Original article

The Treatment Effect Comparison through Level of Microalbuminuria in Type 2 Diabetes Patients: A Bayesian Approach

Atanu Bhattacharjee[1], Dilip C Nath[2]
[1]Statistical Officer, Maulanna Azad Institute of Dental Science
[2]Professror, Department of Statistics, Gauhati University
Correspondence to Atanu Bhatachrjee, E-mail ID: atanustat@gmail.com

Abstract

The microalbuminuria is defined as small quantities of albumin in the urine. It is highly prevalent in type 2 diabetic population and useful to measure the severity of kidney damage. A Poisson and Negative-binomial model have been applied for studying the presence of microalbuminuria in urine among the type 2 diabetes patients. The effect of drug treatment viz. (i) Metformin with Pioglitazone and (ii) Pioglitazone with Gliclazide, have been compared in a clinical trial of type 2 diabetes patients in the present study. It has been found that Metformin with Pioglitazone is more effective to reduce the microalbuminuria as compared to Pioglitazone with Gliclazide.

Introduction:

With the explosive growth of incident the type 2 diabetes has become a major international public health challenge. Moreover, an increasing number of individuals have exposure of the pre-diabetic state, which is dangerous for future risk of developing high diabetes incidence. Earlier findings suggests that type 2 diabetes can be delayed or prevented in individuals by modification of lifestyle and medication (Gerstein et al.(2001); Forman et al. (2006)).The awareness about the prevention is a fundamental public health challenge and there is a great requirement of effective strategies to identify high-risk individuals. Unfortunately, the best available risk stratification method is an Oral Glucose Tolerance Test (OGTT), although it is costly and difficult to perform in a clinical setting. The Microalbuminuria is defined as small quantities of albumin in the urine ranging from 30 to 300 mg/dl. It is highly prevalent in type 2 diabetic population and essential to measure the severity of kidney damage. According to the worldwide survey (Parving et al. (2006)), 40% of the patients with diabetes is in kidney disease. The similar results have been found in a large population of Australian population (Tapp et al.(2004)). Atkin (2005) and Hillege et al. (2001) have showed that the incidence of an individual's moving from a normalbuminuric to a microalbuminuria classification by a rate of approximately 8% in 4 years, which is surprisingly high. Dejong et al. (2006) have reviewed the public health perspectives and challenges of screening and monitoring of albumin in urine in relation to disease prevention. However, the classical view of the effect of microalbumuria is the consequence of renal damage.

Recently, different methods have been employed to analyze the drug effect comparison through Bayesian Inference (Lee et al. (2002)). The Bayesian approach gives consistent results in comparison to frequency approach (Wong et al. (1985)). In case of Bayesian approach the inference of the random effects can be obtained through the Markov Chain Monte Carlo (MCMC), which is not possible in frequency approach. In this work the Poisson and Negative-binomial models have been applied through Bayesian approach. The urinary albumin excretion is increasingly being accepted as an important clinical outcome predictor. Because of the great public health need for a simple and inexpensive test to identify individuals at high risk for developing type 2diabetes, it has been suggested that the albumin might serve this purpose.

Objective:

The objective of this work is to apply different models and approach on the sampled microalbuminuria value in the type 2 diabetes drug effect comparison. This work is contributed to compare the drug viz. (i) Metformin and Pioglitazone and (ii)Pioglitazone with Gliclazide to reduce the albumin level among the type 2 diabetes patients. The biochemical parameter of interest microalbuminuria has been observed in this work in three follow up visits of each patients. The second and third observations of each patient have been considered in third and twelve months in sequence of baseline visit.

Application:

In this work, the secondary data set has been obtained from the clinical trial, conducted in 2008. This trial has been performed in Menakshi Mission Hospital, Madurai. It has been carried out to observe the drug treatment effect on type 2 diabetes patients in south Indian population. The patients are taken from the randomized double blind and parallel group study. The part of the data set has been considered with microalbuminuria sample of 100 patients: 50 of these are grouped as treatment 1 (Metformin with Pioglitazone) and rests of them are as treatment 2 (Pioglitazone with Gliclazide). The patients are followed up for the three occasions during a 12-month period. The microalbumiuria have been measured on each of these three visits.

Model Specification

The level of microalbuminuria of the i^{th} patient's j^{th} visit has been denoted by Y_{ij}. Kocherlakota et al (1992) have explained a broad discussion on Poisson distribution. Berkhout et al (2004) have explained the condition where Y_{i1} and Y_{i2}/Y_{i1} are distributed with Poisson mean. A Negative Binomial model can be derived in close to the Poisson distribution (Winkelmann (2000)).

Model1:- (Negative Binomial distribution)

A discrete random variable $(Y \sim NB(\pi, r))$ becomes Negative Binomial distribution with the probability density function

$$f_{NB}(y;\pi,r) = \frac{\Gamma(y+r)}{y!\Gamma(r)}\pi^r(1-\pi)^y$$

for y = 0, 1, 2, . . . , r and r > 0. (3)

The mean and variance can be denoted by

$E(Y) = r(1-\pi)/\pi$ and $Var(Y) = r(1-\pi)/\pi^2$. (4)

If we assume that,

$Y|u \sim Poisson(\lambda u)$ and $u \sim Gamma(r,r)$. (5)

The resulting distribution of y becomes to

$$f(y) = \int_0^\infty f(y/u)f(u) = \frac{\Gamma(y+r)}{y!\Gamma(r)}\left(\frac{r}{r+\lambda}\right)^r\left(\frac{\lambda}{r+\lambda}\right)^y,$$ (6)

In case of count data modeling, we can use the model coefficient β_j, j = 0, 1 , 2 , . . . , p and the dispersion parameter r in gamma prior distribution. In this work, the free available software WingBugs has been used to add different structures for the dispersion parameter r. It is flexible to add different data structure assumption in the model.

Model2:- (Poisson gamma model)

The Poisson model can be formulated in two ways viz. (I) Poisson-Gamma Model and (II) Poisson-log normal model based on the prior assumption of the mean parameter.

The Poisson-gamma model is useful to model count data with over dispersion by

$Y_i \sim Poisson(\lambda_i u_i)$ (7)

$u_i \sim Gamma(r_i, r_i)$ for i = 1 , 2 , ... *n.* (8)

The covariates of interest can be called by both λ_i and u_i. In this work, the covariate of interest is the drug treatment effects. The parameter λ_i has been replaced by $\lambda_i D_i$, where D_i is applied as the drug index values 1 or 2. The i^{th} individual has been treated as drug treatment effect "Metformin with Pioglitazone" or "Pioglitazone with Gliclazide". The results of Negative-Binomial distribution have

been obtained and compared with the Poisson-gamma and Poisson-log-normal model.

Model 3:- (Poisson-log normal)

The model can be written in the following term with the assumption of the normal distribution to the error term by,

$Y_i \sim Poisson(u_i)$

(9)

$\log(\mu_i) = \beta_1 + \beta_2 X_{i1} + \cdots . + \beta_p X_{ip} + \in_i$

(10)

where, β_1, $\beta_{2\ldots}$ and β_p are the coefficient of interest and the error term ε_i is assumed to be follows

$\varepsilon_i \sim N(0, \sigma_\varepsilon^2)$

(11)

The model can be formulated to

$Y_i \sim Poisson(\lambda_i u_i)$

(12)

$u_i \sim Exp(\in_i)$

(13)

$\log(\lambda_i) = \beta_1 + \beta_2 X_{i1} + \cdots . + \beta_p X_{ip}$

(14)

The model is extended to Poisson-log normal instead of Poisson-gamma. However, the calculation through Poisson-log normal is computationally difficult and complicated as compared to negative binomial. The mean and variance can be calculated by

$E(y/\lambda, \sigma_\epsilon^2) = \lambda e^{\sigma_{e/2}^2}$

(15)

and

$V(y/\lambda, \sigma_\epsilon^2) = \lambda e^{\sigma_{e/2}^2} + \lambda^2 e^{2\sigma_\varepsilon^2} - \lambda^2 e^{\sigma_e^2}$

(16)

Model Diagnostics:

Table 2 gives the different estimated parameters from negative-binomial distribution through MCMC with 20,000 iterations. These two estimates for both the procedures are essentially identical.

Table 3 provides output from the Poisson-gamma model of the posterior distribution. In the Poisson normal distribution model, the parameter estimates and standard errors consistently do not exceed the corresponding estimates in the negative-binomial distribution.

The corresponding DIC (Decision Information Criterion) value of each models are given in table 5. In the three models, the minimum DIC value is in Model 1 followed by Model 2 and Model 3. It can be concluded that Model 1 is appropriate as compared to the Model 2. The standard deviations of coefficient values confirm that Model 1 is suitable as compared to Model 2. However, it is very difficult to make out which model is the best, but keeping in view the problems, Model 1 can be considered the best and appropriate.

Results:

The DIC value for this model is calculated to be equal to 2324.31, which is much higher than the corresponding DIC value for the negative-binomial model (2123.23), indicating a better fit for the latter. However, the computed DIC values are based on the conditional likelihood, as described in the computational note at the end of this section. The insufficient fit of the Poisson-log-normal model is useful to examine the posterior distributions of *E(Y)* and *V(Y)*for each drug group. The E(Y) and V(Y) are the expected mean and standard deviation of the biochemical parameter microalbuminuria. The DI_{ij} has been used to obtain the dispersion index for the i^{th} models j^{th} treatment effect. In case of Negative-Binomial distribution; the DI_{11} and DI_{12} are 184.2 and 101.1 respectively for the drug treatment "Metformin with Pioglitazoen" and "Pioglitazone with Gliclazide" respectively. Where as, in Poisson-Gamma models the posterior mean for DI_1 and DI_2 are 725.7 and 270.4. The Negative-Binomial reveals the λ_1 and λ_2 with 177.00 and 83.61 but the Poisson distribution with the posterior mean 94.61 and 42.58. In presence of Poisson gamma model the posterior mean for λ_i in drug combination Metformin with Pioglitazone comes to 94.61 and 42.58 for drug combination "Gliclazide with Pioglitazone". In case of Negative-Binomial distribution model the computed posterior mean of λ_1 for

"Metformin with Pioglitazone" and "Gliclazide with Pioglitazone" are found to be 177.0 and 83.01. The Poisson-log-normal gives the posterior mean for λ_1 and λ_2 by (92.63) and (41.36) respectively.

Discussion:

This clinical trial could be completed with the conventional statistical approach and p-value. The Bayesian analysis attaches the efforts of how the trial could change our opinion about the treatment effect. It is useful to account more variation in the model. The features of the model are important to consider before applying the small data set in the clinical trial.

Jorge et al (2010) have showed that longer duration of diabetes is positively associated with higher level of albuminuria. They have also been found that the high level of HBA1C (glycosylated hemoglobin) is significantly correlated with the severity of albuminuria. As the early marker of nephropathy tge level of microalbuminuria can be used in type 2 diabetes patients for detecting renal damage. Microalbuminuria , an early marker of nephropathy , can also be considered at the time of diagnosis to the patients with type 2 diabetes. Viberta et al. (2002) have confirmed that enhancing microalbuminuria excretion reduced by valsarun in type 2 diabetes patients with micro-albuminuria. It has been found that the microalbumiuria in the type 2 diabetes patients is presents as the independent risk factor for renal disease. Brantrma et al (2006) have shown that individuals with microalbuminuria had an approximately four times chance to develop new-onset diabetes than those with low normal microalbuminuria levels. However Tonolo et al. (1997), Nakamura et al. (2000) and Gambaro et al. (2002) have proved that statins and glucose aminoglycans lowers the albuminuria. The intervention strategies could be very helpful not only in secondary but also in primary prevention. Thus albumin excretion levels represent the primary marker for success of success of such therapies. This study is attributed to compare the drug treatment effect to reduce the microalbuminuria.

In this paper, the novel models with Bayesian approach have been presented to obtain microalbuminuria level in type 2 diabetes patients and, therefore, the drug effect comparison. The results confirm that Negative-Binomial and Poisson gamma models are useful tools for longitudinal data analysis and, consequently, for the actual application to the drug effect comparison in clinical trial. The Markov Chain Monte Carlo iteration have been employed to estimate the microalbuminuria values for different visits in type 2 diabetes patients. We believe that more research is needed in this area.

The present study confers the presence of microalbuminuria in type 2 diabetes patients. This study extends our knowledge of the efficacy of treatment in patients with type 2 diabetes. The drug treatment group "Metformin with Pioglitazone" has performed better to reduce microalbuminuria in comparison to "Gliclazide with Pioglitazone". There is no significant difference between the (Metformin with Pioglitazone) group and the (Gliclazide with Pioglitazone) group to reduce the microalbuminuria level in the study patients. The kidney failure status in case of both drug treatments is same. The statistical models with prior information need to be considered regarding information about the level of complication. It might be projected that the findings would go a long way towards achieving the goal and may also have an important model fitting with Bayesian approach.

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Table 1:- Microalbuminuria profiles of type 2 diabetes patients included in the study

Type of drug	Number of Patients	Microalbuminuria concentration (mean ±sd)
Metformin with Pioglitazone	50	(83.29±112.29)
Pioglitazone with Gliclazide	50	(167.44±155.29)

Table 2:- Estimated mean of the parameters in the model from negative-binomial model

Parameters	Mean	SD	Highest Posterior Density		Parameters	Mean	SD	Highest Posterior Density	
			2.5%	97.5%				2.5%	97.5%
λ_1	177.0	25.47	132.5	229.7	p_1	0.0057	0.0012	0.0034	0.0085
λ_2	83.61	14.06	60.95	114.7	p_2	0.0104	0.0025	0.0061	0.0158
r_1	0.9978	0.1762	0.6826	1.369	DI_{11}	184.2	43.81	117.5	287.8
r_2	0.8634	0.1548	0.5882	1.197	DI_{12}	101.1	26.01	62.93	163.8

Table 3:- Estimated mean of the parameters in the model from Poisson –gamma model

Parameters	Mean	SD	Highest Posterior Density					Highest Posterior Density	
			2.5%	97.5%				2.5%	97.5%
β_1	4.51	0.11	4.31	4.72	λ_1	94.61	12.97	71.79	121.1
β_2	3.72	0.12	3.49	3.99	λ_2	42.58	6.84	30.32	57.12
τ_1	0.72	0.14	0.46	1.04	DI_{21}	725.7	626.2	232.5	2092.0
τ_2	0.78	0.16	0.49	1.14	DI_{22}	270.4	223.0	90.85	784.1

Table 4:- Estimated mean of the parameters in the model from Poisson –log-normal model

Parameters	Mean	SD	Highest Posterior Density	
			2.5%	97.5%
β_1	4.5	0.13	4.32	4.59
β_2	3.8	0.25	3.59	4.05
τ_1	0.77	0.39	0.49	1.20
τ_2	0.941	0.73	0.35	1.57
λ_1	92.63	10.89	83.56	101.67
λ_2	41.36	8.98	35.36	49.73
DI_{31}	721.65	608.56	106.67	1354.67
DI_{32}	275.16	116.36	155.69	395.74

Table 5:- The computed DIC value for Model-1, Model-2 and Model-3.

Model	DIC
Model-1(Negative Binomial)	2123.23
Model-2(Poisson-gamma model)	2105.12
Model-3(Poisson lognormal Model)	2324.31

"Good health is not something we can buy. However, it can be an extremely valuable savings account."

Anne Wilson Schaef

"The truth is that stress doesn't come from your boss, your kids, your spouse, traffic jams, health challenges, or other circumstances. It comes from your thoughts about these circumstances."

Andrew Bernstein

"Age does not depend upon years, but upon temperament and health. Some men are born old, and some never grow so."

Tryon Edwards