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2018

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SUBJECTIVE SLEEP COMPLAINTS AND THEIR EFFECT ON GLYCAEMIC CONTROL IN ADULT TYPE 2 DIABETICS

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A Research project submitted in part fulfilment for the Degree of Master of Medicine in Internal Medicine, to the Faculty of Health Sciences, Department of Internal Medicine, University of the Witwatersrand Johannesburg 2018.

DECLARATION

I declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Garrison Phutiana Mathole

10 December 2018

DEDICATION

This dissertation is dedicated to

My late mother

Veronica Moyagabo Mathole

My late aunt

Josephine Mmatlekwa Moloisi

ABSTRACT

There is emerging evidence that suggest that sleep disorders are a novel risk factor for diabetes and poor glycaemic control but no data exists for South African populations

Objectives: To describe the prevalence of subjective sleep complaints in adult type 2 diabetics in Chris Hani Baragwanath academic hospital in Soweto and to examine the association between subjective sleep complaints and glycaemic control.

Patients and methods: A cross sectional study, with 150 adult participants attending a diabetic clinic at Chris Hani Baragwanath hospital. A variety of short validated sleep questionnaires including insomnia severity index (ISI) were used.

Results: More patients (46%) in the group with poor glycaemic control had insomnia compared to only 21.6% in the controlled group ($p = 0.014$). The uncontrolled group had a higher Insomnia (ISI) score of 14 compared to the controlled group with (score of 8) ($p = 0.008$). The prevalence of other sleep disorders was high but not significantly related to poor glycaemic control.

Conclusion: There is a high prevalence of sleep disorders in diabetics and insomnia is significantly associated with poor glycaemic control.

PREFACE

This study was approved by the human research ethics committee (medical) of the University of the Witwatersrand Johannesburg, clearance certificate number M140711.

List of abbreviations

AASM: American Academy of Sleep Medicine

ADA: American Diabetes Association

AFS: Awakening from sleep

BFS: Behaviour following sleep

BMI: Body mass index

DKA: Diabetic ketoacidosis

EDS: Excessive daytime sleepiness

ESS: Epworth sleepiness scale

FPG: Fasting plasma glucose

GTS: Getting to sleep

HBA1c: Haemoglobin A one C(refers to glycated haemoglobin)

HHS: Hyperglycaemic hyperosmolar state

ICSD: International Classification of Sleep Disorders

ISI: Insomnia severity index

LSEQ: Leeds sleep evaluation questionnaire

OGTT: Oral glucose tolerance test

OSA: Obstructive sleep apnoea

PLMD: Periodic limb movement disorder

QOS: Quality of sleep

REM Sleep: Rapid eye movement sleep

RLS: Restless leg syndrome

SEMDSA: Society for Endocrinology Metabolism and Diabetes of South Africa

USA: United States of America

VAS: Visual analogue scale

ACKNOWLEDGEMENTS

Dr Alison Bentley my supervisor, thank you for your patience and guidance. Dr V. Khunou thank you for introducing me to the medical ward at Lebowakgomo, it was the beginning of everything.

To my wife Dr Felicity Sebola I really appreciate everything you have done for me and all the encouragement. My parents Tlapa and Taledi Mathole thank you for believing in me.

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Chapter 1: **LITERATURE REVIEW**

1.1 Introduction

Type 2 diabetes mellitus is a major worldwide health burden resulting in significant morbidity and mortality with huge public health implications (Sincree et al., 2009). It is the 8th leading cause of mortality in the world and is an important risk factor for ischaemic heart diseases and stroke which are the commonest causes of death (Skyler et al., 2009). Diabetes is responsible for significant debilitating morbidity and is the leading cause of blindness, non-traumatic lower limb amputation and end stage kidney failure in the world (Ohkubo et al., 1995). Diabetes is a prototype non-communicable life style related disease.

The risk of developing the disease is related to genetics as well as established modifiable risk factors such as obesity, sedentary lifestyle and a calorie rich diet. Sleep disorders are emerging as a significant risk for developing diabetes and have been shown to adversely affect glycaemic control in those who are already diabetic (Cappucio et al., 2010; Barone et al., 2011). Sleep related disorders such as obstructive sleep apnoea are also more likely in patients who are obese, thus as South Africans develop more modifiable non-communicable diseases such as obesity sleep disorders may become more significant in the pathophysiology of other diseases related to the obesity. The relationship between diabetes, obesity and sleep disorders may be quite important. There are no South African studies looking at the prevalence of sleep disorders in type 2 diabetics and their effect on glycaemic control.

1.2 DIABETES

1.2.1. Definition of diabetes

According to the American Diabetic Association, diabetes is a heterogeneous group of metabolic disorders sharing a phenotype of hyperglycaemia due to insulin deficiency, insulin resistance or a combination of both. It is characterised by derangement of carbohydrate, protein and fat metabolism. The disease results in secondary pathological changes in multiple organs such as retinopathy and nephropathy, and also increases the risk of developing cardiovascular diseases (ADA., 2018).

1.2.2 Diagnosis of diabetes

The Society for Endocrinology, Metabolism and Diabetes of South Africa divides glucose tolerance into 3 groups when diagnosing diabetes based on the fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT):

(1) Normal glycaemic state is a FPG of less than 5.6mmol/l or a 2-hour blood glucose of less than 7.8mmol/l following OGTT.

(2) Impaired fasting glucose tolerance is present when FPG is between 5.6mmol/l and 6.9mmol/l and impaired glucose tolerance present when a 2-hour plasma glucose is between 7.8mmol/l and 11mmol/l during an OGTT.

(3) Diabetes is diagnosed when the fasting glucose is above 7mmol/l or a 2-hour blood glucose ≥ 11.1 mmol/l following an OGTT. A glycated haemoglobin ≥ 6.5% and a random blood glucose of above 11.1mmol/l with classic symptoms of diabetes or hyperglycaemic crisis are each also diagnostic of diabetes (SEMDSA.,2017).

A formal laboratory test using validated accredited test methods is preferable over bed side point of care tests in diagnosing diabetes. An abnormal test should be repeated on another day using the same test to confirm the diagnosis of diabetes. Hyperglycaemia can be induced by physiological stress or acute illness and when occurring during such illnesses it must not be regarded as diabetes and testing should be repeated once the illness has resolved.

1.2.3 Epidemiology of diabetes

Data from the International Diabetes Federation shows that there were 371 million people with diabetes In the world by the year 2012 and half of these were undiagnosed (Ford., 2005).The incidence and prevalence of the disease is increasing and it is projected that there will be 552 million people with diabetes by the year 2030 (Whiting et al.,2011). Currently 4.8 million people are dying of the disease every year, and 471 billion US dollars is spent yearly on diabetes across the world.

Africa has 14 million people with diabetes type 2 and this is projected to rise to about 28 million by the year 2030, South Africa has the second largest number of people with the disease with about 1.9 million diagnosed cases, behind Nigeria which has about 3.2 million people living with diabetes (Peer et al., 2014). The local South African authorities estimate that 6.5% of the urban adult population in South Africa has diabetes with an age adjusted prevalence of 13% (Mayosi et al., 2009)

1.2.4 Pathophysiology of diabetes

Insulin resistance and variable insulin deficiency are central to the pathology of diabetes type 2. The pancreatic islet beta cells initially compensate for insulin resistance by increasing the production and output of insulin which delays the onset

of disease by years, until there is decompensation or complete beta cell failure that leads to symptomatic diabetes (Stumvoll et al., 2005). Insulin deficiency is associated with increased glucose production by the liver and reduced glucose uptake by the peripheral tissues which leads to hyperglycaemia. All the cells of the body are bathed in an extracellular environment that is hyperglycaemic, but the cellular damage mediated by high blood glucose level is selective and affects only those cells that lacks a mechanism to tightly regulate glucose influx (Koya et al., 1998). The cells which are susceptible to the tissue damaging effects of hyperglycaemia include: endothelial cells of the blood vessels and capillaries in the retina, mesangial cells of the glomerulus, neurons and Schwann cells in peripheral nerves (Duckworth et al., 2009). It is the intracellular hyperglycaemic environment in these cells that leads to the pathological organ specific damage through the following pathways:

1. Increased activity in the polyol pathway in peripheral nerves, described in the historic 1966 Science paper (Gabbay et al., 1966).
2. Increased formation of advanced glycosylation end products.
3. Hyperglycaemic induced activation of protein kinase in target tissues (Koya et al., 1998)
4. Hyperglycaemia and glycosylation of vascular and neurological tissues giving rise to vascular and non-vascular target organ damage (Brownlee., 2005).

1.2.5 Risk factors for diabetes

The risk of developing diabetes is partly genetic but also largely influenced by behavioural lifestyle risk factors (Billings et al., 2010). The increase in obesity is

partly responsible for the upward trend in the incidence of diabetes in modern society.

The development of diabetes has a strong inherited component with involvement of multiple genes. The national survey by the Center for Disease Control and prevention in the USA showed that the prevalence of diabetes varied in different ethnic groups even when they shared the same environment. People of African origin, native Americans, Indians and Hispanics had a higher incidence and prevalence of diabetes when compared to Caucasians (Geiss et al., 2014). Data from South African studies show higher prevalence rates among the Indian population followed by coloured and black people (Erasmus et al., 2012). Having a parent with diabetes confers the offspring with a 39% chance of being diabetic while in monozygotic twins there is a 90% chance of developing diabetes if one of the twins has diabetes (Meigs et al., 2000).

Other risk factors for developing diabetes include: obesity, advanced age, sedentary life style and a calorie-rich diet (Shai et al., 2006). Obesity is the most established and important modifiable risk factor, in Europe 95% of the newly diagnosed type two diabetics are obese (Astrup., 2001). The Epic–Interact case cohort study showed a doubling of hazard for developing type 2 diabetes when BMI increased by a unit standard deviation (Langenberg et al., 2012). A large cohort of middle aged women showed that a BMI of below 25 kg/m² and a diet rich in high fibre and polyunsaturated fats together with regular exercise was associated with a 90% reduction in new incidents of diabetes. The finding of this study suggests that the incidence of diabetes can be significantly reduced by focusing on modifiable risk factors (Hu et al., 2001).Randomized controlled trials of intensive behavioural lifestyle modification vs standard care showed that the risk of developing diabetes

type 2 can be significantly reduced by weight reduction with diet and exercise having minimal impact independently (Hamman et al.,2006).The lifestyle risk factors are modifiable and present an opportunity for preventative interventions in those who are at risk and can be manipulated to delay target organ damage and prolong life in those who are already diabetic. Interventions focussing on weight loss, increased activity and healthy eating are effective and central to the management of diabetes and reducing vascular complications (Colberg et al., 2010).

The fact that most risk factors for diabetes are modifiable has led researchers to look for other undetermined factors that predispose humans to diabetes. There is increasing evidence showing that sleep deprivation contributes towards insulin resistance and the development of diabetes (Kita et al., 2012; Nilsson et al., 2004). The modern society is sleep deprived and on average sleep for about 6.8 hours per night compared to 8 hours a century ago (Bonnet et al., 1995). All sleep disorders which cause sleep deprivation are now being investigated for their relationship to diabetes.

1.2.6 Complication of diabetes

The complications of diabetes are associated with significant morbidity and mortality and major public health implications. They occur as a result of prolonged hyperglycaemia and the direct and indirect effect on the vascular endothelium and nerves. The complications affect many organ systems and often only manifest after decades of hyperglycaemia. Most of the patients with type 2 diabetes have complications when they are diagnosed because of a prolonged period of undetected diabetes.

The acute complications are diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar state (HHS). DKA is more common in type 1 diabetes and insulin requiring type 2 diabetics while HHS is mostly found in type 2 diabetes (Daugirdas et al., 1989). Both are characterised by insulin deficiency with increased counter regulatory hormones and lead to volume depletion, electrolyte imbalance, with acid-base disturbances especially in DKA. The two complications are medical emergencies which require intensive specialised care, as they are life threatening when missed or incorrectly managed (Kitabchi et al., 2009).

The chronic complications are divided into vascular and non-vascular, with the vascular further subdivided into microvascular complications (nephropathy, neuropathy and retinopathy) and macrovascular complications (peripheral vascular disease, coronary vascular disease and stroke). The risk of developing microvascular complications is directly related to the duration and severity of hyperglycaemia and concurrent hypertension (Bash et al., 2008; Klein et al., 1994). According to the National Kidney Foundation in the USA diabetes is the single leading cause of chronic kidney failure and is responsible for almost 40% of all the patients on dialysis (Inker et al., 2014). Sub-Saharan Africa has a poor renal disease registry but estimates from the available studies puts the prevalence of diabetic nephropathy at around 16% in the diabetic population (Moosa et al., 2015). Diabetic retinopathy is the leading cause of legal blindness globally.

Diabetes is a major cardiovascular disease risk factor and diabetic patients are two to four times more likely to have cardiovascular related mortality compared to non-diabetics of the same age (Riddle., 2010). Diabetes is the leading cause of lower limb amputation and a major risk factor for thrombotic strokes (Janghorbani et al., 2007; Peters et al., 2001).

Poor glycaemic control is the main risk for developing vascular complications together with obesity, dyslipidaemia, smoking and hypertension. The American diabetes association defines poor glycaemic control as a HBA1C of above 7% for the majority of the non-pregnant population and 6.5% for the young and those not at risk of hypoglycaemia. This is the level below which diabetic complications and target organ damage can be avoided. The risks predisposing to poor glycaemic control include old age, lack of education, low income, family history of diabetes, prolonged diabetes, non-compliance to treatment and obesity (Almutari et al., 2013).

The other risk factors for vascular complications include obesity, hypertension, dyslipidaemia and smoking and are not entirely related to glycaemic control alone. Most of the risk factors associated with increased vascular complications are modifiable; in particular obesity, smoking, hypertension and dyslipidaemia (Martin-Timon et al., 2014). A meta-analysis showed that in type two diabetics a 5 kg weight gain was associated with a 30% increase in incidence of coronary heart disease (Anderson et al., 2003). Weight-loss and a calorie restricted Mediterranean diet were associated with an improved glycaemic control, reduction in cardiovascular disease and overall mortality (Williamson et al., 2000; Shai et al., 2008). There is now emerging evidence that associates poor sleep with increased vascular complications in diabetics independent of the other factors (Kim et al., 2013). Abnormal sleep duration (both long and short) is associated with poor glycaemic control and expected to contribute to increased vascular complications (Tsai et al., 2011). A cross sectional study with 1220 Chinese adult patients with diabetes showed an association between short sleep duration and diabetic nephropathy, cardiovascular disease and peripheral neuropathy (Meng et al., 2016)

1.3. Sleep

1.3.1 Definition of sleep

Sleep is a well-organized reversible and regulated periodic physiological state characterised by altered responsiveness and reduced consciousness with decreased physical activity and muscle relaxation (Iber., 2007). It is common to mammals, reptiles, birds and some insects. Sleep is divided into two phase, rapid eye movement sleep (REM) and non-rapid eye movement sleep (NREM). The nocturnal sleep period consists of multiple cycles of NREM alternating with REM, with NREM constituting most of the sleep duration (Siegel., 2009). REM usually only constitute 20% of the total sleep time and is characterised by vivid dreams and rapid eye movement. NREM sleep is further divided into stage 1 to stage 4 which represent slow wave sleep (Borbely et al., 2011). A single cycle last for 90-120 minutes and there are four to five cycles in a normal 8 hours sleep (Espana et al., 2011). Sleep is regulated by intrinsic homeostatic circadian rhythms from the hypothalamus with regulatory inputs from other areas of the brain (Borbely et al., 2011)

1.3.2 Functions of normal sleep

The specific functions of sleep are not well understood and are thought to be restorative, energy conserving and the promotion of optimal brain function. Sleep is important for optimal function of most endocrine systems (Siegel., 2009). Multiple studies have shown that normal sleep affects glucose metabolism. Sleep is associated with glucose intolerance which is worse in the middle of the sleep cycle and improves in the morning (Scheen et al., 1996). On average glucose utilisation decreases by 20% during early sleep. The sleep related hyperglycaemia is due to reduced skeletal muscle glucose uptake and usage and increased secretion of

counter-regulatory hormones in particular growth hormone (Van Cauter et al., 1991). The brain exclusively uses glucose and in fasting states it accounts for almost 50% of total glucose consumption, unlike in awake fasting states. During sleep there is a drop in cerebral function and decreased glucose utilisation which contributes to the sleep related hyperglycaemia (Simon et al., 1994). The sleep associated glucose intolerance varies according to the stage of sleep, NREM sleep is associated with increased hyperglycaemia which improves with REM sleep (Scheen et al., 1996).

The normal sleep associated glucose intolerance worsens with sleep deprivation. An early study by Kuhn et al in the 1960s of 28 healthy young men who had 72 to 126 hours of total sleep deprivation and 5 control nights of normal sleep showed worsening glucose intolerance (Kuhn et al., 1969). Subsequent studies showed increased insulin resistance and a pre-diabetic state associated with sleep deprivation (Spiegel et al., 1999; Tasali et al., 2009)

1.4 Sleep disorders

Sleep disorders are among the commonest medical problems responsible for visits to general practitioners and result in significant morbidity. Many sleep disorders have been independently associated with cardiovascular diseases, metabolic derangement and early mortality (Spiegel., 1999).

The third edition of the International Classification of Sleep Disorders(ICSD-3) produced by the American Academy of Sleep Medicine (AASM) in association with other international sleep societies is globally accepted as the main reference work for the diagnosis of sleep disorders. It divides sleep disorders into seven major categories (Sateia., 2014).

1. Insomnia

2. Sleep related breathing disorders- such as obstructive sleep apnoea
3. Sleep related movement disorders-such as restless leg syndrome
4. Hypersomnias of central origin - such as narcolepsy
5. Parasomnias
6. Circadian rhythm sleep disorders
7. Other sleep disorders

The ICSD-3 classification is an improvement on earlier editions as it takes into consideration the sleep disorders in the paediatric and geriatric populations and there is also a seventh category termed “other sleep disorders” to accommodate those conditions that do not fit into any of the pre-existing categories. Excessive daytime sleepiness is not included under any specific group as it forms part of the diagnostic criteria of most sleep disorders as a daytime-sequelae (Sateia., 2014). A full description of all the conditions classified under the ICSD-3 is beyond the scope of this project and only those sleep disorders which are related to the objective of this study will be explored and this includes insomnia, restless leg syndrome, obstructive sleep apnoea and excessive daytime sleepiness. The selected conditions have been associated with diabetes and cardiovascular diseases and have validated questionnaires for screening and diagnosis

1.4.1 Insomnia

Insomnia is characterised by difficulty initiating sleep, maintaining sleep or waking up too early creating a reduced quantity of sleep hours during the sleep period. According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), the above must occur despite adequate opportunity and circumstance for sleep

and must produce deficiencies in daytime function to fulfil the diagnosis of insomnia. To diagnose insomnia the criteria below must be met.

<u>Criteria for the diagnosis of insomnia adopted from ICSD-3</u>

Criteria 1 to 6 must be met to diagnose insomnia

1. **One or more of the following must be reported by the patient or those close to them**
   - **1.1 Difficulty to initiate sleep**
   - **1.2 Difficulty to maintain sleep**
   - **1.3 Waking up earlier than desired**
   - **1.4 Resistance to go to bed at the appropriate time**
   - **1.5 Difficulty sleeping without caregiver intervention**
2. **One or more of the following related to night-time sleep is observed by patient or others**
   - **2.1 Fatigue/malaise**
   - **2.2 Impairment of concentration, attention or memory**
   - **2.3 Daytime sleepiness**
   - **2.4 Irritability or mood disturbance**
   - **2.5 Impaired social, family, occupational or academic performance**
   - **2.6 Being inclined to commit errors and accidents**
   - **2.7 Concerned and dissatisfaction with sleep**
   - **2.8 Behavioural problems (being impulsive, hyperactive or aggressive)**
   - **2.9 Reduced energy or motivation**

3. **There must be enough time and adequate circumstances for sleep to occur**
4. **The sleep disturbance and daytime symptoms occur at least three time a week**
5. **The sleep disturbance and daytime symptoms have been present for a minimum duration of 3 months**
6. **The sleep disturbance should not be explained by other disorders**

Insomnia is transient when it is less than 3 months duration, usually there is an associated precipitating factor, and chronic when it is of more than 3 months duration (Zucconi et al.,2014). It is the most common sleep disorder in adults, population surveys estimate the prevalence to be around 10% to 15%. Insomnia is more common in females and the elderly, and often associated with serious psychiatric and medical conditions (Costa e Silva et al., 1996).

The loss of daytime function with insomnia may be quite severe and some patients may present with non-specific symptoms of headaches, malaise and irritability but most present with excessive daytime sleepiness. The patient's subjective symptoms are important in determining the diagnosis and the cause of insomnia (Sateia., 2014).

Insomnia is very prevalent in society and an ideal diagnostic tool must be brief, effective, validated and based on the ICSD-3 criteria for diagnosis. An overnight polysomnogram is considered to be the gold standard for diagnosing most sleep disorders but is not recommended for insomnia (Reite et al.,1995). Structured clinical

interviews and sleep diaries are vital when in-depth thorough information is needed about sleep, but they are time consuming and require in-depth knowledge of sleep disorders.

The insomnia severity index (ISI) is a validated 7 component questionnaire that evaluates difficulty with sleep initiation, sleep maintenance, interference of normal daytime function, the patient's perception of the problem and the noticeability of the problem due to the insomnia (Bastien et al.,2001). The components of the ISI correspond with the ISCD-3 diagnostic criteria (Sateia et al., 2014). An overnight polysomnogram may be used to rule out other organic sleep disorders.

Insomnia is treated with cognitive behavioural therapy (CBT) and/or pharmacologically with hypnotics such as benzodiazepines and sedating antidepressants (Saddichha., 2010). The psychosocial and medical condition associated with insomnia must also be treated.

1.4.2 Obstructive Sleep Apnoea (OSA)

Apnoea is defined as a cessation of airflow during sleep for more than 10 seconds while hypopnea is defined as airflow limitation of at least 5 seconds that does not meet the criteria for apnoea (Dempsey et al., 2010). Apnoeas are caused by recurrent episodes of velopharyngeal and oropharyngeal collapse during sleep. The Apnoea-Hypopnoea index (AHI) is the total number of apnoeas and hypopnoeas per hour of sleep and determines the severity of the disorder (Epstein et al., 2009). The apnoeas and hypopneas result in desaturations and recurrent arousals during sleep. OSA is confirmed when a subject has an AHI greater than five events per hour measured objectively by polysomnography with at least one clinical symptom of

sleep disturbance. OSA can also be diagnosed with polysomnography alone when the patient has an AHI≥15 events per night (Epstein et al., 2009)

The risk factors for OSA are, morbid obesity, male gender, craniofacial and upper airway abnormalities and advancing age. It is estimated that 20-30% of males have OSA compared to only 10-15% of females in the general population (Young et al., 2009). The signs of OSA include loud snoring, gasping or choking during sleep and recurrent arousals resulting in interrupted fragmented sleep, which leads to daytime excessive sleepiness and poor concentration with headaches and psychiatric disturbances. OSA is independently associated with hypertension, ischaemic heart disease, cerebrovascular stroke and is associated with increased cardiovascular events and premature mortality (Dempsey et al., 2010).

OSA patients are usually screened with validated sleep questionnaires which mainly focus on the report of snoring, evidence of respiratory pauses and gasping. Most questionnaires include biographic data that predisposes to sleep disordered breathing such as gender and age and questions about other metabolic syndrome related conditions. Validated questionnaires include the STOP BANG Questionnaire, the Berlin questionnaires and the Epworth sleepiness scale (El-Sayed., 2012)). A study by Lou et al showed that the STOP BANG questionnaire has superior predictive value and sensitivity than both the Berlin questionnaire and the ESS in screening for OSA (Luo et al., 2014).

The STOP BANG questionnaire has 8 independent components 3 of which are OSA related symptoms (snoring, daytime tiredness and observed apnoea), 3 anthropometric and physiological parameters (BMI, neck circumference and blood pressure) and the remaining two are age and gender of the patient. The

anthropometric and physiological data are recorded by the researcher, the patient answers the OSA associated questions (Gasfou et al., 2010). The STOP BANG questionnaire has a sensitivity of 97% in identifying subjects at risk of OSA and a positive predictive value of 90%. Of concern is that its specificity is low at 26% and there is a potential for increased false positive results (Chung et al., 2013; El Sayed., 2012). A STOP BANG score of less than 3 shows mild risk for OSA, and a score of 3 to 4 equates to moderate risk while a score of 5 to 8 indicates a high risk for OSA (Nagappa et al., 2017)

The definitive gold standard test to diagnose OSA is an all-night polysomnogram which requires expertise and is costly, thus it is not cost effective to subject everyone suspected of OSA to a polysomnogram. As a result, the validated questionnaires play a crucial role in screening patients in a clinical setting and identifying patients at high risk for OSA in large population studies (Qaseem et al., 2010). OSA can be treated with behavioural modification such as weight loss, reduced alcohol intake or more specifically with nasal continuous positive airway pressure(CPAP) devices. Nasal CPAP has been proven to be effective in relieving the symptoms, prolonging life and preventing the cardiovascular and metabolic complications (Dempsey et al., 2010).

1.4.3 Restless legs syndrome

Restless legs syndrome (RLS) is a movement disorder of the limbs characterised by an urge to move, mainly the legs, in response to an unpleasant sensation in the legs. The subjective symptoms of RLS occur most commonly at rest or during periods of inactivity and in the evening. The discomfort is described as an aching, pulling, stretching and itchy sensation in the deep structures of the legs, which is relieved by

moving the affected limb. RLS can be primary or secondary when associated with other medical conditions such as iron deficiency, rheumatological diseases, multiple sclerosis and diabetes (Krueger et al., 1990).

The prevalence of RLS in the general population is said to be around 5% to 10% and increases with age. RLS is twice as common in females as in males (Ohayon et al., 2012). RLS is associated with fragmented non-restorative sleep accompanied by day time somnolence and great emotional distress. The International Restless Leg Syndrome Group (IRLSG) has developed a diagnostic 5-point series of questions which requires affirmative answers to the following (Allen et al., 2014).

(1) Do you have an urge to move your legs due to an uncomfortable sensation?

(2) Does the urge to move the limbs occur at rest or during periods of inactivity?

(3) Is the discomfort partly or completely removed by moving the limbs?

(4) Is the urge to move worse at night than during the day?

(5) All the above symptoms must not be due to any other medical or behavioural condition.

The treatment of RLS involves non-specific supportive measures such as regular exercise, leg massage or heat therapy for mild disease. Drug therapy is indicated in those with persistent symptoms not responsive to the general measures, and dopamine agonists are the treatment of choice (Trenkwalder et al., 2007).

1.4.4 Excessive daytime sleepiness (EDS)

The American Academy of Sleep Medicine defines excessive daytime sleepiness as an inability to stay awake and alert during most part of the waking episodes of the day, occurring unintentionally daily for at least 3 months. EDS has a prevalence of

10% to 25% in the general adult population (Hara et al., 2004). EDS has commonly been associated with other primary sleep disorders and in the ICSD-3 forms part of the diagnostic criteria for insomnia, narcolepsy, hypersomnia and OSA (Young et al ., 2004). EDS is also associated with medical conditions and risk factors include obesity, depression, cardiovascular and respiratory disorders, extremes of age and sleep deprivation (Slater., 2012). EDS can also be secondary to neuro-psychiatric illnesses and pharmacological drugs used to treat various medical conditions, especially those drugs that have a central nervous system effect such as alcohol, benzodiazepines, opioids and anticonvulsants (Hara et al., 2004).

Recent studies have shown that EDS may represent a separate sleep disorder with its own risk factors and associated conditions. Vgontzas et al have shown an association of EDS with obesity in the absence of OSA (Vgontzas et al., 2000). Other studies have revealed that the treatment of primary sleep disorders such as insomnia and OSA does not necessarily improve the EDS, Patel et al has reported in their study that treatment of OSA with CPAP improves cardiovascular complications but does not improve EDS (Patel et al., 2003).

Patients with EDS present with excessive daytime sleepiness, yawning and difficulty concentrating especially during times of minimal stimulation with an increased risk for motor vehicle accidents and metabolic syndrome resulting in early cardiovascular mortality (Empana et al., 2009; Johnson et al., 2014)). It is diagnosed clinically through history and validated sleep questionnaire such as the Epworth sleepiness scale (ESS) which is a 8-item 4-point self-administered questionnaire that assesses the participants likelihood to fall asleep during certain different soporific situations (Chica- Urzola et al., 2007; Johns., 1992). The ESS is subjective and may be affected by psychological and cultural factors. In some patients the diagnosis may

not be clear on history and a polysomnogram might be indicated for confirmation and to exclude an underlying OSA. In most instances EDS signals an underlying sleep or medical condition and as a result it is imperative to investigate and treat the underlying cause. There is now emerging evidence that link EDS and diabetes, a population-based study by Bixler et al showed a strong link between EDS and diabetes (Bixler et al., 2005). A cross sectional study by Hayley et al found a significant association between EDS and insulin resistance and diabetes: their study also highlighted the confounding factor of obesity (Hayley et al., 2015).

1.5 Sleep disorders and diabetes

There is an increasing evidence from both population based epidemiological cohorts and laboratory sleep studies that show that sleep deprivation caused by behavioural sleep curtailment or primary sleep disorders results in insulin resistance and may be a risk factor for diabetes. Behavioural sleep loss is caused by multiple factors in modern society such as shift work, television watching or using the internet at night. Laboratory controlled sleep studies have shown that sleep deprivation without a primary sleep disorder is associated with endocrine dysregulation and insulin resistance - a known marker for diabetes (Spiegel et al., 1999; Buxton et al., 2010). A cross sectional study on the participants of the sleep heart study by Gottlieb et al have shown that habitual sleep curtailment is associated with increased insulin resistance and new incidence of diabetes independent of other diabetes risk factors and insomnia (Gottlieb et al., 2005). An increase in the general level of sleep deprivation therefore may be related to the rise in diabetes.

There are several population-based studies done in different regions of the developed world which have looked at the association between sleep disorders and

diabetes. In most of these studies information about sleep quality and quantity was subjectively reported by the participants with concurrent objective assessment of insulin resistance and glucose intolerance markers which were used as surrogates for diabetes. Most of the studies employed multivariate statistical methods to overcome the cofounders. The majority of these studies have found a statistically significant aetiological link between insomnia and diabetes (Cappuccio et al., 2010; Tasali et al., 2009).

1.5.1 Insomnia and diabetes

1.5.1.1 Abnormal sleep quantity and diabetes

Both short (sleep of <5 hours) and long (sleep of >9 hours) sleep duration have been associated with a high-risk ratio of developing diabetes. The nurse's health study which was a prospective cohort with 70026 female registered nurses with a follow up of 10 years showed a significant association between sleep duration and diabetes, short and long duration of sleep were positively associated with increased incidence of diabetes and metabolic syndrome. For short sleepers the relative risk was initially significant until the data was adjusted for BMI and the association became attenuated and non-significant, short sleep was not an independent risk for diabetes but may have contributed to the development of insulin resistance through its effects on BMI (Ayas et al., 2003). Short sleep duration is associated with reduced leptin levels (a known anorexigenic hormone) and increased levels of ghrelin (orexigenic hormone) leading to increased appetite, food intake and obesity (Ayas et al., 2003).Another cross sectional study by Chaput et al also showed a significant association between long and short sleep duration with diabetes/impaired glucose tolerance, In contrast to the finding by Ayas et al the association between short sleep

duration and diabetes remained statistically significant after adjusting for BMI (Chaput et al., 2007)

There is no concrete physiological explanation for the association of long sleep duration and diabetes in the nurse's health study and the cross sectional study by Chaput et al, which was statistically significant even after adjustment for confounders. The authors speculated that this association may be secondary to unrecognized factors such as OSA or it may be that long duration of sleep is an early sign of diabetes and not an aetiological risk factor (Ayas et al., 2003)

These isolated studies have been brought together in a systemic review and meta-analysis of 13 population-based cohort studies from different geographical areas of the developed world with a total of 107.576 male and female participants and a follow up of 4.2 to 32 years (Cappucio et al.,2010). The inclusion criteria was any prospective study that had at least 3 years of follow up that assessed the link between sleep disturbances and incidences of diabetes. The results showed that abnormal quantity and quality of sleep were consistently linked to new cases of diabetes. A quantitatively short duration of sleep was associated with a higher risk of diabetes, more so in males than in females. Long duration of sleep was also linked to higher risk of diabetes, but in this case the risk was similar for males and females. Qualitatively both difficulty in initiating and maintaining sleep were linked to a statistically significant risk of diabetes in both sexes. This meta-analysis provided the first pooled assessment of the link between abnormal quantity and quality of sleep and diabetes, which was statistically significant even after adjusting for all the possible confounding variables. The risk ranged from 28% in those with a short duration of sleep to 84% in those who had difficulty maintaining sleep (Cappucio et al., 2010).

1.5.1.2 Insomnia and diabetes

A Japanese prospective study with 2265 men who were healthy and non-diabetic at baseline, followed for 8 years looked at the link between insomnia and diabetes. They showed that those with initial insomnia had a higher age adjusted hazard ratio (2.98, 95%CI; 1.36-6.53) for developing diabetes. Difficulty maintaining sleep had similar statistically significant hazard ratios for developing diabetes (2.23, 95%CI; 1.08-4.61). The overall analysis showed an increased risk of developing diabetes in those with insomnia. This association was adjusted for other risk factors for diabetes (Kawakami et al., 2004).

A Swedish prospective population-based study with 6599 healthy non-diabetic men (mean age 44.5±4 years) at baseline with a follow up of about 15 years examined the relation of self-reported sleep complaints and diabetes. The results showed that in men who developed diabetes, there was a statistically significant link between insomnia or hypnotic use and the development of type 2 diabetes (OR 1.52 [95%CI 1.05-2.20]). The participants who developed diabetes also had an increased heart rate not explained by any other cause. This long-term follow-up supports the hypothesis that difficulty initiating sleep or using hypnotics (a marker for insomnia) results in metabolic derangement, increased sympathetic nervous output and insulin resistance. The shortfall of the study was that it was based on non-validated sleep questionnaires designed to screen for insomnia and other sleep related disorders, and subjects were also asked to self-report alcohol usage, which is always underreported in the general population. As alcohol abuse is a known cause of daytime somnolence and associated with the metabolic syndrome, this may have affected the study results. The other problem that arose in this study was that not all the subjects had an oral glucose tolerance test at baseline, thus some of the

participants may have been diabetic or had glucose intolerance at baseline (Nilsson et., al 2004). The link between insomnia and diabetes was also studied in an adult German population who were diabetes free at baseline. After a follow-up of 7.5 years a high risk of diabetes was found in those with difficulty maintaining sleep in both males and females (Meisinger et al., 2005).

The early studies on insomnia and diabetes did not control for other sleep disorders such as OSA which are known risk factors for metabolic and cardiovascular disorders. A population based study of adult male and female (age above 20 years) by Vgontzas et al was the first large-scale study that showed that objectively measured chronic insomnia and short sleep duration were significantly associated with the development of type 2 diabetes. A polysomnogram was used to objectively measure sleep and the results were adjusted for cofactors such as obesity, alcohol usage and OSA (Vgontzas et al .,2010)

1.5.1.3 Laboratory studies on sleep deprivation and diabetes.

To overcome the cofounding variables which are so common in epidemiological studies there are several laboratory-based studies that look at the impact of sleep disorders and diabetes.

The first laboratory-based study to look at the effect of acute sleep curtailment on metabolic function in 1999 looked at the hypothalamic pituitary axis, carbohydrate metabolism, thyrotropic function and the sympathetic tone in 11 healthy young men who were restricted to 4 hours of sleep per night for 6 consecutive nights. The results showed an impaired hypothalamic pituitary adrenal axis function with raised cortisol, increased glucose intolerance and a heightened sympathetic tone. All of these are known risk factors for the development of type 2 diabetes and

hypertension (Spiegel et al., 1999). A double blinded randomized study of 20 healthy non-obese young men (mean age 26.8 ±5.2 years and BMI 22.3±3.1 kg/m²) also showed that sleep deprivation of 5 hours per night for one week led to a reduction in insulin sensitivity (Buxton et al., 2010). Although these studies had a small sample size they were well carried out and their findings had a significant impact on sleep medicine and the understanding of how sleep deprivation causes diabetes.

The detrimental impact of sleep is not only about the quantity of total sleep. A study by Tasali et al showed that laboratory suppression of non-rem sleep (NREM sleep) in young healthy adults resulted in increased insulin resistance and glucose intolerance even when the duration of sleep was normal. This study highlighted the fact that the stage of sleep lost might be more important than the duration of sleep. Non-REM sleep represents deep restorative sleep and its disruption results in an increased sympathetic output which inhibits pancreatic insulin release and result in hyperglycaemia and glucose intolerance (Tasali et al., 2009).

1.5.2 Obstructive sleep apnoea

1.5.2.1 Obstructive sleep apnoea and diabetes

The aetiological association between type 2 diabetes and OSA is complex and reciprocal, both diabetes and OSA are associated with obesity, insulin resistance, cardiovascular disease and early mortality. The prevalence of both conditions is on the increase and they are becoming global epidemics (Vgontzas et al., 2000). It is important to understand diabetes and OSA independently and also how they interact with each other in causing metabolic syndrome and related cardiovascular mortality. The prevalence of OSA in patients with diabetes diagnosed by polysomnography is between 58% and 86% and a multicentre study (sleep ahead study) showed that

86% of obese diabetics have OSA (Foster et al., 2009). The sleep heart health study showed the lowest prevalence of OSA in diabetics at 58% (Resnick et al., 2003). The difference between the above two studies was the cut off desaturation used to diagnose OSA, the sleep ahead study used a higher desaturation of 4% while the sleep heart health study used 3%. The pathophysiological mechanism that results in a high prevalence of diabetes in those with OSA is not clear, there are studies that report high levels of inflammatory cytokines in OSA and obesity such as tumour necrosis factor alpha and interleukin 6 which are known to lead to lipolysis and insulin resistance (Mantzoros et al., 1997; Vgontjas et al., 1997).

There are several population-based studies that have looked at the relationship between diabetes and OSA. Most of these are cross sectional and they differ mainly in sample size, population groups used and the method used to diagnose OSA. Some use snoring and observed apnoea as a surrogate marker for OSA while others use the more objective polysomnography (Tasali et al., 2008).

Early studies on the aetiological association between OSA and diabetes had non-significant findings because of the confounding effect of obesity which is common to both diseases. This was corrected by findings in large population studies.

The US nurse's health study with 68 852 female subjects with an age range of 30 to 55 years found that snoring and observed apnoea were independent risk factors for diabetes in adult females (Al-dalaimy et al., 2003). The hypothesis that snoring alone might be an independent risk factor for glucose intolerance and ultimately diabetes independent of obesity was confirmed in a Korean study with 2719 non diabetic men with a normal BMI at baseline which found a significant association between snoring and increased incidence of diabetes (Shin et al., 2005). A Swedish population based

prospective study of 2668 males aged between 30 to 69 years showed that self-reported habitual snoring was associated with a higher risk of diabetes (Elmasry et al., 2000).

There are polysomnogram based population studies that shows a strong independent association between OSA and diabetes. In these studies the metabolic parameters of insulin resistance are monitored together with the apnoea-hypopnea index (AHI) and oxygen desaturation. In a study of 116 hypertensive men a high AHI was independently linked to increased insulin resistance (Elmasry et al., 2001). A cross sectional study with 1233 participants found that increased AHI was independently associated with new incidents of diabetes

The challenge with large population studies looking at OSA and diabetes is the control of confounding factors and objective measurement of variables. Studies based on self-reported snoring lack the diagnostic authority of a polysomnogram and those population studies using polysomnograms may have had subjects who under reported alcohol usage which affects sleep, Other studies did not have a baseline oral glucose tolerance test which is the gold standard for excluding diabetes at baseline. Most of the American studies did not highlight the ethnicity of the participants which is a problem as it is well known that the incidence and prevalence of diabetes is higher in people of African origin than Caucasians. There are no studies from the African subcontinent and it is not clear if the findings can be extrapolated to people from the poor and developing world.

1.5.2.2 Laboratory studies on obstructive sleep apnoea and diabetes

Compared to the population cohorts most of the laboratory-based studies controlled for confounders and some studies had normal subjects as control groups to

eliminate the BMI factor (Tasali et al.,2008). A laboratory study by Vgontzas et al looked at three related hypotheses: (1) the effect of OSA on diabetogenic inflammatory markers, (2) the type of adiposity related to OSA (central vs diffuse), (3) the risk of developing diabetes in patients with OSA. Obese middle-aged men with apnoea were matched with obese non apnoeic men and also against lean men with apnoea. The men with apnoea (both lean and obese) had an increased level of diabetogenic inflammatory markers and a high degree of insulin resistance. Obese men with OSA also had significantly higher amounts of visceral fat compared to obese men without OSA (Vgontzas et al.,2000). The mechanisms that lead to insulin resistance in OSA are multiple and include; reduced and fragmented sleep time, increased sympathetic nervous system output, increased diabetogenic inflammatory markers, hypoxia with dysregulation of the hypothalamic-pituitary axis and endothelial dysfunction (Tasali et al., 2008; Vgontzas et al., 2000).

Subjects with OSA and diabetes share anthropometric characteristics and metabolic risk factors and it is estimated that 23 % of patients with established diabetes have OSA (West et al., 2006). Since OSA has already been demonstrated to be a novel risk factor for diabetes it is crucial clinically to know what effect OSA treatment has on glycaemic control in diabetics with OSA. The treatment of OSA with CPAP improves the apnoea and has been shown to decrease cardiovascular outcomes, but it is not yet clear if CPAP therapy will improve glycaemic control in diabetes. There are several studies done and they show conflicting results. Brook et al showed improvement in insulin sensitivity and glucose intolerance in a study with 10 morbidly obese patients with diabetes after 4 months of CPAP therapy (Brooks et al., 1994). Another study observed a significant improvement in HBA1C levels in diabetics with OSA after 3 months of treatment with CPAP, in this study the level of HBA1C

correlated with the duration of CPAP therapy (Babu et al., 2005). A randomized controlled study of 86 subjects assigned to 3 months of CPAP and another 3 months of sham CPAP showed a significant HBA1C improvement in the CPAP group compared to the sham CPAP group (Sharma et al., 2011). There are also multiple studies that show no glycaemic improvement with CPAP treatment in diabetes with OSA. A systemic review and meta-analysis by Feng et al which included six studies showed that CPAP in diabetics with OSA does not affect HBA1C (Feng et al. ,2015). The close association between OSA and diabetes makes the screening of both conditions important in subjects who are at risk and more studies are needed to study the real effect of CPAP on glycaemic control.

1.5.3 Restless leg syndrome and diabetes

The prevalence of RLS is estimated to be around 17% to 29 % in diabetic patients compared to 7% in the general non-diabetic population (Skomro et al., 2001). A study with 124 type 2 diabetics by Merlino et al was the first study to show a significant association between RLS and diabetes. In patients with diabetes RLS was strongly associated with peripheral neuropathy and often diagnosed later than in the diabetic free general population (Merlino et al., 2007). Another cross-sectional study with 100 diabetic patients below the age of 70 showed a high prevalence of RLS (27%) in diabetics, which was also associated with the presence of diabetic polyneuropathy (Lopes et al., 2005).

1.5.4 Excessive daytime sleepiness and diabetes

Excessive daytime sleepiness is a well-recognized symptom of OSA and other sleep disorders. Recent data suggest that the association of EDS and OSA is weak and that EDS may represent an independent sleep related entity with its own risk factors

and metabolic complications (Young et al., 1993). A high prevalence of EDS in overweight patients without OSA has been shown (Vgontzas et al., 1998). A population based Australian study with nearly 2000 participants looked at the relationship between EDS and the metabolic syndrome using the Epworth Sleepiness Scale. In women there was a significant association between EDS and the metabolic syndrome (OR=1.9, 95% CI:1.16-3.09), which was driven by the degree of adiposity, while in men the relationship was driven by advanced age (Hayley et al., 2015). In patients with diabetes EDS adversely affects glycaemic control by inhibiting patients from participating in activities that help improve their blood sugar. EDS is also associated with increased diabetic and non-diabetic mortality, and morbidity such as an increased number of hypoglycaemic attacks. Diabetics also have an increased risk of dozing during motor vehicle driving that may further increase non-diabetic mortality (Inkster et al., 2013).

1.6 Sleep disorders and glycaemic control in diabetes

Emerging evidence shows that the association between diabetes and sleep disorders is a vicious circle whereby sleep disturbances are a risk factor for developing diabetes, and that in established disease poor sleep leads to suboptimal glycaemic control which results in increased target organ damage (Barone et al., 2011). In turn diabetes and poor glycaemic control are associated with an increased incidence of sleep disorders. This relationship is not linear and simple and there is conflicting evidence with some studies showing a positive association between sleep disorders and poor glycaemic control and others failing to prove the link in patients with established diabetes. However, sleep restriction and sleep disorders may be an important modifiable variable that may be manipulated to improve glycaemic control in diabetic patients (Ohkuma et al., 2013).

Cho et al carried out the largest study investigating the prevalence and effect of various sleep complaints in diabetics using validated sleep questionnaires and assessing the effect of sleep complaints on glycaemic control. In their relatively normal weight population there was a high prevalence of sleep disorders in diabetics, with no statistically significant effect on glycaemic control (Cho et al., 2014).

There are limited data on the prevalence of sleep disturbances in patients with diabetes and their effect on glycaemic control from South Africa. There is also a lack of facilities to diagnose sleep disorders or training for doctors and other health care providers in this field. The aim of this study was to survey the prevalence of subjective sleep complaints among adult type 2 diabetics in a South African academic hospital as well as the relationship between sleep disturbances and overall glycaemic control.

Patients with diabetes at South African public hospitals have unique features such as high levels of obesity and hypertension, a lack of diagnosis of sleep disorders and perceived poor glycaemic control. It is currently unknown whether the presence of sleep disorders contributes to a generally poor level of glycaemic control. Highlighting the presence and prevalence of sleep disorders in this population may indicate a reason to introduce training on sleep disorders in the medical curriculum as well as providing a different treatment strategy for managing the diabetic population. Introducing management of obstructive sleep apnea may provide a better way to treat diabetes and hypertension

CHAPTER 2: METHODS

2.1 Aim and objectives of the study

1. To describe the prevalence of subjective sleep complaints in people with type 2 diabetes mellitus attending a diabetic clinic at an academic hospital in South Africa.
2. To investigate the association between subjective sleep complaints and glycaemic control.
3. To compare subjects with sleep disorders to those with no evidence of sleep disturbance.

2.2 Hypothesis

Sleep disorders are a novel risk factor for the development of diabetes and thus diabetic patients will have high prevalence of sleep disorders which are associated with poor glycaemic control.

2.3. Rationale

Evidence from the literature suggests that sleep disorders are a risk factor for diabetes and probably lead to poor glycaemic control in those who are already diabetic. There is lack of data in South Africa on this association.

2.4. Patients

The participants were drawn from a diabetic clinic of an academic hospital in Johannesburg, South Africa. The inclusion criteria were adults with type 2 diabetes with a known recent HBA1C level taken in the three months before the interview. The exclusion criteria were those who have double amputations of the lower limbs,

and subjects with bilateral complete blindness, or other severe complications of diabetes that would have independently affected the sleep quantity and quality.

2.5 Data collection

The participants were drawn from a diabetic clinic at Chris Hani Baragwanath academic hospital in Soweto, South Africa. Patients waiting in line to be seen by the doctor at the Diabetes OPD clinic were approached by the researcher and asked to participate in the study. Participants were interviewed by the researcher and those who consented were given a set of validated sleep questionnaires in English to answer. The researcher translated for patients who were not clear on the language used in the questionnaire. Demographic data (including age, gender, race,) and anthropometric measurements including height, weight and neck circumference were obtained from the patients and or the clinic card. Subjective sleep complaints were assessed with the following validated sleep questionnaires:

2.5.1 Leeds sleep evaluation questionnaire (1-10 on Appendix A) (LESQ)

10 questions which assess four components of sleep using a 100mm visual analogue scale (VAS).

(i) Getting to sleep (GTS): which measures the difficulty in falling asleep calculated from the mean of the first three questions.

(ii) Quality of sleep (QOS): assessing the quality of sleep, from the mean of questions 4 and 5

(iii) Awakening from sleep (AFS): measures the difficulty of getting up from sleep, it is calculated from the mean of questions6 and 7

(iv) Behaviour following sleep (BFW): looks at post sleep behaviour and is calculated from the mean of questions 8, 9 and 10.

To score the LSEQ the subject puts a vertical line on the 100 mm VAS within the two extremes of 0 to 100.If they put their vertical line in the middle it is a score of 50 mm which represent no change in their sleep, a change of 10mm above 50 is considered clinically significant for each question. The LSEQ was cross culturally validated in 2003 (Tarrasch et al., 2003).

2.5.2 STOP BANG Questionnaire (11-17 on appendix a)

This is a validated sleep questionnaire for screening of obstructive sleep apnea. It is made up of two parts, namely the STOP (snoring, tiredness, witnessed obstruction/choking and high blood pressure) part which assess the subjective report of obstructive sleep and the presence of hypertension. The second part is the demographic anthropometric BANG (BMI>35kg/m2, age>50 years, neck circumference> 43 cm, male gender) part. Each item is assigned one point making a maximum of 8. A score of 3 and above indicates an increased risk of OSA, a score of 5 and above puts a subject at high risk of OSA (Gafsou et al., 2010).

2.5.3 Insomnia Severity index (18-22 on appendix a)

This is a validated, subjective, self-reported instrument used to measure the patient perception of his/her insomnia and consists of 7 items

(1) Inability to fall asleep (initial insomnia)
(2) Difficulty to maintain sleep (middle insomnia)
(3) Waking up too early (terminal insomnia)
(4) The last four items measure the noticeability of impairment due to insomnia, and the interference with daily functioning plus level of distress caused by insomnia.

Each item is measured from 0 to 7 with higher scores representing increasing levels of insomnia. A score of 0-7 is clinically insignificant insomnia, 8-14 is subthreshold, 15-21 represents clinically significant moderate insomnia and a score of 22-28 is considered clinically significant severe insomnia (Bastien et al.,2001).

2.5.4 Restless Leg Syndrome questions (23 on appendix a)

The questions for screening and diagnosing RLS are based on the 5-point criteria designed by the International Restless Leg Syndrome study Group, and consists of 4 yes or no questions, RLS can only be diagnosed when all four are answered yes (Allen et al., 2003).

2.5.5 Epworth Sleepiness Scale (24 on appendix a)

The ESS is a validated tool used to determine the average level of excessive daytime somnolence over the past month. It measures retrospective self-reports of daytime dozing in eight different soporific situations. Each of the eight situations are assessed on a four-point scale from 0 to 3. A score of above 10 shows clinically significant excessive daytime sleepiness (Johns., 1992)

2.5.6 Other data collecting methods

All 150 subjects were seen in the consulting room of the diabetic clinic during their normal follow up visits. The latest HBA1C performed on site using a certified machine were obtained from the patients file, only HBA1C taken in the last three months or less were accepted.

2.5.7. Definition of other variables

Obesity: the WHO classification of obesity using body mass index (BMI) was used as indicated in table 2.1

Table 2.1: WHO BMI Distribution

Class	BMI
Underweight	<18.5 kg/m2
Normal BMI	18.5- 24.9 kg/m2
Overweight	25- 29.9kg/m2
Obese class 1	30 -34.9 kg/m2
Obese class 2	35 -39.9 kg/m2
Obese class 3	>= 40kg/m2

2.6 Glycated haemoglobin (HBA1C) measurement

HBA1C used were measured using a Siemens DCA vantage analyser which is a point of care cartridge-based analyser manufactured in Tarrytown New York USA.

The DCA has a 2.3% coefficient of variation with a HBA1C range of 2.5 to 14% (Whitley et al., 2015)

2.7 Data analysis

Data was captured on a Microsoft excel spread sheet and transferred to a graph-pad inStat (version 3) for statistical analysis. Means and standard deviations or medians and interquartile ranges were used to describe numerical data and numbers and percentages for categorical data, All descriptive data from the questionnaires was treated as non-parametric and thus Mann-Whitney tests were used for comparisons. Basic demographic data such as age, BMI neck circumference and HbA1C were normally distributed and unpaired t-tests were used to compare these variables. A Fishers exact test was used to compare proportions between two groups. In all cases a P value of less than 0.05 was considered to be statistically significant

CHAPTER 3. RESULTS

3.1 Patients demographics

The demographics of the participants are shown in table 3.1 and table 3.2, 120(80%) of the 150 patients were over the age of 50 years, with a mean age of 60.1 years, and a range of 33 to 91 years. The majority 102(68%) of the patients were obese with a mean BMI of 33kg/m² and range of 16.8-53kg/m². The mean (SD) neck circumference was 38.2(3.5), range (25- 49). Males had a higher mean (SD)neck circumference of 40.9 cm (3.5) compared to females 37.3 cm(3.1) with p value of <0.0001(Mann Whitney)

Table 3.1 Demographic and anthropometric characteristics

Variables	Results (no(%) or mean (SD)
Total no: of patients	**150**
Female	**110(73.3)**
Male	**40(26.7)**
Blacks	**140(93.3)**
Coloureds	**6(4.0)**
Indians	**4(2.7)**
AGE (years)	**60.1(11.3)**
BMI (kg.m²)	**33(7.0)**
Underweight	**2(1.3)**
Normal BMI	**16(10.7)**
Overweight	**30(20.0)**
Obese class 1	**49(32.7)**
Obese class 2	**34(22.7)**
Obese class 3	**19(12.6)**
Neck circumference (cm)	**38.2(3.5)**
Hba1c (%)	**8.7(2.3)**

Table 3.2 Anthropometric differences between males and females.

Variable	Female(n=110) N (%)	Male(n= 40) N(%)	P values
Age	**59(11.9)**	**60.2(11.1)**	**0.7321**
BMI	**30.6(5.3)**	**33.9(7.3)**	**0.0120***
A. Normal weight	**12(10.9)**	**6(15.0)**	**0.5710**
B. Overweight	**19(17.3)**	**11(27.5)**	**0.1734**
C. Obese class 1	**35(31.8)**	**14(35)**	**0.6994**
D. Obese class 2	**26(23.6)**	**8(20.0)**	**0.8257**
E. Obese class 3	**18(16.4)**	**1(2.5)**	**0.0253**
Neck circumference(cm)	**40.9(3.5)**	**37(3.1)**	**<0.0001***
Hba1c	**8.1(1.9)**	**8.89(2.3)**	**0.0969**

3.2. The prevalence of different sleep disorders

3.2.1 Sleep difficulties through different stages of sleep

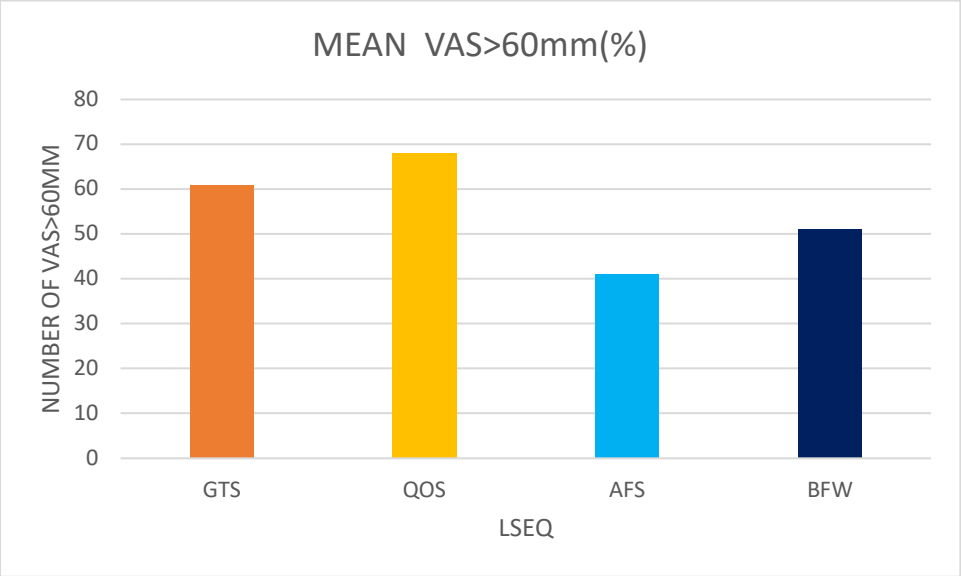
The LSEQ was used to assess difficulties with different stages of sleep, the mean scores are presented in table 3.3 and the higher scores presented in figure 3.1. In this study 61(40.6%) of the patients had difficulty getting to sleep (GTS), with VAS scores (>60mm), with a median GTS of 54.2 mm. Slightly less than half (44.6%) of the patients reported poor quality of sleep (QOS), with a median QOS of 54.3mm. Only 41(27.3%) reported difficulty waking up from sleep (AFS) with a mean VAS of 29.0. About 63(42%) of the patients had abnormal behaviour following wakening (BFW), with mean BFW VAS score of 52.5 mm.

Table 3.3 Leeds Sleep Evaluation Questionnaire group scores

LSEQ ITEM	VAS(mm)
GTS(average)	54.2 (35.7-70.0)
GTS (easy/harder)	57.0 (19.0-75.0)
GTS (quick/slow)	57.0 (20.3-77.0)
GTS (felt more/less drowsy)	65.0 (36.3-77.0)
QOS(average)	54.3 (42.5-75.0)
QOS(restless/calm)	54.5 (24.0-75.0)
QOS(more wakeful periods/less)	69.5 (46.5-81.0)
AFS(average)	29.0 (19.5-66)
AFS(more difficult/less)	22.5 (16.0-65.0)
AFS(longer to wakeup/shorter)	30.0 (19.0-70.0)
BFW(average)	52.5 (27.4-70.7)
BFW (more tired when waking up/less)	59.5 (34.3-86.0)
BFW(more tired now/less)	50.5(29.0-77.0)
BFW(disrupted balanced/less disrupted)	50.5 (30.0-68.0)

GTS-getting to sleep; QOS- quality of sleep; AFS-awakening from sleep; BFW-behaviour following waking. Values given as Median (IQR)

Figure 3.1: LSEQ Scores



3.2.2 Obstructive sleep apnoea symptoms

From the STOP BANG Questionnaire 121(80.6%) of the participants were at risk of having OSA, with STOP BANG score of 3 and above. The mean (SD) score for STOP BANG for all the patients was 4.27 (1.59). Only 48(32%) patients had a STOP BANG score of 5 and above indicating a high possibility of severe OSA. The majority 73(48%) of the subjects had a moderate risk for OSA and 29(19%) had a normal STOP BANG score (Table 3.4).

On the individual items of the STOP BANG - 84(56%) of the patients complained of snoring and 107(71%) woke up tired, while 64(42.6%) reported having a witnessed apnoeic episode at night during sleep (table 3.4). Most of the patients 112(97.3%) out of the 115 at risk of OSA had hypertension.

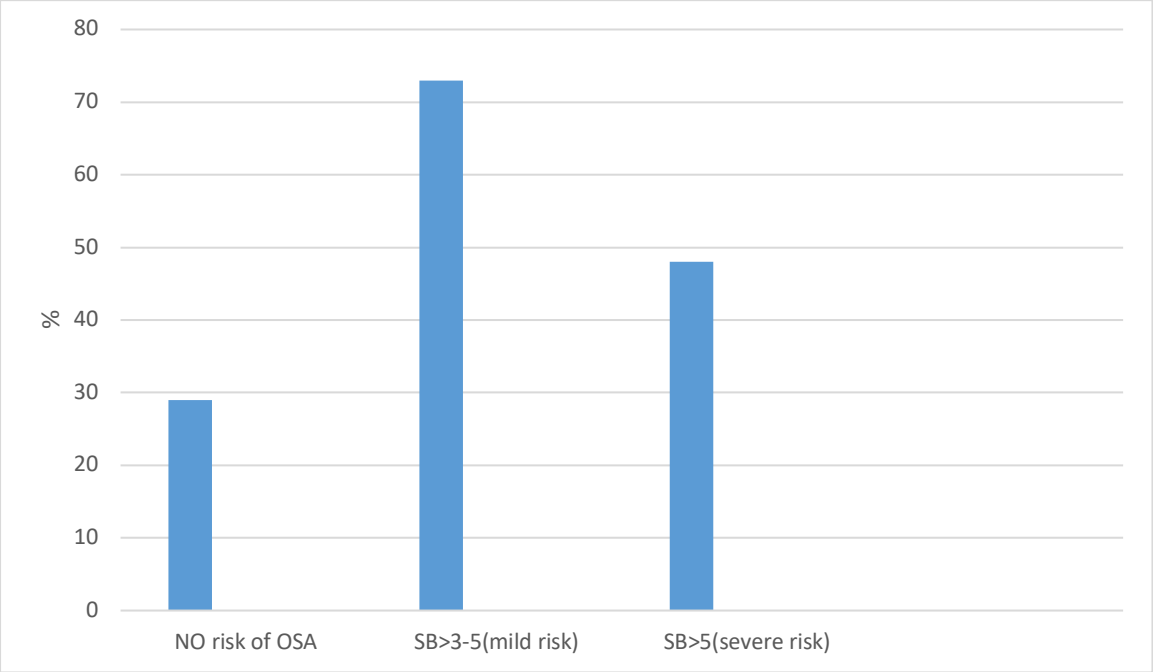
When comparing the prevalence of OSA in different BMI categories the risk of severe OSA (as graded by STOP BANG score) increased with increasing obesity. Of the 19 patients with morbid obesity 95% of them were at risk for moderate to severe OSA, and only 1(5%) had no risk for OSA (Figure 3.2). A total of 83(55.3%) patients had obesity class 1 and 2 with a mean BMI (SD) of 34.5 (7.04), 45(54.2%) of the 83 were at risk of moderate OSA and 24(28.9%) had severe risk for OSA and the remaining 14(16.9%) had no risk for OSA (Table 3.4.)

Table3.4 STOP BANG score with BMI variations

Variable	Underweight	Normal BMI	Overweight	Obese	Morbid obesity
Number	**2**	**16**	**30**	**83**	**19**
Age (years) mean(SD)	**51(11.3)**	**60.1(11.5)**	**59.5(10.9)**	**60.7(11.7)**	**59.4(10.2)**
Gender(f/m) n	**1/1**	**11/5**	**19/11**	**61/22**	**18/1**
BMI mean (SD)	**17.5(0.97)**	**22.3(1.6)**	**27.8(1.3)**	**34.5(7.04)**	**45.5(3.95)**
Neck circumference (CM) mean(SD)	**38**	**33.4(2.1)**	**38.6(3.9)**	**38.9(3.5)**	**38.9(3.1)**
Risk of OSA n (%)					
(1)Low(SBS<3) (2)Moderate(SBS 3-4) (3)Severe(SBS 5-8)	**2(10)** **0** **0**	**6(37.5)** **7(43.8)** **3(18.8)**	**6(20.0)** **14(46.7)** **10(33.3)**	**14(16.9)** **45(54.2)** **24(28.9)**	**1(5.3)** **7(36.8)** **11(57.9)**
Positive response to STOP BANG (n)					
(1) Snoring	**0**	**4**	**14**	**52**	**14**
(2) Tired	**1**	**9**	**21**	**62**	**14**
(3) Apnoea	**0**	**5**	**8**	**39**	**12**
(4) High BP	**1**	**10**	**25**	**75**	**19**
(5) BMI (>35)	**0**	**0**	**0**	**34**	**19**
(6) Age(>50)	**1**	**14**	**24**	**67**	**16**
(7) Neck(>40cm)	**0**	**0**	**8**	**26**	**7**
(8) Gender(male)	**1**	**5**	**11**	**22**	**1**

SBS-STOP BANG Score

Figure 3.2: Prevalence of OSA



SB-STOP BANG, OSA-obstructive sleep apnoea

3.2.3 Insomnia

Out of a total of 150 patients 60(40.0%) had clinically significant insomnia with ISI scores of 15 and above, and 48(80%) of the 60 patients had moderate insomnia with an ISI score of 15-21. The remaining 12(20.0%) out of the 60 had severe insomnia with ISI scores of 22-28. A small proportion (22.7%) patients had subthreshold insomnia which is clinically insignificant. The remaining 56(37.3%) of the patients had no insomnia. Figure 3.3 shows the overall prevalence while figure 3.4 to 3.6 shows the prevalence of different types of insomnia according to the stage of sleep at which the insomnia occurs. In total 87(58.0%) of the patients had initial insomnia of variable severity with difficulty initiating sleep, 116(77.3%) of the patients had difficulty maintaining sleep and reported middle insomnia of variable severity and 105(70%) patients had terminal insomnia complaining of early awakenings of different severity. Satisfaction with sleep was measured with a 5-point scale of 0 to 4,

with 0 representing being very satisfied with sleep and 4 being very dissatisfied with sleep, the median (IQR) ISI score for satisfaction was 2(1-3). A minority (37.3%) of the patients reported that their insomnia or sleep problem greatly interfered with their daytime daily functioning and a similar proportion (31.3%) of the patients reported that it was noticeable to other people that they did not have enough sleep. Only 38(25.3%) of the patients were not worried with their sleep and 55(36.7%) were significantly worried about their sleep problems with a median (IQR) score for distress about their sleep at 2 (0.25-3).

Figure 3.3 Prevalence of insomnia

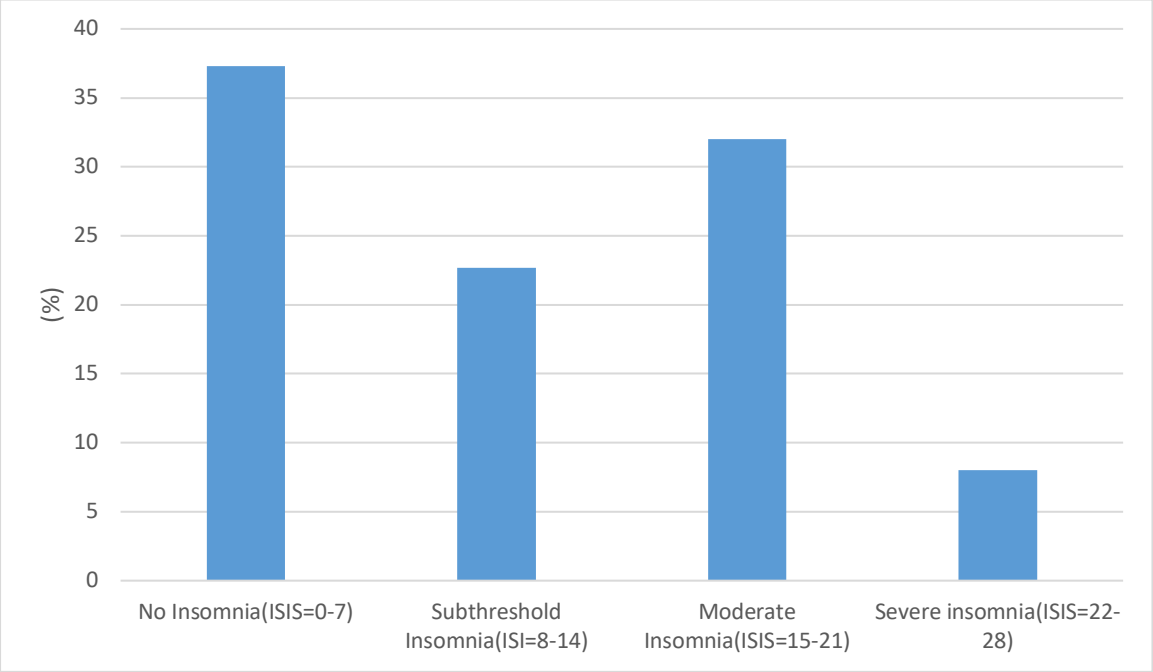


Figure 3.4: Initial insomnia

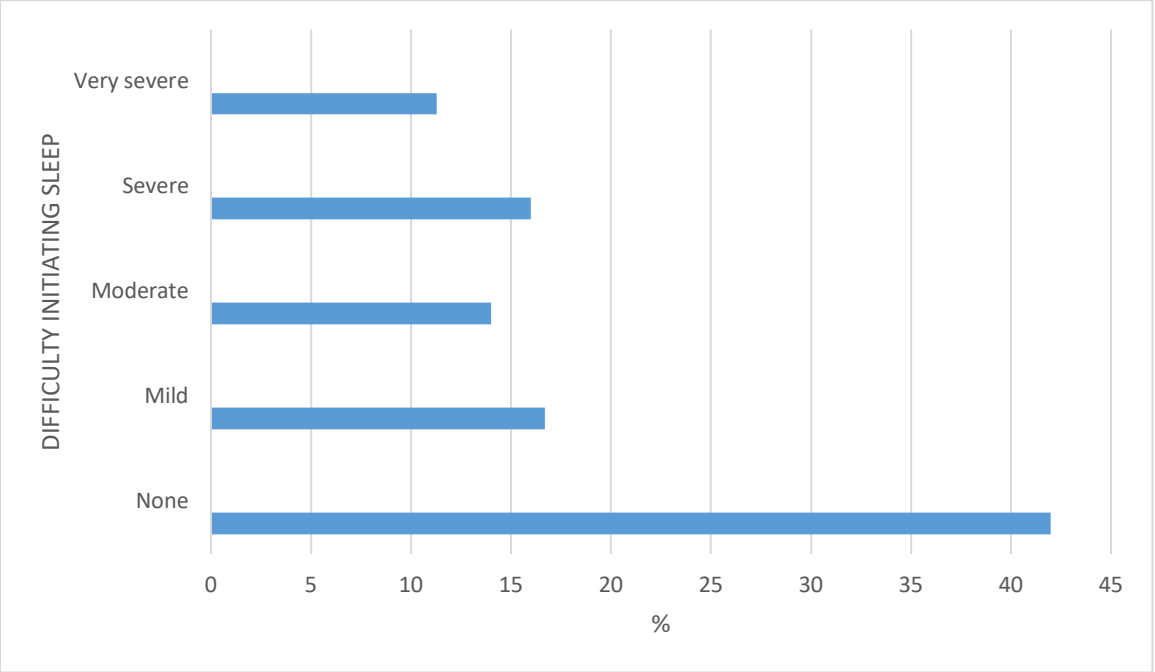


Figure 3.5: Middle insomnia

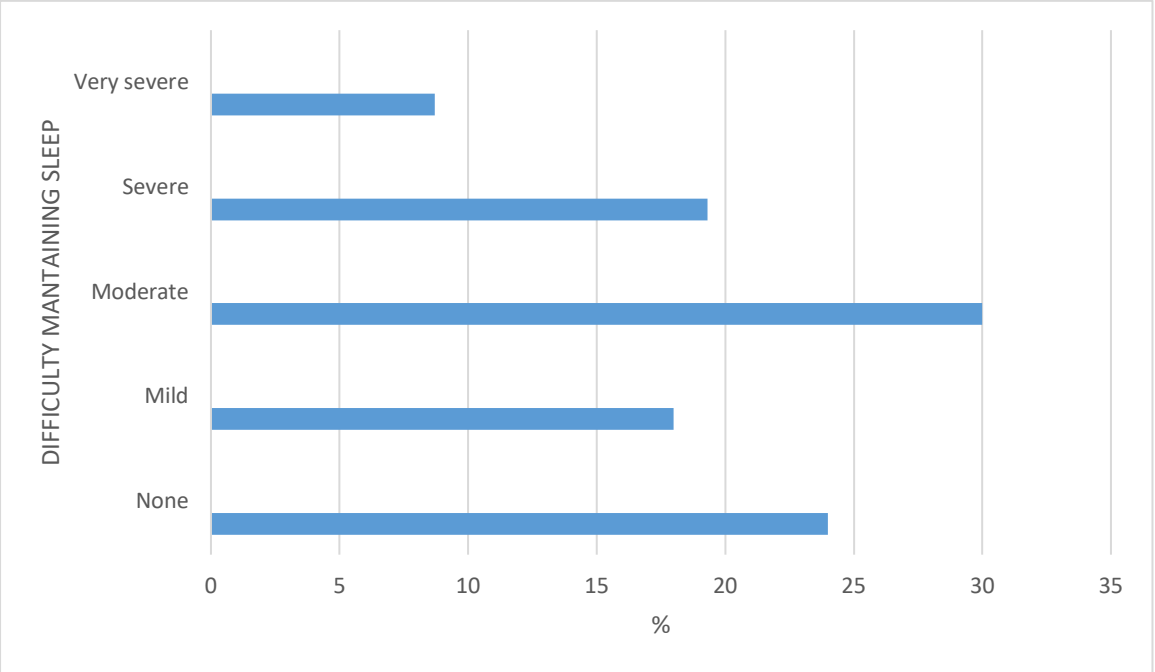
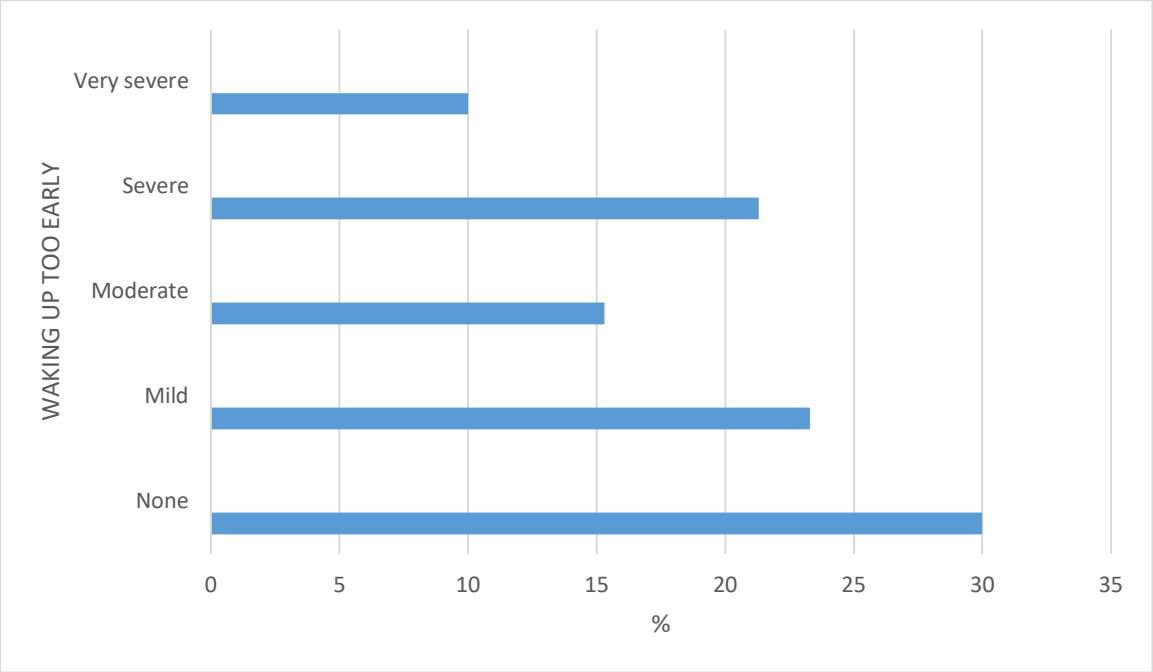


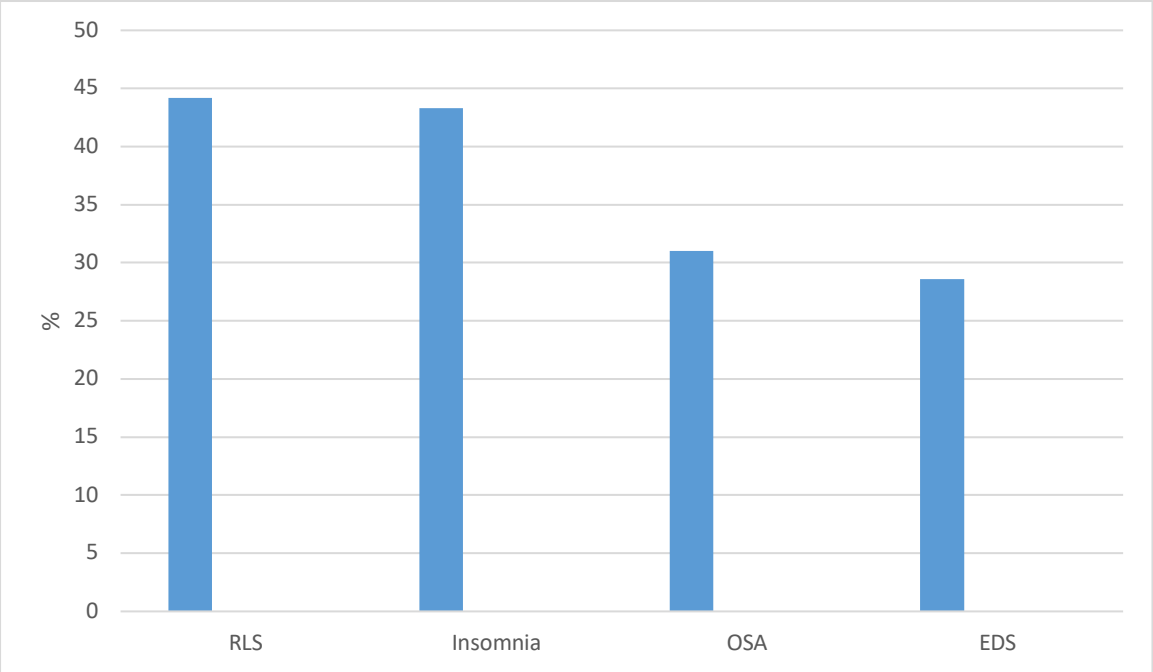
Figure 3.6: Terminal insomnia



3.2.4 Restless leg syndrome symptoms

The prevalence of RLS was 43(29%), and 107(71%) of the patients did not meet the criteria for RLS. The majority were female 39(90.7%). A total of 19(44%) of the patients with restless leg syndrome were on tricyclic antidepressants. This percentage is higher than the usage in the general population and groups with other already mentioned sleep disorders, see figure 3.7

Figure 3.7: Hypnotic/ antidepressant usage



3.2.5 Excessive daytime sleepiness

There were 63(42.0%) patients who had ESS scores of 10 and above which is diagnostic for EDS. The median (IQR) ESS score for the entire group was 9 (5-13).. There was a gender difference in the prevalence of EDS with 45% of the female having significant EDS (ESS>10) compared to only 32% of the males. The association of EDS with other sleep disorders indicated that 76% of the patients with EDS had OSA symptoms with STOP BANG scores of 3 and above followed by insomnia with 52% of the patients having significant ISI scores. Only 36.5% of the patients with RLS had excessive daytime sleepiness. It is worth noting that this group with EDS had the lowest usage of tricyclic antidepressant and other hypnotics that may affect sleep and cause EDS.

3.3 Comparison between Glycaemic controlled and uncontrolled

Participants were divided into controlled and non-controlled groups using the HBA1C level according to the SEMDA guidelines. A HBA1C of 7 and below was regarded as being controlled, while a HBA1C above 7 was considered to indicate uncontrolled diabetes.

3.3.1 HBA1C controlled group vs the uncontrolled group

There were 37(24.7%) patients with a HBA1C of 7 and less who constituted the controlled group with a mean (SD) HBA1C of 6.3(0.5). The majority of the patients had uncontrolled diabetes with an above target HBA1C, there were 113(75.3%) patients in the uncontrolled group with a mean (SD) HBA1C of 9.5(2.1). There were no significant differences in the demographics between the controlled and the uncontrolled groups (table 3.5) apart from the HBA1C which was to be expected.

Table 3.5: Demographic comparison between the controlled and uncontrolled

Variable	Controlled	Uncontrolled	P value
Age (Mean (SD))	60.2(13.7)	60.1(10.5)	0.9429
Gender (female %)	73	72	1.00
BMI (Mean(SD))	33.7 (7.3)	32.8 (6.9)	0.541
Neck circum (cm) median (range)	38 (29-48)	38 (31-49)	0.658
HbA1C median	6.3(5-7)	8.8(7.1-14)	<0.0001
On tryptanol N(%)	13	28	0.2876

3.3.2 The Leeds sleep evaluation questionnaire

The median (IQR) of the scores on each component of the LSEQ are shown in table 3.6. There was no differences in the scores between the two groups when using cut-off scores for significant symptoms (Figure 3.8)

Table 3.6 LSEQ controlled vs uncontrolled group

LSEQ	Controlled	Uncontrolled	P value
GTS (median, IQR)	46.7(34.7-67.5)	56.7(35.7-70.3)	0.3276
QOS(median, IQR)	52.0(46.5-73.9)	54.5(4.5-76.0)	0.8977
AFS(median, IQR)	26.5(20.5-68.5)	30.0(18.5-63.6)	0.7619
BFS(median, IQR)	51.0(36.3-71.9)	52.0(38.3-69.8)	0.7987
GTS >60 n (%)	12 (32.4)	49(43.4)	0.2552
QOS >60 n (%)	16(43.2)	52(46.0)	0.8500
AFS >60 n (%)	11(29.7)	30(26.5)	0.8319
BFS >60 n (%)	16 (43.2)	47(41.6)	1.00

3.3.3: STOP BANG questionnaire

There was no significant difference in prevalence of OSA symptoms between the controlled and the uncontrolled group. The controlled group did not have a significantly different score on the STOPBANG compared to the uncontrolled group (Table 3.7).

Table 3.7 STOP BANG controlled vs uncontrolled

STOP-BANG	controlled	Uncontrolled	P value
Total median(Range)	4(3-5)	3(2-5)	0.4981
>3 n (%)	28(76.0)	81(71.7)	0.6778
>5 n (%)	11(29.7)	30(26.5)	0.8319

3.3.4 Insomnia severity index controlled versus uncontrolled

The most important finding in this study is that insomnia was significantly linked to poor glycaemic control when comparing the two groups. The median ISI score was significantly lower at 8(range:0-23) for the controlled group compared to 14(range:0-28) for the uncontrolled group (P=0.008 Mann-Whitney). In the controlled group 8(21.6%) of the patients had clinically significant insomnia with an ISI of 15 and above compared to the uncontrolled group which had more than twice that rate with 46% of the patients reporting severe insomnia (P=0.014 fisher's exact).

Table 3.8 ISI controlled vs uncontrolled

ISI	controlled	Uncontrolled	P value
Total median (range)	8(3-14)	14(6-19)	0.0080
>15 n	8(21.6)	52(46.0)	0.0114

3.3.5 Restless leg syndrome

There was no difference in the prevalence of RLS between the controlled group 7(18.9%) vs the uncontrolled group 37(31.8%) (P=0.147 fisher's exact test).

3.3.6 Excessive daytime sleepiness

The prevalence of EDS was the same in the uncontrolled and controlled group. Both groups had a median (IQR) ESS score of 9 (5-13) for the uncontrolled and a median (IQR) of 9 (5-11) for the controlled group (P=0.43 Mann-Whitney). In the controlled group 12(32.4%) of the patients had significant EDS with an ESS score of 10 and

above compared to a 53(45.1%) prevalence in the uncontrolled group (P=0.186, fisher exact test).

3.4 OSA group vs group not at risk of OSA (demographics)

There was no age difference between participants at risk for OSA (STOP BANG≥3) and those at low risk (P= 0.91 unpaired t-test). The participants with a higher risk for OSA were significantly more likely to be male (P= 0.026 fisher exact) and obese with a high BMI (P=0.0001 unpaired t-test). The group with a high risk for OSA had higher ESS scores with increased excessive daytime sleepiness however there was no significant difference with the group at low risk for OSA (Table 3.9).

Table 3.9 OSA group vs group without OSA

Variable	STOP BANG ≥3	STOP BANG <3	P value
Age	60.0 (10.5)	60.3 (13.3)	0.9153
Gender	73/34 (68.2/31.8)	37/6 (86.0/14.0)	0.0262
BMI	35.2 (6.5)	27.8 (5.3)	<0.0001
HBA1C	8.76 (2.34)	8.56(2.21)	0.6354
ESS	9.5 (5.19)	7.7 (5.14)	0.0570
Control/uncontrolled	19/55 (25.7/74.3)	18/58 (23.7/76.3)	0.8506

All values given as Mean (SD) and n (%)

CHAPTER 4 DISCUSSION

Diabetes type 2 is a global pandemic which results in significant morbidity and mortality in both the developing and developed world. There are studies from different parts of the world that link sleep disorders with diabetes (Cuppucio et al., 2010).

This study had 150 adult type 2 diabetics from Soweto South Africa. Most of the participants were middle aged, African and female. The majority were obese with a high BMI. Insomnia was significantly associated with poor glycaemic control. The prevalence of other sleep disorders was higher than the reported general non-diabetic population but not significantly linked to poor glycaemic control. A significant number of participants had poor quality of sleep and two thirds of those on tricyclic antidepressant for diabetic peripheral neuropathy had restless legs syndrome. Those at higher risk of OSA were significantly more likely to be men and obese.

In this sample of patients from a diabetic clinic there was a high prevalence of sleep disorders in participants with diabetes, 40.6% of the subjects had difficulty initiating sleep which is higher than the 4.4% to 13.7% previously reported internationally in the general non diabetic population and the South African prevalence which was 18% in whites, 14.5% in South African of Indian origin and 7 % in black South Africans (Petzer.,2012), but similar to previous findings from population based studies comparing patients with diabetes to the general population (Cappucio et al., 2010; Cho et al., 2014). Our study did not show any link between initial insomnia and poor glycaemic control.

In this study 45% of the subjects reported poor quality of sleep which was higher than the general population and in keeping with previous studies that have shown poor quality of sleep among diabetics with recurrent arousals mainly due to hyperglycaemic induced nocturia and pain emanating from peripheral neuropathy (Lamond et al., 2000; Cho et al., 2014). A cross sectional study by Knutson et al in 2006 reported a poor quality of sleep in 71 % of African Americans with type 2 diabetes linked to poor glycaemic control, our study did not show this link. We did not however quantify the suspected nocturia which was responsible for the poor quality of sleep in the previous study (Knutson et al., 2006).

The majority of the participants did not have difficulty waking up from sleep, only 27.3% had difficulty awakening from sleep, and there was no difference between the controlled and uncontrolled groups. Most of the studies done on diabetes and inability to get up from sleep focus on early morning hypoglycaemia and not primarily on sleep disorders. In these studies difficulty awakening was highly associated with hypoglycaemia. Our study did not survey for symptoms of hypoglycaemia.

In our study 40% of the participants had abnormal post sleep behaviour with fatigue and early morning tiredness which was similar to findings from previous studies. Drivsholm et al reported a prevalence of early morning tiredness of about 60% in diabetics (Drivsholm et al., 2005). This study failed to show any relationship between early morning fatigue and glycaemic control, the majority of the participants who had morning tiredness and fatigue were at risk of OSA with a STOP BANG score of 4 and above, this is in keeping with findings from previous studies that have shown

that morning tiredness in diabetes is linked to sleep deprivation and that in males this is associated with OSA while Insomnia is more prevalent in females (Basoglu et al., 2017). Although sleep disorders play a role in morning tiredness in diabetics, the majority of studies already done associated this to non-sleep factors such as diabetic related glucose variability, depression, lack of physical activity and high BMI (Fritschi et al., 2010).

There was a high prevalence of OSA in our patients with 86% of the patients having a positive score for the STOP BANG questionnaire, 42% of the patients had scores suggestive of a risk for mild OSA and 44% had scores predictive of severe OSA. Pamidi et al had similar findings to this study with 86% prevalence of OSA among type 2 diabetics (Pamidi et al., 2012). This prevalence is higher than the reported 20% in the general adult population (Young et al., 2002). The International Diabetic Federation task force on epidemiology and prevention conducted a survey for sleep disorders in subjects from the sleep heart health study and found the prevalence of OSA to be around 58% among type 2 diabetics. The reason behind this difference might be the fact that our patients had a higher mean BMI of 33kg/m² compared to the previous studies. Also the method used to diagnose or screen for OSA was also different, our study used the STOP BANG questionnaire while they used overnight polysomnograms. The other likely reason is that they included only those who were at high risk for OSA, in which case our prevalence of 44% of risk for severe OSA would correlate with their finding (Resnick et al., 2003).

The aetiological association between OSA and diabetes is well known, Aronsohn et al used polysomnography in type two diabetics to objectively determine the prevalence of OSA, which was high at 77% correlating with the findings of this study. In addition to determining the prevalence of OSA, their study was the first to show that severe OSA is linked to poor glycaemic control in patients with established diabetes (Aronsohn et al., 2010). We could not establish a significant link between OSA and poor glycaemic control probably because of multiple confounding factors in our group as well as the cross-sectional nature of the study.

Looking at the demographics of those at high risk of OSA, age was not significantly linked to high risk for the OSA and this is in contrast with other studies that have shown that OSA is associated with older age which is one of the parameters measured by the STOP BANG (Enright et al.,1996; Gafsou et al., 2010). Our study showed that high risk for OSA was significantly linked to male gender and obesity which is in keeping with previous studies. Tasali et al reviewed population and laboratory based studies on OSA and diabetes and established that most studies showed a male predominance and the significant confounding effect of being overweight which is a common risk factor for both OSA and diabetes and may be independently related to both conditions (Tasali et al., 2009). This study did not show a significant association between OSA and excessive daytime sleepiness which have been previously established in other studies (Hayley et al., 2015)

The most important finding of this study is that insomnia was found to be significantly linked to poor glycaemic control. The prevalence of insomnia in this study is higher

than the prevalence in the general population which is estimated to be approximately 10-15% (Summers et al., 2006). The cause of the insomnia may be related to the diabetes. In addition to the already mentioned nocturia and peripheral neuropathy there is emerging evidence that diabetics have abnormal sleep architecture with neuroendocrine dysregulation secondary to the disruption of the normal hypothalamic pituitary axis, with heightened sympathetic output and abnormal cortisol secretion (Pallayova et al., 2010). The results from a population based Finnish study with 1804 diabetics revealed that 28% of the subjects had initial insomnia and 50% reported terminal insomnia (Keinanen-Kiukaanniemi et al., 2006). Previous large population and laboratory-based studies on insomnia and diabetes have reported a higher prevalence of insomnia in diabetics and a significant association with poor glycaemic control and insulin resistance (Cho et al., 2014; Vgontzas et al., 2010). Our findings of a significant association between insomnia and poor glycaemic control in diabetics are similar to those from the above-mentioned studies.

The high prevalence of insomnia in patients with diabetes has significant clinical implications because insomnia has already been positively identified as a risk factor for type 2 diabetes and poor glycaemic control (Cappucio et al., 2010). The laboratory studies done to investigate this link have shown that the insulin resistance can be reversed by restoring sleep (Spiegel et al 1999). Due to this finding some researchers are suggesting that insomnia should be screened and treated in diabetics as part of the overall approach to improve glycaemic control (Knutson et al., 2006).

The prevalence of RLS in our study was 29%. This finding is similar to previous studies which showed a higher prevalence of RLS in diabetics compared to the general population. Two previous studies found similar levels of 24% (Skomro et al 2001) and 27% (Lopes et al., 2005) in diabetics compared to 7% in the general population. A relationship between the prevalence of RLS and peripheral neuropathy has also been reported (Lopes et al., 2005).

The surveillance of peripheral neuropathy and its association with RLS is beyond the scope of this study however it is worth noting that the use of amitriptyline, a tricyclic-antidepressants with an off-label usage against peripheral neuropathy, was higher in this group than the groups with other sleep disorders. There was no association between RLS symptoms and poor glycaemic control in our subjects.

The relationship between RLS and peripheral neuropathy could not be established in our study because we did not screen for peripheral neuropathy. It is possible both that patients diagnosed with RLS could have peripheral neuropathy as well as the opposite that patients identified as having neuropathy may in fact have RLS. Another study to look at this link is needed.

This study showed a high prevalence of excessive daytime sleepiness with 42% of the patients having an ESS score of 10 and above. This correlated with previous studies that found that 50% of diabetics have EDS (Medeiros et al., 2013). EDS is closely linked to other sleep disorders in particular OSA and, as expected, 76% of the 63 patients with EDS had OSA with a positive STOP BANG score. EDS is

associated with increased cardiovascular and motor vehicle accidents mortality (Inkster et al., 2013) and is an early marker of an underlying sleep disorder. Recent research suggests that EDS is an independent sleep related disorder with its own pathophysiological mechanism independent from other disorders (Vgontzas et al., 1998). It is important to screen for this disorder since excessive daytime sleepiness may impede physical activities advocated for good glycaemic control and predispose diabetics to recurrent hypoglycaemic attacks (Inkster et al., 2013)

Of concern is the fact that none of the subjects in our study was on a hypnotic although more than 40% of them have clinical significant insomnia and other sleep disorders as already highlighted, population-based studies report a usage of 8.5-32% of hypnotics in diabetics (Keinanen-Kiukaanniemi et al., 2006). A proper screening program for sleep disorders and appropriate treatment in this population will be imperative in optimizing glycaemic control. It is possible that they were using amitryptaline to help them sleep.

CHAPTER 5 LIMITATIONS OF THE STUDY

This study did not screen for target organ damage especially for peripheral neuropathy which is known to cause nocturnal discomfort and affect sleep. The sleep questionnaires used in this study while validated elsewhere in Africa (LSEQ - Ethiopia) were not validated in our population and thus the diagnostic criteria for certain sleep disorders may not be accurate. There was also no control sample of subjects without diabetes with which to compare the data from the patients with diabetes. Our data is derived from self-reported information and there is a possibility of under reporting sleep symptoms especially those, such as snoring, of which the patient is often unaware. The usage of alcohol in our population was not documented and intake of alcohol can affect sleep and glycaemic control. We did not screen for voluntary sleep curtailment due to night shift and other modern nocturnal activities that leads to short sleep period. Voluntary sleep curtailment has previously been associated with diabetes.

The cross-sectional nature of the study made it difficult to assume any relationship of causality – nevertheless it is an important start indicating a high prevalence of sleep disorders in this population.

CHAPTER 6 CONCLUSION

There has never been a study to look at the prevalence of sleep disorders in the diabetic population in Johannesburg and the surrounding areas. Our participants had a high prevalence of sleep disorders similar to other diabetic populations reported elsewhere. Patients with diabetes in Soweto have difficulty getting to sleep and maintaining sleep. Our study also showed that the majority of diabetics are obese and at risk for OSA and the risk for OSA is significantly associated with male gender and being obese.

The prevalence of insomnia is high in diabetics and in our study is significantly associated with poor glycaemic control but any causative relationship is beyond the scope of this cross-sectional study. Although the prevalence of insomnia was high in our subjects the usage of hypnotics was low in this study compared to other studies and this highlights poor screening and treatment of insomnia in our diabetic population.

The prevalence of RLS was high and was associated with high usage of tricyclic antidepressant, there is a high probability that RLS may be mistaken for peripheral neuropathy and the opposite may be true. Another study is necessary to look into this relationship. There was no association between RLS and glycaemic control in this study.

EDS was associated with high risk for OSA, which correlate with studies from other geographical areas. In contrast to other studies there was no association between EDS and glycaemic control in this study with more than two thirds having sleep disordered breathing problems. Insomnia is significantly associated with poor glycaemic control.

THE FUTURE

There is a need for more objective sleep laboratory studies on diabetics in our population. The relationship between RLS and peripheral neuropathy needs further investigation. There is a need for a large population-based study on sleep and diabetes on the African population.

CHAPTER 7

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APPENDIX A

STUDY FORM NUMBER

SUBJECTIVE SLEEP COMPLAINTS AND THEIR EFFECT ON GLYCAEMIC CONTROL IN ADULT TYPE 2 DIABETICS.

DATA COLLECTION SHEET

Date of data collection: | | | | | | | | |

Demographic data

Age: | | |

Gender | M | F |

Ethnic group (self- identified)

Black	White	Coloured	Indian	Other

Weight(kg)	Height(metre)	BMI	NECK CIRCUMFERENCE(CM)	HBA1C

Medication that may affect sleep

type of psychoanaleptic	TRICYCLIC ANTIDRESSANTS	SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR	BENZODIAZEPINE	OTHERS
Name and dose				

THE VALIDATED SLEEP QUESTIONARE

For the first set of question please mark anywhere on the line which shows how you feel like this:

more difficult than usual — Easier than usual

_____

How would you describe the way you currently fall asleep in comparison to usual?

1.

More difficult Than usual — Easier than usual

_____

2.

slower than usual — More quickly Than usual

_____

3.

I feel less Sleepy than Usual — More sleepy Than usual

_____

How would you describe the quality of your sleep compared to normal sleep?

4.

More restless Than usual

Calmer than Usual

5.

With more wakeful Periods than ever

with less wakeful periods than usual

How would you describe your waking up in comparison to usual?

6.

more difficult than usual

Easier than usual

7.

Requires a period of Time longer than usual

Shorter than usual

How do you feel when you wake up?

8.

Tired

alert

How do you feel now?

9.

Tired

Alert

How would you describe your balance and co-ordination when walking after waking up?

10.

More disrupted Than usual		Less disrupted Than usual

---

11. Do you snore loudly/have you been told that you snore (louder than talking)	**Yes**	**No**
12. Do you often feel tired, fatigued, or sleepy during the daytime?	**Yes**	**No**
13. Has anyone observed you stop breathing during your Sleep?	**Yes**	**No**
14. If you don't have a bed partner have you ever woken Up gasping / choking during your sleep.	**Yes**	**no**
15. Do you have or are being treated for high blood pressure	**Yes**	**no**
16. Do you regularly (three times per week) not get enough Sleep even though you try to get enough	**Yes**	**no**
17. Do you consider yourself to have insomnia (meaning Getting too little sleep at night)	**Yes**	**no**

Please answer the following questions even if you don't think you have insomnia

18. Please rate the current (i.e. last week) <u>SEVERITY</u> of your insomnia.

		none	mild	Moderate	severe	Very severe
A	DIFFICULTY FALLING ASLEEP	0	1	2	3	4
B	DIFFICULTY STAYING ASLEEP	0	1	2	3	4
C	PROBLEM WAKING UP TOO EARLY	0	1	2	3	4

19. How SATISFIED/ DISSATISFIED are you with your current sleep pattern

Very satisfied				very dissatisfied
0	1	2	3	4

20. To what extend do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, ability to function at work/ daily chores, concentration, memory, mood)

Not interfering	A little	somewhat	much	Very much interfering
0	1	2	3	4

21. how NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life

Not at all interfering	A little	somewhat	much	Very much noticeable
0	1	2	3	4

22. How WORRIED/ DISTRESSED are you about your current sleep problem?

Not at all	A little	somewhat	much	Very much
0	1	2	3	4

23. Do you ever have an urge to move your legs usually associated with an uncomfortable sensation in the legs. If your answer is yes please answer the Following three questions

yes	no

A. Is the urge to move or uncomfortable sensation Worse in the evening when compared to the daytime.

yes	no

B. Is the urge to move relieved, even if partially, by moving around

yes	no

C. Is the urge to move worse when you are resting Or lying down

yes	no

24. How likely are you to doze off or fall asleep in the following situations after you've had your usual night 's sleep.

0 = would never doze; 1 = Slight chance of dozing; 2 = Moderate chance of dozing; 3 = High chance of dozing.

Please circle the best answer

Sitting and reading	0	1	2	3
Watching T.V.	0	1	2	3
Sitting inactive in a public place (i.e., theater)	0	1	2	3
As a car passenger for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting & talking to someone	0	1	2	3
Sitting quietly after lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3

Total

APPENDIX B

R14/49 Dr Garrison Mathole

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140711

NAME: (Principal Investigator)	Dr Garrison Mathole
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Subjective Sleep Complaints and their Effect on on Glycaemic Control in Adult Type 2 Diabetics
DATE CONSIDERED:	25/07/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Alison Bentley
APPROVED BY:	Professor Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/11/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES