



Effect of Pharmacists Counseling for Type 2 Diabetes Mellitus Patients on Cost Analysis of Therapy

Adek Chan*

**Faculty of Pharmacy and Common Health,
Health Institute of Helvetia, Medan, 20124, Indonesia**

Abstract : Costs of health care were increased by various factors such as patterns of disease and treatment changed, advanced technology used, public demand and global economic change. One of the diseases that require a high cost for management is a diabetic and cost increase when complications arise. The purpose of this study was to determine the effect of counseling and therapy costs to prevent the possibility of complications in patients with type 2 diabetes. This research was conducted for 3 months involving 24 people with type 2 diabetes mellitus patients, divided into two groups, counseling and without counseling by inspecting Blood Sugar Levels, HbA_{1c} and costs of therapy analysis. The study was evaluated by grouping the patients by sex and age. The results of the study were more type 2 diabetes mellitus female patients (91.67%) than men (8.33%). The cost of therapy in diabetic patients after given counseling was declined from Rp.49.650 to Rp.17.400. The result of statistical test was obtained cost of counseling therapy in patients with DM decreased significantly ($p < 0.05$). The conclusion of this study was patients who were given counseling DM decreased the costs. The provision of counseling affects the cost analysis of therapy in patients with type 2 DM and with counseling can reduce HbA_{1c} levels in patients with DM type 2 thus preventing the occurrence of complications.

Key words : diabetes mellitus type 2, counseling, costs, HbA_{1c}.

Introduction

Recently, the cost of health care is increasing due to factors such as changes in disease and treatment patterns, the increasing use of advanced technology, the increasing of society demand and global economic change. On the other hand costs provided for health can not be improved, because the government capability is very limited. Related to the above, it is necessary to improve the efficiency and use of funds more rationally. Health economics are as a tool to find a way of increasing efficiency and mobilize the funds that can be used to help developing special efforts without neglecting the social aspects of the health sector itself.^{1,2}

Pharmacoeconomics in this relation has an important role as a description and analysis of the cost of therapy in a health care system, more specifically, is a study of the process of identifying, measuring and comparing the costs, risks and benefits of a program, service and therapy as well as the determination of a best alternative. Pharmacoeconomics evaluation estimates that the price of products or services by one or more viewpoints.^{3,4,5}

DM is a disease that requires a high cost for treatment. Results of research at Dr Sardjito, the total cost for managing type 2 diabetes disease ranges between Rp. 208.500 up to Rp. 754.500 per month.^{4,6}

DM is a metabolic disease characterized by hyperglycemia; caused by abnormalities of the metabolism of carbohydrates, fats, and proteins; and can lead to chronic complications such as microvascular, macrovascular and neuropathic. The method used to determine glucose control in all types of DM are glikat measurement of hemoglobin (HbA_{1c}). Hemoglobin in normal circumstances does not contain glucose when it first came out of the bone marrow. When blood glucose levels within the normal range between 70-140 mg% over the last 2-3 months, the HbA_{1c} test results will show the normal value. HbA_{1c} as a single inspection is very accurate for assessing long-term glycemic status. According Dipiro et.al., (2005) achieved treatment targets if 3-6 months HbA_{1c} were $\leq 6.5\%$ - 7.0% . Therapy in the management of type 2 diabetes disease is a groove so that optimal therapy given that begins with interventions such as education, nutrition and exercise which is likely to affect the outcome of patients with diabetes mellitus therapy. According WHO in Indonesia will increase from 4.8 million in 2000 and to about 21.3 million in 2030.^{7,8,9}

Research and drug development conducted at the end of the decade provide some information that can be applied directly to improve patient of DM outcomes. A good and right therapeutic treatment will be very beneficial for patients, both in terms of health or cure illness, costs, and compliance of patients taking the drug, especially for patients who have to take medication for a long time, even a lifetime, such as DM disease, therefore the efficiency and effectiveness of the drugs use and the cost is an important factor considered.^{6,10,11,12}

One major factor is the failure of a treatment non-adherence to therapy is planned, it is one of the important efforts to improve patient's adherence to therapy is counseling and the provision of complete and accurate information about the therapy. Interest patient education is to provide knowledge and skills to participate in the patient's treatment. Research shows that patients who have never received education about diabetes, the risk for major complications increased 4-fold. Counseling in the management of diabetes is very important because diabetes is a disease that is closely associated with lifestyle. Counseling given to people to get the optimal management of diabetes. DM management success relies heavily on the cooperation of patients and their families with health care. Patient compliance to the management program depends heavily on the level of understanding about the disease. DM patients who have enough knowledge about DM generally can control their behavior so that achieve a better quality of life.^{10,12,13}

Some research suggests that the role of pharmacists in the application of health services and pharmacoconomics will help improve the achievement of maximum therapy outcomes with minimum cost, by involving pharmacists actively in health care related to drug use, will be very useful in the healthcare system, including lowering overall health care costs by focusing on optimal drug use, avoid or minimize the problems associated with drug use (Drug Related problems / DRP's), and the achievement of the desired outcomes of patients that improved quality of life. In addition to the intervention of a pharmacist would have an influence, either directly or indirectly to cost savings of treatment. The more the number of pharmacists in clinical practice, the greater the return on investment.^{7,14,15}

Method

The research methodology used in this research was non-experimental studies and Randomized Control Trial of researchers and participants knew which treatment was given. Nonrandom sample was taken by purposive sampling, ie sampling based on certain considerations made by the researcher herself based on the characteristics or properties of existing populations known in advance.^{1,13}

Materials and sources of data in this study were obtained from medical records, details of the cost of drugs, and interviews with type 2 diabetes mellitus patients.

Selection of patients who met the inclusion criteria obtained by searching medical records, patients were divided into two groups: non counseling and counseling. Patients were given a description of the background, objectives and benefits of the research, willing to participate in the study will receive briefings and signed informed consent. Data retrieval beginning of the study, at its next meeting, conducted laboratory tests and questionnaires as a data baseline. In both groups of laboratory examination, covering Glucosilated hemoglobin (HbA_{1c}), blood glucose levels (KGD) when. Pharmacist counseling was conducted on DM disease, lifestyle changes, antidiabetic medication (OHO) and strategies to increase patient compliance. Further data collection ended the study. Having conducted research for three months, then the patient will do laboratory tests (HbA_{1c}) back. This data would be compared to baseline.

The tools used in the study were an ion exchange HPLC for the brand D-10 to measure HbA_{1c} and Easy touch checking blood sugar levels.

Materials used for HbA_{1c} are as much as 300-500 mL EDTA samples derived from 3 ml of blood and reagen220-0101, D-10 Hemoglobin A1c reorder pack for 400 tests.

Data analysis

Data analysis was done in two stages: to test the value before and after counseling was conducted using non-parametric Wilcoxon signed rank test, test sample value after counseling on the control and treatment performed by Mann Whitney utest method.

Result and Discussion

The overview value of HbA_{1c} in Patients with DM Counseling

A total of 12 subjects were observed in this study group who were given counseling there was a percentage reduction in each patient. The largest decrease on patient no. 8 (41.35%) with initial HbA_{1c} value of 10.4 and a final HbA_{1c} value of 6.1. Followed on patient no.9 (34.28%) initial HbA_{1c} value of 10.5 and a final HbA_{1c} value of 6.9, while the percentage increased on patient no. 2 (12.5%) with initial HbA_{1c} value of 6.4 and a final HbA_{1c} of 7.2 (Table 1).

Table 1. The percentage of HbA_{1c} in DM patients with counseling

No	Patients	Nilai HbA _{1c} (%)		Percentage
		Early	End	
1	Mr. M	6,8	6,2	8,82*
2	Mrs. T	6,4	7,2	12,5**
3	Mr. Y	6,7	6,3	5,97*
4	Mrs. S	9,4	10,1	7,45**
5	Mrs. Ms	9,1	7,3	19,78*
6	Mrs. I	10,0	7,1	29,00*
7	Mrs. Z	8,1	7,8	3,70*
8	Mrs. M	10,4	6,1	41,35*
9	Mrs. Sr	10,5	6,9	34,28*
10	Mrs. MI	10,1	8,2	18,81*
11	Mrs. P	12,9	9,2	28,68*
12	Mrs. St	8,4	7,8	7,14*

Explanation:

*) = The percentage of reduction in HbA_{1c} values

***) = The percentage of increase in HbA_{1c} values

Table 2. Analisis value of HbA_{1c} in DM patients with counselling using Wilcoxon Signed Rank Test Method.

	Nilai HbA _{1c} akhir – nilai HbA _{1c} awal
Z	-1,726
Asymp. Sig. (2-tailed)	0,084

Based on the HbA_{1c} value in DM patients with counseling, data analysis used the Wilcoxon Signed Rank Test values obtained by this means meaningfulness = 0,084 counseling does not provide a significant decrease in HbA_{1c} values (p > 0.05).

This is due to several factors such as the level of presence of DM patients during counseling > 50%, non-adherence of patients in carrying out therapeutic diabetic counseling time is short and small sample so it can not be withdrawn statistically, but counseling is given provide value changes HbA_{1c} meaningful on each patient (Table. 1).

Counseling is done expected to give knowledge of DM patients against disease so that it can perform self-care because there is a significant relationship between level of self care and HbA_{1c} in type 2 DM (Yulianti et al., 2010). In this case the self care plays an important role in the management of diabetes, especially to prevent the occurrence of diabetic complications. If complications occur, making the DM disease getting worse and the cost for treatment even more expensive. Individual businesses can be shown in some of the behaviors that reflect self-care activities, such as controlling blood sugar, insulin and meal planning, exercise, and treatment of hypoglycemic.^{15,16,17,18}

However, patients in applying self care there are several obstacles, among others, are very difficult to apply a healthy diet every day because they only ate what was provided and because of the influence of the environment, and in elderly patients will find it difficult to do sports activities due to their limited physical movement. Pharmacists in this case is quite a role to provide services be educating people with diabetes seen in HbA_{1c} reduction in the percentage of each patient even though the majority are not normal HbA_{1c} values (> 6.5%). But this implies that the intervention gave the meaning that is important in managing patients with diabetes.^{19,20,21}

Some studies assert related to the role of pharmacists in the management of diabetes, among other research conducted by the Fremantle Diabetes Study (2005) investigated the effects of counseling given for 12 months against vascular risk in type 2 diabetes, the results showed after being given counseling, blood pressure and glycaemia decreases. Research conducted by Kiel and McCord (2005) evaluated the clinical changes in patients enrolled in a diabetes management program; the results showed that effective diabetes management programs improve clinical outcomes. Real increase observed in HbA_{1c} and LDL values and adherence to prevention. Research conducted by (Arun et al, 2008) in rural India with pharmaceutical care program effectively improve clinical outcome and Health Related Quality of Life (HRQOL) diabetics.^{16,17,18,22,23}

The benefits of lifestyle interventions in the prevention of type 2 diabetes mellitus; the diet only lowers the risk of type 2 diabetes by 31%, while physical activity just dropped 46%. The combination of diet and physical activity lowers the risk by 42%.^{5,24,25}

Their expected counseling can prevent complications in DM patients with patient adherence to medication, lifestyle modification and monitoring of blood glucose levels. The United Kingdom Prospective Diabetes Study (UKPDS) showed each a decrease of 1% in HbA_{1c} (eg from 9 to 8%), will reduce the risk of complications by 35%, with their educational services gives a good influence on the level of knowledge of diabetic patients, especially in terms of compliance. In this study, the parameters used for the assessment of patient compliance is a HbA_{1c} value. HbA_{1c} is a fraction of hemoglobin in the human body that binds to glucose enzymatically. Poor control of glucose metabolism characterized by blood sugar levels continue to rise / hyperglycemia, and in a certain period of time is associated with patient adherence to program management or the checking of blood sugar levels are elevated HbA_{1c} goal.^{14,17,19,26,27}

The role of inspection HbA_{1c} levels necessary to control compliance of treatment and predict the likelihood of complications of various organs in patients with DM. Blood glucose levels and HbA_{1c} be an important clue in the management of diabetes. Therefore, blood glucose tests can not be replaced by HbA_{1c}, but both these examination mutual support to achieve quality control of DM.^{17,28}

HbA_{1c} is very stable in the blood, so that the measurement of HbA_{1c} levels may reflect the levels of sugar in the blood; HbA_{1c} measurement reflects blood sugar levels up to approximately three months prior to the examination.^{19,29}

Some oral hypoglycemic agents (OHO) can lower HbA_{1c} levels by 0.5-2% depending on how drugs work, which will largely increase the secretion and sensitivity to insulin. With pharmacological therapy alone will not succeed in controlling diabetes because the important thing is to change the pattern of life. However, it should be noted also a variety of side effects, such as hipoglikemidan patients need to know how to handle

situations such hypoglycemia, poor HbA_{1c} levels, reflecting the non-compliance of patients in diabetic therapy.^{20,21,22,30,31}

Picture of the value of HbA_{1c} in Patients with DM Without Counseling

Based on the percentage of the value of HbA_{1c} in DM patients, without Counseling, also occurs about percentage decrease and increase. The increasing is highest in patient no. 4 (31.70%) with initial HbA_{1c} value of 8.2 and a final HbA_{1c} value of 10.8. Then the largest decreases in patient no. 6 (29.36%) with HbA_{1c} values of 12.6 and a final HbA_{1c} value of 8.9. Based on the statistical test obtained by value meaningfulness = 0.126, this means that without counseling does not provide a significant decrease in HbA_{1c} values ($p > 0.05$), (Table 3 and Table 4). The increase in the value of HbA_{1c} may occur due to non-compliance of patients in therapy, and patient education background factors that do not know and are not capable of committing self care about DM, while the decrease in HbA_{1c} value that occurs the possibility of patient compliance in therapy, and capable of self care.

Table. 3 Percentage value of HbA_{1c} in patients with DM without counseling

No	Pasients	HbA _{1c} value		Percentage Decrease / Increase
		Beginning	Ending	
1	Ny. Z	8,7	7,6	12,64*
2	Tn. Ar	13,1	11,4	12,98*
3	Ny. E	9,8	7,9	19,38*
4	Ny. Az	8,2	10,8	31,70**
5	Ny. As	9,1	8,9	2,19*
6	Ny. R	12,6	8,9	29,36*
7	Ny. H	9,3	7,7	17,20*
8	Ny. Rh	7,9	8,4	6,33**
9	Ny. Am	6,7	6,1	8,95*
10	Ny. Ru	11,5	11,4	0,87*
11	Ny. Sr	6,2	5,9	4,84*
12	Ny. Rs	6,7	7,0	4,48**

*) = The percentage reduction in HbA_{1c} values

***) = Percentage increase in value of HbA_{1c}

Tabel.4 analysis of HbA_{1c} values in patients with DM without counseling using the Wilcoxon Signed Rank Test

	Initial HbA _{1c} value - the value of HbA _{1c} end
Z	-1,530
Asymp. Sig. (2-tailed)	0,126

Comparative overview of DM patients with HbA_{1c} Values Counseling and Without Counseling

Based on the HbA_{1c} value of the two groups were compared between the two groups using statistical test Mann-Whitney Test, the data obtained is not significant with significance value = 0.260 (Table 5), but the mean in a larger group counseling (14.13) than without counseling (10.88) (Table 5) this means that with counseling greater decrease in HbA_{1c} compared with no counseling this possibility after counseling, patient compliance in therapy and increased knowledge about diabetes so that they can perform self-care of diabetes disease.

Table.5 Comparison of statistical values between the two groups were tested with Mann-Whitney Test

	Mean
Tanpakonseling	10,88
Konseling	14,13
Asymp. Sig. (2-tailed)	0,260

Overview Cost Therapy Counseling Patients with DM

Based on the data obtained it appears that the cost of therapy in diabetic patient after being given counseling decline. In counseling patients before the therapy costs no.9 Rp.49.650 and after being given counseling costs fell to Rp.17.400, followed by counseling patients before the therapy costs no.2 Rp.42.900 after being given counseling costs fell to Rp.14.300. Based on the statistical test obtained by value meaningfulness = 0.03, this means the cost of their counseling therapy in DM patients decreased significantly ($p < 0.05$).

Then the cost of therapy for each diabetic patient counseling meetings has decreased the average cost (Fig.1). Biaya diabetic patient therapy with counseling.

After doing research on type 2 diabetes panderitadr. Djoelham Hospital Binjai then obtained the following results

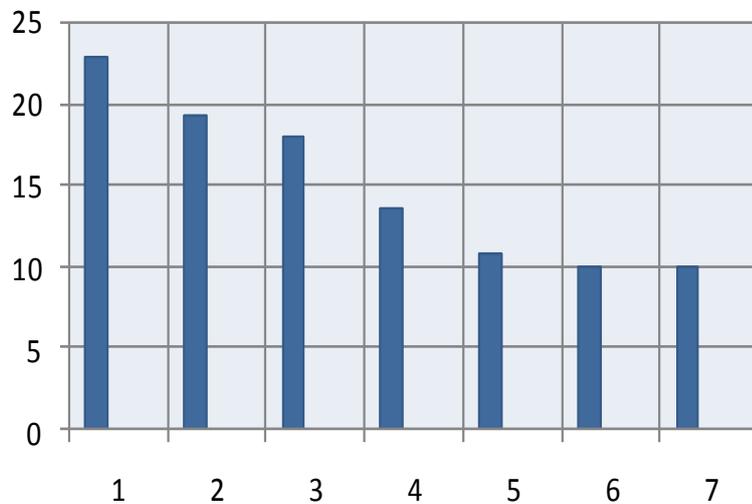


Figure. 1 Graph the average cost per diabetic patient counseling meetings

Counseling is given to influence the cost of therapy in this disease antidiabetic DM. Counseling is given in addition to oral hypoglycemic agents (OHO), also delivered on DM and education to lifestyle changes that control blood sugar levels achieved thus will affect the dose of medication that was given and drug costs decrease. Whereas in patients without counseling (control) therapy costs fixed dose of medication prescribed means no change.^{32,33,34}

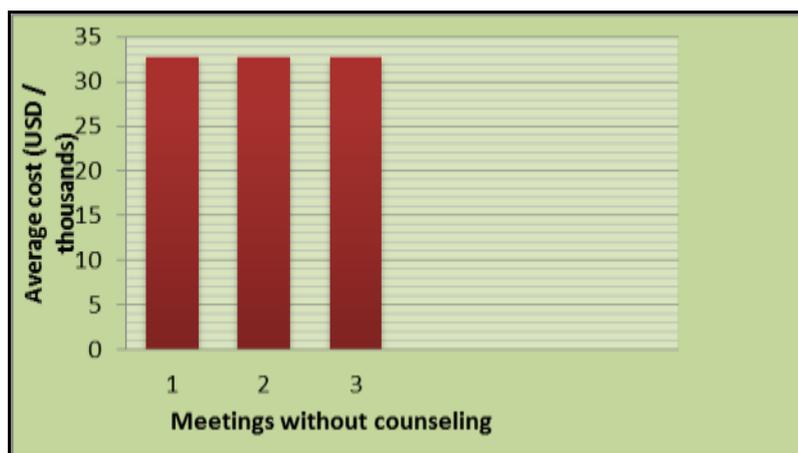


Figure.2 Graph the average cost of DM patients without counseling

Based on the data obtained by the cost of therapy in patients with DM without counseling does not decrease the cost (the cost of therapy remains), appeared at the meeting of 1 to 3 are antidiabetic prescription no change, it's likely the patient perform therapy in accordance with the knowledge that they know without being given education thus affecting the cost of therapy (antidiabetic).^{35,36,37,38,39}

Conclusion

Based on observations and discussions in this study, it can be concluded that in patients who were given counseling a decline in the cost of therapy (drug) whereas in patients without counseling there are no changes in costs, this means the provision of counseling affects the cost analysis of therapy in patients with type 2 diabetes. counseling can reduce HbA1c levels in patients with type 2 diabetes to prevent complications.

References:

1. Kier.LKaren.,Malone, M., danStanovich. J.E. Drug Information.Aguide for Pharmacists.third edition, chapter 8, 2007.
2. Heryanto, I., Iwan S., Ali M., Pharmaceutical Service Quality and Loyalty at Public Hospital in Bandung Indonesia. International Journal of Pharmtech Research, 2016, Vol. 9 No. 7, pp 154-160.
3. Bootman, J.L., Towsend, R.J., and McGhan, W.F., Principles of Pharmacoeconomics, chapter 1. 3td Ed. 315-327, Harvey Whitney Books Company: USA, 2005.
4. Andayani, Tri Murti. Thesis Diabetes Mellitus Treatment Cost Analysis Hospital DR.Sardjito Yogyakarta. Faculty of Pharmacy, University of Gajah, 2006
5. Perkeni,KonsensusPengelolaandanPencegahanPrediabetes, PB Perkeni, Jakarta, 2009
6. Price, S.A, and Wilson, L.M,Patofisiologi: KonsepKlinis Proses-Proses Penyakit, Jakarta, EGC, 2002
7. Dipiro. JT., Talbert., And Yee GC, Pharmacotherapy: a pathophysiologic Approach, 4th Ed., 1334, Appleton and Lange, USA,2005
8. Kumar, R., Couterfeit drugs-Role of Pharmacists and its Prevention , A Review, International Journal of Pharmtech Research, 2014, Vol. 5, No. 2, pp 720-724.
9. Sudheer B., Venkatesh S, Thilagavathi J, Ashok K, and Venkateswarlu NY, Prevalence of Diabetes in Tirupati Urban and Role of Risk Factors Associated with it A Preliminary Survey, International Journal of Pharmtech Research, 2010, Vol. 2, No. 2, pp 1437-1438.
10. Maheshwari P, Impact of Patient Counseling on Health Related Quality of Life in Diabetic and Hypertensive Patients, International Journal of Pharmtech Research, 2016, Vol. 9, No. 1, pp 23-27.
11. Eman EF, Nagwa MB, Samah M, Sally AH, Exercise Therapy Improves Planter Pressur Disstriubution in Patients with Diabetic Peripheral Neuropathy, 2016, Vol. 9, No. 5, pp 151-159.
12. Rao MU, Sreenivasulu M, Chengaiah B, Jaganmohan RK, Chetty CM, Herbal Medicines for Diabetes Mellitus A Review, International Journal of Pharmtech Research, 2010, Vol. 2, No. 3, pp 1883-1892.
13. Notoatmodjo, Medical Research Methodology. Issue 3. Jakarta: Rineka Reserved. 2005, P. 26-27, 88-89.

14. Yulianti, K., Nursiswati., dan Rahayu, U, Hubungan Tingkat self Care dengan Tingkat HbA1c pada Klien Diabetes Melitus Tipe 2 di Poliklinik Endokrin RSUP dr. Hasan Sadikin Bandung. Artikel Self Care, 2010.
15. Shanthi SKV, Kasturi K, and Sivannarayana G, Impact of Pranayama and Amla, an Approach Towards the Control of Diabetes Mellitus, International Journal of Pharmtech Research, 2014, Vol. 6, No. 3, pp 1157-1161.
16. Kiel, J.P., dan McCord, Pharmacist Impact on Clinical Outcomes in a Diabetes Disease Management Program via Collaborative Practice. The Annals of Pharmacotherapy, 2005, vol. 39, No. 11, pp. 1828-1832
17. Suchitra MR, S. Parthasarathy, Effect of Administration of Fenugreek Seeds on HbA1C Levels in Uncontrolled Diabetes Mellitus – a Randomized Controlled Trial, International Journal of Pharmtech Researc, 2015, Vol. 8, No. 2, pp 180-182.
18. Haider K, Mahmoud HH, Diabetes Mellitus type II has not Affected α -tocopherol levels in Sera of Iraqi Diabetic Patients, International Journal of Pharmtech Research, 2016, Vol. 9, No. 2, pp 24-29.
19. Suyono and Slamet, Penatalaksanaan diabetes melitus terpadu: sebagai panduan penatalaksanaan diabetes melitus bagi dokter dan dokter. Jakarta: Balai Penerbit FKUI, 2007.
20. Darmono, Diagnosis and Classification of Diabetes Mellitus: Textbook of Medicine. Issue 3. Jakarta: BP FK UI, 1999.
21. American Diabetes Association, Dystipidemia Management in Adults with Diabetes. Diabetes Care: 27 (Supp I), 2008.
22. Palaian, S., Chetri, A.K., Prabhu, M., Rajan, S., And Shankar, P.R., The Impact of Pharmaceutical Care on the Clinical Outcome of Diabetes Mellitus Among a Rural Patient Population. International Journals of Diabetes in Developing Countries, 2005, 28 (1): 15-18.
23. Cavallerano, J, Optomeri Clinical Practice Guideline. Care of the Patient with Diabetes Mellitus. Edisi 3. St. Louis: Lindbergh Blvd, 2009.
24. Cipolle, J, Pharmaceutical Care Practice. The Clinician's Guide. 2nd edition, 1997
25. Clifford R.M., Davis, W.A., Batty, K.T., dan Davis, T.M, Effect of a Pharmaceutical Care Program on Vascular Risk Factors in Type 2 Diabetes: The Fremantle Diabetes Study, Diabetes Care, 2005, 28 (4): 771-6.
26. Clarke, P., Gray, A., Legood, R. Briggs, A., dan Holman, R, The Impact Of Diabetes-Related Complication on Healthcare Cost. Result from The United Kingdom Prospective Diabetes Study (UKPDS) no.65. Diabetic Medicine, 2003, 20(6) pp.42-450.
27. Depkes RI, Pharmaceutical Care For Diabetes Mellitus, Jakarta, 2005.
28. Eng, J, Sample Size Estimation: How Many Individuals should be Studied? Statistical Concept Series. Radiology, 2003, 227(2): 309-313.
29. Inzucchi, S., Porte, D., Sherwin, R., dan Baron, A, The Diabetes Mellitus Manua : A Primary Care Companion. Edisi 1. New York: McGraw-Hill Companies, 2005.
30. Katzung, B.G, Basic and Clinical Pharmacology, Book II. Edisi 8. Jakarta: Salemba Medika, 2005.
31. Martin. D, Pharmacoeconomics in Psychiatry, United Kingdom, 2002.
32. Muhlis. M, Farmakoekonomi. Article Pharmacoeconomics, 2007.
33. Oliver, S., Michael, H., dan Christian, W., Economic and Clinical Aspects of Diabetes Regarding Self-Monitoring of Blood Glucose. Diabetes Technology and Therapeutics, 2008, vol. 10(S1): S-72-S-81
34. Pallant Julie. SPSS Survival Manual. A step by step guide to data analysis using spss for windows (version 12).
35. Perkeni, Konsensus Pengelolaan Diabetes Melitus Tipe 2 di Indonesia. PB. Perkeni, Jakarta, 2002.
36. Ramsey, S., Kenth, H.S., Stepahnic, A.L., Howard, G.B., Jason, E.K., dan Paul, G, Diabetes Care Productivity and Medical Cost Of Diabetes in a large Employer Population. Diabetes Care, 1999.
37. Subish, P., Anupa, K.C., Mukhyaprana, P., Surulivel, R., dan Ravi, S, Role Of Pharmacist In Counseling Diabetes Patients. The Internet Journal Of Pharmacology, 2005.
38. Tjiptoherijanto. P., Soesetyo. B, Ekonomi Kesehatan. Penerbit Rineka Cipta. Jakarta, 2009.
39. Waspadji, S, Komplikasi Kronik Diabetes Melitus: Pengenalan dan Penangannya: Buku Ajar Ilmu Penyakit Dalam. Edisi 3. Jakarta: BP FK UI, 1999.
