diabetes in Hospital Universiti Sains Malaysia.

Introduction: The important association between tuberculosis and diabetes mellitus is even more prominent in developing countries, including Malaysia, where tuberculosis is endemic and the burden of diabetes mellitus is fast increasing.

Objectives: To determine the prevalence of latent tuberculosis infection among patients with diabetes and factors associated with it.

Methodology: A cross sectional study was conducted from October 2013 to January 2015. Mantoux test was performed on the patients whom are eligible and gave consent to participate in the study and reading was carried out at 72 hours. Respondents with mantoux reading of 10mm or more with a normal chest radiograph were diagnosed with LTBI.

Results: The response rate for this study was 93.7% with 319 respondents tested with tuberculin skin test for latent tuberculosis infection. The prevalence of latent tuberculosis infection among diabetic patients was 11.4%. Education level was significant associated with LTBI; while other factors studied (age, gender, duration of diabetes, HbA1c result, smoking status, presence of any co-morbities and on insulin treatment) showed no significant association with latent tuberculosis infection in diabetic patients.

Conclusion: The prevalence of latent tuberculosis infection in Malaysia was relatively low for an intermediate tuberculosis burden country. However this preliminary evidence provides a baseline data on the reservoir of latent tuberculosis infection among diabetic group in our setting, which is especially important in the issue of tuberculosis chemoprophylaxis for latent tuberculosis infection among patients with diabetes.

Chapter 1

Introduction

CHAPTER 1

INTRODUCTION

1.1 Tuberculosis epidemiology and burden globally and in Malaysia

Tuberculosis (TB) is ranked second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In year 2013, 9 million people fell ill with tuberculosis and 1.5 million died from the disease. The majority of tuberculosis deaths occur in the developing countries. More than half (56%) of the new tuberculosis cases were from South-East Asia and Western Pacific Regions; followed by a further one quarter from African Region, and 24% and 11% from India and China.(1)

It is reported that some countries are showing a major drop in tuberculosis cases; while in others the numbers are dropping very slowly.(2) For example, Brazil and China has a sustained decline in tuberculosis cases over past 20 years; and in Cambodia tuberculosis prevalence fell by almost 50%. In 2002, tuberculosis was classified as the eighth leading cause of death, and it is projected to fall to the twenty third leading cause of death in year 2030.(3) The 2015 Millennium Development Goal (MDG) of halting and reversing TB incidence has been achieved globally, in all six WHO regions and in most of the 22 high TB burden countries, with the tuberculosis incidence falling at an average rate of 1.5% per year between year 2000 and 2013. Meanwhile, worldwide tuberculosis mortality rate has dropped 45% between 1990 and 2013 and tuberculosis prevalence rate fell by 41%. Much need to be done to reach the Stop TB Partnership targets of a

50% reduction by 2015. Among the three 2015 targets for reduction in TB disease burden (incidence, prevalence, mortality), 2 out of 6 WHO regions (the Region of the Americas and the Western Pacific Region) have achieved all three of them. South East Asia Region seems to be on track to achieve the three targets; where in the African, Eastern Mediterranean and European Regions those targets are falling but not in a pace fast enough to meet targets.(1) And it is projected that TB will cause 21.8 million disability life years loss in year 2015, again ranking second only to HIV in this category.(4)

Malaysia is a country with an intermediate burden of tuberculosis; is reported to have a TB prevalence of 131/ 100,000 and incidence of 99/ l00, 000 populations.(5) There is a rise in tuberculosis incidence between year2011 and 2012. A concurrent rise in rate of relapse was also reported, thus rendering tuberculosis still a public health problem in Malaysia.(6) In year 2013, the tuberculosis mortality rate is 5.8/ 100,000 population (excludes HIV + TB); and 1.5/ 100,000 population (HIV+ TB only). The increase in non-communicable diseases and demographic shift towards population senescence has attributed to the resurgence of tuberculosis. Tuberculosis in Malaysia is also compounded by the HIV pandemic, complacency, neglect towards the disease, and international movement.

1.2 Diabetes mellitus prevalence globally and in Malaysia

Diabetes mellitus prevalence is soaring globally, fuelled by obesity, changing patterns of diet and physical activity, and aging populations. The number of people with diabetes, which was 171 million in year 2000, is expected to grow to 366-440 million in year 2030. Three quarters of these patients live in low-income countries.(7-9) In Malaysia the prevalence of diabetes continue to rise; the fourth National Health and Morbidity Survey 2011 showed that the prevalence of type 2 DM for adults age 18 years old and above is 15.2%. In fact, Malaysia has already reached its projected of prevalence of diabetes for the year 2025.(10)

1.3 Double burden of tuberculosis and diabetes mellitus

Although HIV infection is considered the most potent risk factor for TB, many studies showed that the high prevalence of DM worldwide and its effect on TB burden is greater than HIV infection.(11) Worldwide 70% of diabetics live in TB endemic countries. Eight of the ten countries with the highest incidence of DM are also classified as high burden countries for TB.(12) This link of DM and TB is more prominent in developing and low-income countries, where the provision of tuberculosis care are complicated as tuberculosis , poverty, poor access to health services are all closely linked.(13) And at the same time treatment of diabetes poses a large financial burden in these countries with limited resources. In the setting of the increasing overlap of

populations at risk for both diseases, TB and DM combined represent a health threat globally.

1.4 Justification of study

The first report on the association between DM and TB was documented by Avicenna (980-1027 AD) over a thousand years ago. A meta-analysis shows that DM increases the risk of TB, regardless of different study designs, background TB incidence or geographic region.(14) The cohort studies reveal that diabetic patients have approximately 3-fold risk of developing active TB compared to non-diabetics.(14) Diabetic patients with concurrent TB infection have poorer treatment outcomes.(15) Studies available on DM and TB generally focus on active TB disease. A review of 232 patients diagnosed with tuberculosis at a medical facility in Malaysia, 17.7% of the patients have underlying diabetes mellitus – the percentage for this risk factor was the highest in contrast to all other associated risk factors.(16) Active case findings among diabetics are among the interventions carried out to control TB.

However the risk of developing active tuberculosis is a two-step process, the initial exposure and infection by Mycobacterium tuberculosis, followed by subsequent progression to the disease. And reactivation of the disease is largely under the influence of immune sufficiency, thus the reactivation risk to TB from latent TB state is higher in immunocompromised individuals, such as in the diabetic group. With the rise of

diabetic prevalence and an intermediate tuberculosis disease burden in the country, diabetic patients in Malaysia should be considered a high risk population prone to tuberculosis reactivation. Studies on latent TB infection among DM patient are scarce.

A huge gap in global TB control today is the eradication of TB reservoir in human population. A two pronged approach involving the coupling of primary with secondary control is recommended as treatment efficacy of both LTBI and the active disease work in synergy.(17) Currently, screening of LTBI was focused on healthcare workers (HCWs), contacts of tuberculosis patients and drug abusers. But the high rising prevalence of DM globally and in Malaysia deems an early intervention, i.e. screening for latent TB in this at risk population a feasible proposition in the Malaysian context, in the track to control TB transmission.

Chapter 2

Literature Review

CHAPTER 2

LITERATURE REVIEW

2.1 Latent Tuberculosis Infection

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB. It is estimated that one third of the world's population is infected with latent TB.(18) Infected persons are asymptomatic and not infectious, but are at risk of progression to active TB disease.(19) And if untreated, the estimated risk of developing symptomatic tuberculosis disease is 5-10% over a lifetime, with about half of that risk occurring during the first year or two after infection.

The risk of developing TB disease following infection depends on several factors, the most important one being the immunological status of the host, and thus the risk is increased in persons with HIV infection, diabetes, and other chronic conditions; those using immunosuppressant medications; and those with apical fibronodular changes on chest radiography, and children younger than four years.(19-21)

However, in the country, the prevalence of latent tuberculosis infection (LTBI) was studied in only few specific groups, including among healthcare workers, prisoners and tuberculosis contacts. A cross sectional study was conducted at four randomly selected

hospitals in the Klang Valley from December 2008 to May 2009 and the overall prevalence of latent tuberculosis infection among health care workers was 10.6% (CI: 8.6%; 12.6%).(22) Another study carried out among Healthcare workers in the University of Malaya Medical Centre, Kuala Lumpur was done to determine the occupational risk of Mycobacterium tuberculosis infection among healthcare workers and found that 52.1% of the healthcare workers tested had indurations of 10 mm or greater.(23) Among prisoners with and without HIV infection in a prison in Kelantan, a cross sectional survey showed that LTBI prevalence was 87.6%, with significantly lower TST reactivity among HIV infected than non HIV infected prisoners (83.6% vs.91.5%).(24) A cross-sectional convenience survey was conducted to assess the prevalence and correlates of LTBI among attendees at a recently created voluntary drug treatment center, and showed positive TST prevalence of 86.7%.(25)

A cross sectional study was carried out to compare the prevalence of M. tuberculosis infection among the household contacts of HIV-positive and HIV-negative pulmonary tuberculosis patients. 30% of the contacts of HIV-positive PTB had a positive tuberculin compared with 52.8% of the contacts of HIV-negative patients.(26) Targeted testing is an essential TB prevention and control strategies that identify, evaluate, and treat persons who are at high risk for latent TB infection or at high risk for developing TB disease once infected with *M. tuberculosis*. With the alarming increase in the trend of DM in the country, which falls in the high risk groups to progress from latent TB to active TB, the feasibility of screening of this group of patients becomes even more crucial.

2.2 Latent Tuberculosis Infection in patients with diabetes

Patients with diabetes have increased susceptibility M. tuberculosis infection through multiple mechanisms, which include those directly related to hyperglycaemia and cellular insulinopenia, as well as indirect effects on macrophage and lymphocyte function which lead to diminished ability to contain the organism.

The most important effector cells for containment of tuberculosis are phagocytes (alveolar macrophages and their precursor monocytes) and lymphocytes. Diabetes is known to affect chemotaxis, phagocytosis, activation, and antigen presentation by phagocytes in response to M. tuberculosis. In diabetic patients, chemotaxis of monocytes is impaired, and this defect does not improve with insulin.(27) In a study of patients with tuberculosis, alveolar macrophages were less activated and had decreased hydrogen peroxide production in those with diabetes.(28)

Diabetes might adversely affect T-cell production of interferon γ, and T-cell growth, function, and proliferation. Interferon γ potentiates the nitric-oxide-dependent intracellular killing activity of macrophages. In experiments involving mice with induced diabetes that were challenged with M. tuberculosis, concentrations of interferon γ were diminished, and production of inducible nitric-oxide synthase by macrophages was low;(29) and the bacterial burden was also higher than in control mice. (30)

The available studies point to depressed immunological function in diabetes mellitus that might predispose a patient to infections for which cell-mediated immunity plays an important role, such as tuberculosis. Decreased phagocyte and T-cell function are likely contributors.

Studies on latent TB infection among DM patient are scarce. One transversal observational study in Spain was carried out to determine the frequency of Tuberculin positives in diabetic population in a general medicine clinic. It reported 69 (42.2%) of 163 diabetic patients to have a positive tuberculin skin test. There was a statistically significant relationship ($p<0.001$) between positive Mantoux test and the age of patients. (31)

Another observational cross survey to study the prevalence of tuberculosis infection in 235 diabetics, and also to study the relationship of years of the illness and patient's age with the infection. Mantoux test measured at 72 hours yield a prevalence of tuberculosis infection of 11.53%, without significant statistical association with the years of evolution of diabetes ($p=0.097$). The average years of evolution of diabetes, 8.15 was associated significantly with the PPD (in mm) ($p=0.00031$) with a low association power ($r=0.314$). The average age, 62.6 years was significantly associated with PPD (mm) ($p=0.0022$), with a low association power ($r=0.191$).(32)

Leow et.al from Tan Tock Seng Hospital conducted a cross-sectional study to elucidate latent TB infection prevalence and longitudinal follow up to ascertain latent TB

infection to active TB progression rate in 220 diabetic patients. Study results showed prevalence of latent TB infection of 28.2% by reactive T-Spot. None progressed to active TB from year 2007-2013. Furthermore, any co-morbidity was positively associated (p=0.016) while metformin was negatively associated (p=0.008) with latent TB infection.(33)

Results of one study showed the reaction to purified protein derivate (PPD) is significantly correlated to the degree of hyperglycemia.(34) Another cross sectional study showed that poor glycaemic control (hazard ratio 1.39, 95%CI 1.18–1.63 per unit increase in HbA1c) was associated with active TB disease which has Mantoux test ≥10 mm.(35) An Australian cohort study revealed that the risk for TB is higher among people with diabetes who are using insulin; the crude RR of TB of 1.78 (95% CI 1.17 to 2.73) in people with DM and 2.16 (95% CI 1.19 to 3.93) in people with DM using insulin.(36)

Chan-Yeung et al carried out a cross sectional study to determine the prevalence of tuberculous infection and the predictors of positive tuberculin reactivity among old aged home residents in Hong Kong.(37) Of 3682 residents (mean age 82 years) who underwent a TST, 46.3% had a positive reaction. Factors associated with a significantly higher risk of a positive TST included being male, an ex- or current smoker and having a past history of tuberculosis.(37)

2.3 Methods of assessing latent TB infection

Traditionally, LTBI is diagnosed based on the following criteria:

1. No symptoms to suggest active disease
2. Normal CXR/static CXR findings.
3. Smear/culture negative on sputum or bronchoalveolar lavage for Mycobacterium tuberculosis (if collected)
4. Positive TST (Mantoux test). Interferon-gamma release assays (IGRAs) may be used as an alternative test in all situations for adults.

There are two testing methods available for the detection of Mycobacterium tuberculosis infection, namely Mantoux tuberculin skin test (TST) and Interferon-gamma release assays (IGRAs). The TST induces a delayed hypersensitivity reaction that is detectable 2-12 weeks after infection with M. tuberculosis. Positive TST is interpreted on a graded-system based on positive predictive values (PPVs) which are largely dependent on the risk of acquiring the disease and risk of latent TB reactivation.(38) There is no good evidence to support the various cut-off measurements of TST in diagnosing LTBI for individuals living in high prevalence countries with moderate/high risk of developing TB reactivation. Thus, the Development Group of CPG TB Malaysia (3rd edition) suggests that a TST of $\geq$10 mm should be considered as a positive test for LTBI for most individuals investigated in this country except for categories listed in the Table 2.1 below:(39)

Table 2.1**:** Positive TST for LTBI

Positive TST Reaction (Measurement)	**Type of Individual**
≥5 mm	HIV-infected persons Organ transplant recipients Persons who are immunosuppressed for other reasons (such as those taking the equivalent of >15 mg/day prednisolone for ≥1 month or taking TNF-α antagonists)
≥15 mm	Individuals from countries with low incidence of TB
≥10 mm	All other high risk individuals

However, the interpretation of the result is compounded by the fact that the reagent (tuberculin) used in the test cross-reacts with BCG and NTM. This gives rise to false positive results in some individuals.

IGRAs are the newer tests for LTBI screening. These in vitro blood tests evaluate T-lymphocyte responses to M. tuberculosis–specific antigens, such as early secretory antigenic target-6 and culture filtrate protein-10. At the moment, there are two commercial tests available, i.e. the T-SPOT.TB (Oxford, Immunotec) and the QFT-GIT Test (Cellestis). They employ certain antigens like the ESAT-6 and CFP-10 (for T-SPOT and QFT-GIT), as well as TB7.7 (only for QFT-GIT) to stimulate the production

of Interferon-γ from the T-cell lymphocytes. These antigens do not cross-react with the BCG and most NTM.(38) Advantages of IGRAs include single visit, does not cause booster phenomenon, and the tests are not affected by healthcare worker bias, results available within 24 hours, unaffected by BCG and most environmental mycobacteria. Limitations include that of blood sample must be processed within 8-30 hours after collection, limited data on use in children younger than 5 years, persons recently exposed to TB, immunocompromised persons, and those who will be tested repeatedly.

A meta-analysis comparing IGRAs and TST in low TB prevalence countries showed that IGRAs have higher specificity and better PPV and NPV than TST in adult population.(40)

However, in low-income and middle-income countries, WHO recommends that IGRA should not replace TST to test for LTBI.(41) For these countries with high incidence of TB, (usually from low and middle income countries), the expert group commissioned by WHO concluded that the quality of evidence on the use of IGRAs in LTBI screening for healthcare workers, contacts and outbreak investigations in low and middle income countries is very low. The data could not be pooled due to heterogeneity in study designs and outcomes. Majority of studies showed comparable LTBI prevalence by TST or IGRA in contacts; four studies reported a statistically significant difference between positivity rates estimated by TST, T-SPOT or QFT. Both IGRAs and the TST seemed to show positive associations but the strength of the association (after adjustment) varied across studies, irrespective of BCG vaccination. These results indicated that concordance between TST and IGRAs ranged widely.(40)

The Development Group suggests that the situations where IGRAs may be used are as follow: (39)

i. alternative to TST for

• patients who are not expected to/could not come back for Mantoux test reading

• patients who had recent BCG vaccination or past NTM infection

ii. Where a 2-step test is considered (TST followed by IGRA)

• close-contacts whose TST is in the range of 5 - 9 mm

• patients who are offered LTBI treatment but are not convinced that they have LTBI

• individuals who require annual screening of LTBI such as healthcare providers working in high risk areas

CXR helps to differentiate between LTBI and pulmonary TB in individuals with positive tests for TB infection. A CXR should be ordered as part of a medical evaluation for individuals who have a positive TST or IGRA result.(42)

Chapter 3

Objectives

CHAPTER 3

OBJECTIVES

3.1 General objective

To determine the prevalence of LTBI and its associated factors among patients with diabetes in HUSM.

3.2 Specific objectives

1. To determine the prevalence of LTBI among patients with diabetes.

2. To determine associated factors of LTBI among patients with diabetes.

3.3 Research hypothesis

Patient's age, male sex, presence of any co morbidity, duration of diabetes, HbA1c result, smoking, on insulin treatment are significant associated factors for LTBI among patients with diabetes in HUSM.

3.4 Operational definitions

LTBI is diagnosed based on the following criteria:

1. No symptoms to suggestive of TB disease
2. Positive TST (Mantoux test) with a reading of 10mm or more
3. Normal chest radiograph

Presence of any co morbidity includes hypertension, dyslipidemia, bronchial asthma, chronic obstructive pulmonary disease, ischemic heart disease and stroke.

Chapter 4

Methodology

CHAPTER 4

METHODOLOGY

4.1 Study design

Study design: cross sectional study

4.2 Population and sample

4.2.1 Reference population

Diabetes patients in Kota Bharu, Kelantan

4.2.2 Source population

Diabetes patient attending outpatient clinic HUSM from October 2013 to January 2015.

4.2.3 Inclusion criteria

Patient with diabetes mellitus

4.2.4 Exclusion criteria

1) Diagnosed TB (current/ previous)

2) Patients with symptoms suggestive of TB

3) HIV-infected persons

4) Organ transplant recipients

5) Persons who are immunosuppressed for other reasons (such as those taking the equivalent of > 15mg/day prednisolone for ≥ 1 month or taking TNF-α antagonists)

6) Non Malaysian

4.2.5 Sampling method

Systematic random sampling in the ratio 1:1 based on attendance list at outpatient clinic, HUSM.

4.2.6 Sample size calculation

Sample size for objective 1 i.e. to determine the prevalence of LTBI among patients with diabetes was done using single proportion formula.

$n = (z / \Delta)^2 p (1 – p)$

n = minimum required sample size

z = value of standard normal distribution = 1.96

Δ = absolute precision = 0.06

P= Prevalence of LTBI among diabetic patients in Spain was 42% (31)

Minimum sample size was 260, and after considering 20% non-response rate, the calculated sample size was 312.

For objective 2, to calculate the sample size for the associated factors for categorical variable, Power and Sample software comparing two proportions for categorical variables was used.

$\alpha = 0.05$

Power = 0.8

P_0 = proportion of insulin-dependent in active-TB diabetics was 0.24 (43)

P1 = proportion of insulin-dependent in LTBI in diabetics was 0.40

m= ratio between non LTBI to LTBI in diabetics was 1

Minimum sample size was 264 and after considering 20% non-response rate, the calculated sample size was 317.

For objective 2, to calculate the sample size for the associated factors for numerical variable, Power and Sample software comparing two means formula was used. The calculation of sample size was as follows:

$\alpha=0.05$

Power = 0.8

$\sigma = 2.8$ (standard deviation of mean HbA1c) (44)

$\delta = 1.0$ (expected detectable difference mean between LTBI and non-LTBI)

M = 1

Thus, the sample size calculated was 248. After considering non-respond rate of 20%, the number of patients needed in this study was 298.

Summary of the sample size calculation for objective 2 was tabulated in Table 4.1 and Table 4.2. Since the largest sample size calculated was from objective 2, 317 were taken as the sample size for this study.

Table 4.1: Sample size calculation for categorical variables

Variables	P_0	P_1	Minimum sample size (n)	n + 20% non-respond rate
Insulin dependent(39)	0.24	0.40	264	317
Smoker (33)	0.65	0.45	192	212

Table 4.2: Sample size calculation for numerical variables

Variables	σ	δ	Minimum sample size (n)	n + 20% non-respond rate
Age (28)	11.4	5.0	166	199
HbA1c (40)	2.8	1.0	248	298