STATISTICAL ANALYSIS OF LONGITUDINAL DIABETES DATA IN FELEGEHIWOT REFERRAL HOSPITAL, BAHIR DAR, ETHIOPIA

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Abstract

Background: Diabetes is one of the most widespread chronic disease. In Ethiopia, it has been endemic and it is widely distributed. The aim of this paper was to address the determinant factors of diabetes patients blood glucose level over time with respect to different covariates.

Methods: Institution based longitudinal retrospective study was done to explore the factors affecting the change of blood glucose of diabetes patients by taking the routinely collected information from the patients card at FelegeHiwot referral hospital, Bahir Dar, Ethiopia. To analyze the data, generalized estimating equation was used and data was entered in SPSS version 21 and analyzed with SAS 9.2.

Results: Records of 180 diabetic patients enrolled from 2014 September to 2015 August were analyzed. The results revealed that the blood glucose level (mg/dl) was decreased over time, there is an interaction effect between the treatment sex and follow up time and the rate is statistically different for male and female diabetic patients.

Conclusions: The blood glucose rate of change of female is less than that of males; this may be due to different reasons like, maternity, stress and hormonal changes. The blood glucose is decreasing overtime if diabetic patients adhered properly.

Keywords: Diabetic mellitus, GEE, longitudinal model

Background

Diabetes is a group of diseases characterized by high blood glucose (blood sugar). When a person has diabetes, the body either does not produce enough insulin or is unable to use its own insulin effectively. Glucose builds up in the blood and causes a condition that, if not controlled, can lead to serious health complications and even death. The risk of death for a person with diabetes is twice the risk of a person of similar age who does not have diabetes[1].

Diabetes, a lifelong disease that increases sugar levels in the blood, affects over 366 million people in the globe. Paul Madden, Project Hope’s senior advisor for non-communicable diseases, reported that the disease is rapidly spreading throughout sub-Saharan Africa, and even other developing countries around the world, mainly because of lifestyle changes. The prevalence of diabetic in the world was estimated to be 4% in the year 1995 and estimated to be 5.4% by the year 2025. About eighty percent of diabetes deaths occur in low and middle income countries. At 2011, around fourteen million adults in the Africa Region are estimated to have diabetes, with a regional prevalence of 3.8%[1].
Some of Africa’s most populous countries also have the highest number of people with diabetes, with Nigeria has the largest number (3.0 million), followed by South Africa (1.9 million), Ethiopia (1.4 million) and Kenya (769,000). In Ethiopia, the number of deaths attributed to diabetes reached over 23,869.00 in 2012 and there were over 1.33 million cases of diabetes in Ethiopia in the year 2015[1, 2]. The World Health Organization estimated the diabetes populations of Ethiopia by 2000 and 2030 respectively are 796,000 and 1,820,000[3]. It is noted that eating an unbalanced diet, unhealthy food, lack of physical exercise and stress causes diabetes. Another prognostic factor that is associated with increased risk of Type II diabetes is smoking[4-7]. Meta-analysis done by[8] and stated that body mass index, waist circumference, and waist/hip indicators are the risk factors for diabetes.

**Study area and design**

Institution based longitudinal retrospective study was conducted to fit longitudinal model and determine the risk factors that affect the change of blood glucose of diabetic patients by reviewing the record reported from September 2014 to August 2015 years at FelegeHiwot Referral Hospital, Bahir Dar city administration, Ethiopia. FelegeHiwot Referral Hospital is a 245 bed hospital located in Bahir Dar city, northwest Ethiopia. Bahir Dar is special zone and capital city of Amhara National Regional State (ANRS), which is located approximately 578 km northwest of the Capital of Ethiopia, Addis Ababa, having a latitude 11°36’N and longitude of 37°23’E[9]. The average daily temperature is 19°C and the daily rain fall is variable extending from 3mm in the month of February to 438mm in the month of July. The hospital was established in 1955 as district hospital and it was upgraded to referral hospital in 1994. The hospital has Surgery, Medical, Paediatrics, Obstetrics and Gynaecology, Psychiatrics, Dental and Orthopaedics units with both out patient, in patient and follow-up departments. The hospital has total of 415 health professionals including (76 Physicians, 168 Nurses, 6 Psychiatric Nurses, 27 Midwives, 42 Pharmacists, 29 Laboratory Technicians, 4 Sanitarians, 14 Anaesthetists, 14 X-ray Technician(Radiographers), 33 Residents and 2 Health Educations)(References).

A total of one year data on diabetic cases were obtained from the hospital and information were collected on 180 subjects at least five times, diabetic patients were registered for the first time and their baseline blood glucose level (mg/dl) were recorded, and then this record was repeated once within three months for intensive clinical monitoring.

**Ethical Consideration**

Ethical approval was obtained from the Bahir Dar University, college of Science, Research Ethics Committee. Since the research involved secondary data that is without any direct contact with human subjects an informed written consent was sought from the management and the ethical committee of the hospital. The data collection procedures and analysis were free of any personal identifiable information to ensure confidentiality and anonymity.

**Limitations**

Since the data was extracted from routine medical records, a number of variables were unable to be extracted due to technical difficulties and therefore, were not included in the analysis. Such as weight, height, occupation, smoking status, marital status, religion, family history, physical exercise, diet and lack of regular meeting of doctors with diabetic patients. And from the recorded data few missing values were observed. However, the problem was overcome with the imputation mechanisms of the missing observation technique, last observation carried forward (LOCF) using SAS software.
Model variables and measurements
The data routinely collected at the hospital included the diabetic patients’ demographic details, for this analysis, the outcome was measured using different measurement from patient’s card, and the covariates were selected from the various aspects of the collected data. The covariates can be classified as time-independent and time-varying. Measurement and coding of the outcome and covariates is described below.

Time independent covariates:- Baseline demographic and socio-economic variables included in this analysis were age (in years); gender (1 = female, 0 = male); place of residence (0 = urban, 1 = rural); presence of others diseases (0 = no, 1 = yes); systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertension conditions (0 = normal, 1 = prehypertension, 2 = Stage I HNT, 2 = Stage II HTN), types of drug (0 = others, 1 = Metformin, 2 = Glibenclamide).

Time varying covariates—Time was measured as a continuous variable representing monthly follow-up visits to the hospital. The variable time starts with the value 0 for the first follow-up visit, 1 for the second visit, up to 4 for the fifth follow-up visit.

Measurements and Data Quality
The response variable for this study was blood glucose level. A structured questionnaire was used to collect data on patients card. Data quality was assured by using a pre-tested data collection tool and two trained health professionals for data collection purpose were engaged in continuous supervision and monitoring.

Statistical data analysis
In the last 10 years, there has been a growing interest in longitudinal studies and in the statistical analysis of longitudinal data. Longitudinal studies are widely used to measure outcomes over time within and between individuals in which the outcome variable is repeatedly measured. For data-analyses in longitudinal studies special statistical techniques are developed, which take into account that the repeated observations of each individual, are correlated[10-12]. Compared to cross-sectional study designs, longitudinal study designs can be more efficient, less costly, and more robust to model selection, and they can have increased statistical power[13, 14]. The nature of longitudinal data set provides rich information, about the variability of the outcome within and between individuals, and trend of the outcome over time, as well as effect of treatment on outcome[8, 14-17]. This method was used to assess factors associated with the blood glucose (mg/dl) of diabetic patients over time and the collected data were entered into SPSS 21 and then imported to SAS 9.2 format for analysis.

Socio-demographic and clinical characteristics of the study population were summarized using the mean and standard deviation for continuous variables and proportions for categorical variables. To account for multiple measurements of each patient (correlated data), and to allow all diabetic patients, regardless of the number of visits, to be included in the analysis, model selection was done by first including all predictor variables in the model and then evaluating whether any interaction terms needed to be incorporated into the model.

Results
There were 180 patient records extracted from identification card of diabetic patients between September 2014 to August 2015 years. Many diabetic patients were enrolled in FelegeHiwot Referral hospital, Bahir Dar Ethiopia, in the study period. The study showed that, a total of 87 of the 180 patients (48.3%) were from the rural residence. About one third 61 (33.9%), of the diabetic patients were taking Metformin drug and fifty one percent of the diabetic patients from this study had extra diseases. The result showed that 113 (92.8%) of the diabetic patients were
under the normal conditions of hypertension conditions, but very few 18(10%) of them had stage II HTN (Table 3). The autoregressive working correlation structure has been used for data analysis because the nature of the structure seems appropriate and the blood glucose of diabetic patients were decreasing overtime (Table 2).

The result showed that rural diabetic patients have relatively more blood glucose level (mg/dl)/than urban for repeated measures (Table 1 and Figure b). Specifically, the mean blood glucose level (mg/dl) at the baseline for rural diabetic patients is 401.4 with standard deviation of 153 and decreasing to the fifth period 228.1 with 145 standard deviation. However, for Urban diabetic patients the mean and standard deviation at baseline and last measure respectively are 312(142.3) and 172.6 (77) (Table 1). More generally, the overall blood glucose level (mg/dl) is decreasing from baseline period to the end of the study period on average (Table 2). Some of the demographic and clinical variables of a diabetic patients included in the result are presented (Table 3). The average age of diabetic patients was 39.75 with standard deviation 15.7,there were slightly more males than females evaluated in the overall years.

Interaction between Place of residence and follow up time for blood glucose(mg/dl): The diabetic measures decreased overtime for both urban and rural. However, even if the interaction between time and place of residence is not statistically significant, the rate of decrease was not the same for urban and rural after controlling for other covariates in the model. The rate of increase was 7.9 higher for rural than for urban [7.9, 95% CI: (-31, 46.9); P=0.69] (Table 1 and 4, Figure b).

Interaction between treatment sex and follow up time for blood glucose(mg/dl): The rate at which the values of blood glucose(mg/dl) decreased over time differed in the males and females by controlling other variables in the model, the rate of decrease in the values of the blood glucose(mg/dl) for female is 47.8 times that of males [-47.8, the 95% CI: (-80.6, -15): p value= 0.043] (Table 1 and 4, Figure a).

Interaction between hypertension condition and follow up time for blood glucose(mg/dl): This study showed that, the blood glucose of diabetic patients with no hypertension decreased over the follow up periods rapidly compared with the others and in conclusion the diabetic patients will get improvement soon if they were free from hypertension conditions. But if diabetic patients have hypertension, their blood glucose increased over time and the situation becomes more and more complex (Table 4 and Figure e).

This result revealed that the hypertension status of diabetic patients, sex, drug type, and time are the most significant variables that contributed to the improvement of the blood glucose(mg/dl) of diabetic patients(Table 4). The rate of change of decrement of blood glucose(mg/dl) for male diabetic patients is 47.8 females (the reference category=female). Similarly for drug type, the rate of change of the blood glucose for diabetic patients’ not same for three different drugs. The blood glucose for diabetic patients who took Glibenamide was 72.4 times lower forthosediatric patients compared with those of diabetic patients who were under other drugs (Table 4, figure e). The change of the blood glucose for hypertension free diabetic patients were rapid, the measures for normal conditions were 27.6 times lower than those of diabetic patients who are under type II HTN stage (Table e)

Discussion
To evaluate the risk factors for blood glucose and to see the rate of change of this measure over time, we examined 180 people records extracted from identification card of diabetic patients (ID) who received medical check-ups at least five times at the Hospital during the period 2014
September to 2015 August. This study aimed to quantify the contribution of some socioeconomic and biological covariates on the blood glucose level of diabetic patients at FelegeHiwot Referral Hospital, Bahir Dar, Ethiopia followed for a period of one year. There have been no studies conducted on the rate of change of blood glucose of diabetic patients using retrospective longitudinal data analysis in Ethiopia, particularly the study area. Therefore, this paper analysed the rate of change of the blood glucose of diabetic patients over time in addition to determining the effects of risk factors such as age, sex, types of drug, the presence of other diseases, place of residence, and blood pressure for the change of the blood glucose at the baseline using data from FelegeHiwot Referral hospital.

In this study the researchers have shown that sex and types of drug, hypertension condition and follow up time were important predictor risk factors for the change of blood glucose level, whereas age, place of residence, others were not statistically significant variables. By controlling other factors, this result revealed that, sex has its own impact on the sugar level/blood glucose measures and this study is in line with the recent studies which have been suggested that diabetic measures in women and men are not same [18], but contrast with a study by [19].

When diabetic patients are under the treatments, time was seen to be an important risk factor for the rate of change of blood glucose measures. The average measures at the first examination was approximately 254 mg/dl decreased to 198 mg/dl, for example, would constitute 22 % decline. This result is consistent with [20, 21]. In common with [19, 22], the Systolic blood pressure (mm Hg) is significantly associated with blood glucose of diabetic patients, but in contrast with [25] not significantly associated with Diastolic blood pressure (mm Hg). The effect of age on the blood glucose of diabetic patients, elderly people are more affected. Age is an Important Risk Factor for Type 2 Blood glucose [23, 24]. The recent studies revealed that social inequalities in blood glucose were larger in women than in men, similarly in our study the blood glucose over time did differ by sex and the measurements were increased for women than men over the follow up time [25, 26].

Conclusions
It seems that there was no longitudinal study conducted previously to determine the factors that affect the blood glucose of patient’s overtime. Diabetes is still the major health problem in the country. The rate of change of the sugar levels over time was affected by sex of the participants, the hypertension conditions, and the time. Keeping other covariates constant the rate of decrease for female is less than that of males. In this study, age of diabetic patients and types of drug they used had no effect on the change of the rate of blood glucose of the diabetic patients. The result of this paper showed that the blood glucose of diabetic patients under the treatment was decreasing over time, implies there is an improvement. Diabetic patients with hypertension in addition to diabetic, their blood glucose increased over time compared with diabetic patients who were free from the hypertension conditions.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
HM carried out drafting the proposal, involved in data collection and analysis up to final submission. DL and DT participated in proposal review, data analysis and final result review up to final submission. Finally, all authors read and approved the final manuscript.
Acknowledgments

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References

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20. Timothy Adampah1, Derek NgbandorNawumbeni, Sylvester DodziNyadanu, Ruth Polishuk, Mixed-Effects Model for Longitudinal Study of Type-2-Diabetes


23. AlokBhargava (2003), A longitudinal analysis of the risk factors for diabetes and coronary heart disease in the Framingham Offspring Study


## Table 1: Mean and standard deviation of Blood glucose of diabetic patients with some covariates at baseline, second, third, fourth and fifth visits.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>299.3(126.6)</td>
<td>237.120.7)</td>
<td>206.5(104.9)</td>
<td>195.3(78.4)</td>
<td>189.8(89.2)</td>
</tr>
<tr>
<td>Male</td>
<td>380.6(159)</td>
<td>258.6(129.9)</td>
<td>230.8(115.4)</td>
<td>209.6(108.2)</td>
<td>194.8(109.2)</td>
</tr>
<tr>
<td><strong>Place of Residence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>401.4(153)</td>
<td>280.6(145.9)</td>
<td>245.9(126.5)</td>
<td>215(147)</td>
<td>228.1(145)</td>
</tr>
<tr>
<td>Urban</td>
<td>312(140.3)</td>
<td>222.4(97.3)</td>
<td>199(91.4)</td>
<td>194.4(80.5)</td>
<td>172.6(77.4)</td>
</tr>
<tr>
<td><strong>Other diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>354.9(152)</td>
<td>241.6(120)</td>
<td>12(110)</td>
<td>208.7(103.7)</td>
<td>185.6(101)</td>
</tr>
<tr>
<td>No</td>
<td>345.5(153)</td>
<td>259.8(131.9)</td>
<td>231(112)</td>
<td>199.9(91.9)</td>
<td>200(102)</td>
</tr>
<tr>
<td><strong>Drug type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>400.4(151.9)</td>
<td>281.9(132.5)</td>
<td>255.5(123.5)</td>
<td>221.3(112.5)</td>
<td>208(109.5)</td>
</tr>
<tr>
<td>Metformin</td>
<td>288.2(131.7)</td>
<td>216.3(112.5)</td>
<td>182.3(76.3)</td>
<td>186.4(64.4)</td>
<td>180.5(91)</td>
</tr>
<tr>
<td>Glibencamid</td>
<td>271.5(105.8)</td>
<td>187.8(71)</td>
<td>160.7(60)</td>
<td>166.4(81)</td>
<td>146.9(65)</td>
</tr>
<tr>
<td><strong>SBP category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>405.8(143.3)</td>
<td>278.7(132)</td>
<td>238.2(114.5)</td>
<td>220.8(109.6)</td>
<td>204.6(110.3)</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>254(131.7)</td>
<td>222.8(112.4)</td>
<td>196.3(108)</td>
<td>167.7(58.9)</td>
<td>168(70)</td>
</tr>
<tr>
<td>Stage I HTN</td>
<td>252.7(102.5)</td>
<td>196(96)</td>
<td>214.6(105)</td>
<td>193.5(75.4)</td>
<td>107.8(73.8)</td>
</tr>
<tr>
<td>Stage II HTN</td>
<td>264(110.9)</td>
<td>179.9(75.7)</td>
<td>168.2(76.8)</td>
<td>172.4(61.6)</td>
<td>184.3(105.6)</td>
</tr>
</tbody>
</table>

Table 2: the correlation structure of the data

<table>
<thead>
<tr>
<th>Months</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>350</td>
<td>152.6</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>250.8</td>
<td>126.8</td>
<td>0.56</td>
</tr>
<tr>
<td>2</td>
<td>221.7</td>
<td>111.9</td>
<td>0.36</td>
</tr>
<tr>
<td>3</td>
<td>204.3</td>
<td>98</td>
<td>0.28</td>
</tr>
<tr>
<td>4</td>
<td>192.5</td>
<td>101.8</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table 2: the correlation structure of the data
Table 3: Baseline Socio demographic and clinical characteristics of the diabetic patients

Algorithm converged.

GEE Fit Criteria

| Parameter | Standard Error Estimate | 95% Confidence Limits | Z | Pr | | | |
|-----------|------------------------|-----------------------|---|----|---|---|
| Intercept | 39.6696 214.6225 370.1246 | 7.37 | <.0001 | |
| AGE       | -0.4829 0.4478 -1.3605 0.3947 -1.08 | 0.2808 | |
| SEX Female | -47.8004 16.7513 -80.6323 -14.9684 | -2.85 | 0.0043 | |
| SEX Male | 0.0000 0.0000 0.0000 0.0000 | . | . | |
| PR Rural | 7.9662 19.9083 -31.0533 46.9858 | 0.40 | 0.6890 | |
| OTHER_D No | -12.0275 18.5920 -48.4673 | 24.4122 | -0.65 | 0.5177 | |
| OTHER_D Yes | 0.0000 0.0000 0.0000 0.0000 | . | . | |
| DRUGTYPE Glibencamide | -72.4369 27.4602 -126.258 | -18.6159 | -2.64 | 0.0083 | |
| DRUGTYPE Metformin | -36.9742 23.8831 -83.7843 | 9.8359 | -1.55 | 0.1216 | |
| DRUGTYPE Others | 0.0000 0.0000 0.0000 0.0000 | . | . | |
| SBP_CATEGORY Normal | 79.4309 35.2198 10.4014 | 148.4604 | 2.26 | 0.0241 | |
| SBP_CATEGORY Prehypertension | -13.4578 33.9635 -80.0252 | 53.1095 | -0.40 | 0.6919 | |
| SBP_CATEGORY Stage I HTN | 6.9663 30.7254 -53.2545 | 67.1871 | 0.23 | 0.8206 | |
| SBP_CATEGORY Stage II HTN | 0.0000 0.0000 0.0000 0.0000 | . | . | |
| DBP_CATEGORY Normal | 46.1213 35.2198 10.4014 | 148.4604 | 2.26 | 0.0241 | |
| DBP_CATEGORY Prehypertension | 33.9635 -80.0252 | 53.1095 | -0.40 | 0.6919 | |
| DBP_CATEGORY Stage I HTN | 37.7326 35.5204 -31.8861 | 107.3512 | 1.06 | 0.2881 | |
| DBP_CATEGORY Stage II HTN | 0.0000 0.0000 0.0000 0.0000 | . | . | |
| time | -17.8860 10.1663 -37.8115 | 20.395 | -1.76 | 0.0785 | |
| time*SEX Female | 14.4064 5.3629 3.8953 | 24.9175 | 2.69 | 0.0072 | |
| time*SEX Male | 0.0000 0.0000 0.0000 0.0000 | . | . | |
| time*PR Rural | 5.2310 6.2855 -7.0883 | 17.5503 | 0.83 | 0.4053 | |
| time*PR Urban | 0.0000 0.0000 0.0000 0.0000 | . | . | |
| time*OTHER_D No | 8.2936 6.0996 -3.6614 | 20.2485 | 1.36 | 0.1739 |
Table 4: Estimates of the parameters from the GEE model with associated 95% confidence intervals (CI)

Figures: All the two-way interaction plots

Figure 1: Interaction between follow up time visits and sex

Figure 2: Interaction between follow up time visits and place of residence
Figure 3: Interaction between follow-up time visits and drug type

Figure 4: Interaction between follow-up time visits and presence of other disease

Figure 5: Interaction between follow-up time (visits) and hypertension conditions
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**Abbreviation:**
mmHg: unit for blood pressure; millimetre mercury
mg/dl: milligrams per decilitres
HTN: Hypertension
CSA: Central Statistics Agency
WHO: world Health Organization
IDF: *International diabetes federation*
SPSS: Statistical Package for the Social Sciences
CDC: Centre for disease control