

**PHARMACOEPIDEMOLOGICAL AND ECONOMIC EVALUATION OF DIABETES
MELLITUS PATIENTS WITH CO-MORBIDITIES**

*Dr. P. Narayana Swamy¹, Dr. R. Venkateswararao Rao¹, Dr. Karthik Muthusamy², S. Charishma³, K. Satyadurga³, K. Nani Babu⁴ and Prof. Rama Rao Nadendla⁵

¹Department of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Education and Research (RIPER) Anantapur, Andhra Pradesh, India.

²Independent Consultant, Pharmaceutical Research, Chennai, India.

³Pharm.D, Interns of Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, Andhra Pradesh,

⁴Department of Pharmacy Practice, (1a,4) Assistant Professors Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, Andhra Pradesh, India.

⁵Principal, Chalapathi Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India.

*Corresponding Author: Dr. P. Narayana Swamy

Department of Pharmacy Practice, Raghavendra Institute of Pharmaceutical Education and Research (RIPER) Anantapur, Andhra Pradesh, India.

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ABSTRACT

Introduction: Diabetes is one of the most common chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycemia). **Aim and objectives:** The aim of this study was to determine cost of illness and cost of utility in the study population and making recommendations to decrease the economic burden of the treatment by following the life style modifications. **Methodology:** It is a cross sectional pharmacoepidemiological study. Totally 132 diabetic patients both in-patients and out patients of medical and surgical departments in a secondary level referral hospital were included in this study which was conducted for a period of 6 months. All patients with diabetes type-II, continuing anti diabetic drugs (Metformin, Glibenclamide and Insulin,) for their diabetes management are included and patients who are diagnosed as Diabetic type-I and pregnancy and pediatric patients were excluded. Data was analyzed by Carlson comorbidities Index. **Results:** A total of 132 diabetic patients were included, in which male and females were nearly equal in number. Based upon the comorbid conditions, it was found that the most of the subjects (69%) were suffering with diabetes along with hypertension and 9.9% are having comorbidity of hypertension & acute renal failure along with DM and treatment costs more economic burden to the patients. The average utility of drugs is more for the combination of Metformin+Glibenclamide+Insulin than metformin+glibenclamide. **Conclusion:** Finally we concluded that study place is a rural area and most of people are with poor knowledge and having lack of awareness on both disease and treatment. By applying Charlson Co morbidities index we found the patient's economic status by which we found that many of the diabetic patients facing economic burden, especially daily wager are feeling much difficulty to face even therapy cost also. In co morbidities side, we noticed 55% of the study population are having diabetes with hypertension. Although all the patients were provided with education regarding their disease and drugs for improving their quality of life, but it has an influence on very few people.

KEY WORDS: Diabetes, Epidemiology, Antidiabetics, Pharmacoeconomics.

**INTRODUCTION
DIABETES**

Diabetes is a chronic disease. The term "diabetes mellitus" describes a metabolic disorder of multiple aetiologies most common reason considered is when pancreas does not produce insulin and it is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs (WHO 1999).^[2]

There are two main types of diabetes

Type 1 diabetes (T1B) usually patients require life long insulin injections for survival.^[2]

Type 2 diabetes (T2B): This is the most common type of diabetes (representing 90% of diabetic cases worldwide).

Type 2 diabetes (Non-insulin-dependent diabetes mellitus (NIDDM).

➤ It majorly occurs due to insulin resistance which is characterised by hyperglycemia and it develops in adulthood who are at risk of obesity, decreased physical activity and unhealthy diets and can be

managed with the help of oral hypoglycemic agents and lifestyle modifications such as diet, exercise etc.

- Patients are at lower risk of micro vascular and macro vascular complications unlike Type 1 diabetes.

Symptoms^[2]

- ✓ Patients may have no symptoms at all or minimal symptoms such as polyuria, polydipsia, polyphagia, and unexplained weight loss before diagnosing.
- ✓ May also experience numbness in extremities, pain in feet (disesthesias), and blurred vision and may have recurrent and severe infections
- ✓ Patients may present with loss of consciousness or coma but this is less common than in Type-1 diabetes.

Diagnosis²

- ✓ Diagnosis is made by the presence of classic symptoms of hyperglycemia and an abnormal blood test.
- ✓ A plasma glucose concentration ≥ 7 mmol/L (or 126 mg/dL) or ≥ 11.1 mmol/L (or 200 mg/dL) 2 hours after a 75g glucose drink.

- ✓ In a patient without classic symptoms, diagnosis can also be made by HbA1C test which is done to approximate metabolic control over previous 2-3 months and to guide treatment decisions. This test can also be used to diagnose type 2 diabetes.
- ✓ Some patients are diagnosed through "opportunistic screening" of high risk groups who are asymptomatic.
- ✓ For example, age >45 years of age, a BMI >25 kg/m² may, being of certain ethnic group or being hypertensive may prompt a screening test or the patient him/herself requests screening.

Treatment^[2]

The main aim of the treatment is to prevent or delay the complication of diabetes. It is also necessary to provide the education regarding the importance of diet, exercise, and foot care.

Diabetic Treatments

- 1) Oral hypoglycemic therapy.
- 2) Insulin treatment.
- 3) Diet (combined with exercise).

Oral Medications for Type 2 Diabetes

Drug	Initial Dose	Maximum Dose	Usual Dose
Biguanide			
Metformin	500 mg bid	2550 mg/d	500-1000 mg bid
Metformin XR	500 mg/d	2000 mg/d	1500-2000 mg/d
Sulfonylurea			
Glimepiride	1-2 mg/d	8 mg/d	4 mg/d
Glipizide	2.5-5 mg/d	40 mg/d	10-20 mg/d
Glipizide SR	2.5-5 mg/d	20 mg/d	5-20 mg/d
Glyburide	2.5-5 mg/d	20 mg/d	5-10 mg/d
Glyburide Micronized	0.75-3 mg/d	12 mg/d	3-12 mg/d
Thiazolidinedione			
Pioglitazone	15-30 mg/d	45 mg/d	15-45 mg/d
Rosiglitazone	4 mg/d	8 mg/d	4-8 mg/d
α-Glucosidase inhibitor			
Acarbose	25 mg tid	100 mg tid	25-100 mg tid
Miglitol	25 mg tid	100 mg tid	25-100 mg tid
Metiglinide			
Repaglinide	0.5 mg before meals	4 mg before meals	0.5-4 mg before meals
Nateglinide	60-120 mg tid before meals	120 mg tid before meals	60-120 mg tid before meals
DPP4 Inhibitor			
Sitagliptin	100 mg/d	100 mg/d	100 mg/d
Saxagliptin	2.5 mg/d	5 mg/d	5 mg/d
Bile Acid Sequestrants			
Colesevelam	375 mg/day	375 mg/day	375 mg/day

Complications of diabetes

1. Diabetic retinopathy (eye disease).
2. Nephropathy (kidney disease).
3. Neuropathy (nerve disease).
4. Cardiovascular disease.

Charlson Co morbidity Index

EDUCATION & COUNSELING

	Some of the recommendations made were
Educating the patient regarding the <ul style="list-style-type: none"> · Diabetes disease process and treatment options · Nutritional management · Physical activity · Medications · Monitoring · Acute complications · Chronic complications · Psychosocial adjustment · Preconception care, pregnancy and gestational diabetes management. 	Medical Nutrition Therapy (MNT): Subjects with diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian. Physical Activity: A regular physical activity, adapted to prevent the complications, is recommended for all patients with diabetes who are capable of implementing. Patients may need a pre-exercise stress test. It improves insulin sensitivity. Self-Monitoring of blood Glucose (SMBG): Instruct the patient in SMBG and routinely evaluating the technique and ability to use the results to adjust therapy. Foot Care: Patients with diabetes and high-risk foot conditions should be educated regarding their risk factors and appropriate management. Women with diabetes who are contemplating pregnancy should be evaluated and, if indicated, treated for diabetic retinopathy, nephropathy, neuropathy and cardiovascular disease.
Smoking Cessation Counseling	Advise all patients not to smoke. Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. This can be accomplished by assessing the smoking status and history, and counseling on smoking prevention and cessation.

The Charlson Co morbidity Index (CCI) is a method of predicting mortality by classifying or weighting comorbid conditions, has been widely utilized by health researchers to measure burden of disease.

The Charlson co morbidity index predicts the ten-year mortality for a patient who may have a range of co morbid conditions, such as diabetes mellitus heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality. Many variations of the Charlson co morbidity index have been presented, including the Charlson/Deco, Charlson/Romano, Charlson/Manitoba, and Charlson/D'Hoeres comorbidity indices.

Clinical conditions and associated scores are as follows:

1 each: Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular

disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease.

2 each: Hemiplegic, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukaemia, lymphoma.

3 each: Moderate or severe liver disease.

6 each: Malignant tumor, metastasis, AIDS.

For a physician, this score is helpful in deciding the treatment options for a condition. For example, a patient may have cancer with co morbid heart disease and diabetes. These comorbidities may be so severe that the costs and risks of cancer treatment would outweigh its short-term benefit.

Since patients often do not know how severe their conditions are, health care professionals were originally supposed to review a patient's chart and determine whether a particular condition was present in order to calculate the index. Subsequent studies have adapted the comorbidity index into a questionnaire for patients.

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm) Cerebrovascular disease: CVA with mild or no residua or TIA Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) Tumor without metastases (exclude if >5 y from diagnosis) Leukemia (acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
 Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Pharmacoeconomics^[9]

“The field of study that evaluates the behaviour of individuals, firms, and markets relevant to the use of pharmaceutical products, services and programs, and which frequently focuses on the costs (inputs) and consequences (outcomes) of that that use.

Thus, pharmacoeconomics (PE) is a subfield of health economics. Operationally, the field of Pharmacoeconomics consists of comparing outcomes (clinical, economic, humanistic) and costs (resource consumption) of pharmaceutical products, programs and/or services to the next best alternatives from selected perspectives. The aim of this approach is to identify, measure, value, and establish a link between both resource consumption and outcomes so that relative worth of selected pharmaceutical products, programs and/or services can be established.

The basic task of economic evaluation is to identify, measure, value, and compare the costs and consequences of the alternatives being considered.^[2]

The two distinguishing characteristics^[2] of economic evaluation are as follows:

- (1) Is there a comparison of two or more alternatives?
- (2) Are both costs and consequences of the alternatives examined?

A full economic evaluation encompasses both characteristics, whereas a partial economic evaluation addresses only one.

COST –UTILITY ANALYSIS

Cost-utility analysis (CUA) is a method for comparing treatment alternatives and also can compare cost, quality and quantity of patient years that integrates patient preferences and HRQOL.

Cost is measured in dollars, and therapeutic outcome is measured in a quality-adjusted life year (QALY) gained.

Advantages of cost–utility analysis

Cost–utility analysis was developed to address the problem of conventional cost effectiveness analysis, which did not allow decision-makers to compare the value of interventions for different health problems.

Cost–utility analysis can capture the value of improvements in morbidity and mortality.

Cost–utility analysis thus increasingly facilitates the transparency of resource allocation processes.

Disadvantages of cost–utility analysis

- ✓ With many healthcare interventions, there are significant concerns about the ability of cost–utility analysis to capture all the valued characteristics.
- ✓ It is undoubtedly true that QALYs do not capture differences in the process characteristics of interventions, and there is substantial evidence that patients do attach value to these.

- ✓ There is also concern that the descriptive instruments and the utilities they generate are insufficiently sensitive to differences in treatments for milder conditions.
- ✓ For chronic conditions, the assumption that the utility of a health state is independent of the time spent in that health state is considered problematic.
- ✓ Similarly, that the preceding and subsequent health states do not affect the utility of a specific health state is a strong assumption in the context of chronic conditions, especially conditions where disability accumulates over time.

COST-OF-ILLNESS

Cost-of-illness studies measure the economic burden of a disease or diseases and estimate the maximum amount that could potentially be saved or gained if a disease needs to be eradicated. Numerous cost-of-illness studies have been conducted over the past 30 years. Many of these studies have been instrumental in public health policy debates because they highlight the magnitude of the impact of an illness on society or a part of society and it can help policy makers to decide which diseases need to be addressed first by health care and prevention policy. Additionally, these studies can indicate the diseases for which curing would be valuable in reducing the burden of disease. For specific stakeholders, such as the federal government, cost-of-illness studies can show the financial impact of a disease that has on public programs, such as Medicare and Medicaid.

Cost-of-illness studies are often cited in disease studies that attempt to highlight the importance of studying a particular disease, as well as in cost-effectiveness and cost-benefit studies. Cost-of-illness studies can demonstrate which diseases may require increased allocation of prevention or treatment resources, but they are limited in determining how resources are to be allocated because they do not measure benefits.

METHODOLOGY**Study design**

It is a Pharmacoepidemiological study involving cohort study design. Stratified convenience sampling with matching for factors such as gender, age is used. All diabetic type 2 patients under medication of Metformin, Glibelcamide and insulin were included. Medical records and patients reports were assessed for data collection.

Data collection and processing

In-patients and out patients of medical and surgical departments in a secondary level referral hospital were included and study was done for a period of 6 months.

Data was collected from patients diagnosed as Diabetic type-II and continuing anti diabetic drugs (**Metformin, Glibelcamide, and Insulin and others²⁰⁾**) for their diabetes management.

We have collected the data from patients in regular intervals regarding medical history, medication history, and comorbid conditions, drugs used along with the contact details. Data was processed using Microsoft excel.

Inclusion Criteria

1. All in patients and out patients who are diagnosed as Diabetic type-II.
2. Continuing anti diabetic drugs (**Metformin, Glibelcamide and Insulin,**) for their diabetes management.
3. All patients of above 40 years old.
4. Who visit hospital for their regular checkup of disease.
5. Diabetics with Co-morbidities were also involved in this study.

Exclusion Criteria

1. Patient who are diagnosed as Diabetic type-I.
2. Those who are non-compliant.
3. Those who have communication problems.
4. Patients with pregnancy.
5. Pediatric patients.
6. Patients who are not willing to participate in the study.

RESULTS

Patient's demographic details

A total of 132 diabetic patients are considered, in which males are 63 and females are 69 which are almost equal in number.

Table 1: Cost of illness in different co morbidities.

Disease	No of Pt's	Total Drugs cost	Avg drug cost	Total other hosp cost	Other Avg Hosp Cost	Total cost	COI %	COI
DM	19	22,800	1,200	2888	152	25688	1352	1
DM+HTN	41	63,960	1,560	23370	570	87330	2130	1.57
DM+HTN+P.ULCER	11	52,800	4,800	12540	1140	65340	5940	2.78
DM+ HTN+LEU	3	16,200	5,400	4560	1520	20760	6920	1.16
DM+HTN+CHF	5	30,000	6,000	4650	930	34650	6930	1.0
DM+ HTN+LYM	5	31,000	6,200	7325	1465	38325	7665	1.10
DM+ HTN+CRF	9	1,03,644	11,516	15480	1760	119124	13236	1.72
DM+ HTN+ARF	13	1,69,000	10,090	20475	1575	189475	14575	1.10
DM+ HTN+NEURO	3	49,500	16,500	5265	1755	54765	18255	1.25
DM+HTN+ALF	6	1,03,500	17,250	11880	1980	115380	19230	1.05
DM+ HTN+TUMOR	5	93,000	18,600	12850	2570	105850	21170	1.10
DM+HTN+MLD	4	79,040	19,760	7436	1859	86476	21619	1.02

Average Utility of Drugs

Table 2: Comparison of utility and cost of drugs per number of patients.

Drugs	Number of pts	Avg utility	Avg cost
M + Gli	93	0.7	7036
Met+Glib+Ins	39	0.8	10665

Patients with Co morbidity

By involving co morbidity scale we included all the diabetic patients who are suffering with co morbidities.

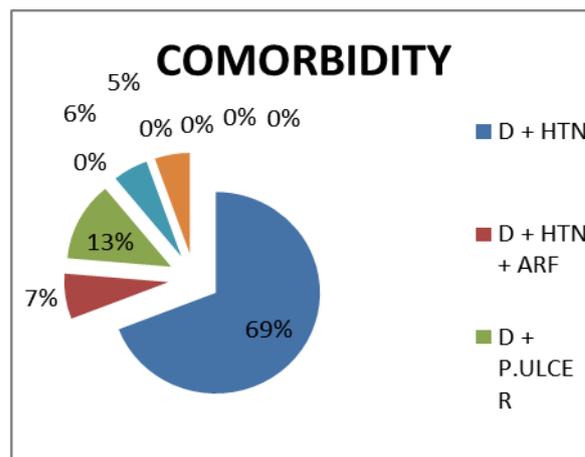


Figure-1: Percentage of co-morbidities in study population.

Cost Analysis for Calendar Year

We calculated cost of therapy according to co-morbidity. No of patients: patients who are suffering from particular disease.

Avg cost of therapy: average cost of entire therapy through one year.

Cost of drugs: total expenditure of amount on medicines from all patients.

Other hospital cost: laboratory and hospital charges.

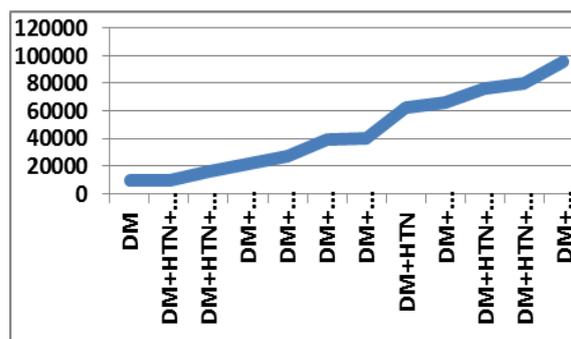
Comparison of Co morbidity with Age Group**Table: CCI in Co morbidity.**

S.NO	Disease	No: of Pts	Avg age	Avg CCI
1.	DM	19	41-55	3
2.	DM+HTN	41	46-59	4
3.	DM+HTN+P,ULCER	11	45-65	5
4.	DM+HTN+CHF	7	56-70	5
5.	DM+HTN+ALF	13	52-79	6
6.	DM+HTN+MLD	4	60-82	9
7.	DM+HTN+ARF	13	50-70	5
8.	DM+HTN+CRF	9	56-80	7
9.	DM+HTN+LEU	3	58-70	6
10.	DM+HTN+LYM	5	62-80	6
11.	DM+HTN+TUMOR	5	59-77	11
12.	DM+HTN+NEU	9	63-89	7

Table. 3: All Patient Data Showing With Charlson Co morbidity Index.

Age group	Number	Avg utility	CCI
41-50	36	0.8	5.0
51-60	40	0.7	6.3
61-70	46	0.6	7.0
71-80	7	0.5	6.7
>80	3	0.5	6.0

Average additional Cost due to Different Co morbidities

**Figure-2: Ascending order of cost of hospitalization.****Comparison of utility with Charlson Co-morbidity index**

Through this average utility of drugs with scoring of Charlson co-morbidity index of every individual for years of disease was explained.

Table 4: CCI for years of disease.

Suffering from years	Numbers	Avg utility	CCI
1-2	23	5	6
2-5	33	5.2	6.01
5-10	38	6.7	7.06
10-20	24	7.9	8.0
Above 20	14	8.8	9.01

DISCUSSION

In this study, a total of 132 diabetic patients were included out of which male and females are nearby equal in number and adults are higher than the geriatric patients.

In our study, higher number of patients are having the comorbidity of hypertension and other comorbidities include peptic ulcer, congestive cardiac failure, acute renal failure, chronic renal failure, leukemia, lymphoma, other tumors, nephropathy, acute liver disease, moderate liver disease.

Diabetes mellitus is lifelong threatening condition which causes the economic burden in subjects with low socio-economic status. However, some government hospitals

are helping the patients from poor economic background by providing health care to all of them without charging money for consultation and providing all the useful medicine.

By this study, we had analyzed cost per individual patients according to their disease status with cost of therapy per year. Finally we concluded that diabetic with co morbidities are facing more economic burden per year wise when compared with subjects having only diabetes.

Average utility of therapy: comparison of utility and cost for number of patients was analyzed and its seems like combination therapy of Metformin + Glibenclamide was most popularly consumed when compared with other combinations. Insulin is advised to very few patients and

other oral antidiabetics were given in combinations based on patient disease condition.

Cost of hospitalization with co morbidities: In total 132 study subjects, 60% of patients are hospitalized with comorbidities and facing economic burden for hospitalization, travelling and other costs like cost of diagnosis. In our study many of the participants are daily wagers, they will loosen their economic source if they get struck with hospitalization.

Basically study place is rural area with most of the subjects are with poor knowledge about disease and its complications. In our study it was identified that, many of the patients are facing economic burden, even sometimes they are not able to consume sufficient quantity of medications due to the high costs.

CONCLUSION

The costs for patients with comorbidities was substantially higher when compared to the patients with out comorbidities and the cost was found to increase progressively with increase in number of complications. Therefore, the burden of this disease was significant for patients as well as their families, so the health policy makers should emphasize on the initiatives to prevent the disease prevalence. Proper care and counseling should be provided continuously to the patients with diabetes to manage the disease effectively and to prevent the devastating complications. Lastly we recommend that more economic studies should be done which play an important role in applying the frame work for resources allocation in diabetes prevention and control.

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