ADHERENCE TO ANTIDIABETIC DRUGS AND ASSOCIATED FACTORS AMONG PATIENTS WITH DIABETES TYPE 2 IN DAR ES SALAAM, TANZANIA

By

Rwegerera, Godfrey Mutashambara (MD)

A dissertation submitted in partial fulfillment of the requirement for the degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences

October 2010

CERTIFICATION

The undersigned certifies that she has read and hereby recommends for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled: **"Adherence to antidiabetic drugs and associated factors among patients with diabetes Type 2 in Dar es Salaam, Tanzania"** in partial fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences.

SUPERVISOR'S SIGNATURE.....

Prof Janeth K. Lutale

Date.....26/11/10.....

DECLARATION AND COPYRIGHT

I, **Godfrey Mutashambara Rwegerera**, hereby declare that this dissertation is my own original work and that it has not been presented and it will not be presented in any other University for a similar or any other degree award.

Signature.....

Date 25/11/2010.....

This dissertation is copyright material protected under the Berne Convention, the Copyright Act of 1999 and other international and national enactments, in that behalf, on intellectual property. It may not be reproduced by any means, in full or in part, except for the short extracts in fair dealing; for research or private study, critical scholarly review or disclosure with an acknowledgement, without the written permission of the Directorate of Postgraduate Studies, on behalf of both the author and Muhimbili University of Health and Allied Sciences.

ACKNOWLEDGEMENT

First, and foremost, I would like to thank my supervisor, Prof Janeth K. Lutale for her valuable efforts to guide me tirelessly from proposal development until completion of my dissertation work

I thank all Members of the department of Internal Medicine, the list is very long, and they deserve special thanks for their guidance and constructive ideas during proposal formulation and completion of the research work.

I would like to acknowledge the work done by Dr Mpembeni of the department of Epidemiology and Biostatistics, MUHAS, and Dr Joel F. Malisa of National Institute of Medical Research for their professional assistance on database management and analysis of research data.

Special thanks to staff of diabetic clinic, Sister Elizabeth Likoko and Mr. Salumu N. for their great assistance in patients recruitments

Special word of thanks to the patients who willingly gave consent to participate in the study, without them, this work would never have been completed.

With great love and affection, my parents, Clement Rwegerera, and Winifrida, for the support they have given me to accomplish my goals.

DEDICATION

To Brian Godfrey, my son for always coming by the table and clicking the computer buttons during tireless moments of this write up, also my wife Liberatha for her great support to enable the completion of this work.

ABSTRACT

Introduction:

Diabetes is the chronic disease that requires long term medical attention to limit the development of complications. Low cost strategies such as lifestyle modifications, increasing physical activity and effective drug use have been shown to reduce the impact of diabetes and associated complications(1). Despite the compelling evidence about the effectiveness of medications, adherence to treatment has been recognized to be a major problem in patients with chronic illnesses. In Tanzania, no studies have been done on the extent of antidiabetic drug adherence and factors affecting drug adherence, information on this area will enhance effective interventional strategies to improve diabetes care and reduce costs associated with preventable morbidity and mortality.

Objective:

To determine extent of adherence to antidiabetic drugs and associated factors among patients with diabetes type 2 in Muhimbili National Hospital, Dar es Salaam, Tanzania

Methodology:

A descriptive cross-sectional study was conducted at the Diabetic clinic of Muhimbili National Hospital from 14th May 2009 to 31st December 2009. A structured questionnaire was used to get patient information. Additionally patient's files/folders were also used to obtain the information. Patients' adherence to antidiabetic treatment was assessed through patient self-reporting modality.

Results:

A total of 216 diabetes type 2 patients were interviewed during the study period. Out of these, 144(66.7%) were females and 72(33.3%) were males, 157(72.7%) of patients were either overweight or obese. Adherence to antidiabetic drugs was found to be 60.2% and 71.2% at one week and three months recall respectively. Good adherence to antidiabetic treatment was observed in patients who were below 40 years and those above 60 years ($p< 0.05$); also addition of extra medications for chronic conditions other than diabetes had positive impact on extent of antidiabetic drug adherence at one week analysis. Religion, education, duration of diabetes, and number of antidiabetic drugs were not significantly associated with antidiabetic

drug adherence. High cost of medication was the major reason for poor adherence accounting for 52.7% of cases. Increased number of other non-diabetic medications was significantly associated with good antidiabetic drug adherence (p=0.002). A significant proportion of patients had poor glycemic control, 145/216(67.1%) assessed by either fasting or random blood glucose measurements or 47/62(75.8%) assessed by HbA1c measurements. Good adherence to antidiabetic treatment had no significant impact on the extent of metabolic control and chronic diabetes complications.

Conclusions

Drug adherence for the previous one week was suboptimal at 60.2% vs. 71.2% at 3 months. As regards to social demographic factors, they were not associated with adherence to antidiabetic drugs.

Cost of antidiabetics, side effects of drugs were associated with poor antidiabetic drug adherence while improved glycemic control or feeling better led to stopping use of medications.

Many patients had poor glycemic control and BP levels regardless of adherence pattern

Recommendations

There is a need to design a mechanism for patients to obtain regular drug supply either for free or at subsidized cost.

Majority of patients in this study were overweight or obese, indicating the need to emphasize adherence to other non pharmacological measures such as strict dietary control and exercises.

There is a need to conduct further studies among patients with good adherence so as to find reasons for them not faring well compared to those with poor adherence.

TABLE OF CONTENTS

Contents **Page**

CERTIFICATION ii
DECLARATION AND COPYRIGHT iii
ACKNOWLEDGEMENT iv
DEDICATION v
ABSTRACT vi
TABLE OF CONTENTS viii
LIST OF TABLES ix
LIST OF ABBREVIATIONS x
INTRODUCTION AND LITERATURE REVIEW 1
Introduction 1
Drug adherence patterns among diabetic patients 3
Factors contributing to drug non adherence 4
PROBLEM STATEMENT 9
RATIONALE 10
OBJECTIVES 11
METHODOLOGY 12
Study design 12
Study setting 12
Study population 12
Inclusion criteria 12
Exclusion criteria 13
Sampling of study subjects 13
Assessment of adherence 14
Clinical evaluation 15
Blood pressure assessment 16
Laboratory assays 18
RESULTS 21
DISCUSSION 35
STUDY LIMITATIONS 42
CONCLUSIONS AND RECOMMENDATIONS 43
Conclusions 43
Recommendations 43
REFERENCES 44
Appendix 1: Questionnaire 49
Appendix 2: CONSENT FORM (English version) 54
Appendix 3: CONSENT FORM (Swahili version) 56

LIST OF TABLES

Page

Table 1. Socio-demographic characteristics of population of patients with diabetes mellitus type 2 22

Table 2 Types of antidiabetic drugs used by patients in the last three months (N = 216) 23

Table 3. Adherence to timing of drug intake and dosing (N=216) 24

Table 4. Pattern of drug adherence to antidiabetic drugs according to calculated number of days of drug use per prescribed dosages in previous one week or past three months (N=216) 25

Table 5Association between antidiabetic drug adherence and socio-demographic characteristics of patients with diabetes mellitus type 2 in the previous one week..... 27

Table 6. Reasons for non- adherence to the antidiabetic treatment..... 29

Table 7. Complications and metabolic parameters among the studied population of patients with diabetes mellitus type 2 (N=216) 31

Table 8. Association between antidiabetic drug adherence, complications and metabolic parameters in the previous one week..... 33

Table 9. Results of logistic regression..... 34

LIST OF ABBREVIATIONS

ABPI	-	Ankle Brachial Plexus Index
AIDS	-	Acquired Immunodeficiency Syndrome
BMI	-	Body Mass Index
BP	-	Blood pressure
CI	-	Confidence Interval
DBP	-	Diastolic Blood Pressure
DM	-	Diabetes Mellitus
FBG	-	Fasting Blood Glucose
GFR	-	Glomerular Filtration Rate
HbA1c	-	Glycosylated Hemoglobin
HIV	-	Human Immunodeficiency Virus
IDF	-	International Diabetes Federation
JNC	-	Joint National Committee
MNH	-	Muhimbili National Hospital
MUHAS	-	Muhimbili University of Health and Allied Sciences
OHA	-	Oral Hypoglycemic Agents
OR	-	Odds ratio
RBG	-	Random Blood Glucose
SBP	-	Systolic Blood Pressure
T2DM	-	Type 2 Diabetes Mellitus
USA	-	United States of America
WHO	-	World Health Organization
<	-	Less than
≥	-	More than or equal to

INTRODUCTION AND LITERATURE REVIEW

Introduction

Diabetes is a significant and growing health problem worldwide. It is a chronic disease that requires long-term medical attention both to limit the development of its devastating complications and to manage them when they do occur. Type 2 diabetes represents 90% of the overall burden of diabetes worldwide with approximately 150 million cases (1) .

Diabetes mellitus is also an important problem in Africa. Amos et al in 1997 projected a 2-3 fold increase in the prevalence of diabetes in the next 20 years in Sub- Saharan Africa(2), rising from 1.1% in the 1995 to 1.3% in the year 2025 with an expected 185% increase in absolute number of people with diabetes from 3 to 8 million (3)

In an earlier study done in three rural Northern areas of Tanzania in 1984, at Ndolage and Kamachumu hospitals in Kagera region and Bugando hospital in Mwanza region (An urban area), Ahren, B. et al, reported overall diabetic prevalence of 0.7%. It was then concluded that the overall prevalence of diabetes in Tanzania was rather low (4). McLarty et all in 1989 reported a prevalence of 0.9% from a population study of an urban area in Tanzania (5). In 2000 another study done in Dar es Salaam rural, Tanzania revealed an increased prevalence of six- to 10-fold within a 10-year period (6) .

The burden associated with diabetes is enormous in terms of increased morbidity and mortality and the economic strains associated with the disease. Poorly managed patients have poor quality of life, have prolonged and frequent hospital admissions. All these impact on the patients and the family members who have to take care of them. They also impact on the health care system, the government and the society as a whole.

Worldwide, 3.2 million deaths are attributed to diabetes (7) every year compared to 3.1 million (2.8-3.5 million) for AIDS (8)

In 1996, McLarty et al reported diabetes to be an important cause of adult mortality in Tanzania, reaching mortality rates comparable to those reported among diabetic patients in the USA. (7).

The adult male mortality rates associated with diabetes were 34, 30, and 15 per 100,000 per year in Dar es Salaam, Hai and Morogoro areas respectively. The corresponding

figures in women were 21, 18, and 4 per 100,000 per year, respectively. This study also showed that the occurrence of acute metabolic complications such as, diabetic ketoacidosis, infection, and stroke each accounted for approximately 30% of all diabetic deaths, which were mostly caused by preventable causes by better case-management of diabetic emergencies .(7)

Microvascular complications are highly prevalent owing to poor levels of glycemic and blood pressure control so commonly noted in Sub-Saharan Africa. (9).When absence of foot pulses was used, the prevalence of peripheral vascular disease was found to be 4-8%, but was substantially higher, to 18-28% when Doppler ultrasound examinations were performed. (10).Another study done in Tanzania among patients with type 2 diabetes in 1997 revealed a prevalence of 12.5% for lower limb vascular disease(11). Another study also conducted in Tanzania in 1980 among diabetic patients showed prevalence of peripheral neuropathy of about 32%, and the prevalence of hypertension and proteinuria were found to be 26% and 14% respectively.(12)

Diabetic nephropathy is a significant problem among patients with type 2 diabetes. A Cross sectional study done in Tanzania among 153 Type 2 diabetic patients found the prevalence of microalbuminuria to be 9.8% and that of macroalbuminuria to be 7.2%. Type 2 patients with abnormal albumin excretion rate had significantly longer diabetes duration 7.5 (0.2-24 yrs) than those with normal albumin excretion rate 3 (0-25 yrs), $p < 0.001$. (13).

An investment in diabetes care brings health gains in other disease areas such as hypertension and coronary artery diseases. Low cost strategies such as lifestyle modification, increasing physical activity and effective drug use have been shown to reduce the impact of diabetes and other associated diseases. (14)

Drug adherence patterns among diabetic patients

Management of type 2 diabetes mellitus (T2DM) starts with non pharmacological approaches like lifestyle modifications, dietary modification, and physical activity. Pharmacologic therapy is usually introduced when the initial strategies fails or are not producing adequate results in lowering the hyperglycemia.

Recently initiatiation of Metformin in all patients with T2DM at diagnosis along with appropriate lifestyle modifications as long as there are no contraindications to the use of Metformin have been introduced (15) In addition to Metformin, there are a number of pharmacologic options for the treatment of Type 2 diabetic mellitus including oral agents, injected insulin, the incretin mimetic agents, amylin analogs, and inhaled insulin. The initiation of therapy depends on the patient's needs, adherence challenges, and physiologic benefit of the agent (16). The addition of pharmacologic therapy during treatment of diabetes mellitus helps to provide needed physiologic support for insulin deficiency or for insulin resistance. The benefit of pharmacologic therapy has been clearly established in improving avoidable and costly microvascular and macrovascular outcomes of diabetes mellitus. (15, 17).

Previous studies in Mexico, Jamaica, United States of America and India which were conducted between 1999 and 2002 respectively found adherence to diabetes treatment generally to be sub-optimal ranging from 23 to 77 % (18-22) In addition, these studies have generated varied results of the factors associated with non-adherence to diabetes treatment. In another study among patients with diabetes type 2, adherence was found to range between 65% to 85% for oral agents and 60% to 80% for insulin (9). Despite compelling evidence about the effectiveness of medications, adherence to treatment has been recognized to be a major problem in patients with chronic illness(23, 24) and a large proportion of patients become non -adherent at six months from treatment initiation (23, 25).

Rates of non-adherence with any long term medication treatment vary from 17% to 60%, depending on the characteristics of the condition, the treatment, the patient, and the setting (26, 27). Of significance, non adherence is the highest when the patients are symptom -free (27).

In a study done in rural area of Virginia in United States of America where the average age of the participants was 59 years; 42% were African-American, and 61% were women. It was found that the average HbA1c level overall was 8.1%. Better metabolic control was associated with increasing age, white race (vs. African-American), and less intense drug therapy (fewer medications, no insulin). Interestingly, there was no association between diabetic control and gender, income, and continuity of care. (21). Another study comparing the effect of diabetic drug adherence on metabolic control showed a significant association, for each 10% improvement in adherence to oral antidiabetic agents, HbA1c levels were reduced by about 0.19% (21)

Factors contributing to drug non adherence

Medication taking can be challenging for the individual with diabetic mellitus because of several factors. Vermeire E et al showed factors including regimen complexity (number of medications and number of doses per day), cost and side effects to be associated with diabetic non-adherence. (28) . Patients who did not understand their drug regimens well had higher risk of non-adherence than those who understood them well.(9, 28, 29) .Other studies conducted on regimen complexity as a reason for non-adherence did not show significant association.(30, 31)

Other studies have implicated several other factors which associate with diabetic non-adherence.

Age

Drug non-adherence has been previously demonstrated with advancing age, this is due to the fact that advanced age is associated with poor/decrease cognition, increased number of drugs due to several cormobidies, and increased number of follow-up clinic attendances (14) . In a meta-analysis of the literature on medication nonadherent rates in the elderly, it was shown that 29-59% of elderly do not take medications as prescribed (32)

In a study conducted in Mulago hospital in Uganda, almost one third of respondents (31.3%) in the age group 36 to 50 years were not adhering, however overall age was not a significant factor affecting adherence (29)

Sex

In Mulago hospital, Uganda, prevalence of non-adherence among patients with diabetics was found to be 28.9%.Women had almost threefold increase in risk of non-adherence as compared to men .Results of this study further revealed sex to be significantly associated with drug non-adherence (29)

Level of education

According to the study performed in Mulago, Uganda, non-adherence to antidiabetic medication was found to be higher in patients with none or primary education(70.7%),compared to those with secondary or tertiary education(29.3%),the difference was statistically significant(29). In another study performed in Brazil, adherence to antidiabetic education improved with increase in level of education, however in this study the association was not significant(33)

Co morbidities

Patients with diabetes mellitus often use several other medications to treat or prevent DM co morbidities, and the use of this greater number of medications results in increased regimen complexity and challenges to adherence and may lead to selective adherence by patients. Several studies have reported that patients with multiple medical conditions associated with increased age such hypertension, hyperlipidemia and acute coronary syndromes actively choose which treatments to forego when pressures cost become a problem. (34, 35)

Drug costs

In a study done in Tanzania from 1989-90, the average annual direct cost of diabetes care was $287 for a patient requiring insulin and $103 for a patient not requiring insulin. Insulin accounted for 68.2% ($156) of the average annual outpatient costs. For patients not requiring insulin the cost of oral hypoglycemic drugs and treatment of chronic

complications and infections accounted for 42.5% ($29.3) and 48.8% ($33.7) of costs respectively. Cost of outpatient care of diabetic patients for the whole of Tanzania was estimated at $2.7m, 32.2% of which was for insulin.(36). The study conducted in Ibadan, Nigeria revealed that 59% of patients were non-adherent with the previous anti-diabetic drugs due to lack of finance (51.7%); (37)

Drug side effects

According to a study done among patients with type 2 diabetes in a tertiary care setting in Ibadan, southwestern Nigeria, oral hypoglycemic agents (OHA) were prescribed for 86% of cohorts while insulin and OHA was prescribed in 14% . About 70.8% of patients on OHA were on combination therapy. The most frequently prescribed OHA combination was glibenclamide and metformin (95.8%). Glibenclamide was prescribed as twice daily regimen in 69% of cohorts. The most frequently documented side effect was hypoglycemia (60.3%). Only 44% of cohorts had adequate glycemic control; of these, 93% were adjudged adherent with prescribed anti-diabetic drugs. The study further revealed that 34.5% of patients were non-adherent with the previous anti-diabetic drugs due to side effects (37).Side effects as a reason for non-adherence was also the most attributing factor in another study(9)

Social stigma

Social stigma in minority of patients with type 2 diabetic mellitus who use insulin injection has been implicated as a barrier for drug adherence: this is due to the fact that patients fear to be labeled as users of substance of abuse. Depression has also been identified to be a significant factor challenging DM medication adherence, with depressed patients less likely to report and demonstrate good adherence (42% of depressed patients reporting good adherence versus 67% non-depressed patients.)(38) Another study on the effects of depression on DM identified medication non-adherence rates of 24.5% for those with depression versus 18.8% for those with no major depression (39)

Alcohol use

It has been shown in different populations, that, the more one drinks alcohol, the less likely to go for outpatient visits. Alternatively, the disinhibitory effects of alcohol might explain poor adherence among regular, heavy drinkers. However, disinhibition would be less likely to explain differences among patients with low vs. moderate levels of alcohol consumption (40)

In a study conducted in Northern California assessing the effect of alcohol consumption on diabetic drug adherence, current alcohol consumption was reported by 50.8% of adults with diabetes. A gradient of increasing risk for poor adherence to diabetes self-care behaviours including drug adherence with increasing alcohol consumption, starting with those who consume even one drink a day was observed. Former drinkers had the greatest compliance for diabetic drug intake (41).In 2001–2002 the prevalence of alcohol abuse and dependence in the general US population were 4.7 and 3.8%, respectively. It is unknown whether people with diabetes have a similarly high prevalence of alcohol consumption and alcohol use disorders compared with the general population (42)

Health system factors

Provider or system factors have also been identified that create barriers to the diabetic mellitus drug adherence, they include a perceived lack of time or resources to train patients and inadequate ability to follow-up or monitor therapy. Several reports characterizing these common barriers to using medications for diabetic mellitus have linked worse diabetes care outcomes to poor diabetes medication adherence.

Patients treated in health systems with poorer treatment coordination may experience even greater differences in their adherence behavior across drug classes. Concurrent management by multiple prescribers with poor coordination may negatively impact patients' therapeutic alliance with their clinicians, a factor that has been found to affect patients' adherence to multiple drug types (43-46)

Furthermore, it was revealed in the study conducted in Uganda that, patients who took longer time to visit a health worker were more likely not to adhere (29). Other studies conducted in United States between 1999 and 2003 have cited other factors like poor

patient-provider relationship and longer time since diabetes education to be associated with poor diabetic drug adherence (19, 30, 47, 48)

The situation of multiple prescribers is also common in Tanzania, whereby patients have to attend different clinics and operations at different clinics are disjointed.

Other social demographic factors

Results from different studies revealed other socio-demographic factors like marital status, occupation of the respondent and religion were not significantly associated with non-adherence (18, 24, 29, 31).Also other studies revealed other factors like duration of diabetes, route of administration and number of antidiabetic drug types prescribed were not significantly associated with non-adherence.(29-31)

Patient-caretaker related factors

Grant R et al found other patient factors attributing to poor drug adherence;- these include patient resistance and fear of weight gain, inconvenience and inadequate support (49).

Perceived inefficacy of prescribed anti-diabetic drugs leading to self-medication with local herbs attributed to d (13.8% (37)

PROBLEM STATEMENT

Non-adherence to prescribed non pharmacological as well as pharmacological treatment schedules has been and continues to be a major problem worldwide for all diseases and in particular the chronic diseases. Studies on this subject show that adherence is about 50% for medications in chronic diseases and much lower for lifestyle prescriptions (18, 50).

Of the chronic diseases, diabetes is considered to be one of the most demanding conditions for psychological and behavioral changes. It requires frequent self monitoring of blood glucose, dietary modifications, exercise, and administration of medications on a schedule (24, 47, 51).

Studies have emphasized the importance of achieving optimal glucose control through strict adherence to medications, diet, and exercise in order to minimize serious long term complications(18, 47, 52) .These complications affect the patient's quality of life, increase mortality, morbidity and economic cost to society (18, 47, 53)

There is no available data on Tanzania on the extent of antidiabetic drug adherence.

RATIONALE

It has been shown that effective management of DM type 2 is associated with lower avoidable morbidity, mortality, and health care utilization hence reducing the cost and burden to government and community at large.

Evidence from previous studies have shown that nonadherent people with diabetes had significant worse clinical outcomes compared to patients who are adherent to treatment (54)

Despite the emphasis put to patients on the importance of appropriate medication use, many patients are poorly adhering to pharmacotherapy (55) and fall short of achievable health goals as a result.

On the other hand in developing countries like Tanzania, where the health system is overburdened by infectious diseases like Tuberculosis and HIV, improving antidiabetic drug adherence pattern is expected to reduce the increased costs associated with preventable morbidity

Some of the studies done previously had included highly selective samples that are not representative of the populations from which they are picked. Furthermore, most of the studies were carried out in developed countries, leaving a gap in knowledge about the prevalence and factors that may be associated with non-adherence to diabetic treatment in developing countries.

This study was conducted to assess the extent of antidiabetic drug adherence among patients with DM type 2, and determine factors that lead to poor drug adherence, it is hoped that the information gathered will help health care workers to have effective intervention strategies to improve problem of poor drug adherence

OBJECTIVES

BROAD OBJECTIVE

To determine the pattern of antidiabetic drug adherence and associated factors among patients with type 2 diabetic mellitus attending Muhimbili diabetic clinic, Dar es Salaam Tanzania.

SPECIFIC OBJECTIVES

1. To determine the magnitude of antidiabetic drug adherence among patients with diabetic mellitus type

2. To determine the association between socio-demographic factors and antidiabetic drug adherence

3. To determine the reasons for not adhering to antidiabetic drugs among patients with diabetic mellitus type 2

4. To determine the association between antidiabetic drug adherence and metabolic control (serum creatinine, random blood glucose, urine for protein and serum HbA1c levels)

5. To determine the association between antidiabetic drug adherence and presence of chronic complications (hypertension, peripheral neuropathy and peripheral vascular disease) among patients with diabetes type 2

METHODOLOGY

Study design: Descriptive cross-sectional study

Study setting: Diabetic clinic, MNH, Dar es Salaam, Tanzania

Muhimbili National Hospital is the largest consultant hospital and teaching hospital in Tanzania. It is located in the city of Dar es Salaam with an estimated population of over 4 million in February 2009.Dar es Salaam has three districts, Ilala, Kinondoni and Temeke. The diabetic clinics in district hospitals of Dar es Salaam were established in 2002, before that, Muhimbili National Hospital used to serve as a primary facility for diabetes patient in the city. Currently, Muhimbili National Hospital serves as a tertiary hospital for diabetes management for patients all over the country and at times it operates as a primary and secondary health facility. Patients are attended two times per week at diabetic clinic of Muhimbili National Hospital, Monday clinic is for Children and adolescents with diabetes mellitus type 1, whereas Thursday clinic is for adults with both type 1 and 2 diabetes mellitus.

Study population: Patients with Diabetic mellitus type 2 attending diabetic clinic of Muhimbili National Hospital

Study duration

This study was conducted from 14th May 2009 to 31st December 2009

Inclusion criteria:

Patients diagnosed to have diabetic mellitus type 2 according to previous diagnosis in the medical files and on drug treatment.

Patients on drug treatment for at least three months prior to the day of the interview.

Exclusion criteria

Patients who did not consent to participate in the study

Those who were on life style modification and exercise only without drugs for diabetes

Sampling of study subjects

Systematic sampling was used to select study patients, whereby during the clinic day (every Thursday), the investigator got the patients list from a nurse at a nursing station where all patients had their weight and blood glucose (fasting or random) measured. For each clinic day, the investigator went through the files to identify patients who met inclusion criteria. Those who met the inclusion criteria were identified and a list made.

For this study, every 5th patient who met the inclusion criteria was included in the study. In cases, where patient did not consent, the 7th patient was asked for participation without affecting the order of selection. With the number of patient in each visit ranging from 50 to 60, about 10 to 12 patients were recruited in each visit.

Sample size determination

Sample size was calculated from the formula of descriptive cross-sectional study;-

$N=Z^2p\,(100-p)/d^2$

Where

N=Estimated minimum sample size, Z=is the standard deviation of 1.96 at 95% confidence interval

p= Prevalence of adherence among diabetic patients at Mulago hospital in Uganda, estimated to be less than 72 %,), d= margin of error on p, 0.06, Hence,

$n=1.96\times1.96\times72\times28/6^2$

N=215

Data collection

Data was collected by the investigator. The process involved, firstly introduction of the study to individual patients, then seeking consent from the patient and signing of consent forms.

Patient demographic characteristics including age, sex, date of first diagnosis were obtained and recorded in a structured questionnaire.

History of previous and currently used drugs was also included in the questionnaire. These informations were obtained from patients and also crosschecked in patient's files/folders.

For the purpose of this study, glycemic control was assessed using random or fasting blood glucose, and HbA1c was also measured. Serum creatinine and urine for protein were used to assess renal functions.

Based on the first 200 subjects, every 4th of the already recruited patients had his/her serum collected for assessment of metabolic control by measuring HbA1c,the 12 extra patients were conveniently selected by including them as they were subsequently recruited.

Assessment of adherence

In this study, adherence was defined as the extent to which a person's behavior in taking medications corresponds with agreed recommendations from a health care provider" (56, 57).

Adherence was determined by patient's self report. Patients were asked about the antidiabetic drugs used in the past one week and three months.

Estimation of antidiabetic drug adherence was based on the number of days drugs missed, for example, if one dispensed drugs for 60 days during last visit and the patient missed 3 days, then 3/60 ×100, as percent non-adherence, so the patient missed 5%, in other words patient was judged to be 95% adherent

Good adherence was considered if the patients calculated adherence was at least 80% of the expected days, patients with less than 80% days of using their medications were judged non-adherent(poor adherence).The cut off point of 80% was considered acceptable as it was also used in other studies of chronic medications (50, 58)

For patients using more than one antidiabetic drug, the worst computed adherence for the drugs was used to represent the patient's overall adherence.

Patients found to have good drug adherence, were encouraged to continue with regular medication, those with poor adherence (non adherence) were counseled on importance of antidiabetic drug adherence, reasons for not adhering were highlighted and ways to combat adherence problems were discussed with patients.

Clinical evaluation

Nutritional status assessment

Nutritional status of the patients was assessed by using Body Mass Index (BMI), which is calculated as a ratio of weight/height x height (W/H X H)

Classification of BMI was according to WHO, (59, 60) as follows;-

1. < 18.5 indicating Underweight
2. 18.5 24.9 indicating Normal weight

3. 25.0 -29.9 indicating overweight

4. More or equal to 30 indicating Obesity

Blood pressure assessment

Three blood pressure measurements taken at intervals of 5 minutes were obtained at the clinic, out of which average blood pressure was obtained from the three readings. Blood pressure was measured by means of calibrated digital BP machine. Classification of Hypertension in this study was according to International Diabetes Federation which defines Hypertension as diastolic blood pressure of $\geq$ 90 mmHg and/or systolic blood pressure of $\geq$ 140mmHg(61)

Peripheral vascular disease assessment

For the purpose of this study, Peripheral vascular disease was categorized according to Ankle Brachial Plexus Index (ABPI), where Doppler probe was used to record pulses of brachial and leg positions. The Ankle Brachial Plexus Index (ABPI) is a measure of reduction in arterial blood pressure of the legs and as such is used to detect evidence of peripheral vascular disease. It is calculated by dividing the highest systolic blood pressure in the arteries at the ankle and foot by the higher of the two systolic blood pressures in the arms. For the purpose of this study, ABPI was calculated using systolic blood pressure of right arm by dividing it to highest of systolic blood pressure of either the dorsalis pedis or anterior tibialis of right leg. The ABPI of greater than 0.9 was considered normal, however a value greater than 1.3 was considered abnormal, and suggests calcification of the walls of the arteries and noncompressible vessels reflecting sever peripheral vascular disease(62).

The following ABPI ratios were used to describe the severity of peripheral vascular disease (62):-

1. Normal→ 0.90- 1.30
2. Mild obstruction→ 0.70- 0.89
3. Moderate obstruction→ 0.40- 0.69
4. Severe obstruction→ <0.40
5. Poorly compressible secondary to medial calcification> 1.30

Peripheral nervous system assessment

Peripheral nervous system was assessed by means of monofilament. The 5.07(10g) monofilament is an acceptable standard for screening of the minimum level of protective sensation in the foot

The monofilament measurements were performed as follows:-

a. Patients were placed in supine or sitting position with shoes and socks removed, and the monofilament wire was touched on 10 identified spots on the plantar and dorsal aspect of the foot.
b. The monofilament was held perpendicular to the patient's foot, it was placed against the foot increasing the pressure until the monofilament bent into a C-shape, and precautions were made not to apply the monofilament over ulcer, scar or necrotic tissue, also not to slide the monofilament over the skin
c. Patients were asked to respond "yes" each time they felt the pressure of the monofilament on their foot during examination, they were instructed to close their eyes with toes pointing straight up during examination
d. Scoring of the presence of peripheral neuropathy was calculated by number of felt spots out of 10 and scored as follows;-

Score of > 8 → Normal perception

Score of 4-7 → Diminished touch

Score of $\leq 3 \rightarrow$ Loss of touch perceptions with more risk for foot ulcers.

For the purpose of this study, patient was classified as having normal perception, diminished touch or loss of touch perception by considering the worst score of the two legs.

Laboratory assays

Glycemic assessment

Random blood glucose or fasting blood glucose were measured using a glucometer and categorized as good or poor control, hypoglycemic patients were also identified and categorized as poor control.

Sub- categorization of glucose levels was according to WHO standard values as follows:-

(a) Good control was considered if the fasting blood glucose was 3.9-7.2mmol/l and or random blood glucose was $\leq$ 11.1 mmol/l
(b) Poor control was considered if the fasting blood glucose was >7.2mmol/l and or random blood glucose was >11.1 mmol/l
(c) Fasting or random blood glucose of $<$ 3.8 mmol/l indicated hypoglycemia and was also considered as an indicator of poor control

Glycosylated hemoglobin of $<$ 6.5% to 7.0% was considered as ideal/normal for metabolic control, between 7.1 to 7.5% as satisfactory for metabolic control and above 7.5% as a marker of poor metabolic control(63, 64)

Renal function assessment

Renal function status was ascertained by measuring protein in urine by dipstick, and serum creatinine was used to calculate estimated GFR.

Using serum creatinine, weight and age of the patient in years, an estimated GFR from creatinine clearance by Cockroft-Gault formula as follows:-

eGFR = (140- Age (years) x weight (kg) x 88.2 x k/serum creatinine (umol/l) x 72

Where k=1 in male, and k = 0.85 in female

Renal function was grouped into five stages (65) as follows;-

Stage I =Creatinine clearance of more or equal to 90 mls/min

Stage II = Creatinine clearance of 60 - 89 mls/min

Stage III = Creatinine clearance of 30 - 59 mls/min

Stage IV = Creatinine clearance of 15 -29 mls/min

Stage V = Creatinine clearance of < 15 mls/min.

Results of proteinuria obtained in dipstick urine test were used to assess extent of nephropathy, however if there was concurrent leukocytes, results of dipstick urine protein were disregarded in such patients.

DATA MANAGEMENT.

Data was entered in SPSS Program version 16 (SPSS Inc. Chicago, Illinois). It was then cleaned and analysis was done through SPSS version 16. Comparison of proportions and statistical significance was tested by using Chi-squared test.

Proportions found to be significant were further tested using ordered logistic regression.

A p-value of less than 0.05 was considered significant.

Ethical consideration

Ethical clearance to conduct the study was sought from Muhimbili University of Health and Allied Sciences Ethical Review Board. Permission to do the study was obtained from Muhimbili National Hospital management. Informed consent to participate in the study was obtained from potential study participants or parents/guardians of the participant if

the participant was legally unable to make decisions. Blood for investigations was obtained by venopuncture; this was done to all study participants.

Disposal of Study patients

All findings (physical and laboratory investigations,) were communicated to patients either during the index visit or subsequent visits by to the investigator or other physicians taking care of the patient and patients continued with standard care as per MNH guidelines.

RESULTS

A descriptive cross-sectional study was conducted at Diabetic clinic of Muhimbili National Hospital from 14th May 2009 to 31st December 2009 with the objective of determining the magnitude of antidiabetic drug adherence and associated factors among patients with type 2 diabetic mellitus.

During the study period, a total of 1234 patients with diabetes mellitus were attended at Thursday adult diabetic clinic. Two hundred and twelve (212) patients were systematically selected, out of which, 216 were enrolled to participate in the study. Six (6) patients were excluded, of these, 3 did not consent (the reasons for decline being subjected to many researches in the past without feedback for one of them, and two refused without giving reason)

Two(2) could not make an appointment for clinical assessment as they were out of town and 1 patient was busy nursing his sick wife.

1. Social demographic characteristics

Majority of patients in this study were in the age groups 51-60 and more than 61 years, i.e. 74 (34.3%) and 73 (33.8%) respectively, the median age of the patients was 55.0 years (34-81 years). Two-thirds of studied patients, 144 (66.7%) were females

Regarding level of education, 111(51.4%) of patients had primary level of education, 48(22.2%) had secondary education, and 31(14.4%) of patients had post-secondary education. Most of the patients had diabetes duration for more than 5 years, 135 (62.5%), the rest, had diabetes for less than 2 years, 38(17.6%) and between 2 -5 years, 43 (19.9%). Patients' nutritional status revealed that, 52(24.1%) had normal BMI, 87(40.3%) were overweight and 70(34.2%) were obese. In total 157(72.7%) had weight above the normal range. (Table1).

Table 1. Socio-demographic characteristics of population of patients with diabetes mellitus type 2

Demographic factor	N= 216	%
Age		
< 40	21	9.7
41-50	48	22.2
51-60	74	34.3
> 61	73	33.8
Sex		
Male	72	33.3
Female	144	66.7
Religion		
Christian	110	50.9
Moslem	106	49.1
Education level		
No formal	26	12.0
Primary	111	51.4
Secondary	48	22.2
Post-secondary	31	14.4
Duration of diabetes(years)*		
≤ 2	38	17.6
2-5	43	19.9
> 5	135	62.5
BMI**		
Underweight	4	1.9
Normal	52	24.1
Overweight	87	40.3
Obesity	70	32.4

* Median duration (range), 7 years (0.3-34 years)

** 3 patients were not as assessed for nutritional status due to inconvenience of measuring either their weight or height.

2 .Types of antidiabetic drugs prescribed to patients.

Metformin was the most used drug, either as a single drug or in combination, its use accounted for 154(71.3%), Glibenclamide was the second most commonly used drug, i.e. 120(55.6%), while 33(15.3%) of the patients were on Insulin injections (Table 2)

Seventy seven patients, 77(35.6%) were on single antidiabetic treatment, 134 (62.0%) were on two antidiabetic drugs while 5 (2.4%) were on three antidiabetic drugs (not shown in the table)

Regarding treatment with more than one antidiabetic treatment, the most used combination was Metformin and Glibenclamide, i.e. 97(45.1%), followed by Metformin and Chlopropamide, 30(14.0%). (Figure 1)

Table 2 Types of antidiabetic drugs used by patients in the last three months (N = 216)

Name of drug	Frequency	Percentage
Metformin	154	71.3
Glibenclamide	120	55.6
Chlopropamide	39	18.1
Insulin	33	15.3
Other drugs*	8	3.8

* Other drugs include Glipizide, Gliclazide, Rosiglitazone, and Pioglitazone

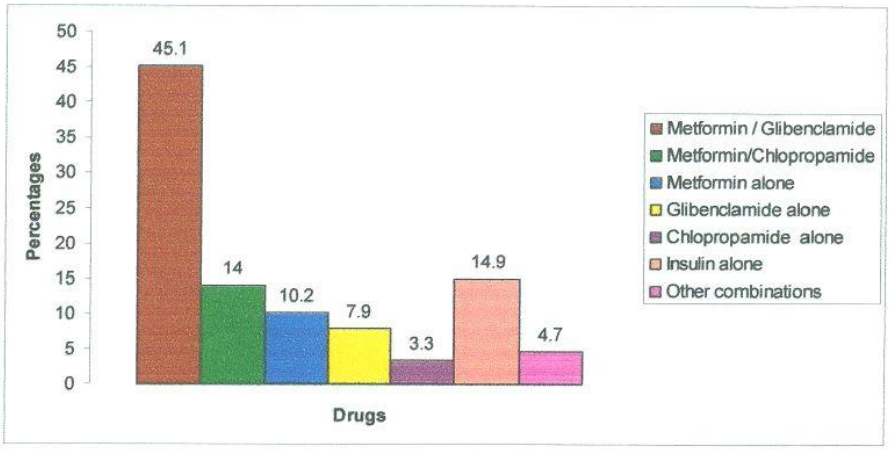


Figure 1: Pattern of drugs used by patients over the last three months

3.1 Pattern of drug adherence by timing of drug intake and prescribed dosage

Adherence of the patients to treatment by abiding to instructed time of medications was reported by 166(76.9%) while 175(81.0%) of the patients reported to adhere to the prescribed dosage (Table 3)

Table 3. Adherence to timing of drug intake and dosing (N=216)

Response	Frequency	%
Medication use according to instructed time.		
Yes	166	76.9
No	50	23.1
Adherence to prescribed dosage		
Yes	175	81.0
No	41	19.0

3.2 Elicited pattern of drug adherence from prescribed dosages

Adherence to antidiabetic treatment was assessed in the previous one week and past three months to elicit short term and long term recall regarding drug adherence. Most of the patients reported good adherence as recalled at one week (60.2%) and at three months recall (71.2%) (Table 4)

Table 4. Pattern of drug adherence to antidiabetic drugs according to calculated number of days of drug use per prescribed dosages in previous one week or past three months (N=216)

Response	Frequency	Percent
Adherence in one week		
Good	130	60.2
Poor	86	39.8
Adherence in three months*		
Good	153	71.2
Poor	62	28.8

Good = adherence of ≥ 80%, Poor= adherence of < 80%

* One patient had duration of diabetes less than three months.

4. Association between antidiabetic drug adherence and social demographic characteristics and other drug factors in the previous one week

Age was found to be significantly associated with drug use adherence (p-value =0.02).Good drug usage adherence was elicited more among the older patients (> 61 years) who had drug usage adherence of 71.2%. Patients in the age group of 41-50 years had the least drug usage adherence (43.8%).The significant good drug use adherence among the older patients was only elicited in one week recall but not in the previous 3 months recall of the patients adherence to drug use.

Gender and religion were found to have no statistical significant association with drug usage adherence in one week and three months recall of patients drug use adherence.

The level of formal education, diabetes duration and whether the patient used one or multiple antidiabetic drugs were also not found to be significantly associated with drug

use adherence in the previous one week and past 3 months. Though not significant, those who used single antidiabetic drug had better drug use adherence compared to those who used more than one antidiabetic drug.

However, when patients used other drugs in addition to antidiabetic drugs, the level of antidiabetic drug use adherence improved. This was exponentially observed with the more number of other drugs used, with addition of 1 other non antidiabetic drug, the reported level of drug use adherence was 68%,with three or more other drugs the level of adherence was 77.4%.This observed increasing drug use adherence was statistically significant with p-value of 0.011(Table 5)

The effect of additional of other non diabetic drugs to antidiabetic treatment reported by patients in the past 3 months recall revealed the same increasing pattern though not statistically significant.

Table 5Association between antidiabetic drug adherence and socio-demographic characteristics of patients with diabetes mellitus type 2 in the previous one week

Adherence in previous week	Total	Good adherence (%)	p-value*
Age (years)			
< 40	21	14 (66.7)	
41-50	48	21 (43.8)	
51-60	74	43 (59.1)	
>61	73	52 (71.2)	0.022
Sex			
Male	72	47 (65.3)	
Female	144	83 (57.6)	0.280
Religion			
Christian	110	61 (55.5)	
Moslem	106	69 (65.1)	0.148
Education level			
No formal	26	15 (57.7)	
Primary	111	68 (61.3)	
Secondary	48	30 (62.5)	
Post-secondary	31	17 (54.8)	0.897
Duration diabetes (years)			
< 2	38	24 (63.2)	
2-5	43	25 (58.1)	
> 5	134	80 (59.7)	0.894
Number of antidiabetics			
1	84	55 (65.5)	
> 1 (2 or 3)	132	75 (56.8)	0.205
Other drugs			

Antidiabetic alone	109	54 (49.5)	
Anti+ 1	48	33 (68.8)	
Anti+ 2	28	19 (67.9)	
Anti+ 3 or more	31	24 (77.4)	0.011

Good = adherence of ≥ 80%

*Chi-square used to calculate p-value

Anti+ indicate antidiabetic drug plus 1/2/3 other non diabetic drugs.

6. Reasons for not adhering to antidiabetic treatment

Of the 86 patients who had poor adherence to antidiabetic treatment, the most common reason for non-adherence was running out of pills which accounted for about 34% of cases. The high cost of antidiabetic drugs and feeling better after using drugs and therefore concluding that there was no need to continue taking drugs, each accounted for 19% of the reasons for non- adhering. Use of traditional medicine, febrile illness and lack of motivation to continue also played a big role as other reasons for non adherence, together they accounted for 20(13.5%) of patients. (Table 6)

Table 6. Reasons for non- adherence to the antidiabetic treatment

Reasons for missing drugs	Frequency, n(%)
Drug cost	78(52.70)
Feeling better	28(18.92)
Other reasons*	20(13.51)
Side effects	17(11.49)
Forgot	4(2.70)
Alcohol intake	1(0.68)
Total	148(100.00)

* Other reasons included use of traditional medicine, febrile illness, and lack of motivation

7. Complications and metabolic parameters among studied patients

Two hundred and sixteen patients were examined using doppler probe for evidence of peripheral vascular disease. Many patients, i.e. 192(88.9%) had no evidence of peripheral vascular disease, and 4.2% of patients were categorized as having severe peripheral disease due to poor compressibility with medial calcification of vessels.

About 32(14.8%) of patients had evidence of peripheral neuropathy judged as loss of touch perception, whereas 120(55.6%) and 64 (29.6%) were found to have normal perception and diminished touch sensation respectively. This was according to monofilament testing. One hundred and thirteen, 52.3% of patients had normal blood pressure levels and one hundred and three, 47.7% had blood pressure levels diagnostic of hypertension.

Renal functional status was also assessed using GFR staging, 83(38.8%) of patients were in Stage I, patients in stage III and IV comprised 51(23.8%) of all patients, there was no patients with chronic kidney disease stage V

Glycemic control of patients was studied using either random blood glucose or fasting blood glucose, majority of studied patients, 145(67.1%) had poor glycemic levels.

Furthermore, metabolic control was also assessed using urine dipstick test for detection of protein, 27(12.9%) of patients had proteinuria. Metabolic control was also assessed using Glycated Hemoglobin, Majority of 62 patients whose HbA1c was measured had poor metabolic control, i.e. 47(75.8%), the remaining 15(24.2%) had levels which were classified as either Ideal or satisfactory (Table 7)

Table 7. Complications and metabolic parameters among the studied population of patients with diabetes mellitus type 2 (N=216)

	Frequency (%)
Peripheral vascular disease (Doppler findings)	
Normal	192(88.9)
Mild obstruction	14(6.4)
Moderate obstruction	1(0.5)
Poorly compressible with medial calcification	9(4.2)
Peripheral neuropathy (monofilament testing)	
Normal perception (≥ 8)	120(55.6)
Diminished touch (4-7)	64(29.6)
Loss of touch perception(≤ 3)	32(14.8)
Blood pressure (mm Hg)	
Normal (<140/ 90 mmHg)	113(52.3)
High BP (≥140/ 90 mmHg)	103(47.7)
Nephropathy (eGFR Staging)	
Creatinine clearance of ≥ 90)	83(38.8)
Creatinine clearance of (60- 89	80(37.4)
Creatinine clearance of (15-59)	51(23.8)
Urinalysis*	
Protenuria	27(12.9)
No protenuria	183(87.1)
Glycemic control (FBG/RBG)	
Good	71(32.9)
Poor	145(67.1)
HbA1c	
Ideal (<6.5 -7.0%)	9(14.5)
Satstifactory (7.1-7.5%)	6(9.7)
Poor (>7.5%)	47(75.8)

*All patients submitted urine for dipstick, 6 (2.8%) patients had proteinuria with leukocytes, and these were subsequently excluded in the analysis

8. Association between antidiabetic drug adherence elicited in previous one week and blood pressure, glycemic control, peripheral vascular disease and presence of neuropathy

Majority of the studied patients who were found to be hypertensive had good antidiabetic adherence, 63(61.2%), on the other hand, 67(59.3%) of normaltensive patients were adherent to antidiabetic treatment. Overall there was no statistical significant association between blood pressure levels and adherence to antidiabetic treatment (p-value= 0.779)
There was a clinically inverse relationship between level of glycemic control and antidiabetic drug adherence.
Majority of patients with good glycemic control had good adherence to antidiabetic treatment, 49(69.0%), this was more proportion compared to those with poor glycemic control in which 81(55.9%), however the difference was not of statistical significance (p-value= 0.064)
Good HbA1c levels represented as ideal and satisfactory had more proportion of patients with good adherence to antidiabetic treatment, 11(73.3%) compared to patients with poor HbA1c levels where 31(66.6%) had good adherence to antidiabetic treatment, the association was not significant (p-value= 0.595)
There was no significant association between peripheral neuropathy and peripheral vascular disease and adherence to use of antidiabetic drugs. (Table 8)

Association between antidiabetic drug adherence with metabolic parameters and complications was also assessed at three months recall, there was no significant association found in either of the complications assessed or metabolic parameters (Results not shown)

Table 8. Association between antidiabetic drug adherence, complications and metabolic parameters in the previous one week

Complications and bio parameters	Total	Good adherence n(%)	p-value*
Peripheral vascular disease(Doppler findings)			
Normal	192	114 (59.4)	
Mild + Mod obstruction	15	12 (80.0)	
Poorly compressible with medial calcification	9	4 (44.4)	0.179
Peripheral neuropathy (monofilament testing)			
Normal perception(>8)	120	78 (65.0)	
Diminished touch(4-7)	64	32 (50.0)	
Loss of touch perception(≤3)	32	20 (62.5)	0.135
Blood pressure (mm Hg)			
Normal(<140/90 mmHg)	113	67 (59.3)	
High BP (≥140/ 90 mmHg)	103	63 (61.2)	0.779
Nephropathy (eGFR staging)			
Creatinine clearance ≥ 90mls/min	83	46 (55.4)	
Creatinine clearance of 60- 89	80	46 (57.5)	
Creatinine clearance of 15-59	51	37 (72.5)	0.732
Urinalysis			
Protenuria	27	17 (63.0%)	
No proteinuria	183	109 (59.6%)	0.736
Glycemic control(FBG/RBG)			
Good			
Poor	71	49 (69.0)	
	145	81 (55.9)	0.064
HbA1c			
Ideal+ satisfactory (<6.5-7.5%)	15	11 (73.3)	
Poor (>7.5%)	47	31 (66.0)	0.595

Good = adherence of ≥ 80%

*Chi-square used to calculate p-value

9. Predictors of drug adherence

Logistic regression was also performed for variables found significant, According to univariate analysis, age and number of other drugs were found significant with p-values of 0.02 and 0.002 repectively.When multivariate analysis was performed, age was found not significant (p-value=0.157),effect of number of drugs other than antidiabetics was still significant even on multivariate analysis (p-value=0.013) (Table 9)

Table 9. Results of logistic regression

Variable	Univariate			Multivariate		
	OR	CI	p-value	OR	CI	p-value
Age	0.97	0.94-0.99	0.02	0.98	0.95-1.01	0.157
Other drugs	0.65	0.50-0.86	0.002	0.70	0.53-0.92	0.013

DISCUSSION

Pattern of antidiabetic drug adherence

Adherence to antidiabetic medications was assessed at three months and also assessed at one week prior to the day of interview so as to reduce the recall bias effect.

Prevalence of adherence to antidiabetic treatment was found to be 60.2% at previous one week recall and 71.2% for last three months recall, this was suboptimal adherence, and it was similar to findings in other parts of the world like United States, Mexico and India where adherence ranges from 23 to 77%(18-22).

A study done at of Mulago (29) which also assessed adherence in the previous one week reported prevalence of 71.1%.This higher prevalence at Mulago could be explained by the fact that patients were free to visit the hospital to refill their drugs any time, while at Muhimbili patients had to wait until their appointment time which is usually around three months.

Adherence to treatment in this study differed between three months and one week recall; this was probably due the fact, patients buying medication delay getting more medications at private pharmacy with the hope of getting free medications when they come for follow up. On the other hand, adherence at three months could be higher because, this is the time closer to patients' last visit to clinic for medication refill. Another possibility to explain the findings of higher adherence at three months compared to previous one week was recall bias.

Additionally, adherence was assessed by eliciting extent to which patients abide to time instructed and follow their prescribed dosages. Prevalence of adherence to time instructed was 76.9% while it was 81.0% for adherence to prescribed dosages.

Majority of patients in this study were either overweight or obese, the two accounted for 72.7% of all patients. Being obese or overweight have been found to have a negative

influence on adherence resulting to patients not following dietary advice or fear of weight gain associated with medication use.(49). Other studies have shown patients with diabetes to have depression twice as much as in matched controls without diabetes, and more research evidence has associated depression with decrease physical activity, hence higher overweight and obesity rates in diabetes, and also depression was associated with poor adherence to antidiabetic medication.(66) .Depression was not assessed in this study; it could have a bearing effect on the pattern of antidiabetic drug adherence.

Social demographic characteristics and antidiabetic drug adherence

Adherence was observed to increase with age, this pattern of adherence was observed both at one week and three months, the effect of age was found to be significant in the previous week (p-value 0.02). These results compares with findings of other studies in United Kingdom and Brazil (31, 33).The results of this study are in contrast to those of Uganda, where age was not found to be associated with antidiabetic drug adherence .(29)

Patients in the middle age group of 41-50 were consistently associated with poorer adherence compared to other age groups with prevalence of 56.2% and 39.6% at one week and three months respectively. This result compares to finding of the study of Mulago hospital, Uganda were majority of patients non-adherent to treatment were in the age group 36-50 years.(29)

Satstifactory adherence was found to increase with age; adherence with age could suggest that with older age patients have more cormobidies, which make them symptomatic, hence more likely to adhere to treatment. This compares to findings of another study on effect of symptoms on adherence.(27)

Effect of gender on adherence did not show significant association, with both males and females having similar levels of adherence. Female patients appeared to have more proportion of non-adherence compared to male patients at one week recall (42.4% versus 34.7%), though this was not statistically significant. Lack of association between gender

and antidiabetic drug adherence was also noted in other studies(18, 20, 51). These findings are in contrast to study done in Mulago hospital, Uganda where female gender was significantly associated with poor adherence.(29).One study conducted on the effect of depression on non-adherence showed that women are more likely to be non-adherent than men because, they are exposed to more stress than men, hence, are more likely to be depressed, resulting to non-adherence, this could also explain the observation of effect of gender on adherence in one week recall(23)

Other social demographic characteristics analyzed were level of education and religion;- they were not associated with antidiabetic drug adherence. This finding is similar to that of other studies, where, religion was not associated with adherence(18, 24, 29, 31).Level of education appeared to have an impact on adherence in another study done in Mexico(18),however in Mexico study, multivariate analysis was not done to rule out possibility of confounding factors. In study of Mulago, level of education was not associated with antidiabetic drug adherence. The findings of this study and that in Mulago (29) are in contrast to those found in Brazil (33), where level of education was found to have positive impact on extent of adherence, the lack of association as regards to level of education on adherence may be due to small number of patients with secondary and post-secondary education in this study.

The duration of diabetes and number of antidiabetic drugs used had no significant association with degree of antidiabetic adherence; however at three months analysis the observation was that, the longer the duration of diabetes, the more the extent of good adherence.

It can be speculated that, patients who have had diabetes for a long duration are expected to have more cormobidies , more diabetes education and are therefore more likely to be adherent to drugs compared to those with shorter duration of diabetes. Lack of association as regards to duration of diabetes is consistent with finding of study done in Brazil(33)

Adherence to medications would be expected to be inversely proportional to the number of pills/medications one uses. In this study however, those patients using other non diabetic drugs had a significant good adherence to antidiabetic drugs at both 3 months and one week reports compared to those who did not have extra non diabetic drugs (p=0.011). The findings were significant even when ordered multivariate logistic regression was done (p=0.013).This could have been due to the fact that patients with multiple other drugs have multiple cormobidies, therefore attending different clinics hence getting more opportunity to have regular health education and more prescriptions.

Reasons for not adhering to medications

Assessing the reasons for missing medication is considered as a key element towards improving diabetes drug adherence, several reasons attribute to antidiabetic poor adherence. Cost was most common reason for poor adherence, accounting for 78(52.70%),cost of buying medications has been found to be a significant factor in determining extent of adherence in most of studies (9, 37),the proportion of patients not adhering due to cost is similar to that found in study of Ibadan, Nigeria, where cost accounted for 51.7% as reason for not adhering to treatment (37)

Side effects have been reported to be one of the commonest reason for non-adherence (30). In this study, side effects as reason for not adhering to treatment was found in 17 (11.49%) of the patients. A study done in Ibadan, Nigeria, side effects accounted for about 34.5% of non-adherence to antidiabetic treatment, the proportion appears small in this study.

Feeling better, forgetting and alcohol intake accounted for 28(18.92%), 4(2.70% and 1(0.68%) as barriers of good adherence respectively. Other reported reasons for non-adherence were use of traditional medicine, lack of food to eat, not feeling well, being tired of drugs, and lack of motivation to take medications which accounted for

20(13.51%), with most of them opting for traditional medicine/herbs because of perceived inefficacy to antidiabetics, a finding also reported in another study(37).
The barriers for good antidiabetic adherence observed in this study provide an opportunity for focused diabetic education on behavior change, also enhancing health care workers to have better understanding of factors for antidiabetic drug adherence.

Association between antidiabetic drug adherence and metabolic parameters

Theoretically it is believed that adherence to antidiabetic treatment would result to better outcomes in terms of reducing morbidity and mortality associated with complications of diabetes, this has been shown in previous several studies.

The key to avoiding complications associated with diabetes is to ensure that patients have good metabolic control. This has been verified on previous studies on effect of good antidiabetic adherence on metabolic control.(21, 67). Glycemic control was assessed using glycemic levels by measuring random blood glucose or fasting blood glucose levels and HbA1c.

In this study, patients who had good glycemic control had better adherence to antidiabetic drugs compared to those who had poor glycemic control (69% versus 56% of patients respectively), though this was not statistically significant. The lack of association between antidiabetic drug adherence and metabolic control was also seen in other studies.(68-70)

Proteinuria was used to assess extent of diabetic nephropathy. Thirteen percent of patients had proteinuria which could be attributed to diabetic nephropathy however the caution should be used to interpret the results due to chance of false negative findings. Quantifying proteinuria by 24-hours urine or creatinine-protein ratio would have been better.

Association between antidiabetic drug adherence and complications

Results of this study showed that 103(47.7%) of patients were hypertensive. This finding appeared to be higher than that of another study done in Dar es Salaam 30 years ago where 26% were hypertensive (12). The difference could have been due to the fact that the previous study was a community setting and it involved a small sample size.

Hypertension as one of the macrovascular complications of diabetes mellitus was also analyzed in association to antidiabetic drug adherence. There was no statistical significance association between adherence and Blood pressure level at previous one week and past three months.

Peripheral vascular disease assessed by doppler ultrasound showed that majority of patients, 89% had no evidence of peripheral vascular disease. There was no significant association between peripheral vascular disease and adherence to antidiabetic drugs.

The proportion of patients with peripheral vascular disease in this study (11.1%) is almost similar to those of previous study in Tanzania,12.5% where also doppler ultrasound was used. (11)

Regarding peripheral neuropathy, 96(44.4%) of patients had evidence of peripheral neuropathy, with 32(14.8%) of them having severe peripheral vascular disease putting them at high risk of traumatic ulcers .Analysis for adherence at three months and one week showed no clinical or statistical difference on the outcome of peripheral neuropathy.

Renal functional status of patients was evaluated using estimated Glomerular filtration rate (GFR),Of 216 patients assessed, 38.8% had normal value of GFR, 37.4% had evidence of mild disease (stage II),Nearly quarter of the patients,i.e 23.8% had either stage III or IV diabetic nephropathy. When the effect of antidiabetic drug adherence on nephropathy was analyzed, patients who were adherent did not have clinical or statistical difference from those who were not adhering to treatment either in the previous one week or past three months recall.

Other studies of self report adherence have also shown lack of significant association between antidiabetic drug adherence and metabolic control and complications of diabetes. One study done in United States of America revealed glycemic control and high blood pressure were not associated with drug adherence, possible explanation for lack of association was that, either patients were over reporting their adherence or doctors were not prescribing sufficient potent doses to achieve metabolic control(71), these explanations could also account for the situation observed in this study.

On the other hand, failure to demonstrate the association between antidiabetic drug adherence and metabolic control/complications should be interpreted with caution, as the sample size in this study was calculated from proportion of adherence, to have the best conclusion; a large sample would have sufficed.

STUDY LIMITATIONS

1. Use of self reporting as a tool to assess adherence could have lead to over reporting of good adherence, recall bias is anticipated in long term medication use especially of more than 2 weeks duration, this was taken care by analyzing data for previous one week.
2. Lack of enough funds to buy reagents for glycated haemoglobin; had enough funds been available, this would enhance increasing sample size to increase power of the study, also extent of metabolic control by HbA1c could be done to large population of study subjects

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

Drug adherence for the previous one week was suboptimal at 60.2% vs. 71.2% at 3 months. As regards to social demographic factors, they were not associated with adherence to antidiabetic drugs.

Use of anti hypertensive was significantly associated with good antidiabetic drug adherence. Cost of antidiabetics, side effects of drugs were associated with poor antidiabetic drug adherence while improved glycemic control or feeling better led to stopping use of medications.

Many patients had poor glycemic control and BP levels regardless of adherence pattern. Furthermore it was shown that presence of hypertension, peripheral neuropathy and peripheral vascular disease were not associated with the extent of antidiabetic drug adherence.

Recommendations

Cost of buying antidiabetic medications accounted for majority of patients with poor adherence; hence there is a need to design a mechanism for patients to obtain regular drug supply either for free or at subsidized cost.

Majority of patients in this study were overweight or obese, indicating the need to emphasize adherence to other non pharmacological measures such as strict dietary control and exercises.

There is a need to conduct further studies among patients with good adherence so as to find reasons for them not faring well compared to those with poor adherence.

REFERENCES

1. Diamond J. The double puzzle of diabetes. Nature. 2003 Jun 5;423(6940):599-602.
2. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med. 1997;14 Suppl 5:S1-85.
3. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998 Sep;21(9):1414-31.
4. Ahren B, Corrigan CB. Prevalence of diabetes mellitus in north-western Tanzania. Diabetologia. 1984 May;26(5):333-6.
5. McLarty DG, Swai AB, Kitange HM, Masuki G, Mtinangi BL, Kilima PM, et al. Prevalence of diabetes and impaired glucose tolerance in rural Tanzania. Lancet. 1989 Apr 22;1(8643):871-5.
6. Aspray TJ, Mugusi F, Rashid S, Whiting D, Edwards R, Alberti KG, et al. Rural and urban differences in diabetes prevalence in Tanzania: the role of obesity, physical inactivity and urban living. Trans R Soc Trop Med Hyg. 2000 Nov-Dec;94(6):637-44.
7. McLarty DG, Unwin N, Kitange HM, Alberti KG. Diabetes mellitus as a cause of death in sub-Saharan Africa: results of a community-based study in Tanzania. The Adult Morbidity and Mortality Project. Diabet Med. 1996 Nov;13(11):990-4.
8. UNAIDS. Global Summary of the HIV/AIDS Epidemic. 2004 December.
9. Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. Am J Med. 2005 May;118 Suppl 5A:27S-34S.
10. Mbanya JC, Sobngwi E. Diabetes in Africa. Diabetes microvascular and macrovascular disease in Africa. J Cardiovasc Risk. 2003 Apr;10(2):97-102.
11. Wikblad K, Smide B, Bergstrom A, Kessi J, Mugusi F. Outcome of clinical foot examination in relation to self-perceived health and glycaemic control in a group of urban Tanzanian diabetic patients. Diabetes Res Clin Pract. 1997 Sep;37(3):185-92.
12. Mhando PA, Yudkin JS. The pattern of diabetic complications in African patients in Dar es Salaam. Trop Geogr Med. 1980 Dec;32(4):317-23.
13. Lutale JJ, Thordarson H, Abbas ZG, Vetvik K. Microalbuminuria among Type 1 and Type 2 diabetic patients of African origin in Dar Es Salaam, Tanzania. BMC Nephrol. 2007;8:2.
14. Diabetes Declaration and Strategy for Africa:Press Release,Cape Town,South Africa. 2006 December.
15. UK Prospective Diabetes Study Group.Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998(352):854-65.
16. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2006 Aug;29(8):1963-72.

17. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405-12.
18. Blanca RBRE, FG. Pharmacological therapy compliance in diabetes. Salud Publica Mexico. 2001;43:233-6.
19. Swaby P, Wilson E, Swaby S, Sue-Ho R, Pierre R. Chronic diseases management in the Jamaican setting: HOPE worldwide Jamaica's experience. P N G Med J. 2001 Sep-Dec;44(3-4):171-5.
20. Bhrett AM, BS. Barriers to adherence in a free medication program for low income individuals with type 2 diabetes (Ph.D).Louisiana State University. 1999.
21. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care. 2002 Jun;25(6):1015-21.
22. Shobhana R, Begum R, Snehalatha C, Vijay V, Ramachandran A. Patients' adherence to diabetes treatment. J Assoc Physicians India. 1999 Dec;47(12):1173-5.
23. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch Intern Med. 2000 Nov 27;160(21):3278-85.
24. Melikian CW, TJ;Vanderplas,A;Dezil,CM;Chang,E. Adherence to oral diabetic therapy in a managed care organization. Clinical Therapy. 2002;24(3):460-7.
25. Sclar DA, Robison LM, Skaer TL, Dickson WM, Kozma CM, Reeder CE. Sulfonylurea pharmacotherapy regimen adherence in a Medicaid population: influence of age, gender, and race. Diabetes Educ. 1999 Jul-Aug;25(4):531-2, 5, 7-8.
26. Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. Diabet Med. 2002 Apr;19(4):279-84.
27. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005 Aug 4;353(5):487-97.
28. Vermeire E, Wens J, Van Royen P, Biot Y, Hearnshaw H, Lindenmeyer A. Interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005(2):CD003638.
29. Kalyango JN, Owino E, Nambuya AP. Non-adherence to diabetes treatment at Mulago Hospital in Uganda: prevalence and associated factors. Afr Health Sci. 2008 Jun;8(2):67-73.
30. Grant RW, Devita NG, Singer DE, Meigs JB. Polypharmacy and medication adherence in patients with type 2 diabetes. Diabetes Care. 2003 May;26(5):1408-12.
31. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 1999 Dec;47(6):555-67.
32. Stewart RB, Caranasos GJ. Medication compliance in the elderly. Med Clin North Am. 1989 Nov;73(6):1551-63.
33. Heloisa Turcatto Gimenes MLZ, Vanderlei Jose Haas. Factors related to patient adherence to antidiabetic therapy. Revista Latino-Americana de Enfermagem. 2009;17(1).

34. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med. 2005 May 23;165(10):1147-52.
35. Sud A, Kline-Rogers EM, Eagle KA, Fang J, Armstrong DF, Rangarajan K, et al. Adherence to medications by patients after acute coronary syndromes. Ann Pharmacother. 2005 Nov;39(11):1792-7.
36. Chale SS, Swai AB, Mujinja PG, McLarty DG. Must diabetes be a fatal disease in Africa? Study of costs of treatment. BMJ. 1992 May 9;304(6836):1215-8.
37. Yusuff KB, Obe O, Joseph BY. Adherence to anti-diabetic drug therapy and self management practices among type-2 diabetics in Nigeria. Pharm World Sci. 2008 Dec;30(6):876-83.
38. Goldman DP, Joyce GF, Escarce JJ, Pace JE, Solomon MD, Laouri M, et al. Pharmacy benefits and the use of drugs by the chronically ill. JAMA. 2004 May 19;291(19):2344-50.
39. Martin BC, McMillan JA. The impact of implementing a more restrictive prescription limit on Medicaid recipients. Effects on cost, therapy, and out-of-pocket expenditures. Med Care. 1996 Jul;34(7):686-701.
40. Karter AJ, Parker MM, Moffet HH, Ahmed AT, Ferrara A, Liu JY, et al. Missed appointments and poor glycemic control: an opportunity to identify high-risk diabetic patients. Med Care. 2004 Feb;42(2):110-5.
41. Ahmed AT, Karter AJ, Liu J. Alcohol consumption is inversely associated with adherence to diabetes self-care behaviours. Diabet Med. 2006 Jul;23(7):795-802.
42. Siminerio L. Challenges and strategies for moving patients to injectable medications. Diabetes Educ. 2006 Mar-Apr;32 Suppl 2:82S-90S.
43. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care. 2002 Dec;25(12):2335-41.
44. Khan S, Rupp J. The effect of exercise conditioning, diet, and drug therapy on glycosylated hemoglobin levels in type 2 (NIDDM) diabetics. J Sports Med Phys Fitness. 1995 Dec;35(4):281-8.
45. Delahanty LM, Halford BN. The role of diet behaviors in achieving improved glycemic control in intensively treated patients in the Diabetes Control and Complications Trial. Diabetes Care. 1993 Nov;16(11):1453-8.
46. Piette JD, Wagner TH, Potter MB, Schillinger D. Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. Med Care. 2004 Feb;42(2):102-9.
47. Ciechanowski PS, Katon WJ, Russo JE, Walker EA. The patient-provider relationship: attachment theory and adherence to treatment in diabetes. Am J Psychiatry. 2001 Jan;158(1):29-35.
48. RUBIN RP, M;Saudek,CD,. Differential effect of diabetes education on self-regulation and life- style behaviors. Diabetes Care. 1999;14(4):335-8.
49. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB, et al. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. Diabetes Care. 2007 Apr;30(4):807-12.

50. Sackett LD HR, Gordon HG,Tugwell P. Clinical Epidemiology.A basic science for clinical medicine;Textbook of Clinical Epidemiology.2nd edn.London:Little,Brown and Company. 1991:249-77.
51. Hernandez-Ronquillo L, Tellez-Zenteno JF, Garduno-Espinosa J, Gonzalez-Acevez E. Factors associated with therapy noncompliance in type-2 diabetes patients. Salud Publica Mex. 2003 May-Jun;45(3):191-7.
52. Barnes L, Moss-Morris R, Kaufusi M. Illness beliefs and adherence in diabetes mellitus: a comparison between Tongan and European patients. N Z Med J. 2004 Jan 30;117(1188):U743.
53. Correlates of expected success at adherence to health regimen of people with IDDM. J Adv NursLo,R. 1999;30(2):418-24.
54. Pladevall M DG, Williams LK,Xi H,Potts LA,Lafata JE,. Clinical outcomes and adherence to medications measured by claims data in patients with diabetes. Diabetes Care. 2004;27:2800-5.
55. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation. 2001 Jun 5;103(22):2668-73.
56. CS R. Measuring adherence with therapy for chronic diseases:Implications for the treatment of heterozygous familial hypercholesteremia. American Journal of Cardiology. 1993;72:68D-74D.
57. RB H. Determinants of compliance:The disease and the mechanism of treatment.Baltimore,John Hopkins University Press. 1979.
58. Dunbar- Jacob J SS, Rohay J,Burke LE. Electronic methods in assessing to medical regimens.In:Krantz D,Baum A,editors.Technology and methods in behavioral medicine.Mahwah,NJ:Lawrence Erlbaum Associates. 1998:95-113.
59. World Health Organization.Physical status:the use and interpretation of anthropometry.Report of a WHO Expert Commitee.WHO Technical Report Series 854.Geneva. 1995.
60. World Health Organization,Obesity:Preventing and managing the global epidemic.Report of a WHO Consultation.WHO Technical Report Series 894.Geneva. 2000.
61. Chobanian AV BG, Black HR et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure.
. Hypertension 2003;42(6):1206-52.
62. Stults B SA, Miller T. Prevention of Diabetic Foot ulcers and Lower Extremity Amputation. American College of Physicians. 2007:51.
63. Goldstein DE LR, Lorenz RA et al. American Diabetes Association.Tests of Glycemia in Diabetes. Diabetes Care. 2003;26(1):S106-8.
64. Federation ID. Clinical Guidelines Task Force,Global Guideline for Type 2 Diabetes,Chapter 6. 2005.
65. National Kidney Foundation "K/DOQI clinical practice guidelines for chronic kidney disease,searched on 29th September 2010. 2001.
66. Elizabeth H.B WK, Michael V.K,Carolyn R,Greg E.S et al. Relationship of Depression and Diabetes Self-care,Medication Adherence and Preventive Care. Diabetes Care. 2004;27(9):2154-60.

67. Wooldridge KL WK, Graber AL et al. The relationship between health beliefs,adherence,and metabolic control of diabetes. Diabetes Educator. 1992;18:495-500.
68. Glasgow RE MK, Schafer LC. Self-care behaviours and glycemic control in type 1 diabetes. J Chronic Disease. 1987;40:399-412.
69. Kravitz RL HR, Sherboure CD et al. Recall of recommendations and adherence to advise among patients with chronic medical conditions. Arch Intern Med. 1993;153:1869-78.
70. Hays RD KR, Mazel RM, et al. The impact of patient adherence on health outcomes for patients with chronic disease in medical outcomes study. J Behav Med. 1994;17:347-60.
71. phillips LS BW, Cook CB,Doyle JP,El-Kebbi IM,Gallina DL,Miller CD,Ziemer DC,Barnes CS. Clinical inertia. Ann Intern Med. 2001;135:825-34.