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# MIXED-EFFECTS MODEL FOR LONGITUDINAL STUDY OF FASTING BLOOD SUGAR LEVEL AMONG TYPE 2 DIABETES PATIENTS

BY

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(UDS/MBM/0012/12)

THESIS SUBMITTED TO THE DEPARTMENT OF STATISTICS, FACULTY OF MATHEMATICAL SCIENCES, UNIVERSITY FOR DEVELOPMENT STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF MASTER OF SCIENCE DEGREE IN BIOMETRY

October, 2015

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# **DECLARATION**

I hereby, declare that this thesis is the result of r	my own original work and that no
part of it has been presented for another degree in	n this university or elsewhere:
Candidate's Signature:	Date: 27/10/2015
Name: ADAMPAH TIMOTHY	

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## ABSTRACT

The main purpose of the study was to determine the pattern of change in Fasting Blood Sugar (FBS) level as well as to obtain the best model for predicting patient's FBS level based on some covariates. A historic data is obtained from the diabetes unit in Ketu-South Municipal Hospital, on 26 (32.5%) males and 54 (67.5%) females of the 80 type 2 diabetes patients on treatment for a 2-year period. Their FBS level, body weight and blood pressure were regularly monitored and thus generating repeated measures. Profile analysis was use to study the pattern of change in the FBS level with respect to the covariates. Linear mixed effect model was use for modeling the FBS level of the patients. The outcome showed that, the trend of the FBS level over time follows cubic function, indicating that initially the FBS level usually increases and then eventually declines only to rise again. The duration of treatment, the body weight, the blood pressure (systolic and diastolic), and the educational status were the factors that significantly influenced the FBS level of patients on treatment. A stepwise selection method was use to fit a reduced regression prediction model from a full prediction model. The trend equation was developed to estimate the rate of change in FBS level. Diagnostic test confirmed that the regression and trend models based on the covariates are adequate for predicting and estimating FBS level of diabetic patients on treatment. It is therefore, recommended that further research should be done to include other risk factors of diabetes in order to improve upon the regression model for the strategic intervention and management of diabetes.



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I say thank you to the staff of Ketu-South Municipal Hospital, especially the diabetic unit for the great help you offered me in the collection of the data.

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# DEDICATION

I dedicate this piece of work to my unstinting friend, Ruth Polishuk, my dearest mother, Vincentia Adampah and my lovely father J.K Adampah.

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# LIST OF ABBREVIATIONS AND ACRONYMS

BMI	Body Mass Index
BP	Blood Pressure
BW	Body Weight
CD4	Cluster of Differentiation Four
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
CI	Confidence Interval
eGFR	estimated Glomerular Filtration Rate
FBS	Fasting Blood Sugar
FI	Fasting Insulin
FG	Fasting Glucose
GWAS	Genome-Wide Association Study
HAART	Highly Active Antiretroviral Therapy
HbAlc	GlycatedHaemoglobinA1c
HIV	Human Immunodeficiency Virus
HOMA	Homeostasis Model Assessment
KSMA	Ketu South Municipal Assembly
LTPA	Leisure-Time Physical Activity
LDL-C	Low-Density Lipoprotein Cholesterol



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MIDD	Maternally inherited Diabetes and Deafness
MODY	Maturity-Onset Diabetes of the Young
OA	Osteoarthritis
OAK	Knee Osteoarthritis
QoL	Quality of Life
RNA	Ribonucleic Acid
SBP	Systolic Blood Pressure
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
TAG	Triacylglycerides
T2D	Type-2-Diabetes
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization



## **CHAPTER ONE**

## **INTRODUCTION**

## 1.1 Background of study

Glucose is the primary and the indispensable source of energy for the cells in the body. The blood glucose level in the body is tightly regulated and maintained at approximately 5mmol/l by the hormones insulin and glucagon. Failure to maintain blood glucose in the normal range leads to chronically high (hyperglycemia) or low (hypoglycemia) glucose levels. In the absence of adequate treatment, hypoglycemia may result in lethargy, loss of consciousness and, in extreme cases, can lead to coma, brain damage and death. In case of persistent hyperglycemia, such as untreated diabetes mellitus, the high glucose level in the blood is a main risk factor for the development of diabetes related complications, including retinopathy, nephropathy, diabetic neuropathy, and erectile dysfunction (Brownlee and Cerami, 1981). Diabetes mellitus is a disease characterized by the inability to regulate blood glucose levels, resulting in chronically increased blood glucose levels, or 'hyperglycemia (Saltielet al., 2001). Multiple types of diabetes mellitus can be distinguished on the basis of the cause of the hyperglycemia, which either results from insufficient or even absence of insulin secretion by the  $\beta$ -cells, referred to as insulin deficient (type 1 diabetes), in combination with a suboptimal response of peripheral target tissues to insulin, a phenomenon referred to as insulin resistance (type 2 diabetes).



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In case of type 1 diabetes, dysregulation of the immune system results in immunological intolerance towards the insulin-producing  $\beta$ -cells. This leads to inflammation of the islets Langerhans and selective destruction of the  $\beta$ -cells of the pancreas (Atkinson and Eisenbarth,2001). Insulin synthesis and secretion are also affected in Maturity-Onset Diabetes of the Young (MODY) (Vaxillaire and Froguel, 2006) and Maternally inherited Diabetes and Deafness(MIDD), due to genetic factors impacting on  $\beta$ -cell development and mitochondrial function (Maasen *et al.*, 2004). Thus the risk factors for type 1 diabetes may include autoimmune, genetic, and environmental factors. About 5-10% of people with diabetes have type 1.

Type 2 diabetes results from an imbalance between insulin sensitivity and insulin secretion. Both longitudinal and cross-sectional studies have demonstrated that the earliest detectable abnormality in type 2 diabetes is an impairment of the body's ability to respond to insulin. Impaired insulin action is observed in several tissues e.g. skeletal muscle, adipose tissue and the liver. It leads to increased insulin secretion from the pancreas to overcome impaired insulin action (Bloomgarden, 1998). Compensatory hyperinsulinemia maintains glucose level within normal range, but in individual at high risk of developing diabetes, beta cells function eventually declines and leads to the development of impaired glucose tolerance and eventually overt diabetes mellitus (Stumvoll *et al.*, (2005); DeFronzo *et al.*, (1992)). Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes. Type 2 diabetes is now increasingly being diagnosed in adult children and adolescents. Type 2



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diabetesmay account for about 90% to 95% of all diagnosed cases of diabetes, (www.diabetesatlas.org).

#### **1.2 Problem Statement**

Non communicable diseases such as diabetes, hypertension, stroke among others which were major health problems in the developed countries are now becoming rampant in the developing countries like Ghana. This disease has added to the already numerous infectious diseases that we are struggling with in the sub-region. The issue of Diabetes has become a worldwide canker; each year more than 396 million people worldwide die from diabetes and its complications (International Diabetes Federation, 2009). This number is expected to increase by more than 50 percent over next decade (www.who.iny/mediacentre.org). Every day, millions of Dollars are being spent on Diabetes worldwide, estimated global healthcare expenditure to treat and prevent diabetes and its complications is at least 376 billion US Dollars (USD) in 2010. By 2030, this amount is projected to exceed some 490 billion USD (www.diabetesatlas.org).

Experts in the medical field work tirelessly to come out with the requisite panacea to help alleviate if not cure the disease. Due to increasing incidence of this deadly chronic non-communicable disease, health practitioners worldwide are trying their possible best to embark on the best treatment and management of the diabetic patients they have, to ensure a better healthcare of the patient. During the treatment of the diabetic patients, it will be very useful to the health practitioners to be predicting the Fasting Blood Sugar (FBS) levels at each stage to enable them know and prepare in advance on the next strategic healthcare management actions



to take as far as the health of the patient is concerned. The health Practitioners and Policy makers find it difficult to predict the FBS level of the diabetic patient, which is very fundamental to the healthcare process in the administration of the drugs. This has triggered biostatistician and/or biometricians to direct their attention towards fitting a linear mixed effects model of the FBS level of Type-2-Diabetics (T2D). In Ghana for instance, some works were done on diabetes but fitting models for prediction of FBS level is limited in literature. This research seeks to unearth a model for reliable prediction of the FBS level of the patients and also to obtain the factors that significantly affect the change in FBS level of patients on treatment.

# **1.3 General Objective**

The main objective of this study is to develop an appropriate linear mixed effects model for predicting the FBS level of type 2 diabetes patients.

### **1.4 Specific Objectives of the study**

- i. To obtain the best model for predicting patients FBS level based on some covariates.
- ii. To determine the pattern of change in FBS level in type 2 diabetes patients on treatment with respect to duration of treatment.
- iii. To determine the factors that significantly affects the changes in FBS level of type2 diabetes patients.



# **1.5 Research Questions**

The following research questions are proposed to be answered in order to achieve the objectives of this research

- i. Can we model the predicting the FBS level of diabetic patients on treatment?
- ii. What factors significantly affect the change in FBS levels of type 2 diabetes patients on treatment?
- iii. What is the pattern of change in FBS levels of type 2 diabetes patient on treatment?
- iv. What is the relationship between FBS level and duration of treatment?

# 1.6 Significance of the Study

The increase in the incidence of type 2 diabetes is strongly associated with obesity and lack of physical activity. Type 2 diabetes is a major cause of kidney failure, lower-limb amputation, blindness, heart disease and is a leading cause of death among adults (Appuhamy*et al*, 2014). Diabetes prevalence studies in southern Ghana have recorded a steady increase (Ama de-Graft Aikins, 2007). This study is aimed to reveal the predisposing factors that influence the epidemiological distribution of type 2 diabetes and to obtain the best model for predicting patients FBS level based on prognostic factors. It will be useful for policy makers and health workers for planning interventions and effective healthcare strategies for addressing the health of type 2 diabetes patients on long-term treatment. Other scholars who show interest in working in this area of study can also make good use of this contribution.

# 1.7 Outline of Thesis

This segment captured outline of the thesis. The chapter two (2) of the work entailed the epidemiology and burden of T2D globally, prevalence of Diabetes mellitus in Ghana, risk factors for T2D, diet and weight, and review of some related works. The chapter three (3) covered the methodology for this study; study population, source of the data collected, modeling approach, model evaluation and profile analysis using mixed effects model. This chapter four (4) presents the results of the data analyses and the discussion based on the results obtained. This final chapter presents the conclusion based on the discussion of the results and the recommendations are made thereafter, list of publication and finally references.



## **CHAPTER TWO**

## LITERATURE REVIEW

#### 2.0 Introduction

This segment captured the epidemiology and burden of T2D globally, prevalence of Diabetes mellitus in Ghana, risk factors for T2D, diet and weight, and review of some related works.

## 2.1 Epidemiology and Socio-economic burdens of Type 2 Diabetes mellitus

Type 2 diabetes is the most common form of diabetes and comprises 90% of people with diabetes around the world (WHO, Fact Sheet No.312, 2009). Type 2 diabetes mellitus has reached epidemic proportions with explosive increase in incidence worldwide over the past few decades. The world prevalence of diabetes in 2010 among adults aged 20-79 years is estimated to 6.4%, affecting 285 million adults (Shaw *et al.*, 2010). Each year more than 396 million people worldwide die from diabetes and its complications (International Diabetes Federation, 2009). This number is expected to increase by more than 50 percent over next decade (WHO, Fact Sheet No.312, 2009). Estimated global healthcare expenditure to treat, manage and prevent diabetes and its complications is at least 376 billion US Dollars (USD) in 2010. By 2030, this number is projected to exceed some 490 billion USD (www.diabetesatlas.org).

Type 2 diabetes mellitus is more prevalent in developed countries; the increase in incidence seems to be more pronounced especially in populations that are experiencing rapid westernization (Zimmet *et al.*, 2002). Apart from microvascular complications, cardiovascular disease, with its attendant morbidity



and mortality, diabetes is now on the rise in the developing countries. Evidence suggests that environmental factors are major determinants of the increasing rates of diabetes (WHO, 1999). Overweight and obesity are increasing dramatically and contribute to the burden of diabetes mellitus and other chronic health conditions. Indeed, the modern environment and sedentary lifestyles promotes the risk factors that cause diabetes.

## 2.2 Prevalence of Diabetes mellitus in Ghana

Although diabetes was thought to be rare in sub-Saharan Africa, recent studies from some countries suggests that the disease may now be more common in sub-Saharan Africa than previously thought (Cooper *et al.*, 1997;Mbanya *et al.*, 1999;Aspray *et al.*, 2000). Though epidemiological data on the prevalence of diabetes in Ghana is scanty, evidence suggests that it is on the increase. In the 1950s, the prevalence of diabetes among an outpatient urban population in Accra was estimated at less than 0.5% (Dodu, 1958). The impression was therefore created among policy makers that diabetes is rare in Ghana. However, a recent study (Amoah *et al.*, 2002) reported a high prevalence rate of 6.3%. A study on the key predisposing factors of diabetes which assessed the prevalence and sociodemographic aspects of overweight and obesity among residents from rural and urban Accra reported an overall crude prevalence of 23.4% and 14.1%, respectively (Amoah, 2003).

## 2.3 Risk factors for type 2 diabetes

The identified risk factors can be classified as non-modifiable and modifiable. Age and ethnicity are the main non-modifiable determinants of diabetes

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prevalence in Africa. Among the modifiable risk factors, residence which defines the environment and lifestyle seems to be a major determinant, since urban residents have a 1.5 to 4-fold higher prevalence of diabetes compared to their rural counterpart (Gill *et al.*, 1997).

Irving et al., (2002), also worked on microvascular correlation of blood pressure, plasma glucose, and insulin resistance in health. The associations between hypertension, insulin resistance and glucose intolerance are poorly understood. Altered microvascular structure and function could contribute by increasing peripheral vascular resistance and decreasing tissue delivery of glucose. They addressed this hypothesis in a sample of healthy men. They studied 105 healthy young men aged 23-33 years. Insulin resistance was calculated using the Homeostasis Model Assessment (HOMA). Video capillaroscopy was used on the dorsum of the finger to measure skin capillary density, and in nail fold capillaries to measure capillary blood velocity. Skin vasodilatation was measured with laser Doppler fluximetry on the forearm following heating and iontophoresis of acetylcholine. The association between hypertension and insulin resistance is unlikely to be explained by altered microvascular structure and function. However, changes in the microvasculature are found in subjects with early and subtle elevations in blood pressure or fasting plasma glucose in advance of their crossing conventional thresholds for the diagnosis of hypertension or diabetes mellitus.

Urban lifestyle in Africa is characterized by changes in dietary habits involving an increase in consumption of refined sugars and saturated fat, and a reduction in



fibre intake (Sharma *et al.*, 1996). Moreover, there is a reduction in physical activity associated with urban lifestyle. Rural populations rely upon foot walk as transportation means and often have intense agricultural activities as their main occupation. Rural dwellers therefore have a high physical activity related energy expenditure compared to urban subjects, thus explaining the higher rates of obesity in the cities. Obesity is also at least 4 times higher in urban areas compared to rural (Aspray *et al.*, 2000) and hence high risk of diabetes among urban folks than the rural folks.

Many studies have elaborated the associations between several risk factors and the risk of type 2 diabetes. Body mass index (BMI), lipids, hypertension, smoking, physical inactivity, low education, dietary patterns, family history, and recently also specific genes are the most frequently documented risk factors for type 2 diabetes (Lyssenko *et al.*, 2008). This means that the health risks for diabetes are multifactorial with a cumulative effect.

## 2.4 Type 2 Diabetes, Diet and Weight

A guiding principle in the treatment of type 2 diabetic patients has been the recommendation to lose of weight (American Diabetes Association, 2004). This is because the health benefits of weight loss have long been recognized (Newburgh, 1942). As weight loss progresses and is maintained, an improvement of glycaemia may be evidenced by a reduction in glycosylated haemoglobin (Kelley *et al.*, 1993). Redmon *et al.*, (2005) reported on the 2-year outcome of weight loss therapies in type 2 diabetic patients that the end result was a weight loss of 4.6 kg sustained over 2 years, which led to a decrease of HbA<sub>1c</sub> of 0.5%.



The approach with regard to weight loss in diabetic patients will need to be more aggressive. A program requires more than educational sessions with dietitians and a manual of instruction on weight loss, as was done here. Behavioral change requires a more engaged and intensive program. This was successful in the Diabetes Prevention Program (Knowler *et al.*, 2002). Also, further research was done in the Redmon study, to investigate ways to increase the amount of weight loss attainable with current treatment modalities and to facilitate long-term weight loss maintenance.

Appuhamy *et al.*, (2014) modeled the effects of diet and exercise interventions on diabetes risk factors in adults without diabetes: meta-analyses of controlled trials. Adults receiving diet and exercise education for approximately one year experienced significant (P<0.001) reductions in FI ( $-2.56 \pm 0.58 \text{ mU/L}$ ), FG ( $-0.18 \pm 0.04 \text{ mmol/L}$ ), SBP ( $-2.77 \pm 0.56 \text{ mm Hg}$ ), TAG ( $-0.258 \pm 0.037 \text{ mmol/L}$ ) and BMI ( $-1.61\pm 0.13 \text{ kg/m}^2$ ). These risk factor changes were related to a mean calorie intake reduction of 273 kcal/d, a mean total fat intake reduction of 6.3%, and 40 minutes of moderate intensity aerobic exercise four times a week. Their study showed that calorie and total fat intake restrictions coupled with moderate intensity aerobic exercises significantly improved diabetes risk factors in healthy normoglycemic adults although normoglycemic adults with glucose, insulin, and lipid abnormalities appear to benefit more.

## 2.5 Related Works

Leon *et al.*, (2003) researched into a 20-year longitudinal observational study of somatic antidepressant treatment effectiveness. Their study revealed that patients



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who received higher levels of antidepressant treatment tended to have more prior episodes more severed expressive symptoms, and more intensive somatic therapy during prior episodes and prior well intervals than those who received lower levels. Treatment effectiveness analyses that were stratified by propensity for treatment intensity demonstrated that those who received higher levels of antidepressant treatment were significantly more likely to recover from affective episodes. In contrast, those treated with lower levels were no more likely to recover than those who did not receive somatic treatment. Despite the indications of more severed expressive illness, those who received higher levels of somatic antidepressant treatment were more likely to recover from recurrent affective episodes.

Chang et al., (2005) modeled the effect of surgical and nonsurgical treatment on longitudinal outcomes of lumbar spinal stenosis over 10 Years. The 10-year rate of subsequent surgical procedures was 23% and 38% for patients initially treated surgically and non-surgically, respectively, and the overall 10-year survival rate was 69%. Patients undergoing initial surgical treatment had worse baseline symptoms and functional status than those initially treated non-surgically.

Klein *et al.*, (2006) examined the relationship of retinopathy in persons without diabetes mellitus to the 15-year cumulative incidence of diabetes mellitus and hypertension. The study showed that Retinopathy was present in 7.3% of the non-diabetic persons in the cohort and 5.4% of the non-diabetic, non-hypertensive cohort at baseline. The 15-year cumulative incidence of diabetes was 12.5% and of hypertension 54.1%. This was estimated by the product-limit method.



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Modeled the parental history and risk of type 2 Diabetes in overweight Latino adolescents. They followed 247 overweight Latino children annually for 5 years. The study deduced that the impact of family history of diabetes on insulin dynamics was confirmed in cross-sectional studies in adults (12, 21) but not in younger children (15, 16). The longitudinal linear mixed-effects modeling was used.

Powers *et al.*,(2008) modeled the effect of a hypertension self-management intervention on Diabetes and cholesterol control. He compared changes in HbA among a subgroup of 216 patients with diabetes and LDL-C among 528 patients with measurements during the study period. Changes in these laboratory values over time were compared between the 2 treatment groups using linear mixed-effects models. For the patients with diabetes, the hypertension self-management intervention resulted in a 0.46% reduction in HbA over 2 years compared with usual care. For LDL-C, there was a minimal 0.9 mg/dL between group difference that was not statistically significant. There was a significant effect of the self-management intervention on the unintended target of HbA, but not LDL-C. Chronic disease self-management interventions might have "spill-over" effects on patients' co-morbid chronic conditions.

Webster *et al.*, (2010) studied the longitudinal association of common susceptibility variants for type 2 diabetes and obesity with fasting glucose level and BMI. Their study showed no significant associations between SNPs and changes in fasting glucose or BMI in the same individuals. The Longitudinal linear mixed-effects models was used.



Kaku *et al.*, (2010) revealed that the pathophysiological features of type 2 diabetes jointly contribute to the development of this disease. It has become widely recognized that the functional pancreatic cell mass decreases over time and type 2 diabetes is a progressive disease. Impaired insulin secretion is characterized by lowered glucose responsiveness. In particular, the decrease in postprandial phase secretion is an essential pathophysiological condition. Glucolipotoxicity, if left untreated, results in the decrease in the functional pancreatic cell mass. The goal of diabetes treatment is to secure a quality of life (QoL) and lifespan comparable to those of healthy people, and a prerequisite for this is the prevention of onset and progression of vascular complications. The need for earlier initiation of proactive intervention must be emphasized, as well as the importance of comprehensive (blood sugar, blood pressure, and lipids) intervention in attaining this goal.

Wu and Briollais (2012) proposed a novel mixed-effects model for longitudinal changes of systolic blood pressure (SBP) over time that could estimate the joint effect of multiple sequence variants on SBP after accounting for familial correlation and the time dependencies within individuals. It was found that multilocus genotypes (GG,TT,AG,GG), (GG,TT,GG,GG), and (GG,TT,AA,AG) were associated with higher SBP and (GG,CT,AA,AA), (AA,TT,AA,AA), and (AG,CT,AA,AG) were associated with lower SBP. The linear mixed-effects model provides a powerful tool for GWAS and the analysis of joint modeling of multilocus genotypes.



Celli *et al.*, (2012) studied the longitudinal inspiratory capacity changes in chronic obstructive pulmonary disease. They used mixed-effects model and Cox regression analysis.

Zheng *et al.*, (2012) modeled the Semi-parametric Mixed Effect Model with Application to the Longitudinal Knee Osteoarthritis (OAK) Data. A stochastic mixed-effect model was used to evaluate the similarity of trajectories associated with increasing disease severity of OA in both knees. Then, a non-parametric mixed-effects model, based on cubic B-spines, was developed to characterize the unknown nonlinear trend of logits as a function of time 1-order. A Markov Transition Model was developed to characterize the transitions among multistates of knee OA. This newly developed approach allows more flexible functional dependence of the ordinal outcome, levels of increasing knee OA severity, on the covariates.

Metcalf *et al.*, (2014) assessed a 10-year coronary heart disease risk in people with Type 2 diabetes mellitus: Framingham versus United Kingdom Prospective Diabetes Study. They compared the 10-year absolute risks of coronary heart disease (CHD) using a Framingham equation and a United Kingdom Prospective Diabetes Study (UKPDS) equation in adults with Type 2 diabetes. Participants were from a cross sectional survey of a randomly selected population. There were 461 people with newly (n = 132) or previously diagnosed (n = 329) diabetes aged 35 to 74 years with no past history of cardiovascular disease or nephropathy. They predicted 10-year CHD risk by age, gender, and newly or previously diagnosed diabetes. Overall the mean 10-year CHD risks predicted by the two equations

were similar. Among men, the UKPDS and Framingham scores were almost identical below 60 years of age but at older ages, the UKPDS score was 4%-11% higher than Framingham. For women, the Framingham score was higher than the UKPDS score between the ages of 40 and 65 years, but the UKPDS score was about 4%-5% higher for women aged 70 years and over. The UKPDS equation tended to give higher risk estimates in people with a predicted 10-year Framingham CHD risk above 15%. It was concluded that, Framingham CHD risk scores tended to be lower than UKPDS scores primarily in people above standard thresholds for drug treatment, so the clinical impact of underestimating risk is likely.

Spangler *et al.*, (2013) modeled the correlation between diabetes prevalence and subsequent cancer mortality in North Carolina counties. Their study assessed the relationship between colorectal, breast and prostate cancer mortality, and diabetes prevalence measured years earlier at the county level in the 100 counties of North Carolina. The multivariate linear regression was carried out to evaluate the contribution of pre-existing diabetes prevalence to cancer mortality, controlling county level covariates. Average North Carolina county level prevalence of diabetes mellitus in 2004 (9%) was higher than the average national prevalence of diabetes in 2004 (7%). Mortality rates for breast, colorectal and prostate cancers at the county level were also higher than those nationally. In multivariate analysis, county level 2005-2009 total cancer mortality as well as mortality from colon and prostate cancers correlated with county level 2004 diabetes prevalence rates. Diabetes mellitus prevalence in 2004 explained 31%, 34% and 42% of the

variance of mortality from prostate, colorectal and total cancers respectively. Their findings supported the relationship between diabetes mellitus and cancer at the population level. Direct and indirect costs of cancer care in North Carolina in 2004 were 5.57 billion dollars. Because diabetes explained 42% of the variance of total county level cancer mortality, prevention and control of diabetes could save the state over 2 billion dollars. This study studied the correlation between diabetes and cancer whiles my work did not compare diseases but rather modeled FBS level and determined the factors or determinants that significantly influenced the FBS level of patients. Nevertheless, the linear mixed-effect model for longitudinal study is employed for both studies.

Adams and Luguterah (2013) also studied the longitudinal analysis of change in CD4 cell counts of HIV patients on ARV in the Builsa District Hospital. Their study revealed that a patient's initial CD4 cell count significantly influence their present CD4 cell count. The duration of treatment was also significant. It was revealed that CD4 cell count increased in about 40 cells/mm<sup>3</sup> in every 6 months. This according to them suggests that there is strong positive association between CD4 count and duration of treatment. The study was estimated using the linear mixed effects model. The method employed by Adams and Luguterah (2013) has coincided with this study, that is longitudinal analysis of change and linear mixed effects model.

Yarkiner *et al.*, (2013) modeled the applications of Mixed Models for investigating progression of chronic disease in a longitudinal data set of patient records from general practice. The applications of these models are illustrated by

analyzing the progression of Chronic Kidney Disease (CKD) over time, and in relation to the impact of known co-morbidities. The results of their model agree with previous research, in regards to the associations between individual comorbidities and CKD. Their model further evaluated the impact of combinations of these co-morbidities on the rate of progression of CKD, as measured by repeated estimated glomerular filtration rate (eGFR) readings. The results provide evidence that the methodological approach used was a useful and appropriate mechanism for investigating dynamic relationships within health-related data. The Generalized linear mixed models was used.

Finucane *et al.*, (2007) Translational methods in biostatistics: linear mixed effect regression models of alcohol consumption and HIV disease progression over time. A significant interaction between alcohol use and adherence to HAART is found: subjects who use alcohol and are not fully adherent to their HIV medications had higher log RNA (ribonucleic acid) viral load levels than fully adherent non-drinkers, fully adherent alcohol users, and non-drinkers who were not fully adherent.



# **CHAPTER THREE**

### **METHODOLOGY**

## **3.0 Introduction**

The methodology for this study is grouped into; study population, source of the data collected, modeling approach, model evaluation and profile analysis using mixed effects model.

## 3.1 Study Area

Ketu-South Municipal Assembly, established by Legislative Instrument (LI) 1469 of 1989, is one of the districts in the Volta Region of Ghana. It is located in the South/Eastern part of the region. The Municipality, which has its capital at Denu, is bordered to the North by the Ketu-North District, to the South by the Gulf of Guinea, East by the Republic of Togo, and to the West by the Keta Municipality. By its strategic location, a common border with the republic of Togo, the district serves as the Eastern Gate-way to Ghana where continuous cross-border trading activities occur. Ketu-South Municipality is relatively low with altitudes from less than 15 meters at the coast and increasing to 66 meters inland. The coastline is fairly smooth and marked by sandbars. The plain nature of the terrain makes movement within the municipal assembly easy. The municipal has Five (5) health demarcated sub-districts. The projected population based on the growth rate of 1.9%, according to 2010 population census is 168,894. The people living in the area are fishermen, fish mongers, petty traders and Kente weavers with a few government workers interspersed between them. The municipality is dominated



by the inhabitants of the traditional worshipers followed by Christians with various denominations and few Moslems. (KSMA, 2006)

The Ketu-South Municipal Hospital is one of the three hospitals and the only government hospital in the municipality, and is also the largest hospital in terms of attendance and infrastructure and the only hospital with a diabetes unit in the Municipality. All other hospitals, clinics and health centers in the municipality refer all diabetes cases to the diabetes unit of the Ketu-South Municipal Hospital.

### 3.2 Study population

The interest population in this study comprises type 2 diabetes patients who are on treatment at Ketu-South Municipal Hospital and whose FBS level, Blood Pressure (BP) and Body Weight (BW) were monitored sequentially from January 2012 to December 2013.

#### 3.3 Source of Data

The data collected was a secondary data from the diabetes unit of Ketu-South Municipal Hospital, where type 2 diabetes patients on treatment were monitored regularly and had their FBS and BP as well as weight measured monthly.

#### **3.4 Modeling Approach**

Generally there are two different types of data that are measured overtime: time series, which takes many measurements on a (usually) small set of individuals, and longitudinal data, which takes a small number of measurements on a (usually) large number of individuals. This research employed the latter, in which there is a small number of time points at which the individuals give responses, but in this case there is a large amount of data measured at any given time point.



Longitudinal data can be analyzed using various methods, such as latent variable models, generalized estimating equations and multivariate analysis of variance, amongst others, but the approach this work took was to fit linear mixed-effects (LME) model. This modeling approach is very flexible enough to account for the natural heterogeneity in the population, and can handle dropout and missing data. It also takes into account within and between sources of variation.

The study considered the changes in the FBS levels in type 2 diabetes patients on treatment over the period of study. By considering changes over time, the mixed effects model for longitudinal data analysis approach has the added advantages of observing changes more accurately by increasing the power and validity of measuring the change in FBS level.

The statistical analysis of the change in FBS level of type 2 diabetes patients over time was done using linear mixed effects models adjusted for potential independent variables, including blood pressure level, weight, time of follow-up, age, drugs taken, gender, marital status, educational level, and religious affiliation.

The general structure for the model is

$$y_{ij} = X_{ij}\beta + Z_{ij}b_i + \varepsilon_{ij} \tag{3.1}$$

where  $y_{ij} = (y_{i1}, y_{i2}, \dots, y_{in})^T, b_i \sim N_q(0, \psi)$  and  $\varepsilon_{ij} \sim N_{ni}(0, \sigma^2 I)$ 

 $\beta$  =Fixed effects, $b_i$  =Random effect for unit *i* 

 $\psi$  =Between-unit covariance matrix



 $\sigma^2 I$  =Within-unit covariance matrix

 $X_{ij}$  is the model matrix for the fixed effects for observations in group i.

 $Z_{ij}$  is the model matrix for the random effects for observation in group i

 $X_{ij}$  is an  $n_i \times j$  matrix with *jth* column, matrix  $Z_{ij}$  is an  $n_i \times k$  matrix. Both  $X_i$ and  $Z_i$  depend on *i*through  $t_i$ . Averaging over the distribution of the latent random effects  $b_i$ , the marginal (population-average) distribution of  $y_{ij}$  is

$$y_{ij} \sim N(X_{ij}\beta, \Sigma_{ij}) \tag{3.2}$$

Where  $\Sigma_i = Z_i \psi Z_i^T + \sigma^2 I$ 

If we take  $Z_{ij} = (1, 1, ..., 1)^T$  as random intercepts, then  $\Sigma$  has compound symmetry. The elements of  $\beta$  represent the effects of the variance in  $X_{ij}$  on the mean response, both for a single subject and on average for the population.

The full model is

$$Y_{ij} = \beta_0 + \beta_1 sex_i + \beta_2 age_i + \beta_3 edu_i + \beta_4 m. status_i + \beta_5 religion_i + \beta_6 preFBS_i + \beta_7 BP_{ij} + \beta_8 weight_{ij} + \beta_9 drug_i + \beta_{10} time_{ij} + \varepsilon_{ij}$$
(3.3)

where  $\beta_0$  is a random-effect intercept that varies according to *i*, where the patient's index *t* is the time.  $\beta_1 \dots \beta_9$  are fixed-effect parameters associated with the non-random predictors. The resulting estimated  $\beta$ , the fixed-effect parameter for each predictor in these models, represents the average change in FBS level for a unit increase in the predictor. Age, weight, BP, and FBS are continuous



variables. The co-variance and correlation matrix were estimated to determine which particular covariance model best fits the data.

# 3.4.1 Correlation and Covariance Structure

The main focus is to look at the component of variance to identify a variance or correlation model for regression in the mixed-fixed model. Estimation of the covariance matrix was used to do this. This is useful for comparing the strength of association between the pair of outcomes particularly when the variance is not constant.

$$\begin{pmatrix} E[(Y_{i1} - \mu_{i1})^{2}] & E[(Y_{i1} - \mu_{i1})]E[(Y_{i2} - \mu_{i2})] & \dots & E[(Y_{i1} - \mu_{i1})]E[(Y_{in} - \mu_{in})] \\ E[(Y_{i2} - \mu_{i2})]E[(Y_{i1} - \mu_{i1})] & E[(Y_{i2} - \mu_{i2})^{2}] & \dots & E[(Y_{i2} - \mu_{i2})]E[(Y_{in} - \mu_{in})] \\ \vdots & \vdots & \vdots & \vdots \\ E[(Y_{i2} - \mu_{i2})]E[(Y_{i1} - \mu_{i1})] & E[(Y_{i2} - \mu_{i2})]E[(Y_{i1} - \mu_{i1})] & \dots & E[(Y_{i2} - \mu_{i2})^{2}] \end{pmatrix}$$

$$(3.4)$$

The covariance is also written in terms of  $\delta_j^2$  and the correlation  $\rho_{jk}$ ;

$$Cov(Y_i) = \begin{pmatrix} \sigma_1^2 & \sigma_1 \sigma_2 \rho_{12} \dots \sigma_1 \sigma_n \rho_{1n} \\ \sigma_2 \sigma_1 \rho_{21} & \sigma_2^2 \dots \sigma_2 \sigma_n \rho_{2n} \\ \sigma_n \sigma_1 \rho_{n1} & \sigma_n \sigma_2 \rho_{n2} \dots \sigma_n^2 \end{pmatrix}$$
(3.5)

and 
$$Corr(Y_i) = \begin{pmatrix} 1 & \rho_{12}, \dots, \rho_{1n} \\ \rho_{21} & 1, \dots, \rho_{2n} \\ \rho_{n1} & \rho_{n2}, \dots, 1 \end{pmatrix}$$
 (3.6)

# 3.4.2 Model for Covariance Structure

In longitudinal data analysis, many covariance structures are possible, depending on how pairs of observations are related. Below are some of these structures.



# i) Autoregressive (1)

The AR (1) structure has the form

$$Corr(Y_i) = \begin{pmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{pmatrix}.$$
 (3.7)

It has homogeneous variance and correlations that decline exponentially with distance. Two measurements that are right next to each other in time are pretty correlated (depending on the value of  $\rho$ ), but as measurements get farther and farther apart they are less correlated.

# ii) Compound Symmetry

The compound symmetry takes the form

$$Corr(Y_i) = \begin{pmatrix} \sigma^2 + \sigma_1^2 & \sigma_1^2 & \sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma^2 + \sigma_1^2 & \sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma_1^2 & \sigma^2 + \sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma_1^2 & \sigma_1^2 & \sigma^2 + \sigma_1^2 \end{pmatrix}.$$
 (3.8)

It has a correlation between two separate measurements, but it is assumed that the correlation is constant regardless of how far apart the measurements are.

## iii) Variance Components

The variance covariance structure is the standard variance components, where there is no correlation between any pair of observations. The covariance structure is given as;

$$Corr(Y_i) = \begin{pmatrix} \sigma_A^2 & 0 & 0 & 0\\ 0 & \sigma_B^2 & 0 & 0\\ 0 & 0 & \sigma_{AB}^2 & 0\\ 0 & 0 & 0 & \sigma_{AB}^2 \end{pmatrix}$$
(3.9)


## iv) Toeplitz

The TOEP structure is similar to the AR(1) in that all measurements next to each other have the same correlation, measurements two apart have the same correlation different from the first, measurements three apart have the same correlation different from the first two, etc.. However, the correlations do not necessarily have the same pattern as in the AR(1). Technically, the AR(1) is a special case of the Toeplitz

$$Corr(Y_i) = \begin{pmatrix} \sigma^2 & \sigma_1^2 & \sigma_2^2 & \sigma_3^2 \\ \sigma_1^2 & \sigma^2 & \sigma_1^2 & \sigma_2^2 \\ \sigma_2^2 & \sigma_1^2 & \sigma^2 & \sigma_1^2 \\ \sigma_3^2 & \sigma_2^2 & \sigma_1^2 & \sigma^2 \end{pmatrix}$$
(3.10)

## v) ARMA(1,1): 1<sup>st</sup> order autoregressive moving average

The measurements are repeated across time, then the time variable will be prominent in this distance function. If measurements are repeated across location, then the distance function will involve some spatial metric reflecting the experimental design's geometry.

$$Corr(Y_i) = \begin{pmatrix} \sigma^2 & \sigma^2 \lambda & \sigma^2 \lambda \rho & \sigma^2 \lambda \rho^2 \\ \sigma^2 \lambda & \sigma^2 & \sigma^2 \lambda & \sigma^2 \lambda \rho \\ \sigma^2 \lambda \rho & \sigma^2 \lambda & \sigma^2 & \sigma^2 \lambda \\ \sigma^2 \lambda \rho^2 & \sigma^2 \lambda \rho & \sigma^2 \lambda & \sigma^2 \end{pmatrix}$$
(3.11)

#### Estimating $\beta$

The regression parameter  $\beta$  and the covariance parameters were obtained by maximizing the likelihood function;

$$L \propto (\sigma^2)^{-N/2} (\sigma^2) \Pi_i |W_i|^{1+2} \times exp\left\{ \sum_i \frac{-1}{2\sigma^2} (y_i - X_i \beta)^T W_i (y_i - X_i \beta) \right\}$$
(3.12)

where  $W_i = (\sigma^{-2}Z_i\psi Z_i^T + I)^{-1}$ , given the covariance parameters, L is maximized at Generalized Least Square estimate.



$$\hat{\beta} = (\Sigma_{i=1}^{m} X_{i}^{T} W_{i} X_{i})^{-1} (\Sigma_{i=1}^{m} X_{i}^{T} W_{i} y_{i}), \qquad (3.13)$$

#### 3.5 Model selection for covariance structures

Akaike's information criterion (AIC) and Bayesian Information Criterion (BIC) are indices of relative goodness-of-fit and may be used to compare models with the same fixed effects but different covariance structures. Both of these criteria apply rather generally for purposes of model selection and hypothesis testing. Formulae for their computation are

$$AIC = L(\hat{\theta}) - q \tag{3.14}$$

$$BIC = L(\hat{\theta}) - (q+2)\log(N^*) \tag{3.15}$$

where  $L(\hat{\theta})$  is the maximized log-likelihood or restricted log-likelihood (REML), q is the number of parameters in the covariance matrix, p is the number of fixed effect parameters and (N for ML and N-p for REML), where N is the number of subjects.

## **3.6 Model Evaluation**

To evaluate linear mixed effects model, Lagrange Multiplier (score) Test, Wald Test and Likelihood Ratio Test were used to check which one of them best fit the model. The tests generated values for the parameters (coefficients) that maximized the value of the likelihood function.

### 3.6.1 Lagrange Multiplier (Score) Test

This test requires estimating only one model. This test was used in testing whether adding another variance to a model will result in a significant improvement in the model fit, for instance if I run a model with only two predictor variables is run.



The test statistic was calculated based on the slope of the likelihood function at the observed values of the variables in the model.

#### 3.6.2 The Wald Test

Wald test tests the null hypothesis that a set of two parameters are simultaneously equal to zero. If the test fails to reject the null hypothesis, it suggests that removing the variables from the model will not substantially harm the fitness of the model, since a predictor with a coefficient that is very small relative to its standard error is generally not doing much help to predict the dependent variable.

## 3.6.3 Likelihood Ratio Test (LRT)

The model is performed by estimating the two models and comparing the fitness of one of them to the other. When you compare the likelihood of the two models, if the difference is significant, the one with more variables will fit the data significantly better than the more restrictive model. Thus the formula for the LR test statistic is

$$T_{LRT} = -2(\log \hat{L}_{reduced} - \log \hat{L}_{full}) = 2\log \hat{L}_{full} - 2\log \hat{L}_{reduced}$$
(3.16)

The test statistic is distributed by chi-square, with degree of freedom equal to the number of parameters.

#### **3.7 Profile Analysis**

Profile plot was staged in order to observe the pattern of change in FBS level over time. The variables used for this plot were sex, marital status, educational level, religious affiliation. Profiles were constructed for the means of FBS levels versus



the time points for the various groups. A scatter plot for the means of change in FBS level over time was staged.

### **3.8 MANOVA**

Multivariate Analysis of variance (MANOVA) was performed to complement and confirm the profile plot of test of parallelism. The MANOVA test is based on the matrices:

Wilks' Lambda (
$$\Lambda^*$$
) =  $\frac{|W|}{|B+W|}$  (3.17)

Lawley-Hotelling Trace =  $tr[BW^{-1}]$ 

Pillai trace =  $tr[B(\dot{B} + W)^{-1}]$ 

Roy's largest root = maximum eigenvalue of  $B(B + W)^{-1}$ 

where  $W = \sum_{i=1}^{g} \sum_{j=1}^{nl} (X_{ij} - \bar{X}_l) (X_{ij} - \bar{X}_l)'$  $B = \sum_{i=1}^{g} n_l (X_{ij} - \bar{X}_l) (X_{ij} - \bar{X}_l)'$ 

## 3.9 Test of Parallel profiles

Profiles are parallel when group differences are constant across variables. Computation of the difference of successive variables for each variable in each group was done and the two-sample Hoteling's  $T^2$  test performed.

## **Hypothesis**

$$H_0: C\vec{\mu}_x = C\vec{\mu}_y \quad \text{vs} \tag{3.18}$$
$$H_A: C\vec{\mu}_x \neq C\vec{\mu}_y$$



Let  $\vec{x}_1, \vec{x}_2, \dots, \vec{x}_n$  denote means of FBS level at the various time points of one level of a group of a sample of *n* from the *p*-variate normal distribution with mean

Let  $\vec{y}_1, \vec{y}_2, \dots, \vec{y}_m$  denote means of FBS level at the various time points of another level of a group of a sample of *m* from the *p*-variate normal distribution with mean vector  $\vec{\mu_y}$  and covariance matrix **S**.

Let

$$C_{(p-1)\times p} = \begin{bmatrix} 1 & -1 & 0 & 0 & \cdots & 0 & 0 \\ 0 & 1 & -1 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 1 & -1 & \cdots & 0 & 0 \\ 0 & 0 & 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 & -1 \end{bmatrix}$$
(3.19)

Then 
$$C\vec{X} = C\begin{bmatrix} X_1 \\ \vdots \\ X_p \end{bmatrix} = \begin{bmatrix} X_1 - X_2 \\ X_2 - X_3 \\ \\ X_{p-1} - X_p \end{bmatrix}$$
 (3.20)

Hoteling's  $T^2$  test

$$T^{2} = \frac{nm}{n+m} \left( C\vec{x} - C\vec{y} \right)' \left( C\mathbf{S}_{pooled} C' \right)^{-1} \left( C\vec{x} - C\vec{y} \right)$$
(3.21)

If  $H_0$  is true then

(3.22)

 $F = \frac{n+m-p}{(p-1)(n+m-2)}T^{2}$ 

has a F distribution with  $v_1 = p - 1$  and  $v_2 = n + m - p$ 

Thus we reject  $H_0$  if  $F > F_\alpha$  with  $v_1 = p - 1$  and  $v_2 = n + m - p$ 



However, if parallelism is proven for any group, further test of equality of profile is performed.

#### 3.10 Test of Equality of Groups (Parallelism assumed)

If parallelism is proven, it is appropriate to test for equality of profiles.

$$H_0: C'\mu_1 = C'\mu_2 = C'\mu_3 = \dots = C'\mu_n$$

$$H_A: C'\mu_1 \neq C'\mu_2 \neq C'\mu_3 \neq \cdots \neq C'\mu_n$$

OR

 $H_0$ : There is no difference between the levels of a factor

 $H_1$ : There is a difference between at least one level and the others

To perform this test, all the variables for each case in each group were averaged and the two-sample t - test performed

$$T^{2} = C' (\bar{X}_{1} - \bar{X}_{2}) [\left(\frac{1}{n_{1}} + \frac{1}{n_{2}}\right) C' S_{pooled} C]^{-1} C' (\bar{X}_{1} - \bar{X}_{2})$$
(3.23)

$$= \left(\frac{c'(\bar{x}_1 - \bar{x}_2)}{\sqrt{\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}c's_{pooled}c}\right)^2 > t_{n_1 + n_2 - 2(\alpha/2)}^2 = F_{1,n_1 + n_2 - 2(\alpha)}$$
(3.24)

Thus  $H_0$  was rejected if  $|t| > t_{\alpha+2}$  with df = n1 + n2 - 2. If equality of groups

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is proven, then flatness was checked.

et 
$$C_{(p-1)\times p} = \begin{bmatrix} 1 & -1 & 0 & 0 & \cdots & 0 & 0 \\ 0 & 1 & -1 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 1 & -1 & \cdots & 0 & 0 \\ 0 & 0 & 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 & -1 \end{bmatrix} \text{ and then } C\vec{X} = C\begin{bmatrix} X_1 \\ \vdots \\ X_p \end{bmatrix} = \begin{bmatrix} X_1 - X_2 \\ X_2 - X_3 \\ X_{p-1} - X_p \end{bmatrix}$$

Le

### 3.11 Test of Flatness of Variables

Basically the average of each segment across groups was used to compute this and each score has zero subtracted from , is squared and divided by the pooled error SSCP matrix (Swg).

$$T^{2} = n(C\vec{x} - \vec{0})'(CS_{pooled}C')^{-1}(C\vec{x} - \vec{0})$$
$$= n(C\vec{x})'(CS_{pooled}C')^{-1}(C\vec{x})$$
(3.25)

If  $H_0$  is true then

$$F = \frac{n-p+1}{(p-1)(n-1)}T^2$$
(3.26)

has a F distribution with  $v_1 = p - 1$  and  $v_2 = n - p + 1$ , thus was rejected  $H_0$  if  $F > F_{\alpha}$  with  $v_1 = p - 1$ 

#### **3.12 Trend Model Diagnosis**

This segment employed the ARCH-LM and the Shapiro-Wilks test in order to diagnose the developed model. This is to check whether there is concordance of the model with the real world observation, in order to make a meaningful conclusion or generalization.

## i) Shapiro-Wilks Test

The purpose of this test is the significance level for testing normality. Given a set of observations  $\bar{x}_1, \bar{x}_2, \bar{x}_3, ..., \bar{x}_n$  sorted in either descending or ascending order, the test statistics of Shapiro and Wilks *W* is defined as:

$$W = \frac{\left(\sum_{i=1}^{n} a_{i} x_{i}\right)^{2}}{\sum_{i=1}^{n} \left(x_{i} - \bar{x}\right)^{2}}$$
(3.27)

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where  $\bar{x} = 1/n \sum_{i=1}^{n} x_i$  is the sample mean and  $a_i$  for i = 1, 2, 3, ..., n are a set of "weight" whose values depend only on the sample size n

## ii) ARCH-LM Test

The conditional heteroscedasticity happens when the variance of the residuals is not constant. To ensure that the fitted model is adequate, the assumption of constant variance must be achieved. The ARCH-LM test was use to test for the presence of conditional heteroscedasticity in the model residuals. The test procedure is as follows;

 $H_0$ : There is no heteroscedasticity in the model residuals

 $H_1$ : There is heteroscedasticity in the model residuals

The test statistic is

$$\mathbf{L} = nR^2 \tag{3.28}$$

Where *n* is the number of observations and  $R^2$  is the coefficient of determination of the auxiliary residual regression.

$$e_t^2 = \beta_0 + \beta_1 e_{t-1}^2 + \beta_2 e_{t-2}^2 + \dots + \beta_q e_{t-q}^2 + v_t$$
(3.29)

where  $e_t$  is the residual. The null hypothesis is rejected when the *p*-value is less than the level of significance and is concluded that there is heteroscedasticity.

## **CHAPTER FOUR**

## **RESULTS AND DISCUSSION**

#### 4.0 Introduction

This chapter presents the results of the data analyses and the discussion based on the results obtained.

## 4.1Preliminary Analysis

The mean, median, standard deviation, minimum, and maximum of FBS level at each measurement point for the sample of 80 patients were stratified by Gender, Education, Marital status, Religious affiliation and drug in table 4.1.

## Table 4.1 Descriptive statistics of FBS level of patients on treatment

Variables	Percentage	Mean	Median	Min.	Max.
	(%)	(fbs)	(fbs)	(fbs)	(fbs)
AGE (years)					
30-39	3.75	8.65556	9.20000	3.00000	12.90000
40-49	20.00	8.80486	8.30000	4.00000	16.50000
50-59	30.00	7.08935	6.80000	3.50000	15.90000
60-69	23.75	7.35263	6.90000	3.70000	13.50000
70-79	18.75	7.45925	7.10000	3.20000	14.20000
80-89	3.75	7.46296	6.90000	4.00000	14.20000
Mean $(Age) = 58$					
Median $(Age) = 53$					
Minimum (Age) = 33					
Maximum (Age) = 84					
GENDER	22.60	7.9(10)	7 40000	2 00000	16 60000
Formale	52.50	7.80190	7.40000	3.00000	16.50000
remaie	67.30	7.52880	7.10000	3.20000	10.40000
EDUCATION					
Non	20.00	7.20347	6.75000	3.80000	15.80000
Primary	27.50	8.20555	7.60000	4.10000	16.40000
JHS	25.00	7.37666	7.05000	3.20000	15.70000
SHS	7.50	7.33888	7.15000	3.00000	13.50000
Tertiary	20.00	7.72638	7.20000	3.50000	16.50000
RELIGION					
		33			

Christian	46.2	5 8.18918	7.60000	3.20000	16.50000
Islamic	16.2:	5 6.45982	6.10000	3.70000	12.80000
Traditional	27.50	7.21161	6.95000	3.80000	13.70000
Other	10.00	8.16666	8.00000	3.00000	15.70000
MARITATAL STA	TUS				
Married	57.50	7.66135	7.20000	3.70000	16.50000
Single	1.2:	5 8.93333	8.60000	6.90000	12.90000
Separated	10.00	8.10138	7.40000	4.40000	15.80000
Divorced	17.50	) 7.39444	7.20000	3.00000	15.90000
Widow(er)	13.75	5 7.38888	7.00000	4.00000	15.10000
DRUG					
Metformin	46.23	5 7.71051	7.10000	3.00000	16.40000
Glibenclami	de 36.2:	5 7.59540	7.20000	3.70000	16.50000
Glimepiride	17.50	) 7.52936	7.20000	3.20000	15.70000
	1	CEDC 1 1 C		1	• 1

The descriptive statistics of FBS level of patients on treatment is shown in the

table 4.1. The ages of the patients ranges from 33 to 84years. The mean and median age was 58 and 53years respectively. Most patients in the study found themselves in the age group of 50-59years, constituting 30% and age group 30-39year and 80-89years were the least, constituting 3.5% each. 32.5% were males and 67.5% were females. Male patients had the least minimum FBS level (3mmol/l) and the highest maximum FBS level (16.5) as compared to female patients who had a minimum and maximum FBS level of 3.2mmol/l and 16.4mmol/l respectively. The educational level category also displayed patients who had primary education as having the highest mean FBS level (8.21mmol/l), followed by tertiary (7.73mmol/l); patients who had no formal education had the minimum which is also the best mean FBS level (7.20mmol/l).

The marital status category shows that patients who are single had the highest and the worst mean FBS level (8.93mmol/l), whereas, the best and the least mean FBS level in the marital status category is (7.388mmol/l) and the patients who were widowed had it. The overall mean FBS level is 7.64mmol/l.

### 4.2 Further Analysis

This segment includes the profile plots of FBS level by groups, the trend analysis of FBS level over time, MANOVA test for groups, Test of parallelism, level and flatness for groups, the parameter estimates of mixed effect model, model diagnosis and the example of the predictive use of the models.

## 4.2.1 Profile plots of FBS Level by Groups

This section entailed profile plots by gender, marital status, educational level, drug and religious affiliation.t0=January,2012, t1= April,2012, t2= July,2012,

t3=octorber,2012, t4=January,2013, t5=April,2013, t6=July,2013,

t7=octorber,2013, t8=January, 2014.

The pattern of change in Fasting Blood Sugar (FBS) level over the period of observation for gender was staged in the profile plots (Figure 4.1). The profiles show that the average change in FBS for males and females are changing over time. Dramatically, the FBS level for both sexes initially increased sharply and at t1, that of the female declined whiles male remained constant until t2 and after that, both seemed to be changing in almost the same pattern.





## Figure 4.1 Profile plot of FBS level by gender

Figure 4.2 shows the change in FBS Level by educational level over time. The profiles show that the average change in FBS Level among different educational levels is different. The FBS level of patients in all the categories rose initially and category; no education, primary education, tertiary education and Junior High School education fall at t1and Senior High School education continued to increase until t2 and then all of them, except patients with JHS education started fluctuating. The change in FBS level of Patients with primary education over time, is ever leading.





Profile plots of Fasting Blood Sugar Level by Educational Levels

# Figure 4.2 Profile plots of FBS level by Educational level.

Figure 4.3 indicates that the average change in FBS level in the marital group is changing over time. The category; single decreased rapidly from time point t0 to t2 and then seemed to assume approximately the same pattern as widow(er), however, others increased initially. Furthermore, married and divorced patients followed the approximately similar pattern and eventually decline. However, the FBS level of separated patients fluctuates as it moves over the time points.





Figure 4.3 Profile plots of FBS level by marital status.

Figure 4.4 indicates that the average change in FBS level in the group is changing over time and that the pattern is approximately the same for Metformin and Glimepiride profiles. However, after all of them rose from t0 to t1, Glibenclamide profile slightly differed in the pattern over time as it flatten from t1 to t2 and then falls rapidly and fluctuates. Averagely, from the profile, even though, is very competitive, metformin seemed to perform worse than glimepiride. Zhu *et al.*, (2013) suggested that Metformin and glimepiride were not significantly different in glycaemic control of Type 2 Diabetes.





Figure 4.4: Profile plot of FBS level by drug.

Figure 4.5 indicates that the average change in FBS level in the religious group is changing over time and that the pattern is approximately similar for all the religious groupings except "Others" which continue to increase until t2 after the rest declined from t1.





Figure 4.5: Profile plots of Fasting Blood Sugar Level by Religion.

## 4.2.2 The Pattern of FBS Level

Equation	Model Su	Model Summary						Parameter Estimates		
	R Square	F	df1	df2	Sig.	b1	b2	b3		
Linear	0.652	1347.957	1	719	0.000	1.147				
Logarithmic	0.693	1623.218	1	719	0.000	4.221				
Inverse	0.566	936.325	1	719	0.000	14.527				
Quadratic	0.853	2081.261	2	718	0.000	3.629	-1.469			
Cubic	0.910**	2407.258	3	717	0.000	6.793	-0.349	0.089		
Compound	0.736	2007.201	1	719	0.000	1.359				
Power	0.771	2420.639	1	719	0.000	1.120				
S	0.584	1009.349	1	719	0.000	0.307				
Growth	0.736	2007.201	1	719	0.000	0.307				
Exponential	0.736	2007.201	1	719	0.000	0.307				
Logistic	0.736	2007.201	1	719	0.000	0.736				

## **Table 4.2 Trend Models**

\*\*means highest variability



Table 4.2 shows the model, parameter estimates and  $R^2$  estimates of the trend of FBS level of Type 2 diabetes patients on treatment. The model with the highest variability was selected and trend of FBS level was fitted.



Figure 4.6: The pattern of FBS level.

Figure 4.6 shows that the general pattern of change in FBS level increases over time and then fall, only to rise again. The cubic function is shown to be a good fit of the change in FBS level over time. The model for the cubic function is given by;

$$FBS = 0.089t^3 - 1.469t^2 + 6.793t \tag{4.1}$$

Where  $t = 0, 1, 2, ..., t_n$ 

The rate of change in  $FBS = \frac{d}{dt}(FBS) = 0.267t^2 - 2.938t + 6.793$ The model accounts for 91% of the variability in the data.



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	ANOVA									
Source	SS	DF	MS	F	Sig.					
Regression	512.393	3	170.798	35.009	.000					
Residual	3493.105	716	4.879							
Total	4005.499	719								

Table 4	.3: Ana	lysis of	<sup>?</sup> Variance
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The regression analysis for the cubic trend model shown in the ANOVA table 4.3 above shows that the trend model is significant (p-value = 0.000)

Table 4.4: Trend model Diagnoses							
Test	Statistics	P-value					
Shapiro-Wilks	W = 0.935	0.0572					
ARCH-LM	Chi-Sq.= 3	0.6207					

The adequacy of the model was checked. The Shapiro-wilks test of normality indicated that the residuals of the model were normally distributed (p-value = 0.0572) and W = 0.935 which is very large and is a good sign for normality as shown in table 4.4 above. The ARCH-LM also indicates that the residuals were free from conditional heteroscedasticity (p-value = 0.6207). Hence the diagnostic test revealed that the model is adequate for the prediction of FBS level.



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## 4.2.3 MANOVA Test for Groups

## **Table 4.5: MANOVA Test for Groups**

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Gender	W	0.9923	1	1.0	65.0	1.50	0.4804 e
	Р	0.0077		1.0	65.0	1.50	0.4804 e
	L	0.0078		1.0	65.0	1.50	0.4804 e
	R	0.0078		1.0	65.0	1.50	0.4804 e
Marital	W	0.9216	4	4.0	65.0	1.38	0.2495 e
Status	Р	0.0784		4.0	65.0	1.38	0.2495 e
	L	0.0851		4.0	65.0	1.38	0.2495 e
	R	0.0851		4.0	65.0	1.38	0.2495 e
Religion	W	0.8547	3	3.0	65.0	3.68	0.0163 e
-	Р	0.1453		3.0	65.0	3.68	0.0163 e
	L	0.1701		3.0	65.0	3.68	0.0163 e
	R	0.1701		3.0	65.0	3.68	0.0163 e
Drug	W	0.9873	2	2.0	65.0	0.42	0.6602 e
-	Р	0.0127		2.0	65.0	0.42	0.6602 e
	L	0.0129		2.0	65.0	0.42	0.6602 e
	R	0.0129		2.0	65.0	0.42	0.6602 e
Education	W	0.9623	4	4.0	65.0	0.64	0.6387 e
	Р	0.0377		4.0	65.0	0.64	0.6387 e
	L	0.0391		4.0	65.0	0.64	0.6387 e
	R	0.0391		4.0	65.0	0.64	0.6387 e
Residual			65				
Total			79				
W = Wilks	'lamb	da  L = La	awley-Hot	telling trace	P = Pillar	i's trace	R = Roy's

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy's largest root e = exact

The Multivariate Analysis of variance tests shown in Table 4.5, indicated that the profiles for the different levels of religion, differed and is therefore not parallel. However, gender, marital status, drug and education did not significantly differ at the 5% significance level and hence their profiles can be tested for parallelism.



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2-group Hotelling's  $T^2 = 13.424512$ 

F test statistic: 
$$F(9,70) = \left(\frac{80 - 9 - 1}{(80 - 2) \times (9)}\right) \times 13.424512 = 1.3386265$$

Thus the hypothesis  $H_0$ : Vectors of means are equal for the two groups, is rejected at 5% significance level since

$$Prob > F(9,70) = 0.2333$$

The results of the Test of Parallelism done using a standard one-way MANOVA followed by a test that used a transformation of the dependent variables are shown in Table 4.6.

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Gender	W	0.8543	1	8.0	71.0	1.51	0.1677 e
	Р	0.1457		8.0	71.0	1.51	0.1677 e
	L	0.1706		8.0	71.0	1.51	0.1677 e
	R	0.1706		8.0	71.0	1.51	0.1677 e
Residual			78				

Table 4.6: Multivariate test of parallelism for Gender

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy'slargest root

e = exact, a = approximate, u = upper bound on F

Table 4.6 shows the results of the test of parallelism for gender .Thus assuming homogeneity, at 5% level of significance, the results confirmed that the profile for the different levels of gender are parallel. Therefore the pattern of change in FBS level in male patients is not significantly different from the pattern of change in FBS level in female patients.

Table 4.7: Test of Equality in Gender.

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Gender	W	0.9906	1	1.0	78.0	0.74	0.3917 e
	Р	0.0094		1.0	78.0	0.74	0.3917 e
	L	0.0095		1.0	78.0	0.74	0.3917 e
	R	0.0095		1.0	78.0	0.74	0.3917 e

Residual

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy's largest root

78

e = exact, a = approximate, u = upper bound on F

The results of the Test of equality of levels of FBS level by Gender are shown in Table 4.7. Since the p-values are greater than 0.05 (p-value = 0.3917 in all cases), the hypothesis that the levels are the same at 5% significance level failed to be rejected. This indicated that the profiles are not significantly different. Thus the average change in FBS level in males is not significantly different from that of the females

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Gender	W	0.3466	1	8.0	71.0	16.73	0.0000 e
	Р	0.6534		8.0	71.0	16.73	0.0000 e
	L	1.8850		8.0	71.0	16.73	0.0000 e
	R	1.8850		8.0	71.0	16.73	0.0000 e

 Table 4.8: Multivariate Test of flatness by Gender

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W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy's largest root

e = exact, a = approximate, u = upper bound on F

Residual

The results of the test of flatness were shown in Table 4.8. At 5% significance level, the null hypothesis that there is no change in FBS level (deviation from flatness) was rejected since the p-value (0.000) is less than 0.05. Therefore, there



is a significant change in the average FBS level over time or, the average FBS level does not remain the same over time.

It is therefore concluded by these three tests for Gender that, there is a significant change in FBS level of patients across the time points, and the pattern and level of change was the same for both sexes.

Table 4.9: Test of parallelism by marital status

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Marital	W	0.7050	4	32.0	252.4	0.78	0.7931 a
Status	Р	0.3279		32.0	284.0	0.79	0.7829 a
	L	0.3734		32.0	266.0	0.78	0.8037 a
	R	0.1965		8.0	71.0	1.74	0.1031 u

Residual75W = Wilks' lambda L = Lawley-Hotelling trace <math>P = Pillai's trace, R = Roy'slargest root

e = exact, a = approximate, u = upper bound on F

In Table 4.9, the test of parallelism for marital status indicated that the difference in the pattern of change for the various levels of marital status is statistically insignificant at 5% significance level. This means that profiles can be said to be parallel. Therefore, the pattern of the average change in FBS level for the levels of marital status is not different.

Table 4.10: Test of level (Equality) by marital status

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Marital	W	0.9760	4	4.0	75.0	0.46	0.7635 e
Status	Р	0.0240		4.0	75.0	0.46	0.7635 e
	L	0.0246		4.0	75.0	0.46	0.7635 e
	R	0.0246		4.0	75.0	0.46	0.7635 e

Residual

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy's largest root

75

e = exact, a = approximate, u = upper bound on F



The results of the Test of equality of levels of FBS by marital status are shown in table 4.10. Since the p-values are greater than 0.05 (p-value=0.7635 in all cases), the hypothesis that the levels are the same at 5% significance level failed to be rejected. That is the test of difference in the levels of marital status is statistically insignificant at 5% significant level. This means the profiles of the average change in FBS level for different levels of marital status are approximately the same.

1 able 4.11 1 est of flatness by marita	n status
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Source		Statistic	Df	F(df1	df2)	F	Prob>F
Marital	W	0.6482	1	8.0	68.0	4.61	0.0002 e
Status	Р	0.3518		8.0	68.0	4.61	0.0002 e
	L	0.5428		8.0	68.0	4.61	0.0002 e
	R	0.5428		8.0	68.0	4.61	0.0002 e

Residual

75

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy'slargest root

e = exact, a = approximate, u = upper bound on F

Table 4.11 shows that the test of flatness by marital status is statistically significant at 5% significant level. This implied that the FBS level by marital status do not remain the same over time.

Table 4.12 Test of Parallelism by drug

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Drug	W	0.8359	2	16.0	140.0	0.82	0.6606 e
	Р	0.1701		16.0	142.0	0.83	0.6556 a
	L	0.1892		16.0	138.0	0.82	0.6659 a
	R	0.1368		8.0	71.0	1.21	0.3035 u

Residual

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy's largest root

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e = exact, a = approximate, u = upper bound on F



Table 4.12 is the test of parallelism by drug. It indicated that at 5% significant level, the difference in the pattern of change for the various types of drug is statistically insignificant. This means that, the average change in FBS level for patients on different drugs are not significantly different.

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Drug	W	0.9980	2	2.0	77.0	0.08	0.9263 e
	Р	0.0020		2.0	77.0	0.08	0.9263 e
	L	0.0020		2.0	77.0	0.08	0.9263 e
	R	0.0020		2.0	77.0	0.08	0.9263 e

Table 4.13: Test of Level (Equality) for drug

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy'slargest root e = exact, a = approximate, u = upper bound on F

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Table 4.13 shows the test of level, that is the test of difference in the types of drug is statistically insignificant at the 5% significant level. This means the profiles of the average change in FBS level for the different types of drug is approximately the same.

Table 4.14 Test of Flatness by drug.

Residual

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Drug	W	0.3613	1	8.0	70.0	15.47	0.0000 e
	Р	0.6387		8.0	70.0	15.47	0.0000 e
	L	0.7676		8.0	70.0	15.47	0.0000 e
	R	0.7676		8.0	70.0	15.47	0.0000 e

Residual

77

W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy'slargest root

e = exact, a = approximate, u = upper bound on F

The results of the test of flatness are shown in Table 4.14. At 5% significance level, we reject the null hypothesis that there is no change in FBS level, since the



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p-value (0.0000) is less than 0.05. This indicated that the FBS level by drug changes over time.

Source		Statistic	Df	F(dfl	df2)	F	Prob>F
Education	W	0.6547	4	32.0	252.4	0.96	0.5333 a
Level	Р	0.3951		32.0	284.0	0.97	0.5135 a
	L	0.4555		32.0	266.0	0.95	0.5539 a
	R	0.2220		8.0	71.0	1.97	0.0627 u

<b>Table 4.15</b>	Test of Pai	allelism bv	VEducational	evel
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W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy's largest root

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e = exact, a = approximate, u = upper bound on F

In Table 4.15 the test of parallelism by educational level indicated that the difference in the pattern of change for the various levels of educational level is insignificant at 0.05 significant level. This means that the profiles of the average change in FBS level for the different levels of education are approximately the same.

4 4.0 75.0 1.18 0.3259 e
4.0 75.0 1.18 0.3259 e
4.0 75.0 1.18 0.3259 e
4.0 75.0 1.18 0.3259 e
4.075.01.184.075.01.184.075.01.18

Table 4.16 Test of Level by Educational level.

Residual

Residual

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W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy's largest root

e = exact, a = approximate, u = upper bound on F

Table 4.16, shows the result of the test of equality of levels of FBS by educational level. Since the p-values are greater than 0.05 (p-value = 0.3259 in all cases), hence a failure to reject the hypothesis that the levels are the same at 5%



significance level. This means that the profiles of the average change in FBS level for the different levels of education are approximately the same.

Source		Statistic	Df	F(df1	df2)	F	Prob>F
Education	W	0.3685	1	8.0	68.0	14.57	0.0000 e
Level	Р	0.6315		8.0	68.0	14.57	0.0000 e
	L	1.7138		8.0	68.0	14.57	0.0000 e
	R	1.7138		8.0	68.0	14.57	0.0000 e

	<b>Table 4.17</b>	Test of	Flatness	by J	Educational	level.
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Residual

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W = Wilks' lambda L = Lawley-Hotelling trace P = Pillai's trace R = Roy'slargest root e = exact, a = approximate, u = upper bound on F

Table 4.17 shows that the test of flatness by educational level is significant. This indicates that flatness is not proven and hence the mean FBS level does not remain the same over time.

## 4.2.4 Statistics for Covariance Structure Model

Table 4.18: Statistics for Covariance Structure Models							
Covariance Structures	AIC	BIC					
Compound Symmetry	3216.1	3225.2					
Variance Component	3214.1**	3218.6**					
Toeplitz	4342.1	6929.3					
AR(1)	3216.1	3225.2					
ARMA(1,1)	3218.1	3231.8					

\*\*means: "Smallest"

Comparison analysis of the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for each of the covariance models is shown in Table 4.18 above. It shows that the variance component model has the smallest value for AIC (3214.1) and BIC (3218.6). This implied that the variance component was selected for modeling.



The cubic trend was incorporated into the linear mixed effect model to obtain the parameter estimates and their significance of the model as shown in table 4.19. The table shows that the age, weight, gender and time of treatment are significant determinants of change in FBS level of patients. Male patients have on average, about the same level as the female patients. The rate of change in FBS level is - 0.2749 per unit increase in time. This suggests that the rate of change in FBS level decreases with time. A unit increase in the age of a patient on treatment is expected to reduce the FBS level by "0.03542" when other factors remain the same. All things being equal, a unit increase in weight of a patient on treatment is expected to increase the FBS level by "0.01262".

In education category, patients with no education are said to have significantly lower change in FBS level than patients with tertiary education. In the category of religion, patients affiliated to Islamic and traditional religion, are expected to have significantly lower change in FBS level as compared to similar patients who are affiliated to no religion "Others". Also, In the marital status category, divorced patients are said to have significantly lower change in FBS level than patients who are widow(er)s. The change in FBS level did not significantly differ by drug.

Table 4.19: Variance Component covariance Structure output								
Effect	Estimation	Standard Error	DF	t value	<b>Pr&gt;</b>  t			
Age	-0.03542	0.00779	700	-4.55	<.0001			
Weight	0.01262	0.00550	700	2.29	0.0223			
Systolic	-0.00024	0.00390	700	-0.06	0.0515			
Diastolic	0.00479	0.00687	700	0.70	0.0585			
Time	-0.27490	0.02966	700	-9.27	<.0001			
GENDER								
Male	10.93980	0.92890	700	11.78	<.0001			
Female	10.81630	0.91820	700	11.78	<.0001			
Education com	pared with to	ertiary						
Non	-0.66960	0.25610	700	-2.61	0.0091			
Primary	0.08598	0.24920	700	0.35	0.7302			
JHS/Middle	-0.12820	0.25030	700	-0.51	0.6087			
SHS	-0.44930	0.34380	700	-1.31	0.1917			
Drug compare	d with Glime	piride						
Metformin	0.27580	0.24240	700	1.14	0.2555			
Glibenclamide	-0.01417	0.25370	700	-0.06	0.9555			
Religion comp	ared with Otl	hers						
Christian	-0.00049	0.28460	700	-0.00	0.9986			
Islamic	-1.91230	0.33240	700	-5.75	<.0001			
Traditional	-0.93610	0.30190	700	-3.10	0.0020			
Marital Status	compared with	ith Widow(er)						
Married	-0.43440	0.26270	700	-1.65	0.0986			
Single	-1.02470	0.80400	700	-1.27	0.2029			
Separated	0.18940	0.37060	700	0.51	0.6094			
Divorced	-0.92930	0.30990	700	-3.00	0.0028			

## 4.2.5 Parameter Estimates of Mixed Effects Model



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4.2.5.1 Full Model for the linear mixed effect model

$$FBS = -0.03542X_{1} + 0.01262X_{2} - 0.00024X_{3} + 0.004793X_{4} - 0.27490X_{5}$$

$$+ 10.9398X_{6} + 10.8163X_{7} - 0.66960X_{8} + 0.08598X_{9}$$

$$- 0.12820X_{10} - 0.44930X_{11} + 0.2758X_{12} - 0.01417X_{13}$$

$$- 0.00049X_{14} - 1.9123X_{15} - 0.9361X_{16} + -0.4344X_{17}$$

$$- 1.0247X_{18} + 0.1894X_{19} - 0.9293X_{20}$$

$$Where X_{1} = Age X_{2} = Weight X_{3} = Systolic X_{4} = Diastolic X_{5} = Time X_{6}$$

$$= Male X_{7} = Female X_{8} = No \ education \ X_{9} = Primary X_{10}$$

$$= JHS X_{11} = SHS X_{12} = Metformin X_{13} = Glibenclamide X_{14}$$

$$= Christian X_{15} = Islamic X_{16} = Traditional X_{17}$$

= Married  $X_{18}$  = Single  $X_{19}$  = Separated  $X_{20}$  = Divorced

Table 4.20: Model Selection for Prediction: Stepwise selection method

Step	Variable Entered	Model (R <sup>2</sup> )	Mallows' C(p)	F-value	Pr>F
1	Diastolic	0.8923	149.619	5958.37	<.0021
2	Weight	0.9052	47.9593	97.42	<.0001
3	Time	0.9083	24.6720	24.55	<.0051
4	Systolic	0.9106	8.5731	17.98	<.0091
5	Education	0.9113	4.8911	5.68	0.0174

All variables left in the model are significant at the 0.0500 level. No other variable met the 0.0500 significance level for entry into the model.

Stepwise selection was use to fit the reduced model for prediction. The stepwise selection method dropped the variables age, drug, religion, marital status and gender, leaving only time, weight, education, diastolic, and systolic as shown in table 4.20.



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Table 4.21: Estimates of reduced model							
Variable	Parameter	Standard	t value	Pr> t			
	Estimate	Error					
Time	-0.18773	0.03345	-5.61000	<.0051			
Weight	0.04375	0.00511	8.56000	<.0001			
Diastolic	0.03643	0.00718	5.07000	<.0021			
Systolic	0.06573	0.00403	3.91000	0.0001			
Education:							
None	-0.51950	0.09312	-0.23000	0.0091			
Primary	0.23611	0.01863	2.13000	0.0102			
JHS/Mid	0.27833	0.00282	2.89000	0.0086			
SHS	-0.20917	0.02809	-1.32000	0.0259			
Tertiary	0.15013	0.06298	2.38000	0.0174			

## 4.2.5.2 Reduced Model for Prediction

 $\hat{Y} = 0.04375X_2 + 0.06573X_3 + 0.03643X_4 - 0.18773X_5 + (0.23611X_9)$ 

 $-\ 0.\ 51950 X_8 + 0.\ 27833 X_{10} - 0.\ 20917 X_{11} + 0.\ 15013 X_{21})$ 

Where  $X_{21}$  = Tertiary.

#### 4.2.5.3 Model Diagnosis

The graphs below show the diagnostic analysis of the residual plots of the FBS level. Figure 4.7a shows the residual versus fitted plot which indicated the assumptions of random distribution of residuals. Figure 4.7b shows the leverage plots with cook's distance less than one, which indicate no influence of outliers in the reduced model. And Fig 4.7c shows the assumptions of normality.



# **Residual Plots of FBS level**



Figure 4.7a Residual vs Fitted values of FBS level



Figure 4.7b Leverage-versus-squared-residual plot





Figure 4.7c Normal Q-Q Plot of FBS

## Example of the predictive use of the models: Regression model

What is the expected FBS level of a tertiary literate with type 2 diabetes and who is on treatment at the diabetes unit for 9months and who is currently weighing 80kg with blood pressure level 170/90 mmHg?

## SOLUTION

The predictive model is

 $\hat{Y} = 0.04375X_2 + 0.06573X_3 + 0.03643X_4 - 0.18773X_5 + (0.23611X_9)$ 

$$-0.51950X_8 + 0.27833X_{10} - 0.20917X_{11} + 0.15013X_{21})$$

Time(t)  $= X_5 = 3$ Weight  $= X_2 = 80$ 

Systolic  $= X_3 = 170$ 

Diastolic =  $X_4 = 90$ 



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Tertiary  $= X_{21} = 5$ 

$$\Rightarrow$$
 X<sub>8</sub> = no edcation = X<sub>9</sub> = primary = X<sub>10</sub> = JHS = X<sub>11</sub> = SHS = 0

Hence the expected FBS level is

$$\hat{Y} = 0.04375(80) + 0.06573(170) + 0.03643(90) - 0.18773(3)$$
  
+ 0.15013(5) = 18.14mmol/L

### **Trend Model**

Consider a type 2 diabetes patient is on treatment, what is his FBS level after 9months.

## **SOLUTION**

The model for prediction is

$$Fbs = 6.793t - 1.469t^2 + 0.089t^3$$

Since the patient was on treatment for 9months,

Time (t) = 3

$$Fbs = 6.793(3) - 1.469(3)^2 + 0.089(3)^3 = 9.561$$
 mmol/L

Therefore the expected FBS level of the patient after 9months of treatment for the predictive and the trend models are 18.14 and 9.561 mmol/l respectively: Both models predict high or abnormal FBS level (> 5.3 mmol/l). This result is actually expected due to the abnormal nature of the blood pressure of the patient (ie. Systolic = 170 > 120 and Diastolic = 90 > 80 mmHg) and the weight which are said to be positively related to the FBS level of the patient from the analysis.



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### **4.2 DISCUSSIONS**

In the study, 101 diabetic patients put on treatment from January 2012 to December 2013 were followed sequentially. Eligibility criterion was used to recruit eighty (80) patients into the study.

The FBS level and other vital statistics of these 80 patients were taken timely through the study period. The minimum age of the patients is 33 years and the maximum age was 84 years. The mean age is 58 years and the median 53 years with majority within the age group of 50-59years, constituting 30% suggesting that aging increases the chances of having type 2 diabetes .The females (67.5%) were almost twice as the males (32.5%). The high number of females as compared to males may be due to the higher physical activity related energy expenditure in males compared to female subjects, hence lower rate of males living with type 2 diabetes (Aspray et al., 2000). The lower rate in males may also be due to the usual unwillingness or lower rate at which males go for medical screening or test as compared to the females. The males and the females slightly differed in their average, as well as minimum and maximum FBS levels. Even though males were half of the females, the average FBS level of males (7.86196 mmol/l) is slightly higher than the average FBS level of females (7.52880mmol/l) which indicates that females seemed to better adhere to the treatment and management plans than the males.

The similar initial increase and then decline in the pattern of change of FBS levels over time for both sexes is a direct indication that the treatment and management plans adopted to bring the situation under control were actually addressing the



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condition in both sexes. The test of parallelism, equality and flatness, showed that the pattern of both male and female patients is not only the same but also identical with the average FBS level changing over time. Thus while gender did not affect the change in FBS level, time did and that there is no time and group interaction. The MANOVA has confirmed that the observed differences in the pattern for the different levels of religion as shown in the profile plot indicated that profiles are not parallel.

The profiles for the effect of drug regimen on the change of FBS level showed that the three main drug regimens metformin, glimepiride and glibenclamide, seemed to have caused a change in FBS level over time, even though, the FBS level of patients on glibenclamide behaved a little strange as compared to the FBS level of patients on metformin and glimepiride. The profiles suggest that these drugs improved the condition of patients on treatment over time as suggested by Garber *et al.*, (2006) that metformin-glibenclamide treatment resulted in significantly greater reductions in HbA1C and FBS compared with metformin plus rosiglitazone in patients with type 2 diabetes. Zhu *et al.*, (2013) also suggested that metformin and glimepiride were not significantly different in glycaemic control of Type 2 Diabetes, suggesting that glimepiride would be a good choice second to metformin in the monotherapy of Type 2 Diabetes. These findings confirmed that the drugs in question are very effective in managing the condition.



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The educational pattern of profiles with consistent leading nature of the FBS level of the patients who had primary education indicated that their understanding of the basics of the condition is low, making them most susceptible. However, the pattern seemed to be approximately similar among the profiles. The result clearly indicates that high educated patients managed the condition better, perhaps they were able to understand the basic disease management and treatment plans better.

The profiling of the FBS level pattern of the different categories of marital status is also expressed and all the marital statuses follow almost the same trend with respect to time. This clearly shows that marital status is not a key indicator of the FBS level of the diabetic patients.

The MANOVA test of parallelism showed that there was significant differential in the pattern of change of the FBS level in religion, however, gender, drug taken, marital status, and educational level of the patients did not show any significant differentials in their pattern of change. The pattern of change in FBS level followed a cubic distribution; the rate of change in FBS level is given by  $\frac{d}{dt}(FBS) = 0.267t^2 - 2.938t + 6.793$  and this is an indication that, the rate of change in FBS level is quadratic and so increases initially and eventually falls. Thus while there is a consistent improvement in the FBS level of patients on treatment, this change decreases with time after having increased initially. This may be due to possible inconsistent use of the treatment and management plans or reduction in the efficacy of the treatment with time possibly by some intrinsic and extrinsic factors. The model accounts for 91% of the variability in the data.



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The variance-covariance structure that was fitted is the variance components which assumed that there is no correlation between any pair of observations of the FBS level that are one or more observations apart.

Obviously, it was observed that age was one of the factors that significantly affect patients FBS level (p-value = <.0001 and estimate of -0.03542). This means that, all things being equal, as the patient continues to grow and committedly on treatment, the expected FBS level slightly averagely decreases. This supports the findings of Ikezaki *et al.*, (2002) that the FBS levels tended to correlate negatively with age, but the correlation was not significant.

One of the factors, that also significantly affect the FBS level of the patient, was the duration of treatment, (estimate of -0.27490 and p-value = <.0001). This means that, averagely, the longer one committedly stay on the treatment, the further the expected FBS level decreases, representing a significant improvement in the condition of the patient.

Furthermore, the weight of the patient is also a significant determinant (p-value = 0.0223 and estimate of 0.01262) of the change in the FBS level of patients on treatment. The positive parameter estimate indicated that the weight of a patient is positively related to the FBS level of the patient. It therefore implies that if weight is reduced, the FBS will also reduced significantly. This is supported by the findings of Kelley *et al.*, (1993) which stated that as weight loss progresses and is maintained, an improvement of glycaemia is evidenced by a reduction in glycosylated hemoglobin.

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The change in FBS level for male and female are not the same (p-value = <.0001) for both and is comfirmed by the linear mixed effect model. The estimate of the FBS level for males is expected to be about 0.1235-fold higher than that of their female counterparts.

Also there were observed educational differentials whereby patients with no education have a significantly lower change in FBS level (p-value = 0.0091 and estimate of -0.66960) when compared to patients with tertiary education.

Patients who were proffesing Islamic and traditional have significantly lower FBS level (p-value = <.0001 and 0.0020 respectively) when compared with patients who belong to "Others or no religion". Their estimated change in FBS level for Islamic and traditional religion patients is 1.9123 and 0.9361 lower than that of "Others", respectively: patients who professed christianity did not significantly differ from "Others".The influence on FBS level by Islamic and traditional religion affiliates could be as a result of some of their religious practices. For instance, moslems do not take alcoholic beverages and most of the traditionalst do not wear footwear no matter what, some do not board car when celebrating their festivals and performing other religious responsibilities which are energy demanding.

Finaly, a stepwise selection method for model selection for prediction was used to fit the reduced model for prediction. The variable; age, drug, religion, marital status and gender were dropped by the selection modeling. The determinants; duration of treatment (time), weight, education, systolic, and diastolic are used to

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fit the reduced prediction model and tested to be adequate for predicting FBS level.

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## **CHAPTER FIVE**

## **CONCLUSIONS AND RECOMMENDATIONS**

#### **5.0 Introduction**

This chapter presents the conclusion based on the discussion of the results and the recommendations are made thereafter.

# **5.1 Conclusions**

In this study, the FBS level of type 2 diabetes patients on treatment were followed retrospectively from January 2012 to December 2013. The analysis revealed cubic distribution trend in the mean FBS level of the patients of the mean age of 53 years. The trend model accounts for 91% of variability in the data.

Even though twice females (67.5%) as males (32.5%) were diabetic, the mean FBS level in males was higher than that of the females (7.5288 and 7.8619 mmol/l respectively). The MANOVA test of parallelism for FBS level differentials with respect to the factors, showed that there was significant differential in the pattern of change of the FBS level in religion. However, gender, drug, marital status, and educational level of the patients did not show any significant differentials in their pattern of change.

The profiles of FBS level among gender, marital status, drug and education were parallel and equal but deviated from flatness. Patients who were on metformin, glimepiride and glibenclamide have a better change in FBS level over time. This suggests that these drugs improved the conditions of patients on treatment over time.

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v. For early detection of the diseases, it is recommended that T2D medical screening or test be organized frequently by the authorities.

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Adampah, T., Luguterah, A., Nyadanu, D., S., and Nawumbeni, N. D., (2014). Longitudinal Study of Type-2-Diabetes: A Profile Analysis at the Ketu-South Municipality.*Journal of Biology, Agriculture and Healthcare, ISSN 2224-3208(Paper) ISSN 2225-093X (Online) Vol. 4, No.25* 

Adampah, T., Luguterah, A., Nyadanu, D. S., and Nawumbeni, N. D., (2014). Mixed-Effects Model for Longitudinal Study of Type-2-Diabetes. *International Journal of Statistics and Applications*, DOI:10.5923/j.statistics.20150502.01

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