1. INTRODUCTION AND BACKGROUND OF STUDY

1.1 Evolution and Definitions of Pharmaco-Economics

Healthcare organizations, governments and individuals have been forced by prevailing circumstances of economic crises to be increasingly oriented towards cost containment due to escalating nature of health expenditure. Allocation to health sector is increasing as a result of cost increment, not only because of growing population but also due to new health development, subsequently, total healthcare spending and per capita spending is increasing.

Moreover, with the depressed nature of the economy in many countries such as Nigeria where per *capita* income is low, there is need for utmost consideration for cost containment measures. Furthermore, the advance in medical technology -"high-tech'', diagnostic and therapeutic options have further complicated the financial picture. Although they offer the potential to improve quality of care, these advances have significantly increased hospitals operating costs.

Health care spending is increasing, both from government and private stand-point, as people make choices to empower themselves (Deborah *et al*., 2003). Pharmacy practitioners and managers face a multitude of economic challenges. The impact of cost containment is causing administrators and policy makers in pharmacy to examine closely the cost and benefits of both proposed and existing programmes. Private employers and public agencies are demanding that health problems be evaluated in terms of clinical and social outcomes related to the cost incurred. Pharmaco-Economic approach can be used to analyze the value of health services to the public, as opposed to the traditional market place scenario where values are measured by the prices that the patient or patron is willing to pay. The use of valid economic evaluation methods to measure the value and impact of new services can increase acceptance of such programs by the medical

profession, third party payers and consumers (Ray, 1979; Mc Ghan, 1993; Bootman *et al.*, 1996).

There is increasing competition among health professionals for the limited dollars and resources available within the institutions and communities. Pharmacists will have to compete increasingly with nursing, medical and other groups for adequate reimbursement and payment (Enright, 1983; Curtiss, 1983). Pharmacists must document the cost-benefits of distinct pharmacy services and must develop priorities for those services to compete successfully within various arena.

In spite of aforementioned inherent and obvious predicaments, public expectations from healthcare providers and government are becoming higher on daily basis (Popcorn and Melby, 1992), therefore, there is need for a useful scientific intervention that can facilitate rational decision. In addition, despite wide use of pharmaceuticals, few data exist regarding actual costs and benefits attributable to specific drug therapy. This problem may be attributed to lack of well defined methodologies to evaluate medical interventions.

The healthcare environment is clearly in a state of rapid evolution. Traditional approach to health care decisions will no longer suffice, therefore, new tools would be required. Medical, ethical and societal concerns about costs, access and quality of care are making healthcare practitioners to consider more comprehensive model for medical decisions.

Consequently, interest in research to assess outcomes of healthcare has been increasing. These trends have led to the evolution of pharmaco-economics: a relatively new discipline in pharmacy (Townsend, 1987; WHO, 1996).

Pharmaco-Economics has been defined as the description and analysis of cost of drug therapy to health care system and society (Townsend, 1987). It is a specialized aspect of health economics which involves the use of economic principles and techniques of

analysis to ensure that scarce healthcare resources are used more efficiently (WHO, 1996). It can also be defined as the branch of health economics that uses cost-benefit, cost-effectiveness, cost minimization and cost utility analysis to compare pharmaceutical products and treatment strategies. It is an economic evaluation of drug therapies, pharmacy services and programmes or pharmacy technology (Cano and Crane, 1999).

Pharmaco-Economics involve balancing the cost with the consequences (outcomes) of pharmaceutical therapies and services. As a type of outcome evaluation, pharmaco-economics look beyond the direct or acquisition cost of a pharmaceutical product by including its impact on total health utilization and costs. As a component of outcome research, it helps pharmacist decide which clinical circumstances, patient characteristics and practice settings are most suitable for a particular intervention (Reeder, 1995). Economic evaluations provide health care decision-makers with valuable information, allowing optimal allocation of limited resources.

Pharmaco-Economics is based on long-term benefits, whereas physicians are typically forced to seek immediate savings (Arenas-Guzman *et al.*, 2005). The objective of pharmaco-economic study is to influence policy formulation and effect decision making, that is to make a person or a group of people change their behaviour and persuade them that a new course of action is a "better" one, "better" simply means that in economic terms, it is more efficient (WHO, 1996). Pharmaco-Economics focuses on the costs and benefit of drug therapy and provide a basis for resource allocation and utilization. It is increasingly becoming important for health policy decision-making. It is a young science that will improve in application. Its need is undeniable, especially in developing countries (Ahuja *et al*., 2004).

How can we meet the ever increasing demand for health care, given our limited resources? Health Economics helps to address this issue. It can be seen as a tool to help

prioritize health care interventions so that maximum health benefits are provided to the population within the resource constraints that exist (Rachael, 2003).

Economic evaluation is a systematic appraisal of costs and benefits of projects or alternative ways of achieving the same outcome, undertaken to determine the economic effectiveness of alternatives (Napper and Newland, 2003). Economic evaluations are tools that health economists use to assess the cost-effectiveness of health care interventions. With new health technologies or a new drug, extra clinical effectiveness will be associated with an extra cost. Once deployed, the resources used to meet these extra costs are no longer available for other interventions. Economic evaluation helps decision makers to determine whether the cost of this extra effectiveness provided by the new drug is worthwhile, within the budget available. They are not supposed to replace the judgment of health professionals, but instead should support both health professionals and decision makers in making informed decisions (Rachael, 2003)

1.2 Statement of Problems

Diabetes Mellitus is a chronic, incurable condition that affects 3% of the Nigerian population (WHO, 2007; WHO, 2010). There is evidence that prevalence of non-communicable diseases is increasing, including diabetes mellitus, which if not adequately managed, can result in a wide range of complications that have clinical, social and economic implications, especially due to decreasing age of onset. Bakari and Onyemelukwe (2004) reported impaired glucose tolerance (IGT) of 7.7% rate among Hausa-Fulani in North-Eastern Nigeria who have no history of diabetes mellitus. They opined that this would increase incidence of diabetes mellitus, as one in three individual with IGT will develop Type II diabetes mellitus. Although, WHO (2007) accorded priority status to diabetes mellitus, many public health planners remain largely unaware of its magnitude and the seriousness of its complications. Of equal consequence is the

increasing prevalence of the disease and the long-term cost of therapy to both patients and the health sector, and its cost to nations in economic terms, due to the fact that use of anti-diabetic drugs in the management of diabetes mellitus is for the lifetime of the patients from the time of diagnosis. This translates into a substantial cost in drug therapy to the patients and government (Cantrill, 1999). This group of drugs is also faced with problem of availability, affordability and non-use of generic names.

The problems/issues here are:

1. To determine whether poverty could be said to be a hindrance to good health (good glycemic control) in terms of drug purchase (non-affordability) and establish whether pharmaco-economic intervention could help.

2. Promoting rational decision on choice of drugs through economic evaluation of drug therapy in healthcare settings, especially government hospitals of which University of Maiduguri Teaching Hospital (UMTH), the only University Teaching Hospital in North-Eastern Nigeria is a good example, with a view to improving effectiveness of drug therapy and efficiency of health service.

3. Determining reliable indicators for effectiveness of anti-diabetic care.

1.3 Aims and Objectives

1.3.1 General Objective

To conduct pharmaco-economic evaluation of anti-diabetic therapy in North-Eastern Nigeria.

1.3.2 Specific Objectives

1. To determine the relationship between socio-economic status, affordability and glycemic control (outcome of anti-diabetic therapy).

2. To determine cost of illness of Type II diabetes mellitus.

3. To determine and compare the mean cost per defined daily dose of branded and generic equivalent anti-diabetic drugs used in Type II diabetes mellitus by cost minimization analysis.

4. To determine and compare the cost-effectiveness of various anti-diabetic drug therapy options in Type II diabetes mellitus.

5. To determine the relationships between degree of knowledge/practice of lifestyle/dietary modification and glycemic control (outcome of anti-diabetic therapy).

6. To determine and compare quality control parameters of branded and generic anti-diabetic drugs.

1.4 Significance of Study

It is essential to consider individual and societal costs of diabetes and search for reliable indicators for the effectiveness of diabetes care (Cantrill, 1999). A form of anti-diabetic drugs utilization study and consequently their economic evaluation is needed to promote rational anti-diabetic drugs prescription and improve economic, clinical and humanistic outcome of anti-diabetic therapy.

Need to verify speculations that anti-diabetic drugs are used as first line management of diabetes mellitus instead of dietary and lifestyle modifications as initial approach and combination of two classes of anti-diabetic drugs without exhausting options of monotherapy.

Diabetes Mellitus is of public health importance because it has no known cure, affects 1 to 2% of the global population and the prevalence is increasing with a wide range of complications that have clinical, social and economic implications (Cantrill, 1999). Upon consideration of the impact of anti-diabetic therapy on the overall cost of healthcare of diabetic patients who uses this class of drugs for lifetime from time of diagnosis, effort

designed to reduce expenditure on this class of drugs as well as use them more effectively would be advantageous (Cantrill, 1999).

The study would indicate whether cost effective spending for management of diabetes mellitus (pharmaco-economics) should be considered in health policy in a depressed economy or impoverished society.

Cost effective therapy of diabetes mellitus will not only ensure rational drug use but also reduce patients dropping out of treatment because of cost, thereby reducing incidence of therapeutic failure by enhancing economic, clinical and humanistic outcome of therapy. Complications due to this disease would be reduced and improvement in spatients' quality of life would be achieved.

Cost Effectiveness and cost minimization analysis, forms of pharmaco-economic tools appear effective when applied properly in therapeutic decision making. The various outcomes of therapy namely: economic, clinical and humanistic (psycho-social) outcomes are considered (Kozma *et al*., 1993).

1.5 Hypotheses

1. There is no association between socio-economic status, affordability and outcome of anti-diabetic therapy.

2. There is no significant difference in the frequency of branded and generic anti-diabetic drugs prescription.

3. There is no significant difference in the mean cost per defined daily dose of branded and generic equivalent anti-diabetic drugs.

4. There is no significant difference in the effectiveness of therapeutic options available for management of Type II diabetes mellitus.

5. There is no association between degree of knowledge/practice of lifestyle/dietary modification and glycemic control (outcome of anti-diabetic therapy).

1.6 Theoretical Framework

Determination of socio-economic status was based on World Bank Socio- Economic Indicators. Social indicators of development/poverty are education, housing, access to water, average household size, access to health, nutrition, access to communication, transportation and electricity while income is an economic indicator (World Bank, 2006). The economic, clinical and humanistic outcome (ECHO) model was adapted for outcome measure. ECHO model is a theoretical framework for planning and conducting a pharmaco-economic evaluation (Kozma *et al*., 1993). ECHO model depicts the value of a pharmaceutical product or service as a combination of a traditional clinical based outcome with more contemporary measures of economic efficiency/quality and humanistic (psycho-social) outcome. The integrated approach provides a theoretical basis for considering potential trade-offs among economic, clinical and humanistic variables in optimizing allocation of health care resources.

1.7 Limitation and Scope of Study

The study was limited to pharmaco-economic evaluation of anti-diabetic therapy in North-Eastern Nigeria, using information generated from patients' interview, case-notes and prescriptions from the only university teaching hospital in the region.

The effectiveness measure was limited to analysis of positive and negative outcome of each treatment option from review of literature to establish probabilities of the outcomes and applying decision analysis for effectiveness (Cano and Fujta, 1988; Suleiman and Tayo, 2001).

Only anti-diabetic drugs dispensed in the study setting were sampled and used for the quality control component of this study.

1.8 Operational Definition of Terms

Adverse Drug Reaction: A measure of noxious or untoward effect of a drug.

Anti-diabetic drugs: Drugs used in management of diabetes mellitus, to control blood glucose.

Bioavailability: A measure of the rate and extent to which a drug reaches the systemic circulation in a pharmacologically active form.

Bioequivalent: Two or more products releases same drug(s), and reaches systemic circulation in a pharmacologically active form at the same rate and extent.

Chemical Equivalent: Two or more products have the same amount of labeled drug(s).

Cost Effective: Achievement of result in the most economical way.

Cost Minimization: Choice of an alternative intervention that would produce the same outcome at a lower cost.

Effectiveness: Measure of outcome. Extent to which current and potential interventions improves population health. Used interchangeably with outcome.

Efficacy: In relation to anti-diabetic drugs, refers to ability and consistency in control of blood sugar.

Frequency of Administration: Indicates the time interval between a dose of a drug and the next dose of the same drug. It is a very important determinant of compliance with dosage regimen.

Glycemic Control: Consistent maintenance of blood glucose level in normal range. It is a measure of outcome of anti-diabetic therapy.

Glycosylated Haemoglobin (HbAc): Fraction of haemoglobin that non-covalently binds glucose; assay providing a measure of average blood glucose level, hence control of diabetes mellitus over about 8 weeks.

Hyperglycemia: Increased blood glucose, usually indicative of diabetes mellitus.

Hypoglycemia: Decreased blood glucose due either to overdosage of hypoglycemic agent or inadequate intake of carbohydrate.

Hypoglycemic agent: Synonym of anti-diabetic drug, that is, drug used in management of diabetes mellitus, to reduce or control blood glucose.

Nephropathy: Kidney disease in which inflammation is not a major component.

Neuropathy: Disease of the nervous system. Loss of function of peripheral nerves, which may be focal or generalized.

Nocturia: Passing urine at night.

Outcome: The result and value of healthcare intervention.

Polydipsia: Excessive Thirst.

Polyphagia: Excessive eating or hunger.

Polyuria: Excretion of excessive amount of urine

Retinopathy: Non inflammatory disease of the retina of the eye.

Safety of Administration: A measure of risk or otherwise of infection, abscess and pain at the site of administration, especially, of injections.

Tachycardia: Excessive or rapid action of the heart.

Therapeutic Equivalent: Two or more drug products produce same pharmacological and therapeutic effect.

2. LITERATURE REVIEW

2.1 Pharmaco-Economics

2.1.1 Overview of Pharmaco-Economic Methodologies

There are four types of economic evaluation that are commonly described in increasing order of methodological and practical difficulty. They are cost minimization analysis, cost effectiveness analysis, cost utility analysis and cost benefit analysis. Although they employ similar methods to define and evaluate costs, they differ in outcome estimation techniques.

Cost Minimization Analysis (CMA): Calculating the cost of two or more alternatives that have the same outcome to identify the lowest cost option e.g. in branded and generic equivalent products (Bootman *et al.*, 1996). Cost Minimization Analysis compares the costs of different interventions that are assumed to provide equivalent benefits. The aim is to decide the least costly way of achieving the same outcome (Napper and Newland, 2003). A good example is a comparison between a branded drug and its generic equivalent. If the assumption of equal effectiveness is substantiated, the decision hinges on finding the least expensive way of obtaining that health benefit. Only the costs are compared and not the benefits. The decision rule is therefore simple because the cheapest intervention will provide the best value for money.

Cost Effectiveness Analysis: Measuring both costs and benefits of alternatives to find the strategy with the best ratio of cost and benefit, measured in the therapeutic or programme effects per money unit. In cost-effectiveness analysis (CEA), benefits are measured in natural units (Bootman *et al.*, 1996).

CEA is used to determine technical efficiency i.e. comparison of costs and consequences of competing interventions for a given patients group within a given budget (Napper and Newland, 2003). The analysis helps to answer urgent questions, such as how much it

would cost to reduce hip fractures in osteoporotic women (Herman *et al.*, 2005).

Cost Utility Analysis (CUA): Same as cost effectiveness analysis except that benefits are measured in “utility” units i.e. healthy years, to which a value has been attached ("utility" units), which are often controversial (Bootman *et al.*, 1996). The best known utility measure is the "quality adjusted life year" (QALY).

In this case, competing interventions are compared in terms of cost per utility (cost per QALY) (Napper and Newland, 2003). Health outcomes are assigned a value based on their contribution to quality of life.

Cost Benefit Analysis (CBA): Comparison of the costs and benefits of an intervention by translating the health benefits into monetary value, so that both costs and benefits are measured in the same unit. The final result is expressed as a net monetary gain (or loss) or as a cost/benefit ratio (Bootman *et al.*, 1996). This type of economic evaluation is one in which all costs and consequences of a program are expressed in the same units, usually money. CBA is used to determine allocative efficiency, that is, comparison of costs and benefits across programmes serving different patients groups. The challenge of CBA is that its analysis require putting a monetary value on all health outcomes and ultimately on life. There is inherent difficulty with this type of analysis and as a result, very few CBA have been performed (Napper and Newland, 2003).

Other Types of Pharmaco-Economic Methodologies

Cost of Illness and Cost of Therapy

An illness consumes resources, thus, it has a cost (Drummond, 1992). The cost of an illness is the sum of three components:

- The medical resources used to treat the illness (direct cost) e.g. hospital care, professional services, drugs and supplies.

- The non-medical resources associated with it (direct cost) e.g. transportation to treatment site and hiring of home care.
- Lost productivity due to illness or disability (indirect cost).

A fourth category, the intangible cost of pain and suffering, is often unquantifiable (Drummond, 1992).

A medical therapy is intended to cure, prevent or reduce the severity of an illness. The cost of therapy also may be classified as direct medical, direct non-medical and indirect. A therapy can cause other resources to be consumed e.g. treating adverse effects of the therapy. This is also considered as part of the total cost of the therapy. For example chronic dialysis may cause anemia, the treatment of which will consume medical resources. In addition, dialysis prolongs life and cost of other treatments during additional years of life though unrelated to dialysis will be included in cost of therapy (dialysis) because they would not have been incurred if the patient had died of end stage renal disease (Drummond, 1992) .

Burden of disease and cost of illness studies quantify the burden of a disease in monetary terms for example, for osteoporosis, the number of fractures occurring and their total cost to the National Health Service (NHS) would be evaluated. However, what is relevant is the relative costs and benefits of different treatments for the condition, rather than the overall cost of the diseases with the highest burden, which will not necessarily result in an efficient use of resources, if the interventions available for that disease or condition are not cost-effective (Rachael, 2003).

Marginal Cost Analysis (MCA) is used to quantify the cost of additional benefit gained from using an alternative intervention. In health, one of the key questions is not whether products/treatments are worthwhile or not, but the extent to which they are worthwhile. Thus the choices in health care are not, for example whether diabetes

mellitus should be treated, rather, should more or less resources be devoted to the management of diabetes mellitus. In this case, it is the marginal (or incremental) costs and benefits of the expansion or contraction of the whole program which are important, not the costs and benefits of the existing programme.

Marginal issues in drug therapy include:

- For what indications should treatment be given?
- What dose to use?
- What frequency to dose at?
- For how long should therapy be continued?

Marginal analysis can also be applied to the benefits of treatment as well as to the cost. Marginal cost analysis assesses the additional cost that one treatment imposed over another, compared with the benefits or success it provides.

2.1.2 Components of Pharmaco-Economic Evaluation

The common components of all types of pharmaco-economic evaluations are that they consider inputs in relationship to output i.e. cost and consequences (outcomes). Involves making informed choices between alternative use of resources, and involve one of the four basic types mentioned above.

2.1.2.1 Cost Determination and Analysis

The price of a drug product is not the same as the cost of drug therapy. Unlike price, which is usually quite easily obtained, cost is more difficult to measure.

The concept of cost deals with the resources that are used or consumed in the production of a good or service. The ultimate products of the healthcare system are therapies that cure, prevent or alleviate diseases and thereby affect health status. In producing these therapies, several services may be used – prescription drugs, laboratory tests, hospital stays, physician's visits and surgical procedures. These services are the inputs in a

production process that produces therapies as its output, and they require basic resources such as personnel, equipment, facilities and supplies. In other words, healthcare services can be viewed as intermediate goods, they consume basic resources and, in turn, they are consumed in the production of therapies.

2.1.2.2 Types of Cost

When discussing cost in any type of economic analysis, several kinds of cost need to be considered, and during any analysis, it is important that the costs quoted are properly identified (Jacob, 1991).

Cost is defined as the magnitude of resources consumed. The cost of a product or service is the monetary value of resources consumed in its production or delivery. Cost can be direct or indirect. A direct cost involves transfer of money – if money is exchanged for the use of a resource, this is a direct cost. An indirect cost is unpaid resource commitment i.e. no money is exchanged e.g. time off work. Cost can also be intangible. Intangible costs cannot easily be measured e.g. pain and suffering experienced by patients (Jacob, 1991).

The different types of cost include:

1. **Fixed Costs:**

   These are costs incurred regardless of the quantity of any output, for example, an employee's salary.

2. **Variable Costs:**

   These are costs which vary with the level of output produced, for example, a sales commission.

3. **Total Costs:**

   These are the fixed cost plus the variable cost.

4. **Average Costs:** This is the resource consumed per unit of output. It is derived by dividing total costs by volume or quantity of output.
5. **Marginal Costs:**

   This is the change in total cost of producing one additional (or one less) unit of output (Drummond, 1992).

2.1.2.3 Framework for Determining Costs

This encompasses five steps:

1. **Specifying the Ingredients:**

The initial step in determining cost of a therapy or programme is to identify the resources consumed by the programme, that is the ingredients used to produce the therapy or service (Levin, 1995). The goal is to develop a comprehensive list of inputs that are used in producing the therapy or service.

- What medical services are used?
- What non-medical services or indirect costs involved?
- What equipment and supplies?

To be meaningful, all relevant resources, and not just the obvious and/or easy to identify and measure ones must be included.

In determining relevance of the resources, scope or perspective of the analysis must be specified. Economic evaluations may assume the view-point of a service provider, insurer, patient, healthcare system or society.

2. **Counting Units**

For each resource, a unit of use or unit of consumption is measured or counted in that unit. For example, the use of a drug product may be measured in doses, physicians' services in procedures and in-patient services in drugs.

3. Assigning Monetary Values

Once resources have been identified and counted, they are assigned a monetary value.

As a general rule, the time and effort spent in assigning a monetary value should be proportional to the importance of that resource. In general, the best measure of a resource value is its opportunity cost.

4. Adjusting for Differences in the Timing of Cost (Discounting)

A time is associated with money. We prefer to receive money now rather than later because they can generate benefits or returns in the interim. We also for the same reason prefer to pay out money later rather than now. Because current and future monies are not valued the same, future costs must be discounted to reflect their current value when a program extends over multiple years (Spiro, 2007).

5. Allowing for Uncertainty

Oftentimes, cost or resource consumption is not known with certainty, assumptions are made and estimated figures are derived. Sensitivity analysis compensates for this uncertainty. It can be viewed as "what if" analysis. The economic evaluation is reworked using different assumptions or estimates of the uncertain cost.

2.1.3 Outcomes

Outcomes describe the results and value of healthcare interventions. However, depending on perspective, the outcomes of health care are multidimensional.

The clinical outcome has traditionally been most concerned with clinical outcomes of treatments. More recently, health care payers and administrators have focused on the economic outcome of healthcare decision, while patients on the other hand, are becoming increasingly knowledgeable and involved in discussions regarding their own health care and are seeking more information regarding the humanistic outcomes of therapy.

The true value of healthcare interventions, programs and policies can be assessed only if all three dimensions of outcomes are measured and considered (Kozma *et al*., 1993).

2.1.3.1 The ECHO Model

The economic, clinical and humanistic outcome (ECHO) model is a theoretical framework for planning and conducting a pharmaco-economic evaluation (Kozma *et al*., 1993). ECHO model depicts the value of a pharmaceutical product or service as a combination of a traditional clinical based outcome with more contemporary measures of economic efficiency/quality and humanistic outcome- psycho-social effects of intervention (drug therapy) The integrated approach provide a theoretical basis for considering potential trade-offs among economic, clinical and humanistic variables in optimizing allocation of health care resources.

a. Economic Outcomes

Economic Outcome Studies assesses the impact of pharmaceuticals on total health resources utilization and cost. The cost of the drug is balanced against its effect on the use of other health care services (inputs).

Economic Outcome includes direct medical, direct non-medical, and indirect costs and consequences. Direct medical costs and consequences include those events that can be directly attributed to the production process or clinical treatment pathway. For example, the direct medical costs of treating asthma may include the cost of pharmaceutical, physician office visits, emergency room care, and patient hospitalization. Direct non-medical costs are those costs incurred by the patient in seeking care and may include care cost and the cost of transportation to the physician's office or the pharmacy (Kozma *et al*., 1993).

Indirect Costs are those related to changes in workers productivity and quality of life and are typically measured in terms of lost wages or absenteeism. Consequences or benefits

of care are often measured in terms of savings or cost avoided. Consequences of pharmaceutical resource utilization may be positive (decreased length of hospital stay, increased quality of life, fewer hospital admissions etc) or negative (adverse drug reactions, unnecessary office visits, decreased quality of life). In a pharmaco-economic evaluation, both positive and negative consequences must be included (Mackeigan and Pathak, 1992).

b. Clinical Outcomes

Clinical Outcomes are the familiar consequences of pharmaceuticals. Mortality, morbidity and disability as well as specific clinical end-point like blood pressure and serum glucose concentration. Eradication of bacteria may be used as clinical outcomes measures in pharmaceutical outcome evaluations and pharmaco-economic studies (Kozma *et al*., 1993).

Clinical outcomes are used to measure changes in health status related to alterations in the physiological disease process. While mortality and morbidity are often the outcomes of greatest interest, many pharmaco-economic studies by necessity rely on clinical indicators or end-points as surrogate measure of those outcomes (Kozma *et al*., 1993).

c. Humanistic Outcomes

Humanistic (psycho-social) outcomes analysis measures the effects of medical care on the physical, social and emotional well being of the patient. This outcome measures is in agreement with World Health Organization (WHO)'s definition of health. Health is a state of complete, physical, mental, social well being and not merely absence of disease or infirmity (WHO, 2001). The ability of an individual to perform routine daily functions and complete normal job duties are very important outcomes that should be measured when assessing the value of a medical or pharmaceutical intervention (Mackeigan and Pathak, 1992).

As a frame work for pharmaceutical outcome evaluations, the ECHO model suggests that all three dimensions of pharmaceuticals should be considered simultaneously rather than focusing on just the drug product cost, the analysis includes the net impact of the pharmaceutical product on total treatment costs and health related quality of life (Reeder, 1995).

2.1.4 Comparisons of Costs and Consequences

As stated earlier, evaluation involves the comparisons of costs and consequences of health care intervention. In economic evaluation, it is essential to distinguish between different types of costs and consequences because it prevents misunderstanding of the words "costs" and consequences (Drummond, 1992).

. Generally, the words costs and benefits raise questions such as:

- Costs to Whom? – society, hospitals, patients?
- Benefits to Whom? – society, hospitals, patients?

Where direct cost is overhead and operating costs, for example, costs of drugs, staff time, capital, equipment, and disposable. Cost to patients e.g. travel costs, treatment cost, Direct consequences could be therapeutic outcomes of a particular intervention. For example, reduction of blood glucose, saving or reallocation of resources to other areas of patient care, improved quality of life measured by quality adjusted life years (QALYs). .

Where indirect cost is costs to patients and their families, for example cost of obtaining home care during illness time, cost to hospitals etc. e.g. time lost from work, indirect consequences could be increased productivity due to the health care intervention. For example, return to work because of a successful by-pass operation.

Where intangible cost is cost related to pain, discomfort and anxiety, intangible consequences could be value of reassurance and counseling, value of life years saved (Drummond, 1992).

2.1.5 Decision Analysis

Decision Analysis is defined as a systematic quantitative method of describing clinical problems (Cano and Crane, 1999). Decision analysis summarizes or presents a decision problem by constructing a decision table or decision tree (Appendix V, VII, IX and XI) for effectiveness (outcome) criteria (Cano and Fujta, 1988).

The decision table is the first analytic tool used in decision analysis. It displays the relationship between pairs of decision elements. Each column of the decision table corresponds to a rating or value given to the characteristic by the decision-maker. The value and assigned weight which determines the criterion rating is somewhat arbitrary hence fairly subjective. However, each option being considered is treated identically with respect to the assigned weight to limit the subjectivity. The value given to each characteristic is determined by decision makers who will make use of the result of analysis in decision making. The outcomes appear as entries in the body of the table. Each criterion value combination has a specific outcome reflecting that the interplay between criterion and value determines the ultimate result and ranking of the desirability of the outcomes. Criterion Value is obtained from analysis of positive and negative outcome of different criteria (characteristic) of a treatment option from review of literature in natural unit e.g. percentages (Cano and Fujta, 1988). For example, criteria for anti-diabetic drug outcome with respective assigned weight are efficacy (0.4), adverse drug reaction (0.2), safety on administration (0.1), frequency of administration (0.1) and bioavailability (0.2).

Steps in Conducting a Decision Analysis

1. Criterion Value X Assigned Weight = Criterion Rating
2. Sum Criterion Ratings for each alternative = Effectiveness Measure

3. Compare alternatives summed criterion ratings

4. Select best option

2.1.6 Steps in Conducting Cost Effectiveness Evaluation

There are six key steps in conducting a cost effectiveness evaluation (WHO, 1996).

Step 1: Define the Objective

For example, in terms of programme output, which drug regimen should be the therapy of choice for the treatment of a named infectious disease? What is the best approach to transporting essential drugs to health facilities?

Step 2: Enumerate the different ways to achieve the objective

For example, short-course chemotherapy with more expensive drugs (Option I), versus traditional long-course chemotherapy with cheaper drugs (Options II).

Purchase of programme vehicles for delivery of drugs to health facilities (Option I) versus a contract with a private transport firm for delivery of drugs (Option II).

Step 3: Identify and measure the costs of each option

All the inputs required for each option should be identified and the costs determined. Capital as well as recurrent costs should be included. When there are joint inputs and outputs, cost allocation methods must be used to determine the share of costs of the relevant option.

Step 4: Identify and measure the benefits of each option

The benefit of each option is identified in natural units e.g. drug effectiveness in terms of eradication of bacteria. Effectiveness measure from decision analysis could also be used. For the transport example, a performance, indicator such as drug consignments delivered on time to a health facility could be used.

Step 5: Calculate and interpret the cost effectiveness of each option

The cost effectiveness ratio is the total cost divided by number of units of output. Better overall efficiency is indicated by a lower cost per unit of output.

Step 6: Perform sensitivity analysis on the conclusion

Sensitivity Analysis measures how different assumptions made in the course of estimating costs and outputs affects the conclusion. Sensitivity Analysis deals with uncertainty in assumptions that underlines the analysis, or with problems of imprecise measurement. Sensitivity Analysis is performed to test whether the decision changes when specific variables (e.g. cost or effectiveness) were altered within reasonable range in favour of less cost effective option. Even though certain costs and benefits cannot be measured accurately, it may be possible to show that the results of the analysis do not change over any reasonable range of cost or benefit (WHO, 1994b).

2.1.7 How to Conduct Cost Minimization Analysis

Cost minimization analysis (CMA) is carried out by calculating and comparing the mean cost per defined daily dose (DDD) of two options that have the same outcome (Branded and Generic products) to identify the lowest cost option (Bootman *et al.*, 1996; Jolicoeur *et al.*, 2002). Cost per DDDs units are recommended by World Health Organization (WHO) for analysis of drug use. DDD represents usual dosage of a drug per day (Jolicoeur *et al.*, 2002).

2.1.8 Applications of Pharmaco-Economics in Healthcare Delivery System

Pharmaco-Economic evaluation is virtually applicable in all areas of pharmacy practice. Some of the applications are as follows, according to Bootman *et al.* (1996):

Formulary System:- Formulary system is a method where the healthcare professionals of an institution, working through pharmacy and therapeutic (P and T) committee,

evaluates, appraise and select from among the numerous available drug entities and drug products those that are considered most cost effective in patient care (ASHP, 2003).

Treatment Guidelines Formulation:- Treatment guidelines are systematically developed statements that assist health professionals and patients in making decisions about appropriate treatment for specific conditions.

The national pharmaceutical treatment guidelines, even local ones, need to incorporate pharmaco-economic data into the treatment recommendations.

National Drug Policy: The National Drug Policy making can be desirably influenced by pharmaco-economic principles in a number of ways. For example, considering the current pharmaceutical problems in the country,

1. The cost profile prescription
2. The existing distribution channels create an avenue for additional cost without justification.
3. Inflationary cost escalation
4. Fake Drugs
5. Ineffective control by regulatory authorities

The only success factor for pharmacists and the health care system at large is an effective pharmaceutical cost management programme, to control cost without adversely affecting the quality of care as perceived by both the recipients and providers of health care. Pharmaco-Economic evaluation is equally useful in quantification and other aspects of supply system since the overall usage pattern of drugs can be evaluated as well. The pharmaco-economic data obtained from the pattern of usage can be used in making decisions in management of drug supply. It can also be applied in designing and implementing cost-effective control by regulatory authorities.

Pharmaceutical Care: A practice in which the practitioner takes responsibility for patient's drug related needs and holds him or herself accountable for meeting those needs. Pharmaco-Economic evaluation ensures more cost-effective option of interventions to be chosen for each patient.

Health Status Monitoring: Monitoring of health status and collection of health status data and quality of life indices especially by community and hospital/clinical pharmacists.

Efficiency Threshold: Setting up standard treatment efficiency threshold for acceptance of new drug into the national formulary system.

Post Marketing Surveillance: Pharmacists such as community pharmacists, being the most accessible, can identify a patient receiving drug for the first time, perform follow-up surveys to determine compliance, side-effects, adverse reactions and ultimately therapeutic and quality of life outcomes.

In conclusion, a collaborative effort between managed care, patient, academia, governmental agencies and pharmaceutical industries can facilitate the design and conduct of valid, objective and timely pharmaco-economic evaluations. This will not only minimize inputs into health care delivery system but also maximize outputs (treatment outcomes) of interventions. In turn, the attainment of health policy goal would be facilitated.

2.2 Previous Pharmaco-Economic Studies

It is essential to consider individual and societal costs of diabetes and search for reliable indicators for the effectiveness of care for diabetes patients (Cantrill, 1999). Educational programmes for patients and professionals are beneficial in rationalizing the use of drug (Costa *et al.*, 1997). There is need to establish process indicators for effectiveness of anti-diabetic care.

Glibenclamide has been documented as a drug of choice in monotherapy of moderate hyperglycemia in non-obese Type II diabetes mellitus patients (ADA, 2005; BNF, 2010). Its comparative cost-effectiveness with chlopropamide indicated in the same condition has not been reported. Metformin is indicated in obese Type II DM (ADA, 2005).

There is no evidence to justify benefit of a combination of anti-diabetic drugs over another, especially on a long term basis (Bernard and Kesth, 2001). It has been shown that less cost-effective antimicrobials are widely used in health institutions even when more cost-effective options are available (Suleiman and Tayo, 2001). There is need to find out the trend with anti-diabetic drugs.

Millennium development goal 7 emphasizes equitable access to essential drugs. One third of world population (1.7-2.1 billion) lacked access to essential drugs (WHO, 2004). A major obstacle to achieving equitable access to drugs is price (WHO, 2008), especially in countries where drugs are paid out of pocket. Drug financing in Nigeria, for example, is generally out of pocket, with 70.2% people living below poverty line of less than 1USD per day (FMOH, 2006). Strategies which would contain and moderate drugs' prices are needed to improve access to drugs. One of such strategies is the efficient use of generic drugs to foster competition in drugs market and therefore provide lower priced drugs in the health system (De-Joncheere *et al.*, 2002; WHO, 2004).

Generic drug is a drug product that compares with pioneer, reference (innovator) drug product in dosage form, strength, route of administration, quality, performance characteristics and in intended use. It could be generic-branded, semi-branded or unbranded generic. Generic medicines are available in all medicine outlets in Nigeria but branded products were found to cost 2 to 7 times the lowest priced generic equivalent (FMOH, 2006). High volume of generic prescriptions does not necessarily translate to maximal cost savings accruable by use of generic medicines (Mrazek and Mossialos,

2000). Savings generated by generic drugs in the last ten years was US 734 billion (GPhA, 2009). Generic drugs generates savings of 25 billion pounds each year for EU healthcare (EGA, 2007).

Branded antimicrobials were prescribed even when generic equivalents were available. This was common in public and private hospitals in Lagos State despite the much more expensive nature of branded products (Suleiman and Tayo, 2003). There is need to establish whether anti-diabetic prescription follow the same pattern. Lack of assurance in efficacy/effectiveness of some generics may also be a factor due to chaotic drug distribution (Swift and Ryan, 1995), which facilitates faking and counterfeit products in Nigeria. Generic substitution has long been applied in formulary system. It has the benefits of discouraging the use of less than optimal drug therapy, competitive bidding and reduce inventory. These benefits have in some cases been quantified as direct drug and inventory savings (Rubin and Kellar, 1983; La-Ruche *et al*., 1995). Generic drug programmes are today probably the most relevant economic strategy for drug supply (WHO, 1996). If generic substitution does not exist, price competition will not exist either and prices of drugs will swell (WHO, 1996).

Generic Substitution which applied CMA stimulates bio-equivalence comparison and help to prevent the stocking of less than optimal products. This can be facilitated in collaboration with the National Agency for Food, Drug Administration and Control (NAFDAC). A mechanism for comparing costs such as CMA can lead to more rational prescribing and limit the number of drug products included in each therapeutic class. Cost of drugs would be reduced as well as patients drop out of treatment because of cost.

Drug availability and affordability are very important components of pharmaco-economic studies (Kara *et al*., 1997). In a study of affordability of available prescribed medicines in selected health care institutions in Nigeria, 65% of available prescribed

medicines were affordable while patients could not afford 35% of available prescribed medicines due to poverty/cost (Giwa, 2001). This trend has negatively affected therapeutic outcome. People may be ill or require medical services but not have enough money to pay for them because of high cost (Kara *et al*., 1997).

Pharmaco-Economic analysis helps to make decisions about whether a new drug should be included in the formulary on the principle that if a drug is not better than a comparable product, it should not cost more. If it is superior to existing therapies but more expensive (a common denominator) and funds are available, any extra expenditure should represent "value for money" (Kara *et al*., 1997).

Brand name drugs are often dispensed when generic alternatives are available resulting in an estimated $8.8 billion in excess expenditures per year in the U.S (Haas *et al.*, 2005).

This avoidable use of brand name drugs may reflect physician and patient beliefs that brand name drugs are superior to their generic counterparts (Banahan and Kolassa, 1997). However, habitual use of brand name terminology may also play an important role in the dispensing of brand name products, as the name recorded on a prescription can impact whether a drug is dispensed in brand or generic form even when the physician would accept the generic version and the pharmacy is empowered to provide it (Suh, 1999; Mott and Cline, 2002). The use of brand names has substantial economic consequence (Fischer, 2003 and 2004). Pharmacists' substitution of generic equivalent is generally allowed and is encouraged by third party payers and several programs have been developed to encourage generic substitution (Haas *et al.*, 2005). However generic substitution is not mandated in most states, can be overridden by the prescribing physician and does not universally occur when allowed by the physician (Suh, 1999; Mott and Cline, 2002).

Persistent use of brand name products has resulted in billions of dollars of excess spending. The use of brand names also has consequences on communication between physicians. Confusion over drug terminology can result in adverse drug events, for example, a patient may inadvertently be given a second formulation of a drug because the prescribing physician fails to recognize that the patient was already taking the medication under a different name (Anton *et al.*, 2002; Schwab *et al.*, 2002). In addition, use of brand names in communication between physicians can undermine efforts to minimize commercial influence on medical practice. The use of branded rather than generic names for the medication can increase health care costs. Physicians refer to most medications by their brand name including drugs with generic formulations, this however, leads to higher healthcare costs (Steinman *et al.*, 2007).

Poverty is a multidimensional problem which includes various forms of deprivation, lack of access to social services and production inputs (World Bank, 2006). According to the World Bank Book for social indicators of development (2006), socio-economic indicators of poverty include income, education, housing, access to water, average household size, access to health, nutrition, access to communication, transportation and electricity. Because sickness reduces productivity, there is a consequent loss of income, which cuts the supply of basic commodities and lowers the standard of essential services. The outcome is a vicious circle of deteriorating health and social mobility: "men and women were sick because they were poor. They became poorer because they were sick and sicker because they were poorer" (Winslow, 1951). Poor health likewise impairs the capacity to learn, which leads to diminishing return on investments in education and training.

What are the real chances of breaking the vicious circle? Is there a health policy that can be applied in conditions of poverty? Do pharmaceuticals rank as a priority and what

roles do they play? If we put a "value" on higher life expectancy and improved quality of life, the "consequences" of better health such as lowered spending for sickness -would have to be considered (Moss, 1973; Usher, 1973).

Further more, hundreds of millions of Third World people are sick today, millions of children are dying today. To wait for long-term improvements means an avoidable waste and lost quality of life. This cannot be acceptable in either human or ethical terms. Clearly, a short-term answer is needed - the role of pharmaceuticals. Examined objectively, it is clear that in the third world, the benefits of drugs outweigh the risks.

Whenever pharmaceutical products have been used rationally, they have had positive effects: prevention of premature death and disability, accelerated cure, prevention of invalidity, alleviation of symptoms of diseases for which there is so far no cure and improved quality of life (Leisinger, 1984).

In these ways, drugs make a major contribution towards raising the quality of life of the sick. In addition, they have many other advantages, particularly, in developing countries where medical infrastructure is badly organized and where there are few well-trained staffs, drugs help to avoid costly hospitalization and shorten out-patient treatment.

2.3 Overview of Diabetes Mellitus

2.3.1 Definitions

In 1999, World Health Organization defined diabetes mellitus as "a metabolic disorder of multiple aetiology, 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". Thus, the metabolic abnormalities of diabetes result from inadequate insulin action on target tissues, due to deficient insulin secretion or insensitivity to insulin action, or a combination of both (WHO, 1994).

Diabetes mellitus has also been defined as a chronic, metabolic, non-communicable disease, characterized by hyperglycemia and eventual glucosuria. It is caused by the inability of tissues to carry out normal metabolism of carbohydrates, fats and proteins, due to an absolute or relative lack of insulin (Walker and Whittlesea, 2008).

An absolute lack of insulin is found in some diabetic patients who developed the disease early in life (juvenile-onset or Type I). Such diabetics are prone to ketoacidosis, usually insulin dependent and often manifest the poly-triad of diabetic symptoms: polyphagia, polyuria and polydipsia. Relative insulin deficiency is usually found in those diabetics who develop the disease later in life (maturity-onset or Type II). They are usually not prone to ketoacidosis and are not insulin dependent. They may be controlled by diet and oral hypoglycemic agents (Walker and Whittlesea, 2008).

2.3.2 Incidence

Diabetes Mellitus is one of the most common non-communicable diseases, and its epidemic proportion has placed it at the forefront of public health challenges currently facing the world. According to WHO (2010), estimated global burden of diabetes mellitus was 135 million cases in 1995, 171 million in 2000 (2.8% prevalence rate) in a worldwide adult population of under 4 billion and has projected that there will be 299 million cases by the year 2025 and 366 million (4.4% prevalence rate) in 2030. A quarter of these populations are over 65 yrs old while 25% of adults affected are less than 44 yrs of age (WHO, 2010).

Increase in the number of people with diabetes is attributable to population growth, increase in ageing population, urbanization, increase in prevalence of obesity (Proceedings of the 4th International Workshop Conference on Gestational Diabetes Mellitus, 1998), and sedentary lifestyle (Sarah *et al.*, 2005). Diabetes is a disease commonly found in any given population. In some parts of Africa, carbohydrate

constitutes about 70% of the diet, so the incidence of diabetes in African would be expected to be higher than 2% estimated for the American Population. It is estimated at 3% (WHO, 2010). About 80% of known diabetic patients are diagnosed after 40 years of age with only 5% being juvenile onset diabetics. Diabetes is reported to increase by up to 10% in any given population over 70 years of age. Among juveniles, there is no age range preference. The disease occurs equally in males and females (Zimmet *et al.*, 2004).

2.3.3 Diagnosis

The diagnosis of diabetes in an asymptomatic individual should never be made on the basis of a single abnormal glucose value. Verification of the diagnosis with repeated testing is required, unless an individual presents with unequivocal hyperglycemia along with its classic symptoms.

According to World Health Organization (2003b) and American Diabetes Association (2009), diagnostic criteria for diabetes mellitus are:

- Fasting Blood Glucose > 6.7 mmole/litre
- Two Hour Post Prandial Blood Glucose > 10 mmole/litre
- Fasting Plasma Glucose > 7.8 mmole/litre
- Two-Hour Post Prandial Plasma Glucose > 11.1 mmole/litre
- Glycosylated Hemoglobin (HbAlc) > 7%

2.3.4 Classification

The classification of diabetes mellitus has evolved considerably over time, taking into account recent advances in the diabetes field. The classification is now primarily based on the etiology (causes) of the disease, rather than its treatment. The revised classification encompasses both clinical stages and etiological types of hyperglycemia and results from improved understanding of the causes of diabetes mellitus (WHO, 1999).

The clinical staging reflects that diabetes mellitus, regardless of its etiology, progresses through several clinical stages during its natural history. Individuals can move from one stage to another in either direction (WHO, 1999).

The severity of hyperglycemia may change over time depending on the extent of the underlying disease processes. While there are autoimmune markers that help identify Type I diabetes mellitus, there are few sensitive or highly specific indicators of the Type II process at present, although these are likely to be revealed in the future. The same disease process leading to Type II diabetes mellitus can cause impaired fasting glucose and/or impaired glucose tolerance without fulfilling the criteria for the diagnosis of diabetes mellitus. In some individuals with Type II diabetes, adequate glycemic control can be achieved with weight reduction, exercise and/or oral hypoglycemic agents. These individuals, therefore, do not require insulin and may even revert to normoglycemia. Other individuals require insulin for adequate glycemic control but can survive without it. These individuals, by definition, have some residual insulin secretion. Individuals with extensive B-cell destruction, therefore, no residual insulin secretion, require insulin for survival. The severity of the metabolic abnormality can even regress (e.g. with weight reduction), progress (e.g. with weight gain), or stay the same (WHO, 1999).

2.3.5 Etiology

Although the precise cause of the dysfunction of insulin-producing pancreas in diabetes mellitus has not been elucidated, it is thought that the disease is inherited as a homozygous recessive trait, with multiple environmental factors influencing the clinical expression of the genetic pattern. These factor can be emotional, physical (infection, trauma), chemical such as drugs (diuretics and steroids), stress, disease processes (pancreatic tumor) and caloric intake. Body weight may also increase the demand for endogenous insulin. This genetic explanation appears to be inadequate for various

reasons. Studies have shown that sometimes only one of identical twin born to parents with diabetes develops the disease. Also only 50% of children with two diabetic parents develop the diabetes (Zimmet *et al.*, 2004)

It is not clear whether the same genetic defect is responsible for both juvenile-onset and maturity-onset diabetes. Other theories proposed but not confirmed include:

1. The production of defective insulin which will not function effectively.
2. The production of an insulin antagonist which may compete for insulin receptors.
3. The formation of anti-insulin antibodies which immunologically inactivate insulin.

These mechanisms may occur together or they could individually precipitate diabetes (Zimmet *et al.*, 2004).

2.3.6 Etiological Types

Etiological types designate defects, disorders or processes that often result in diabetes mellitus.

Type I diabetes mellitus

Type I indicates the processes of Beta-cell destruction that may ultimately lead to diabetes mellitus in which insulin is required for survival to prevent the development of ketoacidosis, coma and death. An individual with a Type I process may be metabolically normal before the disease is clinically manifested, but the process of Beta-cell destruction can be detected. Type I is usually characterized by the presence of anti-glutamic acid decarboxylase (anti-GAD) anti-bodies, islet cells or insulin anti-bodies which identify the autoimmune processes that lead to Beta-cell destruction. In some subjects with this clinical form of diabetes, particularly Non-Caucasians, no evidence of an auto-immune disorder is demonstrateable and these are classified idiopathic Type I diabetes mellitus (ADA, 2005).

Brittle Diabetes

Brittle Diabetes refers to patients with Type I diabetes mellitus who exhibit wide and severe fluctuations in blood glucose despite efforts to modify and adjust their daily activities, meal planning and insulin regimen. They have common occurrences of hypoglycemia, frequently severe hyperglycemia and episodes of diabetic ketoacidosis. Treatment of patients in this category has been a frustration for most health-care providers. The cause of the brittleness is unclear, but may be due to a combination of psychosocial, lifestyle, neuro-humoral and hormonal abnormalities. It can occur in Type II diabetes mellitus patients requiring insulin, but this is rare (WHO, 2003a).

Type II Diabetes Mellitus

Type II diabetes mellitus is the most common form of diabetes and is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that this form of diabetes is clinically manifested. The specific reasons for the development of these abnormalities are not yet known (ADA, 2005). Ketoacidosis is very rare in Type II diabetes. The insulin resistance that occurs in this type is partly explained by the obesity that often co-exist with the disease.

Other Specific Types

Diabetes Mellitus in Special Groups and Circumstances

Children and Adolescents (WHO, 1999)

While Type II diabetes mellitus used to be almost non-existent in children, its prevalence has been increasing rapidly over the past two decades, mostly because of the rapid increase in childhood obesity. A recent study showed Type II to be the leading cause of diabetes in children aged 6-18 years.

Type II diabetes mellitus should be screened for in children aged over 10 years if the child is overweight (greater than 120% of the ideal body weight) and if two of the following characteristics are present: positive family history of Type II diabetes mellitus (first or second-degree relative), signs associated with insulin resistance (polycystic ovarian syndrome, hypertension, dyslipidemia). Testing should be repeated every two years in children at risk.

Gestational Diabetes

Gestational Diabetes is a state of carbohydrate intolerance resulting in hyperglycemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has previously gone unrecognized. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy (WHO, 1999; ADA, 2005). Women who are known to have diabetes mellitus and who subsequently become pregnant do not have gestational diabetes but have "diabetes mellitus and pregnancy" and should be treated accordingly before, during and after the pregnancy.

In the early part of pregnancy (e.g. first trimester and half of second trimester), fasting and post-prandial glucose concentrations are normally lower than in normal, non pregnant women. Elevated fasting or post-prandial plasma glucose levels may well reflect the presence of diabetes that antedates pregnancy, but criteria for designating abnormally high glucose concentration at this time in pregnancy have not yet been established. The occurrence of higher than usual plasma glucose levels at this time in pregnancy mandates careful management and may be an indication for carrying out an Oral Glucose Tolerance Test (OGTT). Nevertheless, normal glucose tolerance in the early part of pregnancy does not itself establish that gestational diabetes will not develop later.

Individuals at high risk for gestational diabetes include older women, obese women, those with previous history of glucose intolerance, any pregnant woman who has elevated fasting or casual blood glucose levels, those with history of gestational diabetes mellitus, those with history of large-for-gestational-age babies, strong family history of diabetes mellitus (ADA, 2005).

It may be appropriate to screen pregnant women belonging to high risk population groups during the first trimester of pregnancy in order to detect previously undiagnosed diabetes mellitus. Women at high risk who screen negatively and average risk women should be tested between 24 and 28 weeks of gestation (ADA, 2005).

2.3.7 Metabolic Syndrome

Often, a person with impaired glucose tolerance (IGT or diabetes) will be found to have at least one or more of the other cardiovascular disease risk factors such as hypertension, central (upper body) obesity, and dyslipidaemia. This clustering has been labeled diversely as the metabolic syndrome, syndrome X, or the insulin resistance syndrome (WHO, 1999). Alone, each component of the cluster conveys increased cardiovascular disease risk, but as a combination they become much more powerful. This means that the management of persons with hyperglycemia and other features of the metabolic syndrome should focus not only on blood glucose control, but also include strategies to reduce the impact of other cardiovascular disease risk factors.

The metabolic syndrome with normal glucose tolerance identifies the subject as a member of a group at very high risk of future diabetes. Thus, vigorous early management of the syndrome may have a significant impact on the prevention of both diabetes and cardiovascular disease, especially as it is well documented that the features of the metabolic syndrome can be present for up to 10 years before glycemic disorder is detected (WHO, 1999).

2.3.8 Diabetes Complications

2.3.8.1 Acute Complications of Diabetes Mellitus

Hypoglycemia

Hypoglycemia in patients with diabetes mellitus is an abnormally low concentration of glucose in the blood caused by insufficient food intake, excessive exercise, or over dosage with oral hypoglycemic agents or insulin (Bastaki, 2009).

The development of hypoglycemia is an ever-present possibility in all patients with diabetes treated with insulin or oral hypoglycemic medications. A person with hypoglycemia may feel nervous, shaky, weak, or sweaty. They may have headache, blurred vision, and be very hungry. In more serious instances, they may become unconscious (WHO, 1999). Taking small amounts of sugar or glucose-containing juice or food wi11 usually help the person feel better within 10-15 minutes.

Eric and Gourley (1993) reported parasympathetic responses (nausea, hunger), diminished cerebral function (confusion, Lethargy, agitation or personality changes). There is also a reflex sympathetic response (tachycardia, sweating or tremor), convulsion, ataxia and coma as symptoms of hypoglycemia.

All manifestations of hypoglycemia are relieved rapidly by glucose administration. In unconscious patients, injection of glucagon or I.V glucose or dextrose may be required. Because of potential dangers of insulin reactions, diabetics should always carry packet of table sugar or candy for use at the onset of hypoglycemic symptoms (Eric and Gourley, 1993).

Hyperglycemic Crisis

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Ketoacidosis mainly affects people with Type I diabetes mellitus. Diabetic ketoacidosis remains a potentially lethal condition with mortality as high as 10%-15%. However,

At-least 50% of cases are avoidable. Many new patients with Type I diabetes mellitus present with ketoacidosis, so early recognition and diagnosis are clearly of importance.

Ketoacidosis occurs when the body breaks down fatty acids and produces ketones, which are acidic. Some of the ketone bodies are lost through the urine, but those that remain will build up in the blood and lead to ketoacidosis with signs as nausea, vomiting, dry skin, dry mouth, deep, rapid breathing and low blood pressure (WHO, 1999).

If the person is not given fluids and insulin right away, ketoacidosis can lead to death. It is crucial to educate patients and health care personnel about precipitating factors and actions to be taken to avoid ketoacidosis. Major precipitating factors include infection and other acute illnesses. In such situations, insulin requirements are likely to increase. Omission or insufficient insulin intake is a major cause of diabetic ketoacidosis in some parts of the world. With proper instruction on monitoring of blood glucose and urine ketones, insulin dose adjustment and maintenance of fluid intake, many potential cases of diabetic ketoacidosis can be prevented. If vomiting occurs, early referral for intravenous therapy is required (ADA, 2005).

It is rare for people with Type II diabetes mellitus to develop ketoacidosis. It is much more common for them to develop the hyperglycemic hyperosmolar state in the face of severe infection or other major intercurrent illness (WHO, 1994).

Common symptoms of hyperglycemia include: polyuria, polyphagia, polydipsia. others include fatigue (due to inability to utilize glucose) and marked weight loss (due to

breakdown of body protein and fat as an alternative energy source to glucose). Blurred vision (caused by a change in lens refraction) may occur. Slow wound healing and candidiasis may also occur. Other symptoms associated with hyperglycemia include tingling or numbness of the extremities, skin infection, itching and drowsiness.

2.3.8.2 Chronic Complications of Diabetes Mellitus

Macrovascular Complications

Diabetes is associated with a substantial increase in the risk of cardiovascular mortality through ischaemic heart disease and stroke. Furthermore, the risk is substantially enhanced by other cardiovascular risks such as hypertension, hyperlipidemia, obesity and smoking (Michael and Karen, 2009).

Atherosclerosis is the most common macrovascular complication of diabetes mellitus (Ramachandran, 1999; WHO, 2001a). It accounts for 75% of diabetes-related deaths, a figure two to three times higher than that in people without diabetes. Studies have reported that the occurrence of clinical events related to coronary artery disease are four times higher in patients with diabetes (Haider and Obaidullah, 1981; Shera, 1999). Coronal and cerebrovascular diseases are also two to three times more common, and post-infarction mortality higher. These increases in atherosclerosis in diabetic individuals are seen in all populations. People with diabetes should therefore be screened for risk factors of macrovascular diseases (cardiovascular, cerebrovascular and peripheral vascular).

There is ample evidence that aspirin intake confers both primary and secondary prevention against cardiovascular diseases in patients with diabetes. Its use is highly recommended (WHO, 2001a).

Microvascular Complications

Pathological changes in the microcirculation lead to nephropathy and retinopathy. The mechanism of damage is thought to be due to hyperglycemia, leading to glycation of structural proteins and the toxic effects of free radicals and glycation end products. Accordingly, there is good evidence that good glycemic control may limit these complications (Michael and Karen, 2009)

Retinopathy

Diabetic Retinopathy is the leading cause of blindness and visual impairment in adults in many societies. Almost everyone with younger-onset Type I diabetes will develop diabetic retinopathy after 20 years of the disease. At sometime during their lives, 75% will develop the most severe stage, proliferative diabetic retinopathy. In older-onset Type II diabetes mellitus, almost 60% will develop diabetic retinopathy and at some time during their lives about 10% will develop proliferative retinopathy and about 2% becomes blind (WHO, 1999).

Both younger- and older-onset diabetic people are at risk of developing another sight-threatening manifestation of diabetic retinopathy, namely macular oedema, a swelling of the central part of the retina. Epidemiological data also suggest that loss of vision due to open-angle glaucoma and cataract may be more common in people with diabetes than in non-diabetics (WHO, 1999).

To prevent retinopathy and visual loss, the following are recommended: promotion of good glycemic control, control of blood pressure, detection and treatment of cataract, detection and treatment of glaucoma at an early stage (WHO, 1999).

Diabetic nephropathy

Diabetic Nephropathy (kidney disease) is the most common cause of renal failure (Alzaid *et al.*, 1994; Al-khader, 2001b) and a major cause of premature death in diabetic patients. Diabetic patients are 17 times as prone to kidney disease as non-diabetic people. It is a multistage condition that requires several years to become clinically overt.

The stages are as follows: Incipient nephropathy, defined by a persistent increase in albumin excretion rate, referred to as microalbuminuria without frank proteinuria. It is represented by an albumin excretion rate of 20 - 200 µg/minute (30-300 mg/24 hours). Microalbnminuria may be accompanied by a rise in blood pressure.

Clinical nephropathy is defined by the presence of persistent proteinuria, i.e. albumin secretion > 200mg/minute (>300 mg/24 hours), and is usually accompanied by hypertension. In advanced Nephropathy, there is a significant decline in glomerular filtration rate and the appearance of symptoms of uremia and/or nephrotic syndrome.

End-stage renal disease necessitates dialysis or renal transplantation (Alzaid *et al.*, 1994; Al-khader, 2001b).

Tighter blood pressure and glycemic control is needed in patients at risk of developing diabetic nephropathy. Vigorous treatment of clinical nephropathy may delay the development of end stage renal disease.

One of the highest priorities at the present time is the education of patients and their physicians about the potential for early detection and prevention of diabetic kidney disease. The likelihood of success in preventing and reducing the consequences of diabetic kidney diseases will depend on the availability of resources to implement educational programmes and to monitor them continuously (WHO, 1994; ADA, 2005).

Diabetic Neuropathy

Diabetic Neuropathy is a nerve disorder that may be clinically evident or sub clinical, and which occurs in diabetes mellitus in the absence of other evident etiology. Manifestations may occur in both the peripheral and the autonomic nervous systems (Morgan *et al.*, 2000).

Peripheral neuropathies include: poly-neuropathies, e.g. distal sensory-motor neuropathy and proximal motor neuropathy; focal neuropathies, e.g. mono-neuropathies (including cranial) and entrapment neuropathies, multifocal neuropathies.

Autonomic Neuropathies may involve the following systems: cardiovascular gastrointestinal and genitourinary (WHO, 1994).

The highest priority at present is the education of patients and their physicians about the potential for detection and treatment of early neuropathy.

Neuropathic Foot

More hospital beds are occupied by diabetic patients with foot problems than by those with all other consequences of diabetes mellitus. The problem of limb amputation in people with diabetes is of such a serious and global nature (WHO, 1994; ADA, 2005).

Diabetes Mellitus is associated with increased frequency of lower-limb amputations, many of which are potentially preventable. Epidemiological data suggest that more than 50% of the 120, 000 non-traumatic lower-limb amputations in the United States of America are associated with diabetes and that the overall risk of amputation in people with diabetes is 15 times than in people without diabetes (WHO, 1994; ADA, 2005).

The underlying lesions that often result in chronic ulceration and amputation have been termed the diabetic foot. This is defined as infection, ulceration and destruction of deep tissues, associated with neurological abnormalities (loss of pain sensation)'and various

degrees of peripheral vascular disease in the lower limb. A number of preventive strategies (careful self-examination, specially fitted shoes, minimization of trauma, etc.) alongside earlier detection and more aggressive management of foot ulcers (e.g. local debridement, provision of special supports and early antibiotic therapy) will prevent or delay lower-limb amputations. In developing countries, lack of proper footwear and inadequate hygiene, together with poorly controlled diabetes, are major causes of lower limb amputations (WHO, 1994 and ADA, 2005).

Education is the most important contribution to the prevention of foot lesions in diabetes (WHO, 1994; ADA, 2005). The first objective should be to increase the knowledge of all those who care for diabetic patients concerning the dangers inherent in the development of diabetic foot lesions and the different skills needed to examine feet and to treat lesions. Another goal is to establish an educational programme for patients at special risk of developing foot ulcers.

The programme should include: regular attendance by patients for the reinforcement of knowledge and motivation for continuing to care for their feet, formal teaching sessions to explain the reasons for the vulnerability of the diabetic foot, and the importance of everyday matters such as suitable footwear and foot hygiene, the provision of appropriate written and/or audiovisual material.

Education of patients has to be centered on appropriate skills aimed at preventing foot lesions. Patients should learn: not to walk bare-footed, to examine shoes daily and look for foreign bodies, to avoid "bathroom surgery" (no scissors, no razor blades, no chemical skin loosener for hyperkeratosis), to treat fungus disease and minor cuts early, to use a mirror to observe the plantar surface of the foot, to test the degree to which pain sensation has been lost and to prevent burns (no hot water or electric heaters) (WHO, 1999).

2.3.9 Screening for Diabetes Mellitus

The question of mass community screening for diabetes remains controversial. The underlying philosophy of screening has been that detection of diabetes in asymptomatic or minimally symptomatic individuals will result in effective treatment that may retard its progression and reduce the risk or the severity of complications, thus diminishing premature morbidity and mortality. This is brought into focus by the frequent presence of specific complications at the time of clinical diagnosis and the estimate that on average subjects had had Type II diabetes mellitus for 4-7 years prior to diagnosis (WHO, 1994; ADA, 2005).

Over the years, opinions have changed frequently on the value of mass screening. Initially it was widely recommended, however, at present, it is recommended only for individuals at risk or for epidemiological studies. This position is supported by many well-designed screening programmes that have provided valuable information about the prevalence of diabetes and their natural history in different populations. Such data are essential for public health planning and provide information for continued evaluation of the current diagnostic criteria. Screening programmes can also improve community awareness and pave the way for education about diabetes mellitus (WHO, 2003b).

2.3.9.1 Screening Approaches

A positive result in a screening test indicates only a high probability of the individual having the disease. The diagnosis of diabetes cannot be made on the basis of a single abnormal blood glucose value in an asymptomatic individual (WHO, 1999). Confirmatory tests are always necessary for a definitive diagnosis to be made. There are three different approaches to screening: population, selective and opportunistic.

Population Screening

Population screening is worthwhile only for health care planning, for epidemiological

research purposes or in high-prevalence populations. It can be used to identify individuals with IGT provided the OGTT is employed. In most societies, it is ineffective in terms of cost and effort to screen low-risk individuals for Type II diabetes mellitus, such as children and young adults (WHO, 1999 and 2003c).

Selective Screening

Selective screening is undertaken in groups known to have risk factors for developing Type II diabetes mellitus. In low-prevalence communities, an even more selective approach should be adopted (WHO, 1999 and 2003c).

Opportunistic Screening

Opportunistic screening occurs when high-risk individuals present themselves to some sector of the health care system. It is the most employed method and is highly cost effective in that no resources are needed to organize the screening or call for subjects (WHO, 1999 and 2003b).

2.3.9.2 Screening Tools

Glucose Measurement

At present there is no satisfactory substitute to glucose measurement. Alternatives, such as measurements of glycated haemoglobin and glycated proteins, although specific, are too insensitive to reliably detect lesser degrees of glycemic disturbances. There are many methods available for measuring blood glucose, ranging from visually-read test-strips to sophisticated automated methods. Precision and accuracy are required for screening. If portable meters are to be used, they should be checked under a full quality assurance programme and a coefficient of variation greater than 5% should not be accepted. When automated procedures are used, care must be taken to minimize the risk of errors in sample identification (WHO, 1999).

Oral Glucose Tolerance Test (OGTT)

The oral glucose tolerance test remains the definitive confirmatory diagnostic test for diabetes mellitus. Glucose levels >11.1 mmol/L (200 mg/dL) 2 hours after a 75 g oral glucose load are diagnostic of diabetes(WHO, 1999) .

Fasting Plasma Glucose

Fasting is defined as avoiding the consumption of any food or beverage other than water for at least 10-16 hour before testing. Fasting Blood and plasma glucose levels are interpreted as follows according to WHO (1999):

<5.6 mmole/l (<100 mg/dl): excludes diabetes (probably)

Between 5.6 and 6.0 mmole/l inclusive (100-109 mg/dl): low probability, may be an indication for diagnostic testing among high-risk individuals (OGTT)

6.1-6.9 mmole/l (110-125mg/dl): indication for diagnostic testing (OGTT)

>7.0 mmole/l (≥126 mg/dl): indicates diabetes, confirmatory test required.

Casual Blood Glucose Measurement

Levels greater than 7.8 mmole/l should be an indication for further testing. A value equal to 10.0 mmole/l in venous whole blood or 11.1 mmol/L in venous plasma is suggestive of diabetes. Sensitivity and specificity can vary, depending on the cut-off used (ADA, 2005).

Urine Glucose Measurement

Urine glucose measurement is insensitive, but relatively specific, for the detection of diabetes. It may be used if reliable blood glucose measurements are not available. Sensitivity is improved by using postprandial urine samples. A positive urine test result indicates the need for confirmatory blood glucose testing (WHO, 1994).

2.3.9.3 Screening for Type II Diabetes Mellitus

A screening programme should identify individuals with one or more diabetes mellitus risk factors. This can be done by means of a written or verbal questionnaire. Individuals with more than one risk factor should be referred for evaluation and testing (WHO, 2003a).

The main reasons for the current interest in screening for Type II diabetes mellitus are:

There is a long, latent, asymptomatic period, in which the condition can be detected, a substantial proportion of people with Type II diabetes mellitus are undiagnosed, a substantial proportion of newly referred cases of Type II diabetes mellitus already have evidence of the micro-vascular complications, the rising prevalence of Type II diabetes mellitus, the seriousness of the immediate effects and long-term complications of Type II diabetes, evidence supporting the efficacy of intensive blood glucose control, blood pressure control and blood lipid control in Type II diabetes, and accumulating evidence sthat treatment of hypertension, dylipidaemia can prevent cardiovascular disease in people with Type II diabetes mellitus (WHO, 2003b).

Screening of asymptomatic adults for Type II diabetes mellitus should be done in the following groups, and if normal should be repeated every three years. High Risk characteristics include: Individuals aged greater or equal to 35 years of age, overweight (body mass index greater than or equal to 25 kg/m^2), first degree relative with Type II diabetes, women with previous history of gestational diabetes mellitus or who delivered a baby weighing greater than 4 kg , individuals diagnosed previously with increased fasting glucose (IFG) or impaired glucose tolerance (IGT), hypertensive individuals with blood pressure greater than 140/90 mmHg and history of vascular disease (ADA, 2005).

2.3.10 Evaluation

Screening for diabetes is justified on the grounds that early detection allows effective early intervention, thus diminishing the likelihood of the development of complications. Selective high-risk and opportunistic screening must be accompanied by confirmatory diagnosis and appropriate follow-up of new cases. Screening for IGT may be justified in high-risk populations but requires an OGTT for identification and a lifestyle intervention programme. Screening programmes should, therefore, be evaluated in terms of: numbers of new cases detected, cost per new case detected, actions taken for individuals with positive test results and long-term benefits of early detection (ADA, 2005).

2.4 Management of Type II Diabetes Mellitus

The goal of treatment of diabetes mellitus is to control blood glucose and ultimately prevent long-term complications, as shown by The Diabetes Control and Complications Trial Research Group (1993) and UK Prospective Diabetes Study Group (1998).

Insulin Therapy is necessary to control hyperglycemia in Type I diabetes mellitus (The Diabetes Control and Complications Trial Research Group, 1993; ADA, 2009). Provided hyperglycemia is mild in Type II diabetes mellitus, patients may be given at least a one month trial of diet, exercise and weight management in order to control hyperglycemia. If this regimen does not lead to adequate blood glucose control, the physician will need to prescribe oral hypoglycemic agents and/or insulin (United Kingdom Prospective Diabetes Study Group, 1998; ADA, 2009).

2.4.1 Objectives of therapy

The main objectives of therapy for Type II DM are: to eliminate symptoms of hyperglycemia, achieve optimum glycemic control, reduce or eliminate microvascular and macrovascular complications of diabetes mellitus, treat associated disorders and to allow the patient to achieve as normal a lifestyle as possible (ADA, 2007).

2.4.2 Treatment Thresholds and Goals

Treatment thresholds are fasting blood glucose (FBG) ≥ 7.5 mmole/l and glycosylated hemoglobin (HbAlc) > 7% while goals of therapy are fasting blood glucose (FBG) < 7.0 mmole/l and glycosylated hemoglobin (HbAlc) < 7% (ADA, 2009).

2.4.3 Treatment options

The backbone of diabetes mellitus management is proper diet and regular exercise, which have to be individualized (Pan, 1993; WHO, 2003). Both could be the only management needed for controlling blood glucose in gestational diabetes, IGT and in Type II diabetes mellitus in its early phase.

Patients with Type II diabetes mellitus may require oral hypoglycemic agents and/or insulin, while Type II patients need insulin therapy to survive. The treatment plan for Type II diabetes mellitus may include: diabetes education, meal planning and nutritional recommendations, exercise, anti-diabetic agents, insulin, management of associated conditions and complications (WHO, 2003c; ADA, 2005; ADA, 2007; ADA, 2009).

The care of an individual with diabetes mellitus requires a multidisciplinary team. Central to success of this team are the patients' participation, input, and enthusiasm. Members of the health team include primary care provider and/or diabetologist, nutritionist, and a diabetes educator. When the complications of diabetes mellitus arise, sub-specialists including neurologists, nephrologists, vascular surgeon, cardiologists and ophthalmologists are essential. Comprehensive diabetes care, therefore, means that optimal diabetes therapy involves more than plasma glucose management. It should also detect and manage diabetes mellitus complications and modify diabetes mellitus-related risk factors (Pan, 1997).

2.4.4 Non Pharmacological Management: Dietary and Lifestyle Modification

Dietary and lifestyle modification are the mainstay of management of Type II diabetes mellitus. Majority of people with Type II DM are overweight and usually have other metabolic disorders of the insulin resistance syndrome, so the major aims of dietary and lifestyle changes are to reduce weight, improve glycemic control and reduce the risk of coronary heart disease (CHD), which account for 70-80% of death among those with diabetes (Bethesda, 1995).

It has been shown that weight reduction and an increase in daily energy expenditure decrease insulin resistance and increase glucose tolerance (Stoffers, 1997). Even, modest weight reduction is associated with a reduction in insulin resistance, a reduction in hepatic glucose production and perhaps, an improved islet B-cell function (Goldstein, 1992).

2.4.4.1 Dietary Modification (Medical Nutrition Therapy)

Diet is the first line in management of Type II diabetes mellitus. Adherence to dietary modification has led to a 25% reduction in overall mortality due to poor glycemic control, and a 33% reduction in deaths from cardiovascular disease (Trichopoulou *et al.*, 2003a).

Carbohydrates

By tradition, most of the recommendations for people with diabetes were low carbohydrate diets. More emphases were placed on the use of complex carbohydrate or starches and avoidance of simple sugars or carbohydrate on the belief that simple sugars would be digested and absorbed more quickly. Carbohydrate at a higher level is acceptable provided it is of low glycemic index and the consumption is rich in soluble fiber (Bastaki, 2005).

Dietary carbohydrate from cereal, breads, other grain product, added sugars should provide 50-60% of the individual energy requirement (Health and welfare, Canada, 1990). Current guidance for carbohydrate consumption still emphasizes the importance of total carbohydrate intake but it focuses on selecting carbohydrate with a lower glycemic index (Walker and whittlesea, 2008).

With regard to carbohydrates, there is strong evidence that the total amount of carbohydrate in meals or snacks is more important than the source or type. Hence sucrose and sucrose-containing foods do not need to be restricted by people with diabetes mellitus. It is important to note, however, that sucrose must be substituted for other carbohydrates gram for gram and not simply added to the meal plan (ADA, 2005).

Non-Nutritive sweeteners are safe for people with diabetes when consumed within the acceptable daily intake levels established by the Food and Drug Administration (FDA). There is strong evidence that large amounts of dietary fibre (50gm/day) may have beneficial effects on glycemia, insulinaemia, and lipidaemia (Pan, 1997).

Proteins

During moderate hyperglycemia, obese subjects with Type II diabetes mellitus have an increased turnover of proteins compared to non-diabetic obese subjects. Based on this evidence, the protein requirements for diabetics may be greater than the recommended daily amount, but not greater than the usual intakes of 10%-20% of the total daily energy requirement (ADA, 2005). Limited evidence suggests that it may be important to avoid protein intake greater than 20% of total daily energy, so as not to advance the development of diabetic nephropathy (Pan, 1997). For adults without nephropathy, protein intake is recommended as less than 1gm/kg of body weight/day. Current evidence indicates people with diabetes has similar protein requirement with those of the general population, about 0.86gm/kg/day (Health and welfare Canada, 1990).

While there is no evidence that a high protein diet contributes to the pathogeneses of early diabetic nephropathy, there is certainly no need for a high protein diet among people with diabetes in general (Bastaki, 2005).For those with nephropathy, protein intake may need to be further restricted but this requires expert dietetic advice and supervision (walker and Whittlesea. 2008).

Fat

The primary goal regarding dietary fat in patients with diabetes is to decrease intake of saturated fat and cholesterol. Saturated fat is the principal dietary determinant of low-density lipid (LDL) cholesterol. Compared to non-diabetic subjects, diabetic subjects have an increased risk of coronary heart disease with higher intakes of dietary cholesterol (Pan, 1993; WHO, 2003a).

Fat is the most energy rich of all nutrients and reduction of fat intake helps to reduce total energy intake which is important for many people with Type II diabetes mellitus. Population consuming a low saturated fat diet have lower incidence and mortality from cardiovascular heart diseases compared with those living in countries with a high intake of saturated fat, and reduced saturated fat intake is associated with reduced level of LDL cholesterol (Bastaki, 2005). Clinical trials in diabetics who lower their cholesterol level achieved a 25-55% reduction in risk of major CHD events, high blood pressure control and achieved 21% reduction in CHD (UK prospective diabetes study group, 1998). For this reason, restriction of saturated and trans unsaturated fats/fatty acids to 10% or less of total energy has been advised.

Diets high in mono-saturated fatty acids e.g. olive oil are associated with improved peripheral insulin sensitivity and improved glycemic control (Parillo *et al.*, 1992). Diets that are very low in saturated fat can reverse insulin resistance (Barnard, 2007).

Dietary Fibers

Dietary fibers has useful properties in that they are physically bulky and they delay the digestion and absorption of complex carbohydrates thereby minimizing hyperglycemia. For the average person with Type II diabetes mellitus, 15gm of soluble fiber (vegetable) is likely to produce a 10% improvement in fasting blood sugar, glycated hemoglobin and low density lipid cholesterol (Walkers and Whittlesea, 2008).

General Dietary Recommendations for Diabetes Mellitus Patients

If the diabetic subject has a normal lipid profile, then the carbohydrate intake can be decreased to 55% of daily intake and the fat intake decreased to 25%-30%. Many individuals with Type II diabetes mellitus are overweight (body mass index greater than or equal to 25 kg/m^2), and approximately 36% are obese (body mass index greater than or equal to 30 kg/m^2).

As body adiposity increases, so does insulin resistance (WHO, 2003b; ADA, 2005).

Obesity may also aggravate dyslipidaemia and hypertension in patients with Type II diabetes mellitus. Because of the effects of obesity on insulin resistance, weight loss is an important therapeutic objective for obese individuals with Type II diabetes mellitus (WHO, 2003c; ADA, 2005).

2.4.4.2 Lifestyle Modification

Lifestyle modification can be a very effective way to keep diabetes mellitus in control.

A comprehensive lifestyle programme have been reported by Toobert *et al.* (2003) to improve glycemic control, lower the risk of cardiovascular diseases which are potential complications of Type II diabetes mellitus and improves quality of life outcomes. Research shows that intensive lifestyle changes may prevent and even reverse CHD (Ornish *et al.,* 1998) which occur 2.5 times more in diabetics than in non-diabetics

(Haffner *et al.*, 1998). Furthermore, evidence points to the effectiveness of lifestyle and behavioral changes, including diabetes self-management training, in Type II diabetes mellitus patients (Wing *et al.*, 2001). Lifestyle changes that focus on healthy eating, physical activity, weight control and diabetes care can prevent or delay the complications associated with Type II diabetes mellitus. Infact, The Diabetes Control and Complications Trial Research Group (1993) confirmed that people with Type II diabetes mellitus who improve their metabolic control through an intensive self-care regimen significantly decreased the onset and progression of microvascular complications.

Alcohol

In diabetics, alcohol consumption should be eliminated in those suffering from hypertriglyceridaemia, in those that are overweight and in those with hypertension. (Christiansen *et al.*, 1993; Koivisto *et al.*, 1993). In general, alcohol use is discouraged in diabetes patient, but individual diabetics should be assessed to determine if the advantages of alcohol consumption (e.g. reducing emotional tension, anxiety etc), out-weigh the potential effects on blood glucose control (Eric and Gurley, 1993). One of the major risk with alcohol consumption among individuals with diabetes is the potential danger of hypoglycemia, especially among those who use sulphonyl ureas.

Smoking

Cigarette Smoking markedly increases the risk of Coronary Heart Disease (CHD) in diabetes mellitus patients (Bastaki, 2005). Smoking cessation can have an important effective on CHD risk reduction in diabetes patients (Baskaki, 2005). In one study, compared to those who never smoked, the relative risk (RR) for CHD across categories of smoking was 1.21 for past smokers and 1.66 for current smokers of 1-14 cigarette/day respectively, and 1.66 for current smokers with more than 15 cigarette/day (Al-Delaimy *et al.*, 2002). Smokers with diabetes have an increased risk of death, high LDL

cholesterol level, nerve damage, kidney diseases and foot ulcers. As such, smoking should be avoided in diabetics (Bastaki, 2005).

Physical Activity

Exercise improves insulin sensitivity and insulin induced glucose metabolism (glycolysis, glycogenesis and conversion of glucose to fats) (Tayo, 1975). Exercise improves circulatory function, an important factor in diabetes management. It helps maintain normal body weight, aids in breathing, digestion and metabolism (Eric and Gourley, 1993). Exercise contributes positively to well-being physically and mentally. It also increases glucose utilization. Diabetics should participate in some form of regular exercise as it will enhance stable blood glucose.

Exercise burns calories and helps to control weight, eases stress and tension, and maintains a feeling of well-being (WHO, 2004). In addition, regular exercise improves the body's response to insulin and may make oral anti-diabetic drugs and insulin more effective. It also promotes circulation and lowers cholesterol and triglyceride levels, thus reducing the risk of cardiovascular diseases (Tuomilehto, 2001a).

Diabetics should be encouraged to live a normal life and participate in sports and exercise programmes. Generally they should not be excluded from physical activities or games, unless there are complications and on the advice of a physician. The main risk when exercising is hypoglycaemia, therefore blood glucose should be checked before exertion, and if appropriate, medication dosage may need to be reduced before exercise, or the individual may need to take an extra carbohydrate snack. Before starting any exercise programme, the health provider should do a thorough physical examination to find out whether or not it is safe for the patient to exercise (Alwan *et al.*, 1996; Knowler, 2002).

2.4.5 Pharmacological Therapy

When lifestyle modification fails, therapeutic methods should be used that consist of the following options: insulin sensitizers, insulin secretagogues, α-glucosidase inhibitors and insulin. They are usually initiated after 2-3 months of inadequate results with non-pharmacological approaches. The commonly used drugs include sulphonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors and meglitinides.

Commonly Used Hypoglycemic Agents (Colagiudi, 2002; American Association of Clinical Endocrinologist, 2007)**:**

Sulphonylureas: They stimulate insulin secretion by B-Cells, thereby enhancing functioning of B-cells. They increase peripheral glucose uptake and utilization. They cause hypoglycemia/weight gain as side effects.

Examples are glibenclamide, chlopropamide, glimiperide, glipiride and glyburide.

Biguanides: They decrease hepatic glucose production and increase insulin sensitivity in peripheral tissues. They are suitable for obese patients and are contra-indicated in severe renal dysfunction. Example is metformin.

Meglitinides: They are short acting anti-diabetic drugs, similar in action to sulphonylureas and taken 3 times daily before meals. It should be skipped if meal is skipped. It is not to be combined with sulphonylureas. Examples are nateglinides and repaglinides.

Thiazolidinediones: They act on liver and peripheral tissues to regulate carbohydrate and lipid metabolism. They can cause weight gain and oedema. They are contra-indicated in class III and IV heart failure. Examples are rosiglitazone and pioglitazone.

Alpha-Glucoside Inhibitors: They decrease carbohydrate absorption in the intestines. Most effective in post prandial glucose control. They exhibit diarrhoea and abdominal

discomfort as adverse effects. Examples are miglitol and acarbose (Colagiudi, 2002; American Association of Clinical Endocrinologist, 2007).

Therapeutic Doses of Commonly Used Anti-Diabetic Drugs:

1. **Oral Hypoglycemic Agents:**

   Sulfonylureas:

   Glibenclamide 5 - 7.5mg twice daily.

   Chlopropamide 250 - 500mg daily.

   Biguanides e.g. Metformin 500-750mg three times daily.

2. **Insulin**

   a. Soluble Insulin, 10 - 20 i.u. three times daily.

   b. Insulin Zinc, 10 i.u. daily.

   c. Biphasic Isophane Insulin , 20 i.u. am., 10 i.u. pm.

2.4.6 Limitations of Some of the Existing Oral Hypoglycemic Agents:

The following side effects are common with some of the existing oral hypoglycemic agents: Hypoglycemia (sulphonyloreas, meglitinides), gastro-intestinal effects (biguanides, alpha-glucosidase inhibitors), lactic acidosis (biguanides), fluid retention (thiazolidinediones) and weight gain (sulphonylureas) (Colagiudi *et al.*, 2002; American Association of Clinical Endocrinologist, 2007).

The use of chlopropamide is no longer recommended for the management of Type II diabetes mellitus due to its exaggerated hypoglycemic and other side effects when compared with other drugs in the same class. This is due to its relatively longer half life (35hours) compared with 24 hours for glibenclamde in the same class. It is also the only drug in its class that exhibit disulfiram like reactions (BNF, 2010).

2.4.7 Newer Anti-Diabetic Drugs

In the past decade, newer anti-diabetic drugs that do not have some of these side effects have been developed with new mechanisms of action, for management of Type II diabetes mellitus. These are: Glucagon-Like peptide I agonists (GLP-I Agonists), Dipeptidylpeptidase-4-inhibitors and Amylin Analogues (Goldberg and Pham, 2007).

Glucagon – Like Peptide I Agonist: They are synthetic versions of exendin - 4 (incretin). They suppress appetite (Triplit, 2007). They delay gastric emptying and suppress glucagon secretion. Examples are:

Exenatide: First GLP-I agonist approved by FDA (2005), which is available as an injection (subcutaneous), administered as 5mcg twice daily (60 minutes before meal). Dose can be increased to 10mcg twice daily after one month (Buse *et al*., 2004; Defronzo *et al*., 2005). In combination therapy, it reduces HbA_C value by 0.7 – 10%.

Side Effects include nausea (self limiting) (Goldberg and Pham, 2007; Loli and Clement, 2008), long term weight loss (Buse *et al*., 2004). It is contra-indicated in Type I diabetes mellitus.

Liraglutide: This is another GLP-I-agonist approved by the US FDA in January 2010, marketed officially as victoza and available as an injection in 0.6mg.

Liraglutide: Dose can be increased to 1.8mg for adequate glycemic control. It is administered independent of meals. It induces Beta cell proliferation and prevent Beta cell apoptosis. It can be used in combination with metformin or sulphonylureas (Garber *et al*., 2008).

Dipeptidyl Peptidase-4-Inhibitors (DPP-4-inhibitor): This is another new class of drugs for Type II diabetes mellitus. They inhibit dipeptidyl peptidase-4 enzyme and prolong the action of glucagon (like peptides -I agonist).

Side effects are gastro intestinal effects, such as flatulence, and diarrhea (Goldberg and Pham, 2007; Garber *et al*., 2008)**.** Examples are:

Sitagliphin: This is the first approved DPP-4 inhibitor by FDA, in October 2006. It is marketed under the brand name Januvia™ by MSD. It is an adjunct in Type II diabetes mellitus management. It is administered as 100mg tablet once daily. Dosage adjustment in patients with severe renal impairment is necessary**.**

Saxagliptin: Recently approved by FDA in August 2009 and marketed by Bristol – Myers Squibb/Astrazeneca as Onglyza™ · It is an adjunct to diet and exercise in glycemic control and can be used in combination with sulphonylureas/metformin/thiazolidines to reduce HbA_C. It is administered as either 2.5mg or 5mg regardless of meals ones daily. Dosage adjustment in necessary in severe renal impairment. Side Effects include upper respiratory tract infection, urinary tract infection and headache.

Amylin Analogue: Another new class of anti-diabetic drugs. They are synthetic analogues of human amylin. They Inhibit post prandial glucagon secretion and delay gastric emptying (Garber *et al*., 2008). Current amylin analogue in market is **pramlintide**, available as a 5ml vial injection, given at a dose of 60 mcg in patients with Type II diabetes mellitus. Side Effects include nausea, vomiting, headache, hypoglycemia. Pramlintide is contraindicated in patients with gastroporesis.

Diabetes Mellitus is a life threatening disease if untreated. New (Novel) anti-diabetic agents offer hope in achieving adequate glycemic control.

2.5 Prevention of Type II Diabetes Mellitus

Primary prevention of Type II diabetes mellitus is possible. Primary prevention has an impact by reducing both the need for diabetes care and the need to treat diabetic complications (Alwan *et al.*, 1996; WHO, 2001a).

Secondary and tertiary preventions are key to reducing the risk of costly diabetic complications, as well as their associated disabilities. There is great potential for tertiary prevention in diabetes, especially with regard to blindness, limb amputation and adverse pregnancy outcomes. Rehabilitation and special assistance are required for those who do develop disabling complications. Overall, action taken early in the course of diabetes is more beneficial in terms of quality of life as well as being more cost-effective, especially if this action can prevent hospital admission.

Many barriers exist at the prevention level, including: lack of knowledge and awareness by individuals and communities, inadequately trained personnel in the preventive health care field, inadequate use of media for creating awareness for health education, changing of deeply-rooted lifestyles is very difficult and social problems (WHO, 2001a).

Primary Prevention

Lifestyle changes aimed at weight control and increased physical activity are important objectives in the prevention of Type II diabetes mellitus. The benefits of reducing body weight and increasing physical activity are not confined to Type II diabetes, they also play a role in reducing heart diseases and high blood pressure.

Lifestyle is the key to reversing these trends. Ministries of health, other ministries and the private sector need to have a commitment to a healthy lifestyle in order to reduce the risk of Type II diabetes and its complications developing in populations. The management of high blood pressure and raised blood lipids is equally important (WHO, 1997 and 2001b).

Randomized controlled trials have shown that in subjects at high risk for developing Type II diabetes mellitus (e.g. those with IGT, IFG), the adoption of favourable lifestyle changes brings about a significant reduction in the incidence of Type II. The Da Quing Study from China, reported by Pan (1997) showed that diet and exercise alone or in

combination in patients with IGT led to a 31 %-46% reduction in the risk of diabetes mellitus over a follow-up period of 6 years. A study conducted in Finland by Tuomilehto (2001c) in individuals with IGT showed that the incidence of Type II diabetes was 23% in the control group compared to 11 % in the intervention group (exercise and diet modifications) over a 4-year period.

The Diabetes Prevention Programme Research Group (2002), randomly assigned 3234 non-diabetic subjects (mean age 51 years, mean body mass index 34.0 kg/m^2) with elevated fasting and post-load plasma glucose concentrations to either placebo, metformin (850 mg twice daily), or a lifestyle modification programme. The objective was to achieve at least a 7% weight loss and at least 150 minutes of physical activity per week. The incidence of Type II diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups respectively.

Community Awareness and Secondary Prevention

The above studies highlight the importance of physical inactivity and unhealthy diets as strong risk factors for diabetes mellitus. A reasonable exercise programme and a modest amount of weight loss led to a marked decrease in diabetes incidence by more than 50%.

Due to the importance of the prevention of Type II diabetes and its complications, priority should be given to the development of community based healthy lifestyle programmes that focus on: maintaining a 'healthy' weight (WHO, 2004), an active lifestyle which includes regular physical activity, early identification of subjects at risk of developing Type II diabetes mellitus, identifying subjects at high risk of non-communicable diseases, such as hypertension, diabetes and heart disease.

The programme should also involve optimal maternal nutrition and weight maintenance, cessation of smoking, introduction of healthy lifestyle programmes in the early school

years. These should focus on the prevention of risk factors, which will predispose to non-communicable diseases in later life.

The primary purpose of secondary prevention activities such as screening is to identify individuals without symptoms who already have the disease, are at high risk of developing complications related to the primary disease, and where intervention could have a beneficial effect. Secondary prevention is the key to reducing the risk of costly and disabling diabetic complications. There is now conclusive evidence that good control of blood glucose levels can substantially reduce these complications. The United Kingdom Prospective Diabetes Study Group (1998) has proven that the risk of diabetic complications can be reduced significantly in people with Type II diabetes.

Therefore, action taken early in the course of diabetes is more beneficial in terms of quality of life and is more cost-effective, especially if this action can prevent hospital admission. The management of high blood pressure and raised blood lipids (fats) is equally important.

Tertiary Prevention

Tertiary prevention of diabetes includes every action taken to prevent or delay the consequences of diabetic complications, such as blindness, foot amputation and adverse pregnancy outcomes. Strategies for tertiary prevention involve prevention of the development of complications by strict metabolic control, education and effective treatment. They also involve screening for early stages of complications, when intervention and treatment are generally more effective. Such screening for complications aimed at early intervention and treatment has proved successful and may be even more effective than strategies aimed at preventing the development of complications. For example, the introduction of laser photocoagulation in the treatment of retinopathy has led to a dramatic decrease in diabetes-related blindness. Rehabilitation

of persons with diabetic complications is essential since many individuals with diabetes may develop disabling complications with high associated costs.

2.6 Biopharmamaceutics Classification System

One method of assessing bio-availability and bio-equivalence is by *in vitro* dissolution based on the Biopharmaceutics Classification System (BCS).

The Biopharmaceutics Classification System is a scientific frame work proposed by Amidon *et al*. (1995), classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, BCS take into account three major factors that govern the rate and extent of drug absorption from immediate release solid oral dosage forms: dissolution, solubility, and intestinal permeability (FDA, 2000).

The system divides actives pharmaceutical ingredients (API) into four classes based on their solubility and permeability properties:

Class I – High solubility/high permeability

Class II – Low solubility/high permeability

Class III – High solubility/low permeability

Class IV – Low solubility/ permeability

The background of this classification is the understanding that dissolution from dosage forms depends considerably on the solubility of drug ingredient and that absorption form the gastro-intestinal tract is dependent on permeability properties of the drug substance.

In addition, immediate release oral dosage forms are categorized as having very rapid, rapid or not rapid dissolution characteristics (WHO, 2006), since dissolution is affected by the biopharmaceutical characteristics of the formulation and absorption from the intestine may be influenced by certain ingredients (e.g. those modifying GI transit or membrane permeability) (Blume and Schug, 1999). Differences observed in the extent

and rate of absorptions of two pharmaceutically equivalent drugs *in vivo* may be due to *in vivo* dissolution differences, but in cases where dissolution is rapid *vis a vis* gastric emptying time and the drug has high intestinal permeability, then the rate and extent of absorption is not likely dependent on drug dissolution (FDA, 2000).

In order to be considered by FDA for a bio-waiver procedure, a pharmaceutical product

- Should contain a class I substance
- Should be rapidly dissolving, meaning it should release at least 85% of its content in 30 minutes in three different buffers (pH 1,2 – 6.8) in a paddle (50rpm) or basket (100rpm) apparatus at 37^0C and a volume of 900ml
- Should not contain excipients which could influence the absorption of the drug
- Should not contain a drug with a narrow therapeutic index
- Should not be designed to be absorbed from oral cavity

Apart from Class I drugs that has consensus of FDA and European regulations on bio-wiavers, arguments were made for bio-waivers for class III (highly solubility/low permeability) in literature (Blume and Schug, 1999; Cheng *et al.*, 2004; Kortajarvi *et al*., 2005).

WHO in its technical report extended the scope of application to class II and Class III, the scope of application was broadened in three directions:

1. The criteria for classification of an API as class I was relaxed with respect to dose solubility and permeability
2. Allows for API classified as class III to qualify for bio-waiver under a more stringent dissolution conditions
3. Set bio-waiver criteria for a category of class II API.

3. METHODOLOGY

3.1 Choice and Description of Study Area

The study was conducted at the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Borno State, Nigeria. The hospital was chosen because it is the only University Teaching Hospital in North-Eastern Nigeria, serving catchment states with 2010 projected population of Adamawa (3,551,898), Bauchi (5,345,611), Borno (4,859,516), Gombe (2,669,949), Taraba (2,556,750) and Yobe (2,664,076), representing 21,647,800 (14%) of 2010 projected national population (158,689,093).

Diabetes Mellitus cases were usually referred to UMTH from these catchment states.

The bed complement for the hospital was 570 as at December 2006. The hospital runs a medical out-patient department comprising of a general out-patient and specialist medical out-patient clinics. Diabetes clinic is one of the specialist medical out-patient clinics and it is run every Tuesday.

3.2 Ethical Considerations

Letters of introduction were obtained from the Department of Clinical Pharmacy and Bio-pharmacy, University of Lagos to Research and Ethical Committee, Health Records Department, Department of Medicine/Diabetes Clinic and Pharmacy Department of UMTH.

The selected diabetic patients were told that they would be interviewed and that their prescriptions and case-notes would be examined and used for research purposes. Their consent was sought and obtained at the point of exit from the pharmacy, before interview and data collection.

3.3 Objective

There is evidence that effectiveness of anti-diabetic drugs in the management of Type II diabetes mellitus decreases progressively after initiation of monotherapy, hence by about three years after initiation of therapy, practically all Type II diabetes mellitus patients on anti-diabetic drugs are on combination therapy and this is for life, therefore economically significant (Costa *et al*., 1997; WHO, 2007). For this reason, identified options of anti-diabetic therapy in Type II diabetes mellitus in UMTH were subjected to pharmaco-economic evaluation.

3.4 Study Population

Type II diabetes mellitus patients that were registered with and attend the diabetes clinic of UMTH were the subjects for the study.

3.5 Sample Size Determination

Type II diabetes mellitus patients registered with diabetes clinic from inception of UMTH in 1983 to December 2006 was obtained from Medical Records Department and is assumed /used as the estimate of the population size of serviced Type II diabetes mellitus patients. This was found to be 2,528.

Using this estimate (2,528) in Fischers' formula for population size less than 10,000,

$$\text{Given by } n_f = \frac{n}{1+ n/N} \qquad \text{Equation 1 (Araoye, 2003)}$$

Where n_f = the desired sample size when population is less than 10,000

n= the desired sample size when population is more than 10,000

N= the estimate of the population size, which is 2,528 for this study

But Fischers' formula for population size greater than 10,000 is given by Araoye (2003) as:

$$n = \frac{Z^2\ p\ q}{d^2} \qquad \text{Equation 2}$$

Where n= the desired sample size when population is greater than 10,000

Z= the standard normal deviate, usually set at 1.96, which corresponds to the 95% confidence level

P= the proportion in the target population estimated to have a particular characteristic. If there is no reasonable estimate, then use 50% (i.e. 0.50)

q = 1.0-p = 0.50

d= Degree of accuracy desired, usually set at 0.05

Therefore n= $\frac{(1.96)^2 (0.50)(0.50)}{(0.05)^2}$ = 385

Substituting this in Equation 1, gives

= $\frac{385}{1 + 385/2,528}$ = $\frac{385}{1 + 0.1523}$ = 351

The required sample size = 351, but because of available resources and to reduce study error, 1,200 of estimated population size was studied, bearing in mind that some of the patients that constitute the population estimate were either dead or dropped out of treatment or even not fit into the inclusion criteria of this study.

3.6 Subjects Selection

A crossectional study of old and new cases of Type II diabetes mellitus by systematic random sampling (using sampling interval of 1) of diabetic patients and their prescriptions at the point of exit from out-patient pharmacy was carried out on diabetes clinic days until a total of 1,200 cases that fall within the inclusion criteria were obtained. This was carried out on diabetes clinic days, which had pool of the cases. A retrospective review of their case-notes was also carried out.

3.6.1 Inclusion Criteria

1. Type II diabetes mellitus out-patient registered with UMTH Diabetes clinic regardless of sex and concurrent illness.

2. Old and new cases of Type II diabetes mellitus.
3. Adult of > or = 18years old.

3.6.2 Exclusion Criteria

1. Type I diabetes mellitus patients.
2. Type II diabetes mellitus in-patients.
3. Type II diabetes mellitus patients with severe complications that may require increased dose of hypoglycemic agents (oral and insulin) e.g. foot gangrene, infections e.t.c.

3.7 Questionnaires Development

Two separate questionnaires were developed for socio-economic indicators of subjects (Appendix I) and degree of knowledge/practice of life style/dietary modification (Appendix IV).

The questionnaires were developed based on literature reviews that identified socio-economic indicators of poverty and issues associated with diabetes education on lifestyle and dietary modification. Identified socio-economic indicators were refined and framed into questions for the instrument on socio-economic status of subjects.

The socio-economic indicators were identified as follows:

- Education, housing, access to water, average household size, access to health, nutrition, access to communication, transportation and electricity (World Bank, 2006)
- Income (World Bank, 2006)

Literature on diabetes education about lifestyle and dietary modification were evaluated to identify the following:

- Role of comprehensive lifestyle programme in improving glycemic control (Toobert *et al.*, 2003)

- Potential danger of hypoglycemia with alcohol consumption in diabetes mellitus (Bastaki, 2005)
- Why smoking should be avoided in diabetes mellitus (Al-Delaimy *et al*., 2002; Bastaki, 2005)
- Role of exercise in glycemic control (Eric and Gourly, 1993)
- Roles of dietary modification in management of diabetes mellitus (Trichopoulou *et al*., 2003)
- Carbohydrate intake recommendation in diabetes mellitus (Bastaki, 2005; ADA, 2009)
- Merits of monosaturated fat and demerits of saturated fat in diabetes mellitus (Parillo *et al.,* 1992)

Probable questions were derived for the questionnaires from the issues identified.

3.7.1 Questionnaires Validation Process

Face and Content Validity

The developed questionnaires were reviewed by project supervisor for face validity of questions. They were also assessed for content validity in terms of content, scope, depth and appropriateness of each item of the questionnaires.

Pre-testing of Questionnaires

The two questionnaires were pre-tested by administering to Type II diabetes mellitus patients (n=120 for each of the questionnaires) attending Diabetes clinic in State Specialist Hospital, Maiduguri. Appropriate corrections were made based on analysis of the pre-tested questionnaires.

Reliability Analysis of Questionnaires

The questionnaires were assessed for reliability using split halves method, with cronbach alpha values of 0.698 and 0.721 for questionnaires on socio-economic indicators of subjects and degree of knowledge/practice of life style/dietary modification respectively.

3.8 Determination of Relationship between Socio-Economic Status, Affordability and Glycemic Control (Outcome of Anti-Diabetic Therapy)

3.8.1 Study Design

A crossectional study, where by, each selected subject is seen and interviewed once in the study at the point of exit from out-patient pharmacy of UMTH was adopted for collection and grading of World Bank socio-economic indicators of poverty (World Bank, 2006). Prospective study of their filled prescriptions and retrospective review of their traced case-notes was also carried out.

3.8.2 Data Instrument

A pre-tested, standardized interviewers' administered questionnaire (Appendix I) with sections on socio-demographic data, socio-economic indicators of poverty (World Bank, 2006), affordability of anti-diabetic drugs and glycemic control based on latest monitoring tests was designed and used for this study.

3.8.3 Data Collection

The Instrument (Appendix I) was used to obtain information on socio-demographic data and socio-economic indicators of poverty from the subjects at the point of exit from out-patient pharmacy of UMTH on consecutive diabetes clinic days (Tuesdays) in a systematic random sampling (using a sampling interval of 1) of subjects that fall within the inclusion criteria until a total of 1,200 subjects were interviewed.

Information on affordability of anti-diabetic drugs and glycemic control category based on latest monitoring tests were extracted from filled prescriptions and traced case-notes

respectively, into respective questionnaires, coded by the hospital number of individual subject.

3.8.4 Computation of Data

For every question or indicator in the instrument, there are four alternative categories. The four categories were assigned a rating interval in ascending order 1-25%, 26-50%, 51- 75% and 76-100%.

The average performance in percentage, for each socio-economic indicator per subject was determined by taking the median of the applicable rating interval of each indicator. For example, rating intervals 1-25%, 26-50%, 51-75% and 76-100% had median value of 13%, 38%, 63% and 88% respectively.

The average performance in percentage, of all measured socio-economic indicators was calculated for each subject by determining the mean of the median values of the measured ten indicators. This was used to categorize each patient into either core-poor, moderately poor or non-poor. For example, if the median values of all ten measured indicators (Appendix 1, Indicator 1-10) for a particular subject are respectively 38%, 13%, 38%, 63%, 63%, 38%, 38%, 88%, 63% and 13%,

Then, the average performance = mean = $\frac{38+13+38+63+63+38+38+88+63+13}{10}$

= 45.5%

In categorizing the subject, the conventional examination scores assessment system was assumed i.e. 0 to 39 is failure ≡ core poor,

40 to 49% is below average ≡ moderately poor,

50 and above is average/above average respectively ≡ non –poor.

Therefore in the above example, the subject with average performance 45.5% would be categorized as being moderately poor.

3.8.5 Data Analysis

The collected data were analysed using EPI- INFO software version 3.4.1 2007. Data were presented as frequency distribution tables and charts. Chi-Square analysis was used to compare proportions and test hypothesis. P-Values < 0.05 were considered significant.

3.9 Cost of Illness Analysis (CIA)

3.9.1 Study Design

A retrospective study of 120 (10%) randomly sampled case-notes out of a total of 1200 case-notes of the subjects that participated in this research work was done. Time and motion study was involved.

3.9.2 Objective

To determine the cost of illness of Type II diabetes mellitus.

3.9.3 Economic Perspective

Economic perspective of the subjects and the hospital were considered since the drug, diagnostic and transport costs were borne by the subjects, while personnel costs were borne by the Hospital Management.

3.9.4 Data Instrument

A pre-tested, standardized data collection form (Appendix II) was designed with columns for Code Number as the Patient's Hospital Number, date of visit, demographic data, detailed address, concurrent illness (s), fasting blood sugar on visit, blood pressure on visit, drugs prescribed with duration (generic/branded) on each visit and cost, diagnostic/monitoring tests on each visit and cost, transport cost on each visit (to and fro), personnel cost and total cost.

3.9.5 Data Collection

The study addressed Type II diabetic out-patients of the hospital. It involved review of 960 prescriptions. These were the prescriptions of 120 diabetic patients obtained from their randomly sampled case-notes, over one year period (July 2009 to June 2010).

The following data were noted and recorded from the case notes in to the data collection form (Appendix II) : Date of Visit, demographic data, fasting blood sugar level at each visit, blood pressure at each visit, concurrent illness (s), number of visits and prescribed drugs (ant-diabetics and anti-hypertensives) at each visit as well as duration of therapy. Evidence of diagnostic/monitoring test were also noted and recorded.

3.9.6 Cost Measure

Only the direct costs were considered. These include the cost of drugs, diagnostic/monitoring tests, transportation and personnel.

Drug costs were obtained from the pharmacy department of the hospital and the cost per defined daily dose (C/DDD) were calculated, taking the duration of therapy into consideration to obtain total cost of drug.

Cost per Defined Daily Dosage (C/DDD) units as recommended by World Health Organization (WHO) for analysis of drug use was applied. DDD represents usual dosage of a drug per day (Nertheimer, 1986).

The costs of diagnostic/monitoring tests were obtained from the laboratory of the hospital. Time and motion studies were carried out to calculate the personnel costs for physicians, pharmacists and nurses. Average time for 15 random observations for completion of task such as consultation, dispensing and measurement of blood pressure was determined and recorded.

The salary of health professionals were obtained form the accounts department of the hospital. The average was considered where necessary. The mean salary per minute was calculated as follow:

$$\text{Mean Salary/Minute} = \frac{\text{Annual Salary}}{\text{Hours/wk x no. of wks/annum x 60}}$$

(Roberts, 1986; Suleiman and Tayo, 2001; Giwa *et al*., 2009).

In the calculations, the respective number of visits were considered.

3.9.7 Cost of Illness

- All these costs were added up for each subject, and for all the 120 subjects to obtain the total cost of illness for the 120 subjects. The average cost of illness (cost per subject) was then calculated and recorded.
- The average cost calculated is the annual average cost of illness for diabetes mellitus (DM).
- The annual cost of illness for diabetes mellitus in North-Eastern Nigeria =

  Annual average cost of illness for DM X 21,647,800 (North-Eastern Nigerian Projected Total Population for 2010) X 3% (Prevalence Rate).
- The National (Nigeria) annual cost of illness for diabetes mellitus =

  Annual average cost of illness for DM X 158,689,093 (National Projected Total Population for 2010) X 3% (Prevalence Rate).

3.9.8 Data Analysis

The collected data were analysed manually. Data were presented as frequency distribution tables.

3.10 Cost Minimization Analysis (CMA)

3.10.1 Study Design

A prospective study of filled prescriptions of the selected subjects at the point of exit from out-patient pharmacy and a retrospective study of their case-notes were done.

3.10.2 Treatment Options

Branded and their generic equivalents used in UMTH were the two options available for each of 5mg glibenclamide tablet, 500 mg metformin tablet and 250 mg chlopropamide tablet.

Innovator products were considered as branded while others were assumed to be generic for each of these anti-diabetic drugs used in UMTH.

The equivalents were evaluated using the same dosage form, equal strength and the same frequency of dosing for all the drugs considered.

3.10.3 Objective

To determine which anti-diabetic options (generic or branded) is a lower cost option and compare frequency of their prescription as at the time of this study in UMTH.

3.10.4 Economic Perspective

Economic perspective of the subjects was considered since the drug cost was borne by the subjects.

3.10.5 Data Instrument

A pre-tested, standardized data collection form (Appendix III) was designed with columns for code number as the patients' hospital number, diagnosis, weight, height, age of onset (year of first diagnosis), prescriptions (generic/branded), duration of present regimen, relevant diagnostic/monitoring test result [fasting blood sugar (FBS) and glycosylated haemoglobin (HbAlc)], blood pressure (B.P), physician's remark/comments, number of anti-diabetic drugs on prescription, total number of prescribed anti-diabetic drugs available in the pharmacy, number out of stock, number of anti-diabetic drugs that is affordable, number of the available anti-diabetic drugs the subjects did not buy due to cost (not affordable), defined daily dose (DDD) and cost/DDD.

3.10.6 Data Collection

Filled prescriptions at the point of exit from out-patient pharmacy was used to extract information for the section of the designed data collection form (Appendix III) relating to the code number, number of anti-diabetic drugs on current prescription, total number of

currently prescribed anti-diabetic drugs available in the pharmacy, number out of stock indicated by o/s written against the anti-diabetic drug on the prescription sheet by the pharmacist, number affordable (assumed to be anti-diabetic drug a subject paid for immediately after costing at the out-patient pharmacy) indicated by a tick against the anti-diabetic drug on the prescription sheet by the pharmacist, number not affordable (assumed to be anti-diabetic drug a subject did not buy immediately after costing at the out-patient pharmacy) indicated by having no mark against anti-diabetic drug on the filled prescription. DDD and cost/DDD was also entered as subjects come to fill their prescriptions consecutively at the out-patient pharmacy.

Patients' code number from the selected prescriptions was used to trace their case-notes at Medical Record Department to obtain other relevant information required in the data collection form (Appendix III) that were not available on the filled prescriptions for each of the subject whose prescriptions have been sampled for this study (n=1,200).

The information include weight, height, diagnosis, year of first diagnosis, duration of present regimen, physician's remark on glycemic control and regularity on medication, relevant diagnostic/monitoring test (latest FBS, HbAlc) and blood pressure.

Data collection continued in a systematic random sampling (using sampling interval of 1) on diabetes clinic days (Tuesdays) until 1,200 anti-diabetic prescriptions and their case-notes within the inclusion criteria were obtained.

3.10.7 Cost Measure

Cost per defined daily dosage (DDD) units, as recommended by World Health Organization (2007) for analysis of drug use was applied. DDD represents usual dosage of a drug per day (Nertheimer, 1986; WHO, 2007). This was applied to the branded and generic equivalents that were used in UMTH. Mean cost/DDD of branded and generic equivalents anti-diabetic drugs available at UMTH was used.

3.10.8 Cost Minimization Analysis

Cost minimization analysis (CMA) was carried out by calculating and comparing the mean cost per defined daily dose (DDD) of two options that have the same outcome (branded and generic products) to identify the lowest cost option (Bootman *et al*., 1996; Nermeither, 1986; WHO, 2007). This was carried out for all the oral anti-diabetic drugs for branded and generic equivalents.

Being chemically equivalent, it was assumed that branded and generic anti-diabetic drugs have the same outcome as required in a cost minimization analysis.

3.10.9 Sensitivity Analysis

Sensitivity analysis was performed to test whether decisions change when specific variables (e.g. cost/DDD) were altered within reasonable range (10-25%) in favour of higher cost option (Appendix VIII).

3.10.11 Data Analysis

The collected data were analysed using EPI- INFO software version 3.4.1 2007. Data were presented as frequency distribution tables. Chi-Square analysis was used to compare proportions and students't-test was used to compare mean and hypothesis testing. P-Values < 0.05 were considered significant.

3.11 Cost Effectiveness Analysis (CEA)

3.11.1 Study Design

A prospective study of filled prescriptions of selected subjects at point of exit from out-patient pharmacy, involving standard cost-accounting technique was carried out, followed by a retrospective review of case-notes of the selected subjects for treatment option identification with diagnosis.

3.11.2 Treatment Option

The treatment options available for different stages (moderate and severe hyperglycemia in obese and non-obese subjects) of Type II diabetes mellitus was identified from case-notes of the subjects. Pattern of usage of each identified option was determined in an anti-diabetic drugs utilization study.

3.11.3 Objective

To determine which of the identified options for different stages of Type II diabetes mellitus were more cost effective**.**

3.11.4 Economic Perspective

Economic perspective of the subjects was considered since the drug cost was borne by them.

3.11.5 Data Instrument

The same data collection form designed for cost minimization analysis (Appendix III) was used to capture data relating to cost component of cost effectiveness analysis.

A standardized effectiveness rating format (Appendix V) and decision analysis table (Appendix VI) were designed to document, rate and analyze effectiveness indicators of anti-diabetic drugs generated from literature.

3.11.6 Data Collection

Patients' code number by hospital number and anti-diabetic drugs prescriptions were filled into the data collection form (Appendix III) from information on the filled prescriptions at the point of exit of subjects from out-patient pharmacy of UMTH on diabetes clinic days (Tuesdays).

Patients' code number was used to trace patients' case-notes at Medical record department to obtain other relevant information required in the data collection form (Appendix III) that were not available on the filled prescriptions for each of the subjects whose prescriptions have been sampled for this study (n=1,200).

The information include diagnosis and FBS on diagnosis, year of first diagnosis, duration of present regimen, Physician's remark on glycemic control and regularity on medication, relevant diagnostic/monitoring test (latest FBS, HbAlc) and blood pressure.

Data collection continued in a systematic random sampling (using sampling interval of 1) on consecutive diabetes clinic days (Tuesdays) until 1,200 anti-diabetic prescriptions and their case-notes within the inclusion criteria were obtained.

3.11.7 Cost Measure

In this study, only drug acquisition cost was considered. Dispensing Cost and transport cost to patients were assumed to be the same for all the treatment options identified.

Anti-Diabetic therapy is a life long management but follow up visit to the physician is usually every two months (60 days) for mild hyperglycemia, one month for moderate hyperglycemia and two weeks for severe hyperglycemia (ADA, 2005). Duration of therapy was therefore respectively set at these periods for each hyperglycemic category identified.

Total Cost of a Treatment Option = Mean Cost per Defined Daily Dosage (DDD) x Duration of Therapy. Mean cost/DDD of treatment options available at UMTH was used. To avoid bias, average cost of available generic equivalents were considered for all the treatment options.

3.11.8 Effectiveness (Outcome) Measure

The effectiveness measure involved theoretical framework by analysis of positive and negative outcome of each treatment option from review of literature as in Appendix V to

establish probabilities of the outcomes and applying decision analysis as in Appendix VI for effectiveness (Cano and Fujta, 1988; Suleiman and Tayo, 2001) of chlopropamide and glibenclamide options.

Effectiveness of a treatment option (in natural unit) = Sum of all criterion rating, where Criterion Rating = Criterion Value X Assigned Weight.

The criterion value and assigned weight which determines the criterion rating is somewhat arbitrary hence fairly subjective. However, each option being considered was treated identically with respect to the assigned weight to limit the subjectivity.

More so, the value given to each characteristic (criterion) is determined by decision-maker(s) who will make use of the result of analysis in taking decision (Cano and Fujta, 1988; Suleiman and Tayo, 2001).

Criterion Value was obtained from analysis of positive and negative outcome of different criterion (characteristic) of a treatment option from review of literature in natural unit e.g. percentages (Cano and Fujta, 1988; Suleiman and Tayo, 2001). For example, criteria for anti-diabetic drugs effectiveness (outcome) and respective assigned weight include efficacy (0.4), adverse drug reaction 0.2), safety of administration (0.1), frequency of administration (0.1) and bioavailability (0.2) (Appendix VI).

3.11.9 Confounding Variables

Confounding variables were identified and solutions were proffered to them right from the study design (Appendix VII).

3.11.10 Cost Effectiveness Analysis (CEA)

Cost Effectiveness Analysis indicates which intervention provides the highest "value for money" and helps to choose the intervention which maximizes health for the available resources (Jolicoeur *et al*., 2002).

Cost Effectiveness Analysis was carried out by calculating:

(i) The cost i.e. the resources required to implement an intervention.

(ii) The effectiveness i.e. the extent to which current and potential interventions improves population health. It is otherwise known as outcome.

$$\text{CEA} = \frac{\text{Total cost of a treatment option (in monetary unit)}}{\text{Effectiveness of the treatment option (in natural unit)}}$$

(Murray, 2000; Jolicoeur *et al*., 2002).

This was determined and compared for available options in each hyperglycemic category.

3.11.11 Sensitivity Analysis

Sensitivity Analysis was performed to test whether the decisions change when specific variables (e.g. cost, effectiveness) were altered within reasonable range (10-25%) in favour of less cost-effective option, as in Appendix IX for chlopropamide and glibenclamide in the management of moderate hyperglycemia in non- obese Type II diabetes mellitus patients.

3.11.12 Data Analysis

The collected data were analyzed using EPI- INFO software version 3.4.1 2007. Data were presented as frequency distribution tables. Chi-Square analysis was used to compare proportions and hypothesis testing. P - Values < 0.05 were considered significant.

3.11.13 Limitation

The criterion value and assigned weight which determines the criterion rating is somewhat arbitrary hence, fairly subjective. However, each treatment option was treated identically with respect to the assigned weight to limit the subjectivity (Appendix VI).

The value to be given to each characteristic (criterion) is determined by the decision maker who will use the result of analyses in taking decision (Cano and Fujta, 1988).

3.12 Determination of Relationships between Degree of Knowledge/Practice of Lifestyle/Dietary Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

3.12.1 Study Design

A crossectional study whereby each selected subject was seen and interviewed once in the study at the point of exit from out-patient pharmacy was adopted for collection of information about rating or degree of subjects' knowledge/practice of lifestyle/dietary modification based on set criteria for assessment (Appendix XI) (Parrilo *et al*., 1992; Eric and Gourley, 1993; Toobert *et al*., 2003; Bastaki, 2005).

3.12.2 Data Instrument

A pre-tested, standardized interviewer's administered questionnaire (Appendix IV) with sections on socio-demographic data, degree of subjects' knowledge/practice of lifestyle/dietary modification and glycemic control based on latest monitoring tests and physician's remark extracted from case-note of each subject into the questionnaires coded by the hospital number of each subject was designed and used for this study.

3.12.3 Data Collection

The instrument (Appendix IV) was used to obtain information on socio-demographic data, degree of subjects' knowledge/practice of lifestyle/dietary modification from the subjects at the point of exit from out-patient pharmacy on consecutive diabetes clinic days (Tuesdays) in a systematic random sampling (using sampling interval of 1) of subjects that fall within the inclusion criteria until a total of 1,200 subjects were interviewed.

Criteria for assessing degree of subjects' knowledge about lifestyle and dietary modification (Appendix X) were obtained from the literature and used in rating the

degree of knowledge/ practice of specific lifestyle/dietary modification into excellent, good, fair or poor.

Glycemic Control category based on latest monitoring tests and physician's remark was extracted from traced case-note of each subject into their respective questionnaires, coded by the hospital number of individual subject.

3.12.13 Data Analysis

The collected data were analysed using EPI- INFO software version 3.4.1 2007. Data were presented as frequency distribution tables and charts. Chi-Square Analysis was used to compare proportions and test hypothesis. P-Values < 0.05 were considered significant.

3.13 Determination and Comparative Assessment of Quality Control Parameters of Branded and Generic Anti-Diabetic Drugs

3.13.1 Drug samples, collection and storage:

The branded and generic drugs investigated were all conventional, immediate release, solid oral dosage forms of anti-diabetic drugs used in the study setting (UMTH). Generic glibenclamide tablet 5mg (A) was compared with innovator brand of glibenclamide 5mg Daonil® (D). Glibenclamide is a sulphonylurea oral hypoglycemic agent used in the management of Type II diabetes mellitus.

Generic metformin tablet 500mg (B) containing metformin hydrochloride was compared with innovator brand of metformin hydrochloride 500mg Glucophage® (E). Metformin hydrochloride is a biguanide oral hypoglycemic agent used in the management of Type II diabetes mellitus.

Generic chlopropamide tablet 250mg (C) was compared with innovator brand of chlopropamide tablet 250mg Diabenese® (F). Chlopropamide is a sulphonyl urea oral hypoglycemic agent used in the management of Type II diabetes mellitus.

Glibenclamide and Chlopropamide are completely absorbed after oral administration (>90%). They belong to BCS Class 1 (high solubility/high permeability) (Volgelpoel *et al*., 2005). These drugs qualify for bio-waiver under the FDA and WHO guidelines (Volgelpoel *et al*., 2005). Metformin is 60% absorbed and defies hepatic degradation. It is in BCS Class III. WHO (2004) in its technical report extended the scope of application of bio-waiver to Class II and Class III API. All drugs analyzed in this study, therefore, qualify for bio-waiver.

All the drugs were collected from UMTH out-patient pharmacy and stored in their packs under conditions specified by the manufacturers prior to assay, which was done before their expiry dates at National Agency for Food and Drug Administration and Control, Maiduguri, Borno State, North-Eastern Nigeria.

3.13.2 Identification Test

Glibenclamide tablets

The light absorption of the solution obtained in the assay of sample A and D were observed under UV Spectrophotometer in the range 230 to 350 nm. Exhibition of a maximum at 300 nm and a less intense maximum at 275 nm were considered passed for glibenclamide (BP, 2002).

Metformin tablets

A quantity of the powdered tablets containing 50 mg of sample B was triturated with 10 ml of *water* and filtered. To 5 ml of the filtrate was added 1.5 ml of 5M *sodium hydroxide*, 1 ml of *strong 1-naphthol solution* and, drop-wise with shaking, 0.5 ml of *dilute sodium hypochlorite solution.* An orange-red colour produced which darkens on standing was considered passed for metformin (BP, 2002). The test was repeated, using sample E.

Chlopropamide tablets

A quantity of the powdered Sample C tablets containing 1g of chlopropamide was extracted with five 4-ml quantities of *acetone*, filtered and the filtrate was evaporated carefully to dryness on a water bath. 0.1g of the residue was heated with 1g of *anhydrous sodium carbonate* at a dull red heat for 10 minutes and cooled. The residue was extracted with water and filtered. The filtrate was acidified with 2M *nitric acid* and *silver nitrate solution* was added. A white precipitate produced was considered passed for chlopropamide (BP, 2002). The test was repeated, using sample F.

3.13.3 Hardness Test

Hardness of each tablet was determined using the Mosanto Stokes hardness tester and the average hardness between 5-7 kgf inclusive was considered acceptable for tablets (B.P., 2008).

3.13.4 Weight Uniformity Test

Ten tablets of each sample were selected randomly and weight singly using an analytical balance (Mettler, UK) (B.P., 2008). Average tablet weight, standard deviation and percentage deviation for each of the six drug samples were calculated. Permitted percentage deviation of not more than 5% for tablet weighing 250 mg or above 250mg (Chlopropamide and Metformin) and not more than 10% for tablet weighing 80mg or less (Glibenclamide) was taken as the acceptable limit (B.P., 2008).

3.13.4 Friability Test

Friability is a measure of the resistance of tablet and granules formulations of pharmaceutical products to abrasion.

Tablets were dedusted, weighed and agitated in a Roche friabilator. After a time interval of 5 minutes at 25 rpm, they were then dedusted, and re-weighed. The measure of abrasion, B, calculated as the percentage loss in weight (% weight variation) was done using the expression:

$B= (w_0 – w)/ w_0 X 100$

Where B= measure of abrasion (% loss in weight).

W_0= weight before agitation.

W = weight after agitation and dedusting.

Values of B not exceeding the upper limited of 1 % were considered acceptable (B.P., 2008).

3.13.5 Disintegration Time Test

The disintegration time of six randomly chosen tablet of each of the six drug samples (A, B, C, D, E and F) was determined (separately for each sample) in the specified liquid using a multi-unit disintegration time apparatus set at 50 rpm. The time taken for the last tablet of a drug sample to break up into small aggregates was noted as the disintegration time (B.P., 2008)). This was repeated four more times for each sample. The mean disintegration time was determined for each sample. Mean disintegration times not exceeding 15 minutes (900 seconds) were considered acceptable (B.P., 2008).

3.13.6 Assay for Content of Active Ingredient

Glibenclamide

20 tablets of sample A were weighed and powdered. A quantity of the powder containing 20 mg of glibenclamide was shaken with 40 ml of 0.1M *methanolic hydrochloric acid*, heated gently and centrifuged. The extraction was repeated with three further 20 ml quantities of 0.1M *methanolic hydrochloric acid*. To the combined extracts was added sufficient 0.1M *methanolic hydrochloric acid* to produce 200 ml, which was filtered. The *absorbance* of the resulting solution was measured at the maximum at 300 nm, using in the reference cell 0.1M *methanolic hydrochloric acid* heated to the same degree.

The content of glibenclamide ($C_{23}H_{28}ClN_3O_5S$) was calculated using 63 as the value of A (1%, 1 cm) at the maximum at 300 nm (B.P., 2008).

Content of glibenclamide, 95 to 105.0% of the stated amount was considered passed (B.P., 2008). The test was repeated, using sample D.

Metformin

20 tablets of sample B were weighed and powdered. Shake a quantity of the power containing 0.1 g of Metformin Hydrochloride was shaken with 70 ml *water* for 15 minutes. This was diluted to 100 ml with *water* and filtered, discarding the first 20 ml. The *absorbance* of the resulting solution was measured at the maximum at 232 nm. The content of the metformin hydrochloride ($C_4H_{11}N_5$, HCl) was calculated, taking 398 as the value of A(1%, 1 cm) at the maximum at 232 nm (B.P., 2008).

Content of metformin, 95 to 105.0% of the stated amount was considered passed (B.P., 2008). The test was repeated, using sample E.

Chlopropamide

20 tablets of sample C were weighed and powdered. A quantity of the powder containing 0.25g of chlopropamide was shaken with 40ml of *methanol* for 20 minutes. Sufficient *methanol* was added to produce 50 ml, mixed and filtered. 5ml of the filtrate was diluted to 100 ml with 0.1M *hydrochloric acid*. 10 ml of this solution was diluted to 250 ml with 0.1M *hydrochloric acid*. The *absorbance* of the resulting solution was measured at the

maximum at 232 nm. The content of chlopropamide ($C_{10}H_{13}ClN_2O_3S$) was calculated, taking 598 as the value of A (1%, 1 cm) at maximum at 232 nm (B.P., 2008).

Content of chlopropamide, 92.5 to 107.5% of the stated amount was considered passed (B.P., 2008). The test was repeated, using sample F.

3.13.7 Dissolution Rate Test

Glibenclamide

Using as the medium 1000 ml of a 0.68% w/v solution of *potassium dihydrogen orthophosphate* adjusted to pH 6.8 by the addition of 1M *sodium hydroxide* and rotating the paddle at 50 revolutions per minute for 45 minutes. A 10-ml sample of the medium was withdrawn and the *absorbance* of the filtered sample of drug A was measured at the maximum at 300nm. The total content of glibenclamide in the medium was calculated, taking 63 as the value of A (1%, 1cm) at the maximum 300nm (B.P., 2008), by applying Beer's lambert law, A/CL = A1%.

The experiment was repeated three more times for the same sample A, and the average determined. Value of percentage average dissolution (release) of 70% and above was considered acceptable (B.P., 2008). The test was repeated, using sample D.

Metformin

The dissolution rate test conducted above was repeated, using sample B and E, but the total content of metformin in the medium was calculated, taking 806 as the value of A (1%, 1cm) at the maximum 233 nm (B.P., 2008) for each of sample B and E.

Values of percentage average dissolution (release) of 70% and above were considered acceptable (BP, 2008)

Chlopropamide

The dissolution rate test conducted above was repeated, using sample C and F, but the total content of chlopropamide in the medium was calculated, taking 469 as the value of A (1%, 1cm) at the maximum 230 nm (BP, 2008) for each of sample C and F.

Values of percentage average dissolution (release) of 70% and above were considered acceptable (B.P., 2008).

4. RESULTS

Preamble

The data were generated through data collection forms into which information extracted from case-notes and filled prescriptions were entered. The socio-demographic data, socio-economic indicators of poverty and information on degree of knowledge/practice of lifestyle /dietary modification was obtained directly by interview of the subjects. One thousand two hundred subjects were studied.

The results of the data analysis were presented in tables and charts below:

4.1 Socio-demographic /Background Information

4.1.1 Age Distribution of Subjects

Most, 780 (65.0%) out of 1200 subjects were between 41 and 60 years of age while 324 (27.0%) were between 61-75 years of age. About 28 (2.3%) and 68 (5.7%) were below 41 years and above 75 years of age respectively.

Table 1: Age Distribution of Subjects

Age Group (Years)	Frequency	Percentage
28-40	28	2.3
41-60	780	65.0
61-75	324	27.0
76-85	68	5.7
Total	1200	100

Mean age = 56.54 ± 0.29; Range = (28-85) =57

4.1.2 Sex Distribution of Subjects

There was slightly higher number of male subjects, 624 (52.0%) out of 1200, over the female subjects, 576 (48.0%).

Table 2: Sex Distribution of Subjects

Sex	**Frequency**	**Percentage**
Male	624	52
Female	576	48
Total	1200	100

4.1.3 Distribution of Subjects according to address of Residence by State

Five Hundred and Seventy Two (47.7%) out of 1200 subjects were residing in Borno State while 244 (20.3%),

One Hunderd and Ninety Three (16.1%), 113 (9.4%), 44 (3.7%) and 27 (2.3%) were residing in Yobe, Adamawa, Taraba, Bauchi and Gombe States of North-Eastern Nigeria. Only 7 out of 1200 subjects were residing in Plateau State of North-Central Nigeria.

Table 3: Distribution of Subjects according to address of Residence by State

State of Residence	**Frequency**
Borno	572 (47.7%)
Yobe	244 (20.3%)
Adamawa	193 (16.1%)
Taraba	113 (9.4%)
Bauchi	44 (3.7%)
Gombe	27 (2.3%)
Plateau	7 (0.5%)
Total	**1200 (100%)**

4.1.4 Distribution of Subjects according to Time of First Diagnosis of Diabetes Mellitus (DM)

Six Hundred and Seventy Two (56%) out of 1200 subjects had been diagnosed as Type II diabetes mellitus patients more than 10 years ago. One Hunderd and Sixty Two (13.5%) of the subjects were diagnosed less than 1 year ago.

Table 4: Distribution of Subjects according to Time of First Diagnosis of Diabetes Mellitus (DM)

Time of First Diagnosis	**Frequency**
Less Than 1 Year	162 (13.5%)
1-5 years	138 (11.5%)
6-10 years	228 (19%)
11-15 years	138 (11.5%)
16-20 years	216 (18%)
> 20 years	318 (26.6%)
Total	1200 (100%)

4.1.5 Distribution of Subjects by Level of Hyperglycemia on Diagnosis

Eight Hundred and Sixty Four (72%) out of 1200 subjects were undergoing treatment for moderate hyperglycemia, 276 (23%) for severe hyperglycemia and 60 (5%) for mild hyperglycemia.

Table 5: Distribution of Subjects by Level of Hyperglycemia on Diagnosis

Level of Hyperglycemia on Diagnosis	**Frequency**
Mild Hyperglycemia (FBS>5.0 but < 7.8mmole/litre)	60 (5%)
Moderate Hyperglycemia (FBS 7.8-11.1mmole/litre)	864 (72%)
Severe Hyperglycemia (FBS>11.1mmole/litre)	276 (23%)
Total	1200 (100%)

4.1.6 Distribution of Subjects according to Duration of Present Regimen

Nine Hundred and Forty Eight (79%) out of 1200 subjects have been on their present regimen for at least 5 months. Two Hundred and Fifty Two (21%) of the subjects have been on their regimen for less than 5 months.

Table 6: Distribution of Subjects according to Duration of Present Regimen

Duration of Present Regimen	**Frequency**
Less Than 2 month	72 (6%)
2-4 month	180 (15%)
5-8 month	672 (56%)
9-12 month	168 (14%)
>12 month	108 (9%)
Total	1200 (100%)

4.1.7 Distribution of Subjects according to Glycemic Control Based on Latest Fasting Blood Sugar (FBS), Mean Glycosylated Haemoglobin (HbAlc) and Physician Remark on Regularity on Medication.

Five Hundred and Twenty Three (43.6%) out of 1200 subjects had poorly controlled glycemia, 274 (22.8%) had fairly controlled glycemia while 403 (33.6%) had good glycemic control based on latest FBS and mean value of glycosylated haemoglobin.

The physician remarked that these subjects were respectively not regular, fairly regular and regular on medication. UMTH normoglycemic range is 2.5-5mmole/litre.

Table 7: Distribution of Subjects according to Glycemic Control Based on Latest Fasting Blood Sugar (FBS), Mean Glycosylated Haemoglobin (HbAlc) and Physician Remark on Regularity on Medication

Glycemic Control Based on Latest FBS	Glycemic Control Based on HbAlc	Physician Remark	Frequency	Percent
Poor (FBS>7.0mmole/litre)	Poor (HbAlc>10%)	Not Regular on Medication	523	43.6
Fair (FBS>6.0 and <7.0mmole/litre)	Fair (HbAlc>7% and <10%)	Fairly Regular on Medication	274	22.8
Good (FBS<6.0mmole/litre)	Good (HbAlc<7%)	Regular on Medication	403	33.6
Total			1200	100

4.1.8 Distribution of Subjects according to Weight, Body Mass Index And Hyperglycemic Range by Obesity Based on Body Mass Index (BMI)

BMI was determined to established the presence or otherwise of obesity in the subjects. It is based on two simple measurements: height (in meters), without shoes and weight (in kg), with minimal clothing. Patients' weight and height are routinely measured on diabetes clinic days and recorded in their case notes. BMI = weight (kg)/Height^2 (m^2)

4.1.8.1 Weight Distribution of Subjects

Eight Hundred and Ten (67.5%) out of 1200 subjects were above 60kg weight while 390 (32.5%) were below 61kg weight. There was a significant difference in these proportions*.

Table 8: Weight Distribution of Subjects

Weight Group (kg)	Frequency	Percent
≤50	6	0.5
51-60	384	32.0
61-70	336	28.0
71-80	288	24.0
81-90	66	5.5
91-100	48	4.0
> 100	72	6.0
Total	1200	100

*(χ^2 = 24.5; df = 1; p = 0.0000007)

4.1.8.2 Distribution of Subjects by Body Mass Index (BMI)

Eight Hundred and Forty (70%) out of 1200 subjects had their BMI greater than 25kg/m^2 while 360 (30%) had their BMI to be between 20 and 25kg/m^2 inclusive

Table 9: Distribution of Subjects by Body Mass Index (BMI)

BMI (kg/m^2)	**Frequency**	**Percent**
20-25 (Normal Subjects)	360	30.0
26-29 (Grade I Obesity)	444	37.0
30-40 (Grade II Obesity)	234	19.5
> 40 (Grade III Obesity)	162	13.5
Total	1200	100

.Garrow, 1981 Classification of Obesity

4.1.8.3 Distribution of Subjects in Each Range of Hyperglycemic Level by Obesity Based on BMI

Eight Hundred and Forty (70%) out of 1200 subjects were obese while 360 (30%) were non-obese. Sixty of these subjects had mild hyperglycemia while 864 and 276 had moderate and severe hyperglycemia on diagnosis respectively.

Table 10: Distribution of Subjects in Each Range of Hyperglycemic Level by Obesity Based on BMI

Level of Hyperglycemia	**Obese**	**Non-obese**	**Total**
Mild Hyperglycemia (>5.0mmole/litre but <7.8mmole/litre)	36 (60%)	24 (40%)	60 (100%)
Moderate Hyperglycemia (FBS 7.8-11.1mmole/litre)	684 (79.2%)	180 (20.8%)	864 (100%)
Severe Hyperglycemia (FBS>11.1mmmole/litre)	120 (43.5%)	156 (56.5%)	276 (100%)

4.2 Relationship between Socio-economic Status, Affordability and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.2.1 Distribution of Subjects according to Average Income per Month, Level of Education Attained Type of Housing, Family Size/Number of Dependants and Subjects' Assessment of Their Nutrition Based on Balance Nature of Diet.

About 178 (14.8%) out of 1200 subjects earn below N7, 500 (National Minimum Wage) monthly while 275 (22.9%) earn between N7, 500 – N15, 000, 352 (29.4%) earn between N15, 000 - N30, 000 and 395 (32.9%) earn above N30, 000 monthly.

Almost 262 (21.8%) out of 1200 subjects had no formal education while 426 (35.5%), 315 (26.3%) and 197 (16.4%) had primary, secondary and tertiary/above education respectively.

Only 117 (9.8%) out of 1200 subjects live in single room apartment while 383 (31.9%), 345 (28.8%) and 355 (29.5%) live in room and parlour, two bedroom and three bedroom/above apartments respectively.

Almost 262 (21.8%) out of 1200 subjects had family size/dependants greater than 10 while 670 (55.8%) and 268 (22.4%) had family size/dependants between 6-10 and 2-5 respectively. None (0.0%) had family size/dependant of 1.

About 539 (44.9%) out of 1200 subjects assessed their nutrition to be unsatisfactory while 228 (19.0%), 432 (36.0) and 1 (0.1%) assessed their nutrition to be fairly satisfactory, satisfactory and very satisfactory respectively in terms of balance nature of diet.

Table 11: Distribution of Subjects according to Average Income per Month, Level of Education Attained, Type of Housing, Family Size/Number of Dependants and Subjects' Assessment of their Nutrition Based on Balance Nature of Diet

Average Income per Month	Level of Education Attained	Type of Housing	Family Size/ Dependants	Nutrition
<N7,5000 178 (14.8%)	No Formal Education 262 (21.8%)	Single Room 117 (9.8%)	.>10 262 (21.8%)	Unsatisfactory 539 (44.9%)
N7,500-N15,000 275 (22.9%)	Primary 426 (35.5%)	Room and Palour 383(31.9%)	6-10 670 (55.8%)	Fairly Satisfactory 228 (19.0%)
N15,000-N30,000 352 (29.4%)	Secondary 315 (26.3%)	Two Bedroom Apartments 345 (28.8%)	2-5 268 (22.4%)	Satisfactory 432 (36.0%)
>N30,000 395 (32.9%)	Tertiary and Above 197 (16.4%)	Three Bedroom Apartments and Above 355 (29.5%)	1 0 (0%)	Very Satisfactory 1 (0.1%)
Total 1200 (100%)	**Total** 1200 (100%)	**Total** 1200 (100%)	**Total** 1200 (100%)	**Total** 1200 (100%)

4.2.2 Distribution of Subjects according to Accessibility to Portable Water, Type of Healthcare Facility Accessible, Type of Communication Facility Accessible, Usual Means of Transportation and Electric Power Supply

About 498 (41.5%) out of 1200 subjects rarely have supply of portable water while 263 (21.9%), 315 (26.3%) and 124 (10.3%) have supply of portable water monthly, weekly and everyday respectively.

Almost 263 (21.9%) out of 1200 subjects patronize Traditional healers while 540 (45.0%) and 397 (33.1%) patronize health centers and hospitals respectively for their healthcare.

Approximately 384 (32.0%) out of 1200 subjects had postal services as their frequent means of communication while 746 (62.2%), 70 (5.8%) and none (0.0%) had telephone, e-mail/internet and fax as their frequent means of communication respectively.

All the 1200 subjects (100.0%) use road as their usual means of transportation.

608 (50.7%) out of 1200 subjects had no supply of electric power while 465 (38.7%), 127 (10.6%) and none (0.0%) had irregular, regular and very regular supply of electric power respectively.

Table 12: Distribution of Subjects according to Accessibility to Portable Water, Type of Healthcare Facility Accessible, Type of Communication Facility Accessible, Usual Means of Transportation and Electric Power Supply

Supply of Portable Water	Healthcare Facility	Frequent Means of Communication	Usual Means of Transportation	Electric Power Supply
Rarely	Not Available	Postal Services	Water	Not Available
498 (41.5%)	0 (0.0%)	384 (32.0%)	0 (0.0%)	608 (50.7%)
Monthly	Traditional Healer	Telephone (G.S.M)	Rail	Irregular
263 (21.9%)	263 (21.9%)	746 (62.2%)	0 (0.0%)	465 (38.7%)
Weekly	Health Center	E-mail/Internet	Road	Regular
315 (26.3%)	540 (45.0%)	70 (5.8%)	1200 (100.0%)	127 (10.6%)
Everyday	Hospital	Fax	Air	Very Regular
124 (10.3%)	397 (33.1%)	0 (0.0%)	0 (0%)	0 (0.0%)
Total	**Total**	**Total**	**Total**	**Total**
1200 (100%)	1200 (100%)	1200 (100%)	1200 (100%)	1200 (100%)

4.2.3 Distribution of Subjects according to Socio-economic Status

Majority, 760 (63.3%) out of 1200 subjects were poor while 440 (36.7%) were non-poor. There was a statistically significant difference in the proportion of poor and non-poor subjects*.

Table 13: Distribution of Subjects According to Socio-economic Status

Poverty Summary	**Frequency**	**Percent**
Poor	760	63.3
Non-poor	440	36.7
Total	1200	100.0

*(χ^2 = 12.5; df = 1; p = 0.0004)

4.2.4 Distribution of Subjects according to Affordability of Available Prescribed Drugs

Most, 721 (60.1%) out of 1200 subjects could not afford one anti-diabetic drug or the other while 479 (39.9%) could afford all available prescribed anti-diabetic drugs.

There was a statistically significant difference in the proportion of subjects that could afford all available prescribed anti-diabetic drugs and those that could not afford one anti-diabetic drug or the other*.

Table 14: Distribution of Subjects according to Affordability of Available Prescribed Anti-Diabetic Drugs

Affordability	**Frequency**	**Percent**
Yes (afford all available prescribed anti-diabetic drugs)	479	39.9
No (could not afford atleast one of the available prescribed anti-diabetic drugs)	721	60.1
Total	1200	100.0

*($\chi^2 = 46.96$; df = 1; p = 0.0000)

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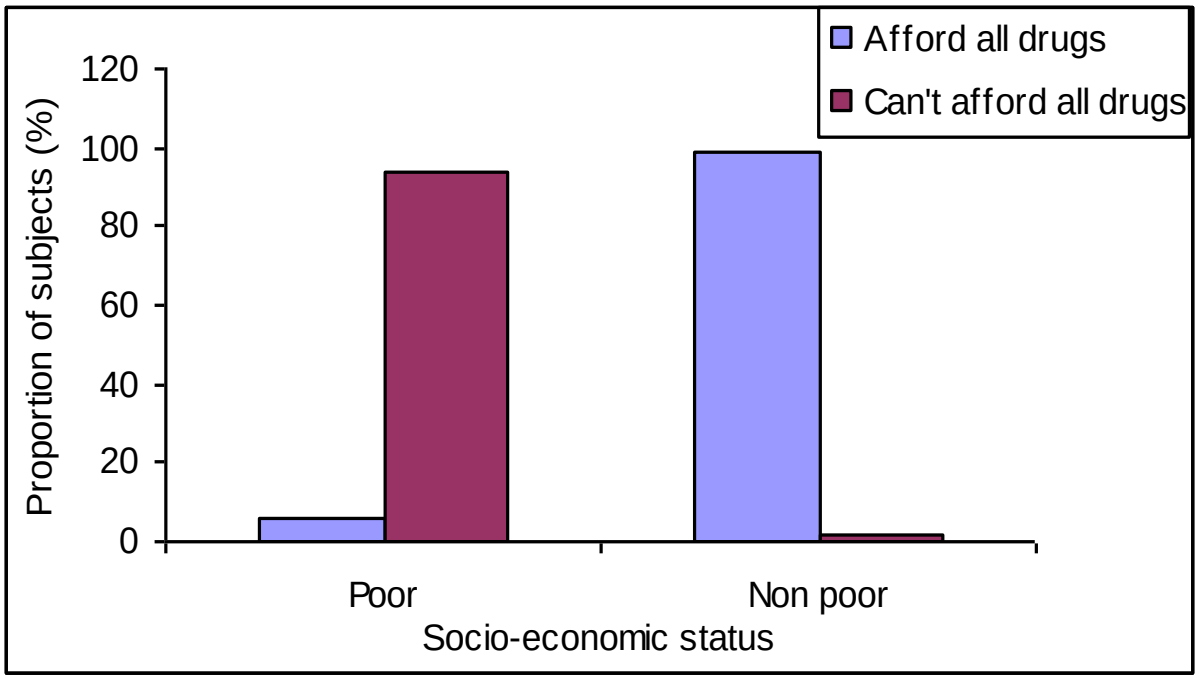
4.2.5 Relationship between Socio-economic Status of Subjects and Affordability of Available Prescribed Anti-Diabetic Drugs

Majority, 715 (93.8%) out of the 762 poor subjects could not afford one anti-diabetic drug or the other while 47 (6.2%) could afford all available prescribed anti-diabetic drugs. Most, 432 (98.6%) out of 438 non-poor subjects could afford all available prescribed anti-diabetic drugs while 6 (1.4%) could not afford one anti-diabetic drug or the other. Poor and non-poor subjects significantly differ in affordability of anti-diabetic drugs*.



*(χ^2 = 169.7, df = 1, p = 0.000).

Figure 1: Relationship between Socio-economic Status of Subjects and Affordability of Available Prescribed Drugs

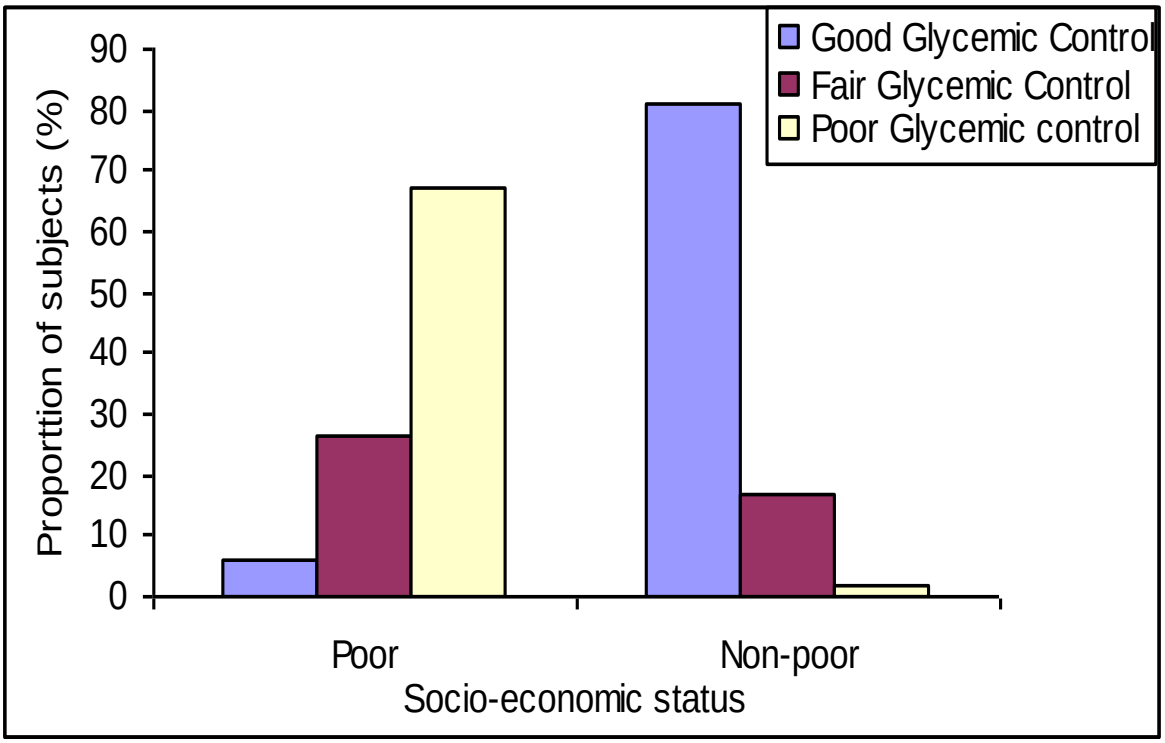
Can't afford all drugs = could not afford atleast one of the prescribed anti-diabetic drugs.

4.2.6 Relationship between Socio-economic Status and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Majority, 514 (67.4%) out of 762 poor subjects had poor glycemic control while 201 (26.4%) and 47 (6.2%) had fair and good glycemic control respectively.

Almost 356 (81.3%) out of 438 non-poor subjects had good glycemic control while 74 (16.9%) and 8 (1.8%) had fair and poor glycemic control respectively.

Poor and non-poor subjects significantly differ in glycemic control (outcome of anti-diabetic therapy)



*(χ^2 = 128.77; df = 2; p = 0.000).

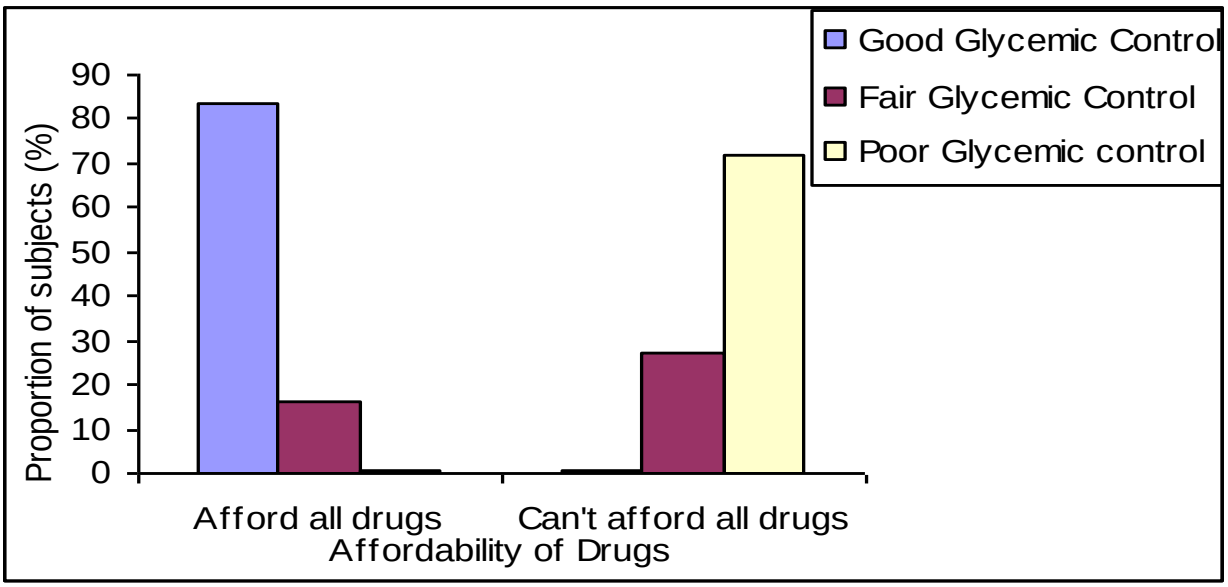
Figure 2: Relationship between Socio-economic Status and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.2.7 Relationship between Drug Affordability and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Majority, 399 (83.3%) out of 479 subjects that could afford all available prescribed anti-diabetic drugs had good glycemic control while 78 (16.3%) and 2 (0.4%) had fair and poor glycemic control respectively.

Almost 520 (72.1%) out of 721 subjects that could not afford at-least one of the available prescribed anti-diabetic drugs had poor glycemic control while 197 (27.3%) and 4 (0.6%) had fair and good glycemic control respectively.

Subjects that could afford all their drugs and those who could not, significantly differ in glycemic control (outcome of anti-diabetic therapy)*.



*(χ^2 = 154.86; df = 2; p = 0.000).

Figure 3: Relationship between Drug Affordability and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Can't afford all drugs = could not afford atleast one of the prescribed anti-diabetic drugs.

4.3 Cost of Illness Analysis (CIA)

4.3.1 Total Cost per year of Individual Drug for the 96 Diabetic Patients on Oral Agents

The total cost per year of individual drug for the 96 diabetics patients on oral agents and corresponding percentage of total drug cost to the 96 diabetic patients on oral agents are: N440, 780 (16.0%), N6, 768 (0.2%), N483, 560 (17.6%), N1, 185,730 (43.1%), N506, 863 (18.4%), N39, 900 (1.4%), N68, 000 (2.5%), N2, 550 (0.1%), N9,100 (0.3%) and N10, 033.95 (0.4%) for glibenclamide, chlopropamide, metformin, lisinopril, nifedipine, methyldopa, captopril, frusemide, hydrochloro-thiazide and aspirin respectively.

Table 15: Total Cost per year of Individual Drug for the 96 Diabetic Patients on Oral Agents

Drug	Total Cost/Year Naira ($)	% of Total Drug Cost	% of Annual Cost of Illness	No. Patients involved	% of Patients involved
Glibenclamide	440,780 (2938.53)	16.0	12.0	94	97.9
Chlopropamide	6,768 (42.24)	0.2	0.2	2	2.1
Metformin	483,560 (3223.73)	17.6	13.1	90	93.8
Lisinopril	1,185,730 (7904.87)	43.1	32.2	84	87.5
Nifedipine	506,863 (3379.09)	18.4	13.8	37	38.5
Methyldopa	39,900 (266)	1.4	1.1	12	12.5
Captopril	68,000 (453.33)	2.5	1.8	11	11.5
Frusemide	2,550 (17)	0.1	0.1	10	10.4
Hydrochloro-thiazide	9,100 (60.67)	0.3	0.2	7	7.3
Aspirin	10,033.95 (66.89)	0.4	0.3	90	93.8
Total	2,753,284 (18,352.35)	100.0	74.8		

4.3.2 Annual Cost of Illness for the 96 Diabetic Patients on Oral Agents

The annual cost of illness for the 96 diabetic patients on oral agents was N3, 678,384.95, with drug, diagnostic/monitoring tests, transport and peronnel cost components of N2, 753,284.95 (74.9%), N150, 000 (4.1%), N525, 000 (14.3%) and N250, 100 (6.7%) respectively.

Table 16: Annual Cost of Illness for the 96 Diabetic Patients on Oral Agents

Cost Component	**Total Cost Naira ($)**	**% of Annual Cost of Illness**
Drug	2,753,284.95 (18,352.35)	74.9
Diagnostic/Monitoring Tests	150,000 (1,060)	4.1
Transport	525,000 (3,500)	14.3
Personnel	250,100 (1,667.33)	6.7
Total (Annual Cost of Illness)	3,678,384.95 (24, 579.68)	100.0

4.3.3 Total Cost per year of Individual Drug for the 24 Patients on Insulin

The total cost per year of individual drug for the 24 diabetics patients on insulin and corresponding percentage of total drug cost to the 24 diabetic patients on insulin are: N1, 636,000 (94.0%), N38, 560 (2.2%), N64, 100 (3.7%) and N978.00 (0.1%) for insulin, metformin, lisinopril and aspirin respectively.

Table 17: Total Cost per year of Individual Drug for the 24 Patients on Insulin

Drug	**Total Cost Naira ($)**	**% of Total Drug Cost**	**% of Total Cost of Illness**	**No. of Patients involved**	**% of Patients involved**
Insulin	1,636,000 (10,906.67)	94.0	78.9	24	100.0
Metformin	38,560 (257.07)	2.2	1.9	18	75.0
Lisinopril	64,100 (427.33)	3.7	3.1	8	33.3
Aspirin	978 (6.52)	0.1	0.1	12	50.0
Total	1,739,538 (11,579.59)	100.0	84.0		

4.3.4 Annual Cost of Illness for the 24 Patients on Insulin

The annual cost of illness for the 24 diabetic patients on insulin was N2, 072,538, with drug, diagnostic/monitoring tests, transport and personnel cost components of N1,739,538 (84.0%), N37, 500 (1.8%), N233, 000 (11.2%) and N62, 500 (3.0%) respectively.

Table 18: Annual Cost of Illness for the 24 Patients on Insulin

Cost Component	Total Cost Naira ($)	% of Annual Cost of Illness
Drug	1,739,538 (11,597.59)	84.0
Diagnostic/Monitoring Tests	37,500 (250)	1.8
Transport	233,000 (1,553.33)	11.2
Personnel	62,500 (416.67)	3.0
Total (Annual Cost of Illness)	2,072,538 (13,817.59)	100.0

4.4 Cost Minimization Analysis (CMA)

4.4.1 Anti-Diabetic Drugs Utilization: Prescriptions, Availability and Affordability

Almost 1242 (78.6%) out of 1580 anti-diabetic drugs prescriptions were in branded names while 338 (21.4%) were in generic names. There was a significant difference in these proportions*.

All, 1580 (100%) of prescribed branded and generic equivalent anti-diabetic drugs were available, none were out of stock in UMTH Pharmacy.

Subjects were able to afford more prescribed generic anti-diabetic drugs, 329 (97.3%) out of 338 times compared with 802 (64.6%) out of 1242 times for branded. The difference was statistically significant**.

Table 19: Anti-Diabetic Drugs Utilization: Prescriptions, Availability and Affordability

	Frequency of Prescription			**Available**				
				Generic	**Branded**	**Generic**	**Branded**	
Drug Prescribed	Generic	Branded	Total	Yes	Yes	No	No	
Metformin	148	568	716	148 (100%)	568 (100%)	0 (0%)	0 (0%)	1
Chlopropamide	16	66	82	16 (100%)	66 (100%)	0 (0%)	0 (0%)	
Glibenclamide	174	608	782	174 (100%)	608 (100%)	0 (0%)	0 (0%)	1
Total	338 (21.4%)	1242 (78.6%)	1580 (100%)	338 (100%)	1242 (100%)	0 (0%)	0 (0%)	3
Chi-square	χ^2 =64.98; df=1; p =0.000							

*(χ^2 =64.98; df=1; p =0.000)
**(χ^2 =31.22; df=1; p = 0.000).

4.4.2 Identified Treatment Options for Cost Minimization Analysis in Type II Diabetes Mellitus in UMTH

Branded Products were more frequently prescribed than generic equivalent products for all anti-diabetic drugs used. There was a statistically significant difference in the frequency of prescription of branded and generic anti-diabetic drugs for Metformin*, Chlopropamide** and Glibenclamide*** respectively.

Table 20: Identified Treatment Options for Cost Minimization Analysis in Type II Diabetes Mellitus in UMTH **Multiple Response n=1580**

	Option I Generic	**Option II Branded**	**Total**	**Chi- square**
Anti-Diabetic Drug	**Frequency of Prescription**	**Frequency of Prescription**	**Frequency of Prescription**	
a. Metformin	148 (20.7%)	568 (79.3%)	716 (100%)	* χ^2=64.98; df=1; P=0.000
b. Chlopropamide	16 (19.5%)	66 (80.5%)	82 (100%)	** χ^2=74.42; df=1; P=0.000
c. Glibenclamide	174 (22.3%)	608 (77.7%)	782 (100%)	*** χ^2=60.50; df=1; P=0.000

4.4.3 Cost Minimization Analysis

Cost Minimization Analysis (CMA) was carried out by calculating and comparing the mean cost per defined daily dose (DDD) of two options that are assumed to have the same outcome (Branded and Generic Products) to identify the lowest cost option.

This was carried out for all anti-diabetic drugs where branded and generic equivalent products were found to be used

in UMTH.

4.4.3.1 Mean Cost/DDD of Anti-Diabetic Drugs

Students' t-test showed that there was a statistically significant difference in the mean cost per DDD of branded and generic equivalent product for all anti-diabetic drugs applicable for cost minimization analysis.

Table 21: Mean Cost/DDD of Anti-Diabetic Drugs

	DDD	**Mean Cost /DDD (Naira)**		**Students' t-test**
		Generic	**Branded**	
a. Metformin	1.5gm daily	15.0 ± 0.15 (n =148)	30.0 ± 1.9 (n=568)	t=185.87; df=714; P<0.05
b. Chlopropamide	250mg daily	7.50 ± 0.1 (n=16)	30.0 ± 2.5 (n=66)	t=72.08; df=80; P<0.05
c. Glibenclamide	5mg daily	5.0 ± 0.2 (n=174)	12.50 ±2.8 (n=608)	t=66.08; df=780; P<0.05

4.4.3.2 Sensitivity Analysis for Cost Minimization Analysis of Antidiabetic Drugs

Sensitivity Analysis was performed to test whether the decision changes when specific variables (e.g. Mean Cost/DDD) were altered within reasonable range in favour of higher cost options.

Sensitivity Analysis (what 'if' analysis) indicates that the decision is still valid, showing that generic products are lower cost options to branded equivalents for all anti-diabetic drugs applicable for cost minimization analysis.

Table: 22: Sensitivity Analysis for Cost Minimization Analysis of Anti-Diabetic Drugs

Alteration in Variable	**Mean Cost/DDD (Naira)**
i. Increasing the Mean Cost/DDD of Generic Chlopropamide Tablet by 25% (N1.88)	9.38
ii. Decreasing the Mean Cost/DDD of Branded Chlopropamide Tablet by 25% (7.50)	22.50
iii. Increasing the Mean Cost/DDD of Generic Glibenclamide Tablet by 25% (N1.25)	6.25
iv. Decreasing the Mean Cost/DDD of Branded Glibenclamide by 25% (N3.13)	9.37
v. Increasing the Mean Cost/DDD of Generic Metformin Tablet by 25% (N3.75)	18.75
vi. Decreasing the Mean Cost/DDD of Branded Metformin Tablet by 25% (N7.50)	22.50

4.5 Cost Effectiveness Analysis (CEA)

4.5.1 Anti-Diabetic Drugs Utilization/Identified Treatment Options for Cost Effectiveness Analysis in UMTH

Twenty Four (2%) and 36 (3%) out of 1,200 subjects were managed with diet/lifestyle modification only (for mild hyperglycemia in non-obese Type II DM) and metformin only (for mild hyperglycemia in obese Type II DM) respectively.

Almost 150 (81.5%) out of 184 non-obese subjects with moderate hyperglycemia were managed with glibenclamide tablet monotherapy while 34 (18.5%) were managed with chlopropamide tablet monotherapy. There was a significant difference in this distribution.

Almost 632 (92.9%) out of 680 obese Type II diabetes mellitus patients with moderate hyperglycemia were managed with metformin + glibenclamide combination therapy while 48 (7.1%) were managed with metformin + chlopropamide combination therapy.

Almost 90 (57.7%) out of 156 non-obese Type II diabetes mellitus patients with severe hyperglycemia were managed with soluble insulin + insulin zinc suspension while 66 (42.3%) were managed with biphasic isophane insulin. There was a significant difference in the proportions.

Ninety (75%) out of 120 obese Type II diabetes mellitus patients with severe hyperglycemia were managed with soluble insulin + insulin zinc suspension + metformin while 30 (25%) were managed with biphasic isophane insulin + metformin. There was a significant difference in these proportions.

Overall, 900 (75%) of the subjects were managed with oral hypoglycemic agents.

Table 23: Anti-Diabetic Drugs Utilization/Identified Treatment Options for Cost Effectiveness Analysis in UMTH

Condition	Frequency of Anti-Diabetic Drugs Used		Total	Chi-Square Analysis
Mild Hyperglycemia in Non-obese DM	**Diet and Lifestyle Modification Only** 24 (100%)		24 (100%)	
Mild Hyperglycemia in Obese DM	**Metformin Only** 36 (100%)		36 (100%)	
Moderate Hyperglycemia in Non-obese DM	**Chlopropamide** 34 (18.5%)	**Glibenclamide** 150 (81.5%)	184 (100%)	χ^2 =79.38; df=1; p =0.0000
Moderate Hyperglycemia in Obese DM	**Metformin + Chlopropamide** 48 (7.1%)	**Metformin + Glibenclamide** 632 (92.9%)	680 (100%)	χ^2=144.50; df=1; p =0.0000
Severe Hyperglycemia in Non-obese DM	**Soluble Insulin + Insulin Zinc** 90 (57.7%)	**Biphasic Isophane Insulin** 66 (42.3%)	156 (100%)	χ^2 =4.50; df=1; p =0.034
Severe Hyperglycemia in Obese DM	**Soluble Insulin + Insulin Zinc + Metformin** 90 (75%)	**Biphasic Isophane Insulin+Metformin** 30 (25%)	120 (100%)	χ^2 =48.02; df=1; p =0.0000

4.5.2 Distribution of Glycemic Control According to Treatment Option of Each Subject.

Nineteen (55.8%) out of 34 and 107 (71.3%) out of 150 subjects respectively managed with chlopropamide monotherapy and glibenclamide monotherapy had good glycemic control, but the occurrence of good glycemic control with glibenclamide, 71.3% was significantly higher than with chlopropamide, 55.8% *.

Eighteen (50.0%) out of 36 subjects managed with metformin monotherapy had good glycemic control, while 6 (16.7%) and 12 (33.3%) had poor and fair glycemic control respectively. There was a statistically significant difference in these proportions**.

There was no significant difference in the proportions of subjects that had good, fair and poor glycemic control with metformin + chlopropamide combination therapy***.

There was a significant difference in the proportions of subjects that had good, fair and poor glycemic control with metformin + glibemclamide combination****.

Sixty (66.7%) out of 90 subjects managed with soluble insulin + insulin zinc combination had poor glycemic control while 27 (30.0%) and 3 (3.3) had fair and good glycemic control respectively. There was a significant difference in these proportions*****.

Twenty One (31.25%) out of 66 subjects managed with biphasic isophane insulin had poor glycemic control while 16 (25%) and 29 (43.75%) had fair and good glycemic control respectively. There was a statistically significant difference in these proportions******.

Diet and lifestyle modification only had 75% (18 out of 24 subjects) occurrence of good glycemic control and 25% (6 out of 24 subjects) occurrence of fairly controlled glycemia, with no occurrence of poor glycemic control. There was a significant difference in these proportions*******.

Almost 523 (43.6%) out 1200 subjects had poor glycemic control based on monitoring test while 274 (22.8%) and 403 (33.6%) had fair and good glycemic control respectively. There was a significant difference in these proportions********.

Table 24: Distribution of Glycemic Control According to Treatment Option of Each Subject.

n = 1200

Treatment Option	Glycemic Control				Chi-Square Analysis
	Poor FBS>7.0mMole/L HbAlc> 10%	**Fair FBS>6 & < 7mMole/L HbAlc> 7% < 10%**	**Good FBS< 6.0mMole/L HbAlc> 7%**	**Total**	
Chlopropamide Monotherapy	4 (11.8%)	11 (32.4%)	19 (55.8%)*	34 (100%)	χ^2 =43.68; df =2; p =0.0000
Glibenclamide Monotherapy	6 (4%)	37 (24.7%)	107 (71.3%)*	150 (100%)	χ^2 =105.69; df =2; p =0. 0000
Metformin Monotherapy	6 (16.7%)	12 (33.3%)	18 (50.0%)	36 (100%)	** χ^2 =24.51; df =2; p =0.000005
Metformin + Chlopropamide	18 (37.5%)	12 (25.0%)	18 (37.5%)	48 (100%)	*** χ^2 =4.71; df =2; p=0.09
Metformin + Glibenclamide	324 (51.3%)	130 (20.5%)	178 (28.2%)	632 (100%)	**** χ^2 =20.58; df =2; p =0.00003
Soluble Insulin + Insulin Zinc	60 (66.7%)	27 (30.0%)	3 (3.3%)	90 (100%)	***** χ^2 =92.91; df =2; p =0.0000
Biphasic Isophane Insulin	21 (31.25%)	16 (25%)	29 (43.75%)	66 (100%)	****** χ^2 =14.38; df =2; p =0.0008
Soluble Insulin + Insulin Zinc + Metformin	75 (83.3%)	15 (16.7%)	0 (0%)	90 (100%)	χ^2 = 173.01; df =2; p =0.0000
Biphasic Isophane Insulin + Metformin	9 (30%)	8 (27%)	13 (43.3%)	30 (100%)	χ^2 =4.90; df= 2; p= 0.08
Diet and lifestyle Modification only	0	6 (25%)	18 (75%)	24 (100%)	******* χ^2 = 131.25; df =2; p =0.000

Total	**523 (43.6%)**	**274 (22.8%)**	**403 (33.6%)**	**1200 (100%)**	******** χ^2 = 9.93; df =2; p =0.007

*(χ^2 =4.23, df=1, p =0.04)

4.5.3 Cost Effectiveness Analysis (CEA) of Chlopropamide and Glibenclamide in the Management of Moderate Hyperglycemia in Non-Obese Type II Diabetes Mellitus Patients

There was no statistically significant difference in the effectiveness of chlopropamide and glibenclamide tablet.

Glibenclamide cost less (N1.76) per unit of effectiveness while chlopropamide cost more (N2.97) per unit of effectiveness. Glibenclamide therefore appeared to be more cost effective than chlopropamide in the management of moderate hyperglycemia in non-obese Type II diabetes mellitus patients.

Table 25: Cost Effectiveness Analysis (CEA) of Chlopropamide and Glibenclamide in the Management of Moderate Hyperglycemia in Non-Obese Type II Diabetes Mellitus Patients

Treatment Option	**Total Cost (C) in Naira**	*** Effectiveness (E)**	**CEA (C/E)**
Option I Chlopropamide Tablet 250 mg o.d x 1/12	225.00	75.66	N2.97/ Unit of Effectiveness
Option II Glibenclamide Tablet 5 mg o.d x 1/12	150.00	85.0	N1.76/Unit of Effectiveness

*(χ^2=2.04; df=1; p =0.153)

4.5.4 Sensitivity Analysis for CEA of Chlopropamide and Glibenclamide in the Management of Moderate Hyperglycemia in Non-Obese Type II Diabetes Mellitus Patients

Sensitivity Analysis was performed to test whether the decision changes when specific variables (e.g. cost or effectiveness) were altered within reasonable range in favour of less cost effective option (chlopropamide).

Sensitivity Analysis indicates that the decision remain valid, confirming glibenclamide to be more cost effective.

Table 26: Sensitivity Analysis for CEA of Chlopropamide and Glibenclamide in the Management of Moderate Hyperglycemia in Non-obese Type II Diabetes Mellitus Patients

Alteration in Variable	**CEA**
i. Decreasing the Cost of Chlopropamide by 25% (N56.25)	N2.23/unit of effectiveness
ii. Increasing the Effectiveness of Chlopropamide by 25% (18.91)	N2.38/unit of effectiveness
iii. Increasing the Cost of Glibenclamide by 25% (N37.5)	N2.21/unit of effectiveness
iv. Decreasing the Effectiveness of Glibenclamide by 25% (21.25)	N2.35/unit of effectiveness

4.5.5 Cost Effectiveness Analysis (CEA) of Metformin + Chlopropamide and Metformin + Glibenclamide in the Management of Moderate Hyperglycemia in Obese Type II Diabetes Mellitus Patients

There was no statistically significant difference in the effectiveness of metformin + chlopropamide and metformin + glibenclamide*. Metformin + Glibenclamide cost less (N7.63) per unit of effectiveness while metformin + chlopropamide cost more (N9.74) per unit of effectiveness. Metformin + Glibenclamide therefore appeared to be more cost effective than metformin + chlopropamide in the management of moderate hyperglycemia in obese Type II diabetes mellitus patients.

Table 27: Cost Effectiveness Analysis (CEA) of Metformin + Chlopropamide and Metformin + Glibenclamide in the Management of Moderate Hyperglycemia in Obese Type II Diabetes Mellitus Patients

Treatment Option	**Total Cost (C) in Naira**	***Effectiveness (E)**	**CEA (C/E)**
Option I Metformin Tablet 500 mg tid x 1/12 + Chlopropamide Tablet 250 mg o.d x 1/12	675.00	69.33	N9.74/unit of effectiveness
Option II Metformin Tablet 500 mg tid x 1/12 + Glibenclamide Tablet 5 mg o.d x 1/12	600.00	78.67	N7.63/unit of effectiveness

*(χ^2 =2.10; df=1; p = 0.147).

4.5.6 Sensitivity Analysis for CEA of Metformin + Chlopropamide and Metformin + Glibenclamide in the Management of Moderate Hyperglycemia in Obese Type II Diabetes Mellitus Patients

Sensitivity Analysis indicates that the decision becomes invalid, showing that metformin + glibenclamide combination was not necessarily more cost effective than metformin + chlopropamide.

Table 28: Sensitivity Analysis for CEA of Metformin + Chlopropamide and Metformin + Glibenclamide in the Management of Moderate Hyperglycemia in Obese Type II Diabetes Mellitus Patients

Alteration in Variable	**CEA**
i. Decreasing the Cost of Metformin + Chlopropamide by 25% (N168.75)	N7.30/unit of effectiveness
ii. Increasing the Effectiveness of Metformin + Chlopropamide by 25% (17.33)	N7.79/unit of effectiveness
iii. Increasing the Cost of Metformin + Glibenclamide by 25% (150)	N9.53/unit of effectiveness
iv. Decreasing the Effectiveness of Metformin + Glibenclamide by 25% (19.67)	N10.17/unit of effectiveness

4.5.7 Cost Effectiveness Analysis (CEA) of Soluble Insulin + Insulin Zinc and Biphasic Isophane Insulin in the Management of Severe Hyperglycemia in Non-Obese Type II Diabetes Mellitus

There was no statistically significant difference in the effectiveness of soluble insulin + insulin zinc and biphasic isophane insulin*.

Soluble insulin + insulin zinc cost more (N30.37) per unit of effectiveness while biphasic isophane insulin cost less (N12.65) per unit of effectiveness. Biphasic Isophane Insulin therefore appeared to be more cost effective than soluble insulin + insulin zinc in the management of serve hyperglycemia in non-obese Type II diabetes mellitus patients.

Table 29: Cost Effectiveness Analysis (CEA) of Soluble Insulin + Insulin Zinc and Biphasic Isophane Insulin in the Management of Severe Hyperglycemia in Non-Obese Type II Diabetes Mellitus

Treatment Option	**Total Cost (C) in Naira**	***Effectiveness (E)**	**CEA (C/E)**
Option I Soluble Insulin 20 i.u tid x 2/52 + Insulin Zinc 10 i.u o.d x 2/52	2,450.00	80.67	N30.37/unit of effectiveness
Option II Biphasic Isophane Insulin 20 i.u am, 10 i.u pm	1,050	83.0	N12.65/unit of effectiveness

*(χ^2 =0.03; df=1; p = 0.854)

4.5.8 Sensitivity Analysis for CEA of Soluble Insulin + Insulin Zinc and Biphasic Isophane Insulin in the Management of Severe Hyperglycemia in Non-Obese Type II Diabetes Mellitus

Sensitivity analysis indicates that the decision remain valid, confirming biphasic isophane insulin to be more cost effective.

Table 30: Sensitivity analysis for CEA of Soluble Insulin + Insulin Zinc and Biphasic Isophane Insulin in the Management of Severe Hyperglycemia in Non-Obese Type II Diabetes Mellitus

Alteration in Variable	**CEA**
i. Decreasing the Cost of Soluble Insulin + Insulin Zinc by 25% (N612.50)	N22.78/unit of effectiveness
ii. Increasing the Effectiveness of Soluble Insulin + Insulin Zinc to equal that of Biphasic Isophane Insulin (83.0)	N29.52/unit of effectiveness
iii. Increasing the Cost of Biphasic Isophane Insulin y 25% (N262.50)	N15.81/unit of effectiveness
iv. Decreasing the Effectiveness of Biphasic Isophane Insulin by 25% (20.75)	N16.87/unit of effectiveness

4.5.9 Cost Effectiveness Analysis (CEA) of Soluble Insulin + Insulin Zinc + Metformin and Biphasic Isophane Insulin + Metformin in the Management of Severe Hyperglycemia in Obese Type II Diabetes Mellitus

There was no statistically significant difference in the effectiveness of soluble insulin + insulin zinc + metformin and biphasic isophane insulin + metformin*.

.Soluble Insulin + Insulin Zinc + Metformin cost more (N34.45) per unit of effectiveness while biphasic isophane insulin + metformin cost less (N15.91) per unit of effectiveness. Biphasic Isophane Insulin + Metformin therefore appeared to be more cost effective than soluble insulin + insulin zinc + metformin in the management of serve hyperglycemia in obese Type II diabetes mellitus patients.

Table 31: Cost Effectiveness Analysis of Soluble Insulin + Insulin Zinc + Metformin and Biphasic Isophane Insulin + Metformin in the Management of Severe Hyperglycemia in Obese Type II Diabetes Mellitus

Treatment Option	**Total Cost (C) in Naira**	***Effectiveness (E)**	**CEA (C/E)**
Option I Soluble Insulin 20 i.u tid x 2/52 + Insulin Zinc 10 i.u o.d x 2/52 + Metformin Tablet 500 mg tid x 2/52	2,660.00	77.21	N34.45/unit of effectiveness
Option II Biphasic Isophane Insulin 20 i.u am, 10 i.u pm + Metformin Tab 500mg tid x 2/52	1,260	79.17	N15.91/unit of effectiveness

*(χ^2 =0.03; df = 1; p = 0.864)

4.5.10 Sensitivity Analysis for CEA of Soluble Insulin + Insulin Zinc + Metformin and Biphasic Isophane Insulin + Metformin in the Management of Severe Hyperglycemia in Obese Type II Diabetes Mellitus

Sensitivity Analysis indicates that the decision remain valid, confirming biphasic isophane insulin + metformin to be more cost effective than soluble insulin + insulin zinc + metformin

Table 32: Sensitivity Analysis for CEA of Soluble Insulin + Insulin Zinc + Metformin and Biphasic Isophane Insulin + Metformin in the Management of Severe Hyperglycemia in Obese Type II Diabetes Mellitus

Alteration in Variable	**CEA**
i. Decreasing the Cost of Soluble Insulin + Insulin Zinc + Metformin by 25% (N665.00)	N25.84/unit of effectiveness
ii. Increasing the Effectiveness of Soluble Insulin + Insulin Zinc + Metformin by 25% (19.30)	N27.56/unit of effectiveness
iii. Increasing the Cost of Biphasic Isophane Insulin + Metformin by 25% (N315)	N19.89/unit of effectiveness
iv. Decreasing the Effectiveness of Biphasic Isophane Insulin by 25% (19.79)	N21.22/unit of effectiveness

4.6 Relationship between Degree of Knowledge/Practice of Lifestyle/Dietary Modification and Outcome (Glycemic Control) of Anti-Diabetic Therapy

4.6.1 Knowledge about Lifestyle/Dietary Modification

4.6.1.1 Distribution of Subjects according to degree of Knowledge about Lifestyle/Dietary Modification

Three Hundred and Fifteen (26.3%), 90 (7.5%), 359 (29.9%) and 436 (36.6%) out of 1200 subjects had excellent, good, fair and poor knowledge about signs and symptoms of hyperglycemia respectively.

Three Hundred and Two (25.2%), 93 (7.7%), 356 (29.7%) and 449 (36.4%) out of 1200 subjects had excellent, good, fair and poor knowledge about signs and symptoms of hypoglycemia respectively.

Three Hundred and Forty (28.3%), 105 (8.8%), 317 (26.4%) and 438 (36.5%) out of 1200 of subjects had excellent, good, fair and poor knowledge about beneficial effects of exercise respectively.

About 313 (26.1%), 87 (7.2%), 355 (29.6%) and 445 (37.1%) out of 1200 subjects had excellent, good, fair and poor knowledge about dietary modification respectively.

Almost 310 (25.8%), 95 (7.9%), 364 (30.4%) and 431 (35.9%) out of 1200 subjects had excellent, good, fair and poor knowledge about lifestyle modification respectively.

Three Hundred and Eight (25.7%), 102 (8.5%), 366 (30.5%) and 424 (35.3%) out of 1200 subjects had excellent, good, fair and poor knowledge about complications associated with diabetes mellitus respectively.

Almost 318 (26.5%), 96 (8.0%), 365 (30.4%) and 421 (35.1%) out of 1200 subjects had excellent, good, fair and poor knowledge about their treatment respectively.

About 315 (26.3%), 90 (7.5%), 359 (29.9%) and 436 (36.6%) out of 1200 subjects had excellent, good, fair and poor practice of self monitoring respectively.

Subjects significantly* differ in degree of knowledge about signs and symptoms of hyperglycemia/hypoglycemia, beneficial effect of exercise, dietary modification, lifestyle modification, complications associated with diabetes mellitus, treatment and practice of self monitoring, with majority having poor knowledge in all cases and poor practice of self monitoring.

Table 33: Distribution of Subjects according to degree of Knowledge about Lifestyle/Dietary Modification

Item	**Excellent**	**Good**	**Fair**	**Poor**	**Total**	
	Frequency	**Frequency**	**Freq**uency	**Freq**uency	**Freq**uency	***Chi-Square Analysis**
Signs and Symptoms of Hyperglycemia	315(26.3%)	90 (7.5%)	359 (29.9%)	436 (36.3%)	1200 (100.0%)	χ^2 =23.25, df= 3, p=0.00004
Signs and Symptoms of Hypoglycemia	302 (25.2%)	93 (7.7%)	356 (29.7%)	449 (36.4%)	1200 (100.0%)	χ^2 =24.43, df=3, p= 0.00002
Beneficial Effect of Exercise	340 (28.3%)	105 (8.8%)	317 (26.4%)	438 (36.5%)	1200 (100.0%)	χ^2 =21.87, df=3, p= 0.00007
Dietary Modification	313 (26.1%)	87 (7.2%)	355 (29.6%)	445 (37.1%)	1200 (100.0%)	χ^2 =26.35, df=3, p= 0.000008
Lifestyle Modification	310 (25.8%)	95 (7.9%)	364 (30.4%)	431 (35.9%)	1200 (100.0%)	χ^2 =23.25, df= 3, p= 0.00004
Complications Associated with DM	308 (25.7%)	102 (8.5%)	366 (30.5%)	424 (35.3%	1200 (100.0%)	χ^2 =22.72, df=3, p= 0.00005
Treatment	318 (26.5%)	96 (8.0%)	365 (30.4%)	421 (35.1%)	1200 (100.0%)	χ^2 =22.81, df=3, p= 0.00004
Practice of Self Monitoring	315 (26.3%)	90 (7.5%)	359 (29.9%)	436 (36.3%)	1200 (100.0%)	χ^2 =23.25, df=3, p= 0.00004

4.6.2 Practice of Lifestyle Modification

4.6.2.1 Distribution of Subjects According to Frequency of Smoking

Two Hundred and Eighty Seven (23.9%) out of 1200 subjects never smoked while 594 (49.5%), 203 (16.9%) and 116 (9.7%) smoked occasionally, frequently and very frequently respectively.

Table 34: Distribution of Subjects according to Frequency of Smoking

Smoking	**Frequency**	**Percent**
Never (0)	287	23.9
Occasional (1-4 cigarette /week)	594	49.5
Frequently (1-4 cigarette/ day)	203	16.9
Very Frequently (5 and above cigarette /day)	116	9.7
Total	1200	100.0

4.6.2.2 Distribution of Subjects according to Frequency of Alcohol Intake

Two Hundred and Sixty Four (22.0%) out of 1200 subjects never drank alcohol while 618 (51.5%), 202 (16.8%) and 116 (9.7%) drank alcohol occasionally, frequently and very frequently respectively.

Table 35: Distribution of Subjects according to Frequency of Alcohol Intake

Alcohol Intake	**Frequency**	**Percent**
Never (0)	264	22.0
Occasional (1-2 bottle/week)	618	51.5
Frequently (1-4 bottle/day)	202	16.8
Very Frequently (5 and above bottle/day)	116	9.7
Total	1200	100.0

4.6.2.3 Distribution of Subjects according to Frequency of Exercise

Five Hundred and Eighty Five (48.8%) out of 1200 subjects never exercised (except essential exercise) while 285 (23.7%) and 330 (27.5%) exercised occasionally and daily respectively.

Table 36: Distribution of Subjects according to Frequency of Exercise

Exercise	**Frequency**	**Percent**
Never	585	48.8
Occasionally	285	23.7
Daily	330	27.5
Total	1200	100.0

4.6.3 Practice of Dietary Modification

4.6.3.1 Have you modified your diet after diagnosis of your diabetes mellitus (DM)?

All Subjects, 1200 (100.0%) responded to have modified their diet one way or the other after diagnosis of their diabetes mellitus

Table 37: Have you modified your diet after diagnosis of your DM?

Have you modified your diet after diagnosis of your DM?	**Frequency**	**Percent**
Yes	1200	100.0
No	0	0.0
Total	1200	100.0

4.6.3.2 Distribution of Subjects according to Practice of Dietary Modification by Food Type

Seven Hundred and Twenty Three (60.3%) out of 1200 subjects reduced carbohydrate intake while 477 (39.8%) did not change in carbohydrate intake after diagnosis of their diabetes mellitus.

One Hundred and Eighty One (15.1%) out of 1200 subjects reduced protein intake while 411 (34.3%) and 608 (50.7%) increased and did not change in their protein intake respectively.

Five Hundred and Sixty (46.7%) out of 1200 subjects reduced fat intake while 640 (53.3%) did not change in fat intake after diagnosis of their diabetes mellitus.

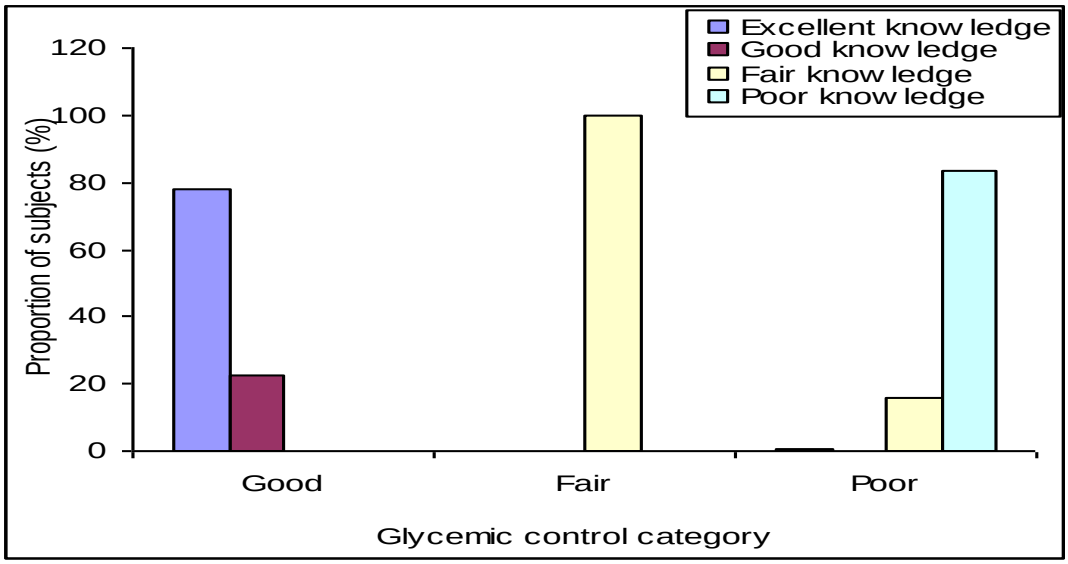
Table 38: Distribution of Subjects according to Practice of Dietary Modification by Food Type

Food Type	Reduce		Increase		Not Changed		Don't Know		Total	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Carbohydrate	723	60.3	0	0	477	39.8	0	0	1200	100.0
Protein	181	15.1	411	34.3	608	50.7	0	0	1200	100.0
Fat	560	46.7	0	0	640	53.3	0	0	1200	100.0

4.6.4 Relationship between Degree of Subjects' Knowledge about Signs and Symptoms of Hyperglycemia/Hypoglycemia, Beneficial Effect of Exercise, Lifestyle/Dietary Modification, Complications, Treatment, Practice of Self Monitoring and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.1 Relationship between Degree of Subjects' Knowledge about Signs and Symptoms of Hyperglycemia and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Three Hundred and Thirteen (77.7%) out of 403 subjects who had good glycemic control were those who had excellent knowledge about signs and symptoms of hyperglycemia. About 275 (100%) out of 275 and 436 (83.5%) out of 522 subjects who had fair and poor glycemic control were those who had fair and poor knowledge about signs and symptoms of hyperglycemia respectively. There was an association between degree of subjects' knowledge about signs and symptoms of hyperglycemia and glycemic control*.

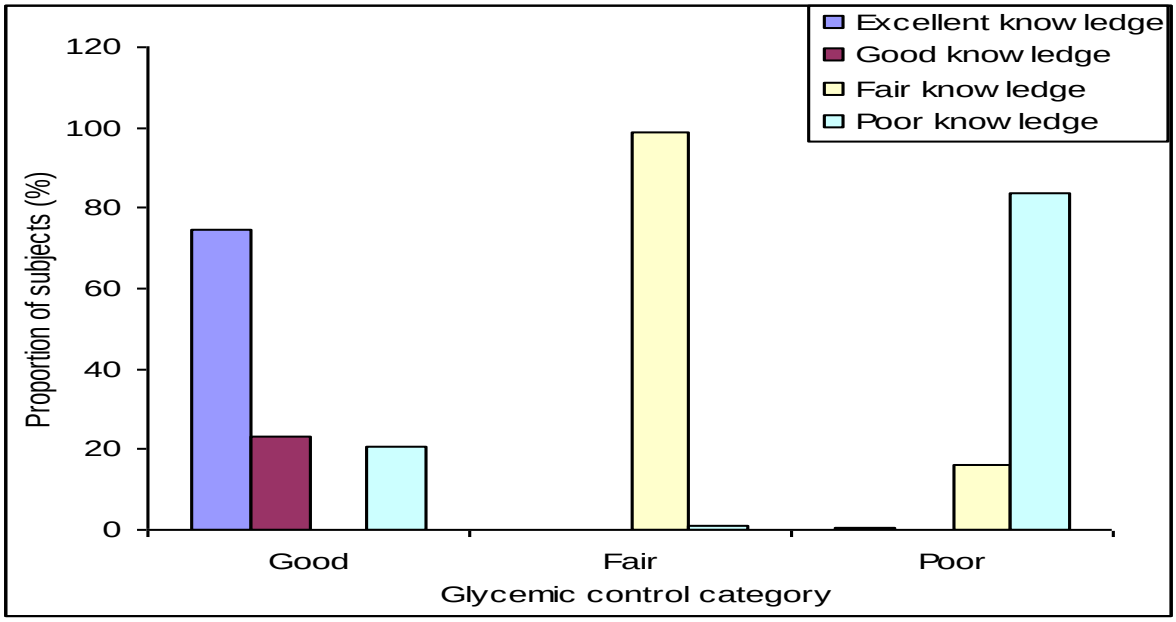


***(**χ^2=1960.8; df=6; p=0.000**).**

Figure 4: Relationship between Degree of Subjects' Knowledge about Signs and Symptoms of Hyperglycemia and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.2 Relationship between Degree of Subjects' Knowledge about Signs and Symptoms of Hypoglycemia and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Three Hundred (74.4%) out of 403 subjects who had good glycemic control were those who had excellent knowledge about signs and symptoms of hypoglycemia. Two Hunderd and Seventy Two (98.9%) out of 275 and 436 (83.5%) out of 522 subjects who had fair and poor glycemic control were those who had fair and poor knowledge about signs and symptoms of hypoglycemia respectively. There was an association between degree of subjects' knowledge about signs and symptoms of hypoglycemia and glycemic control*.

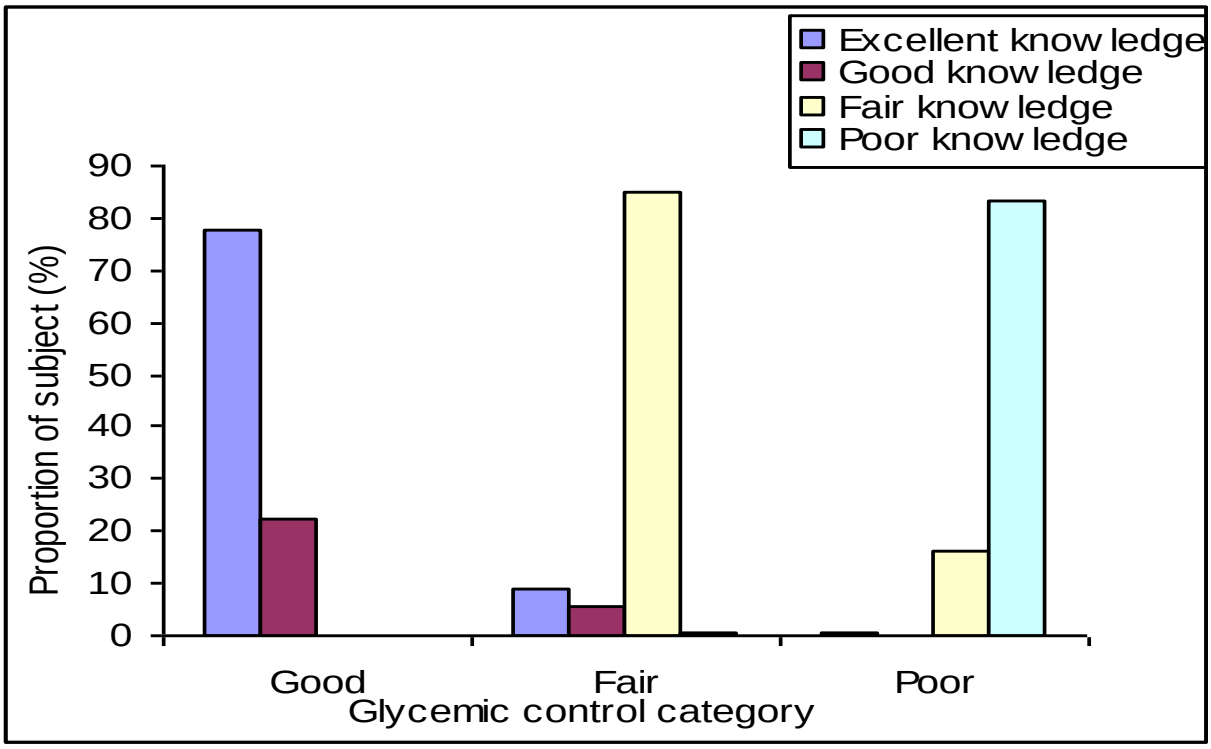


(χ^2 =1890.78; df = 6; p = 0.000**)**

Figure 5: Relationship between Degree of Subjects' Knowledge about Signs and Symptoms of Hypoglycemia and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.3 Relationship between Degree of Subjects' Knowledge about Beneficial Effect of Exercise and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Three Hundred and Thirteen (77.7%) out of 403, 233 (84.7%) out of 275 and 436 (83.5%) out of 522 subjects who had good, fair and poor glycemic control were those who had excellent, fair and poor knowledge about beneficial effect of exercise respectively. There was an association between degree of subjects' knowledge about beneficial effect of exercise and glycemic control*.

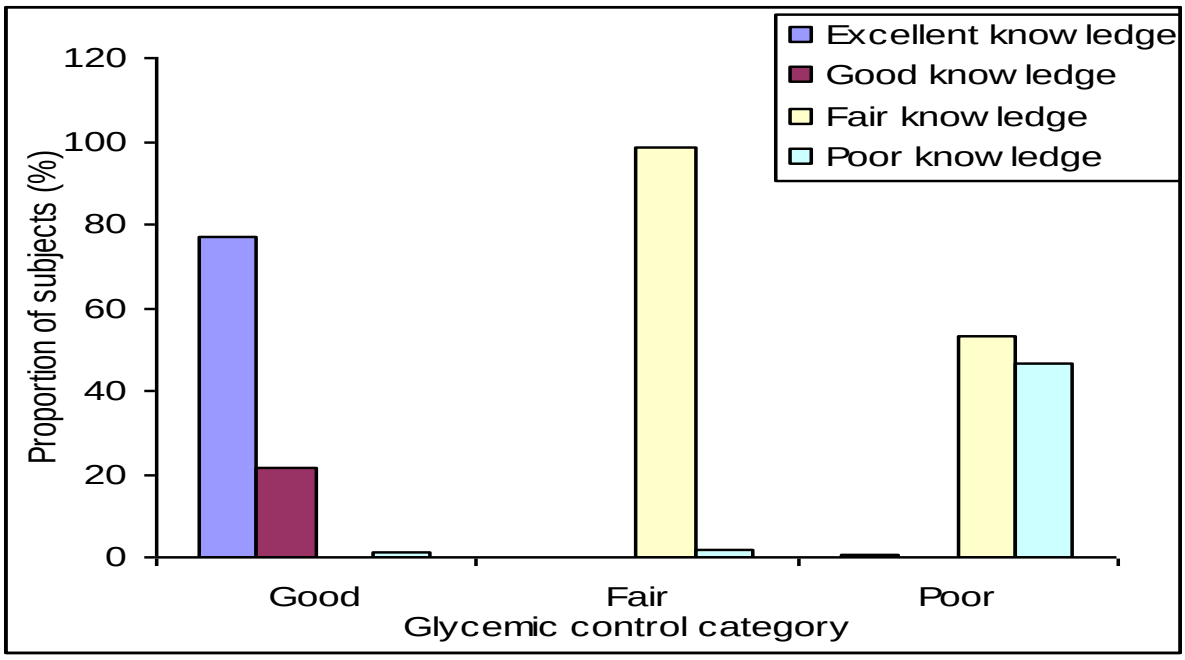


*(χ^2 = 1701.33; df = 6; p = 0.000)

Figure 6: Relationship between Degree of Subjects' Knowledge about Beneficial Effect of Exercise and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.4 Relationship between Degree of Subjects' Knowledge about Dietary Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

About 311 (77.2%) out of 403, 271 (98.5%) out of 275 and 278 (53.3%) out of 522 subjects who had good, fair and poor glycemic control were those who had excellent, fair and fair knowledge about dietary modification respectively. There was an association between degree of subjects' knowledge about dietary modification and glycemic control*.

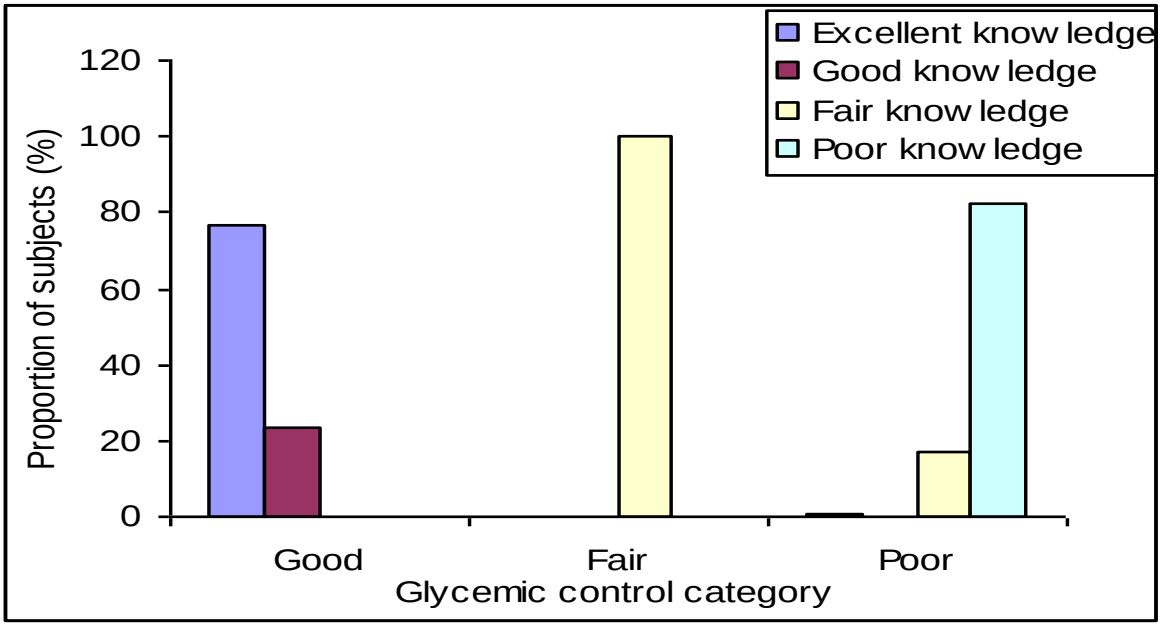


*(χ^2 = 1423.52; df = 6; p = 0.000)

Figure 7: Relationship between Degree of Subjects' Knowledge about Dietary Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.5 Relationship between Degree of Subjects' Knowledge about Lifestyle Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Almost 308 (76.4%) out of 403, 275 (100%) out of 275 and 431 (82.6%) out of 522 subjects who had good, fair and poor glycemic control were those who had excellent, fair and poor knowledge about lifestyle modification respectively. There was an association between degree of subjects' knowledge about lifestyle modification and glycemic control*.

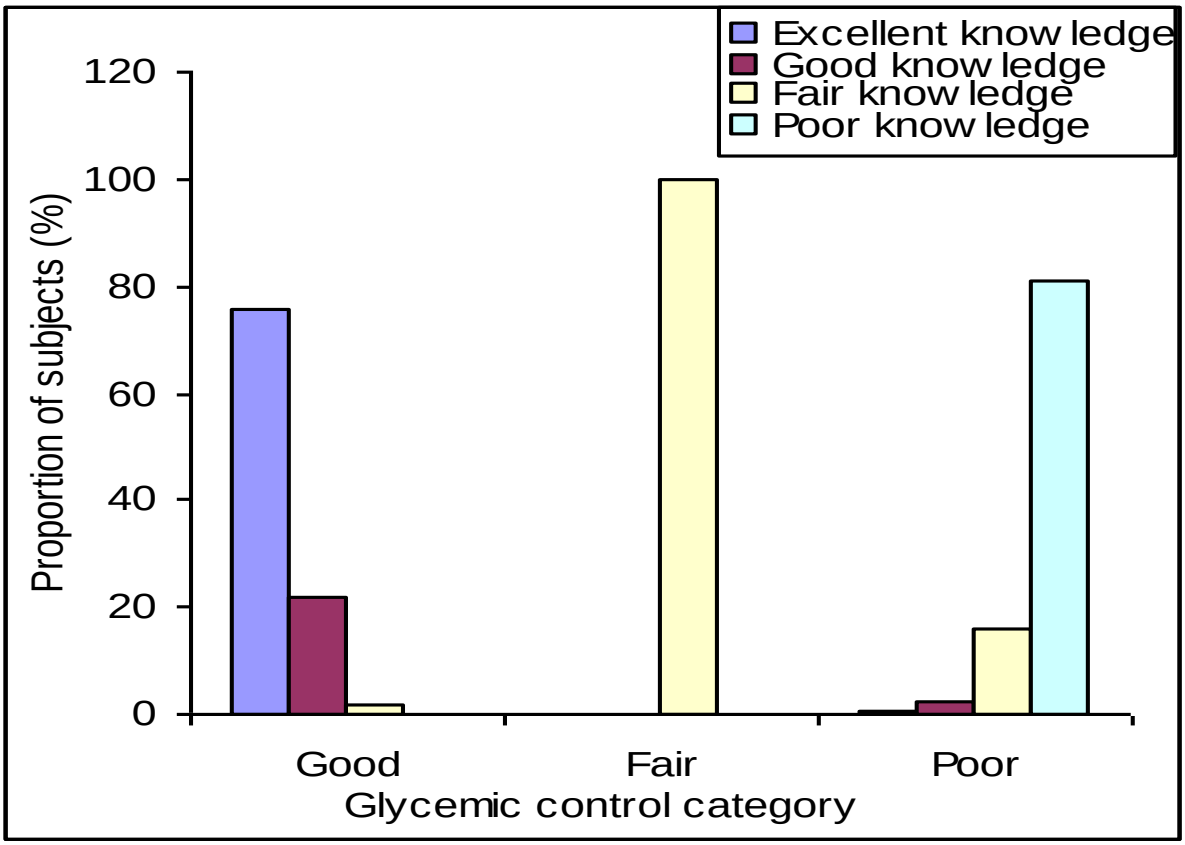


***(**χ^2 = 1941.54; df = 6; p = 0.000**)**

Figure 8: Relationship between Degree of Subjects' Knowledge about Lifestyle Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.6 Relationship between Degree of Subjects' Knowledge about Complications of Diabetes Mellitus (DM) and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Three Hundred and Six (75.9%) out of 403, 275 (100%) out of 275 and 424 (81.2%) out of 522 subjects who had good, fair and poor glycemic control were those who had excellent, fair and poor knowledge about complications of diabetes mellitus respectively. There was an association between degree of subjects' knowledge about complications of diabetes mellitus and glycemic control*.

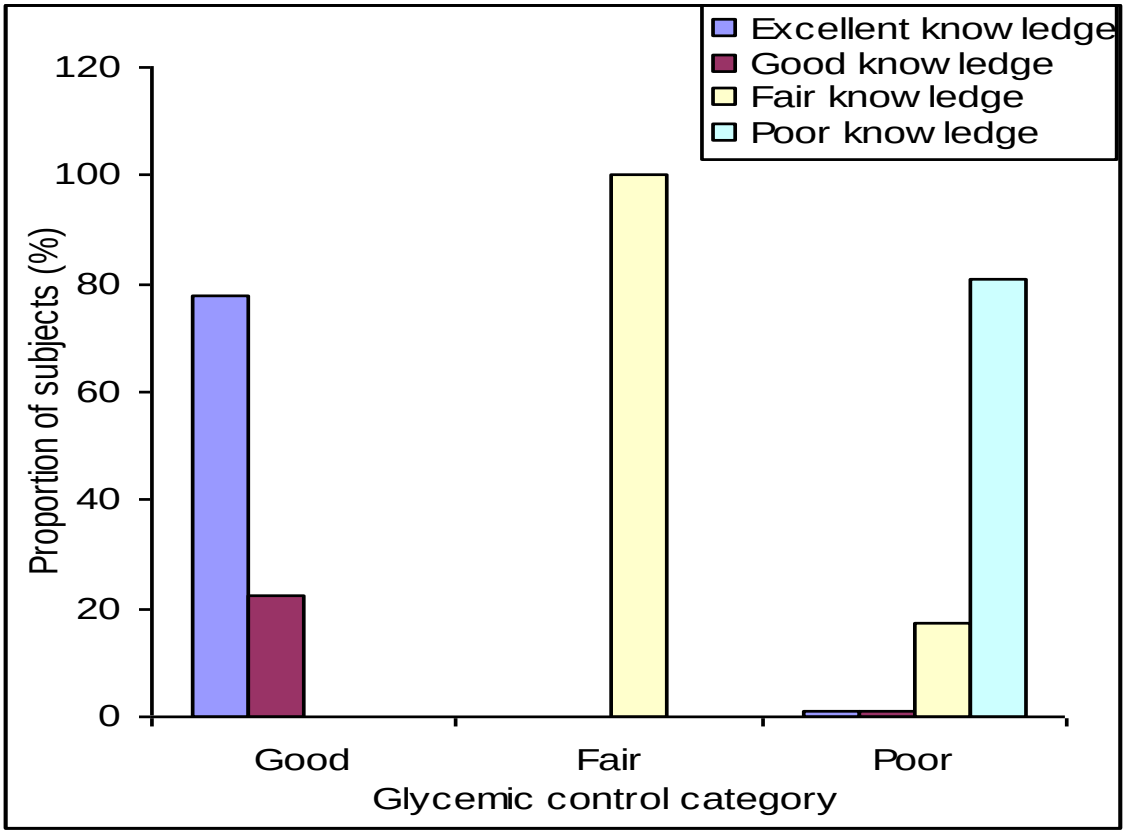


***(χ^2 = 1860.69; df = 6; p = 0.000)**

Figure 9: Relationship between Degree of Subjects' Knowledge about Complications of Diabetes Mellitus (DM) and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.7 Relationship between Degree of Subjects' Knowledge about Treatment and Glycemic Control (Outcome of Anti-Diabetic Therapy)

About 313 (77.7%) out of 403, 275 (100%) out of 275 and 421 (80.7%) out of 522 subjects who had good, fair and poor glycemic control were those who had excellent, fair and poor knowledge about their treatment respectively. There was an association between degree of subjects knowledge about their treatment and glycemic control*.

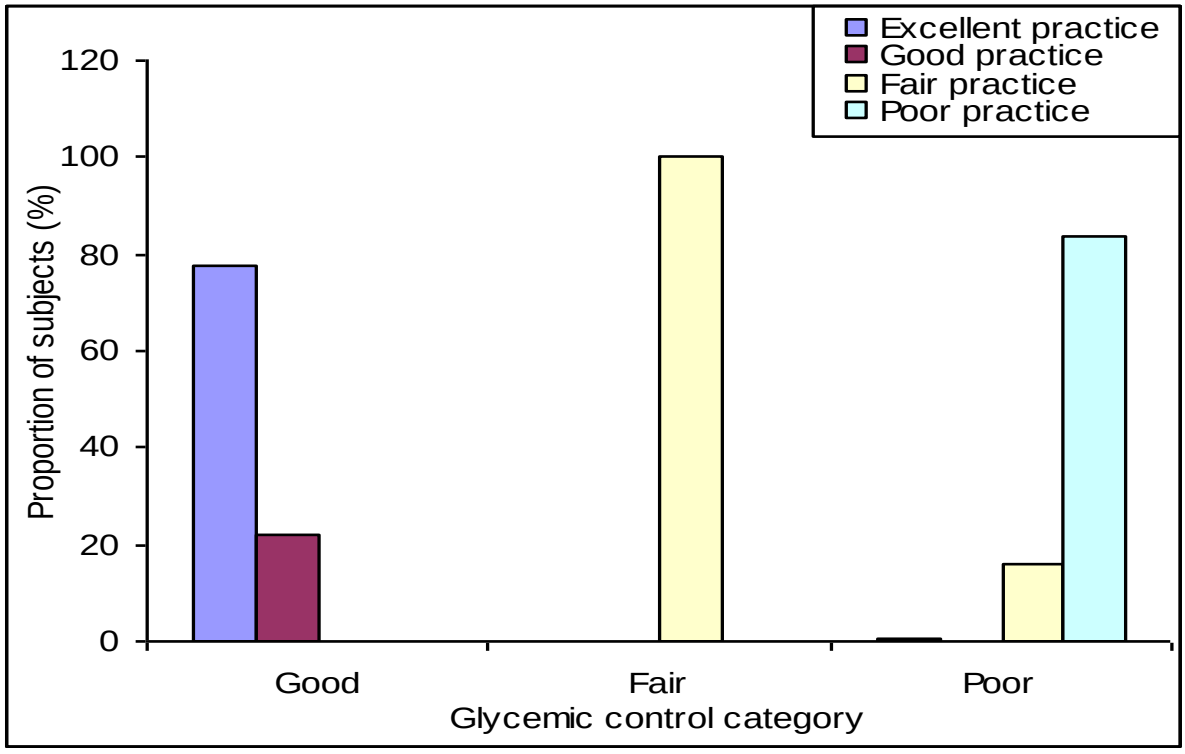


***(χ^2=1892.58; df = 6; p = 0.000)**

Figure 10: Relationship between Degree of Subjects' Knowledge about Treatment and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.4.8 Relationship between Degree of Practice of Self Monitoring and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Three Hundred and Thirteen (77.7%) out of 403, 275 (100%) out of 275 and 436 (83.5%) out of 522 subjects who had good, fair and poor glycemic control were those who had excellent, fair and poor practice of self monitoring respectively. There was an association between degree of subjects' practice of self monitoring and glycemic control*.



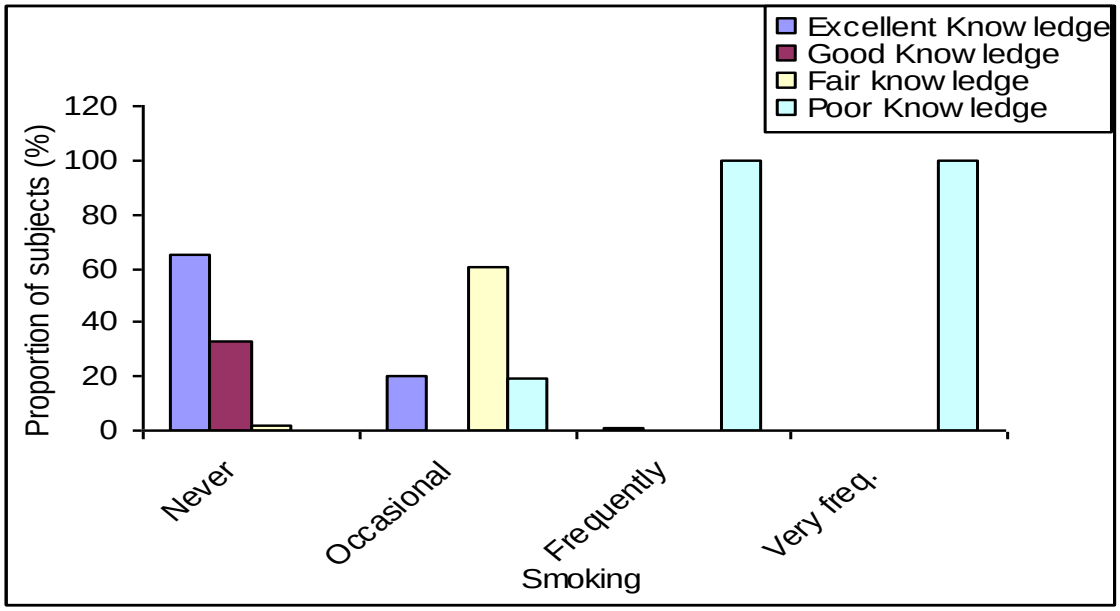
(χ^2 = 1960.81; df = 6; p = 0.000**)**

Figure 11: Relationship between Degree of Practice of Self Monitoring and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.5 Relationship between Knowledge and Practice of Lifestyle Modification among Subjects

4.6.5.1 Relationship between Degree of Subjects' Knowledge about Lifestyle Modification and Smoking.

Almost 187 (65.2%) out of 287, 359 (60.4%) out of 594, 202 (99.5%) out of 203 and 116 (100%) out of 116 subjects who never smoked, smoked occasionally, smoked frequently and smoked very frequently were those who had excellent, fair, poor and poor knowledge about lifestyle modification respectively. There was an association between degree of subjects' knowledge about lifestyle modification and practice of cigarette smoking*.

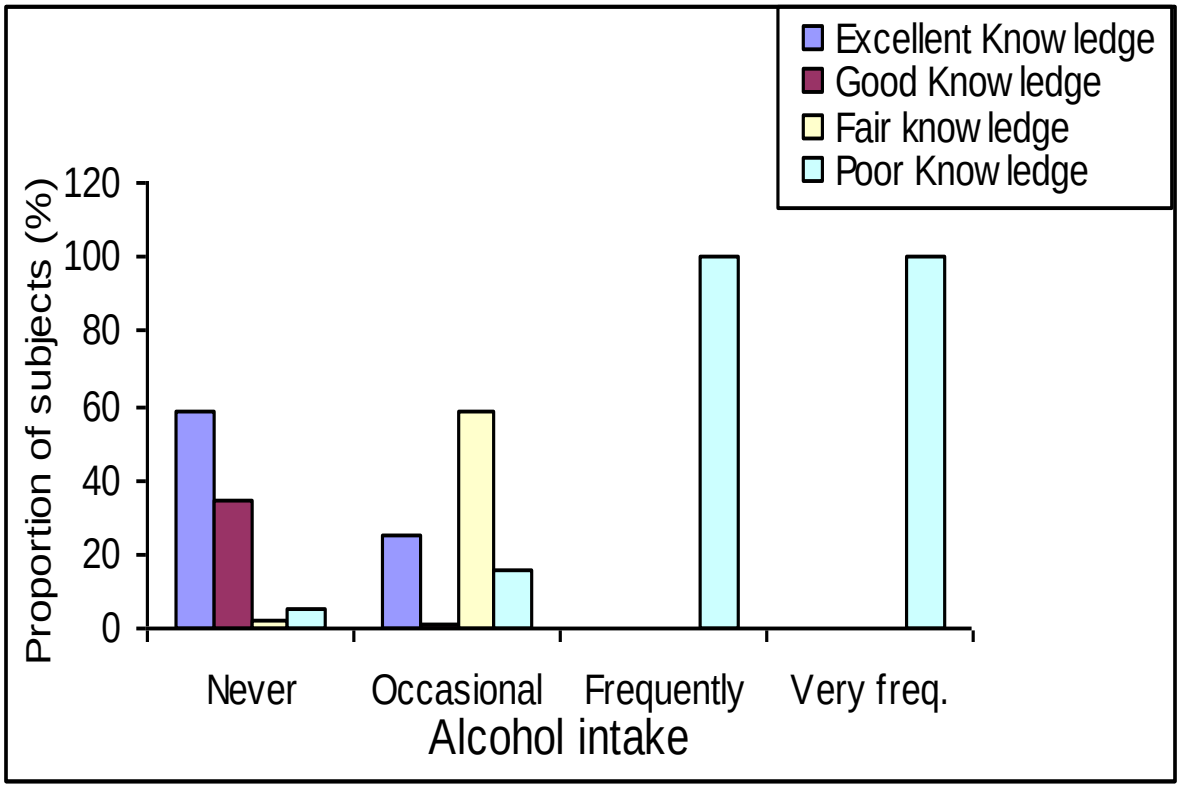


*(χ^2 =1423.9; df=9; p =0.00)

Figure 12: Relationship between Degree of Subjects' Knowledge about Lifestyle Modification and Smoking

4.6.5.2 Relationship between Degrees of Subjects' Knowledge about Lifestyle Modification and Alcohol Intake.

About 154 (58.3%) out of 264, 359 (58.1%) out of 618, 202 (100%) out of 202 and 116 (100%) out of 116 subjects who never took alcohol, took alcohol occasionally, frequently and very frequently were those who had excellent, fair, poor and poor knowledge about Lifestyle modification respectively. There was an association between degree of subjects' knowledge about lifestyle modification and practice of alcohol intake*.

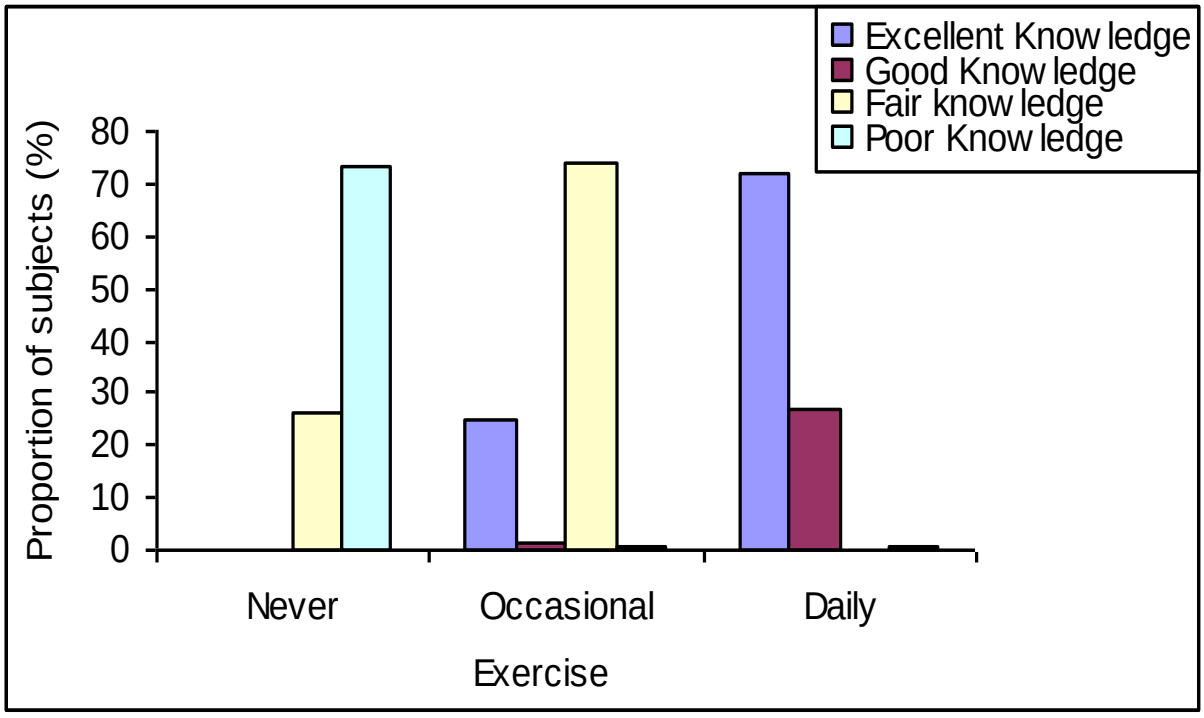


*(χ^2 =1307.1; df= 9; p =0.00)

Figure 13: Relationship between Degree of Subjects' Knowledge about Lifestyle Modification and Alcohol Intake.

4.6.5.3 Relationship between Degree of Subjects' Knowledge about Lifestyle Modification and Exercise.

About 427 (73.2%) out of 431, 210 (73.7%) out of 364 and 239 (72.0%) out of 310 subjects who never exercised, exercised occasionally and daily respectively were those who had poor, fair and excellent knowledge about Lifestyle modification respectively. There was an association between knowledge about lifestyle modification and practice of exercise*. Overall, there was an association between knowledge about lifestyle modification and practice of lifestyle modification among subjects.



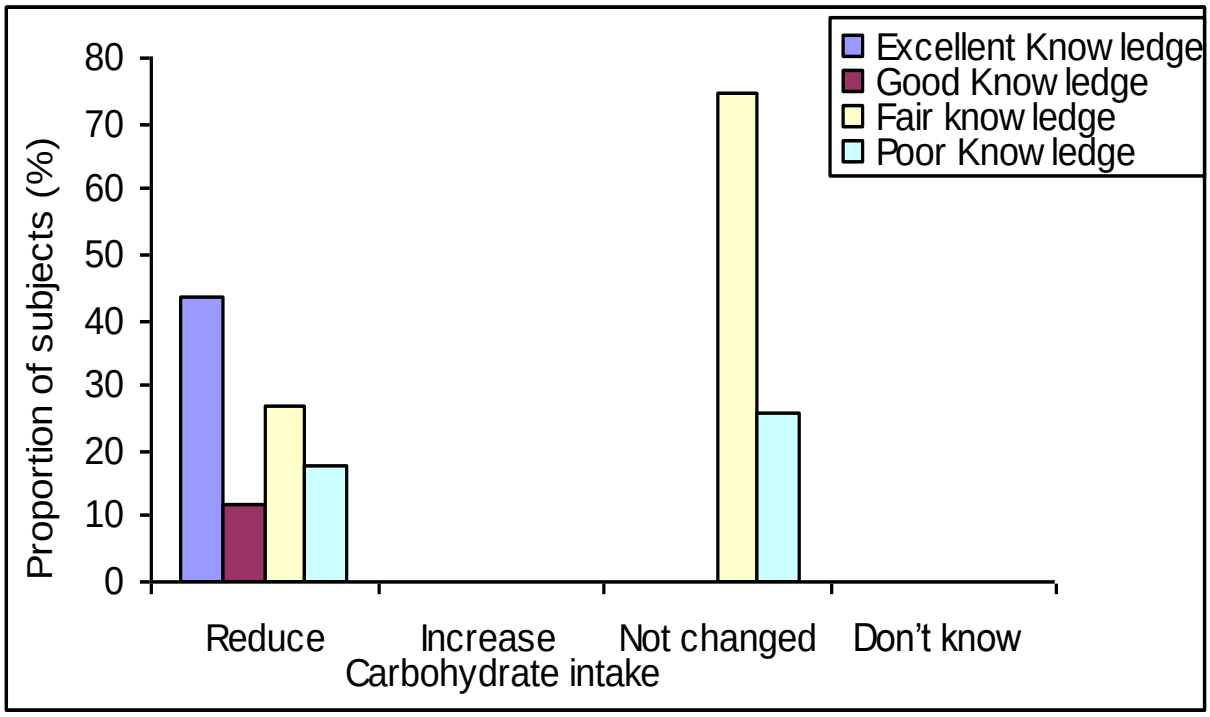
*(χ^2 =1363.1; df=6; p =0.00)

Figure 14: Relationship between Degree of Subjects' Knowledge about Lifestyle Modification and Exercise.

4.6.6 Relationship between Knowledge and Practice of Dietary Modification among Subjects

4.6.6.1 Relationship between Degree of Subjects' Knowledge about Dietary Modification and Carbohydrate Intake

Almost 313 (43.3%) out of 723 and 355 (74.4%) out of 477 subjects who reduced carbohydrate intake and those who did not change their carbohydrate intake after diagnosis of their diabetes mellitus were those who had excellent and fair knowledge about dietary modification respectively. There was an association between degree of subjects' knowledge about dietary modification and modification of carbohydrate intake*.

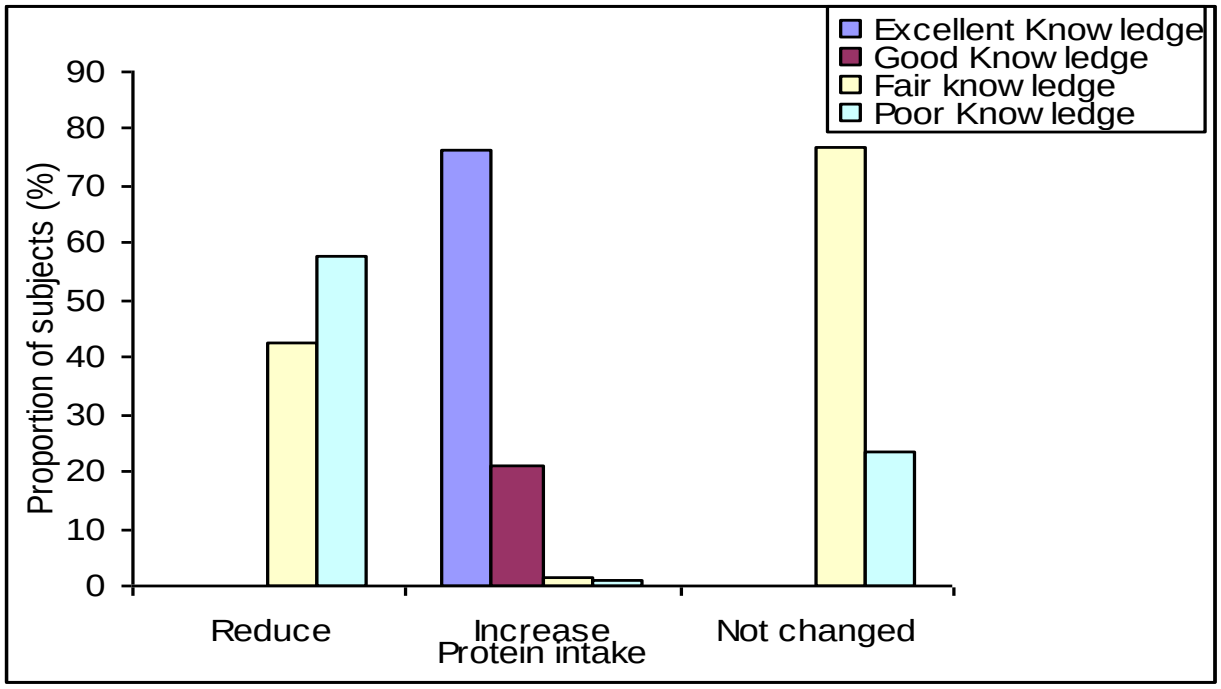


*(χ^2 = 414.4; df = 3; p =0.00)

Figure 15: Relationship between Degree of Subjects' Knowledge about Dietary Modification and Modification of Carbohydrate Intake

4.6.6.2 Relationship between Degree of Subjects' Knowledge about Dietary Modification and Modification of Protein Intake

One Hundred and Four (57.5%) out of 181, 313 (76.2%) out of 411 and 466 (76.6%) out of 603 subjects who reduced protein intake, increased and did not change their protein intake after diagnosis of their diabetes mellitus were those who had fair, excellent and fair knowledge about dietary modification respectively. There was an association between knowledge about dietary modification and modification of protein intake*.



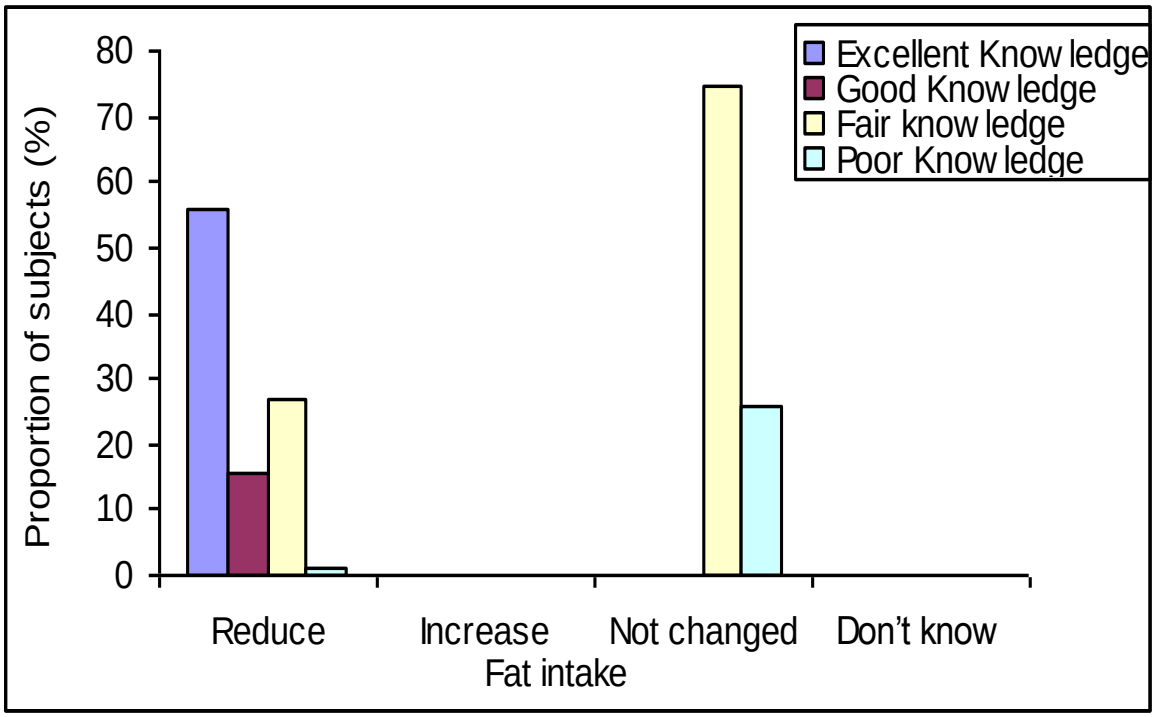
*(χ^2 =1264.9; df=6; p =0.000)

Figure 16: Relationship between Degree of Subjects' Knowledge about Dietary Modification and Modification of Protein Intake

4.6.6.3 Relationship between Degree of Subjects' Knowledge about Dietary Modification and Modification of Fat Intake

Three Hundred and Thirteen (55.9%) out of 560 and 394 (74.4%) out of 640 subjects who reduced their fat intake and those who did not change their fat intake after diagnosis of their diabetes mellitus were those who had excellent and fair knowledge about dietary modification respectively. There was an association between knowledge about dietary modification and modification of fat intake*.

Overall, there was an association between knowledge about dietary modification and practice of dietary modification among subjects.



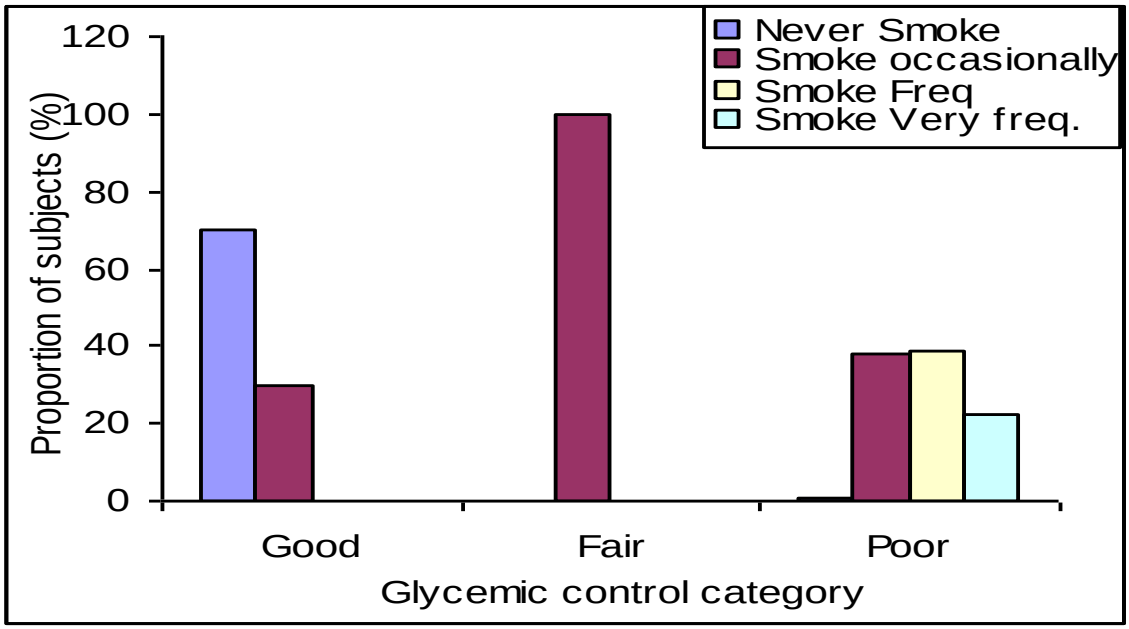
*(χ^2 =733.4; df=3; p =0.00)

Figure 17: Relationship between Degree of Subjects' Knowledge about Dietary Modification and Modification of Fat Intake

4.6.7 Relationship between Practice of Lifestyle Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.7.1 Relationship between Degree of Subjects' Cigarette Smoking and Glycemic Control (Outcome of Anti-Diabetic Therapy).

Two Hundred and Eighty Two (70.0%) out of 403 and 275 (100.0%) out of 275 subjects who had good and fair glycemic control were those who never smoked and those who smoked occasionally respectively. There was an association between degree of cigarette smoking and glycemic control*.

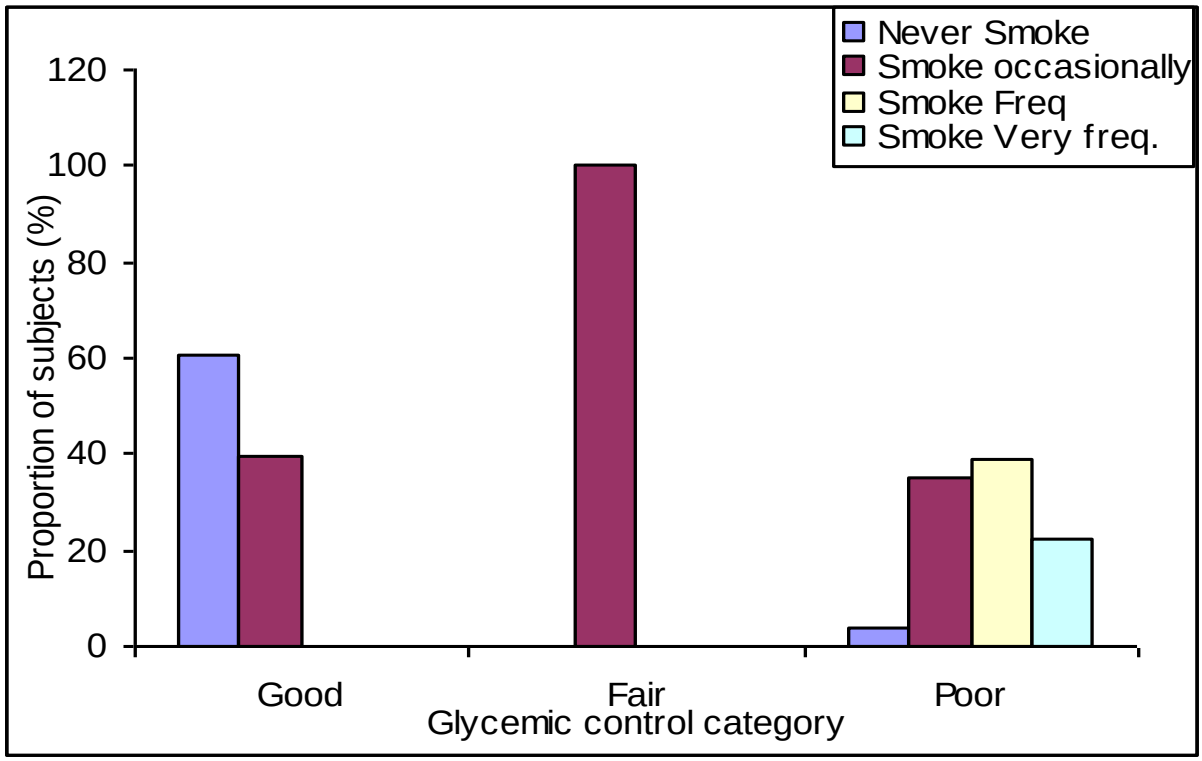


*(χ^2 =987.8; df=6; p = 0.00)

Figure 18: Relationship between Degree of Subjects' Cigarette Smoking and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.7.2 Relationship between Degree of Subjects' Alcohol Intake and Glycemic Control (Outcome of Anti-Diabetic Therapy).

Two Hundred and Forty Four (60.5%) out 403 and 275 (100.0%) out of 275 subjects who had good and fair glycemic control were those who never took alcohol and those who occasionally took alcohol respectively. There was an association between degree of alcohol intake and glycemic control*.



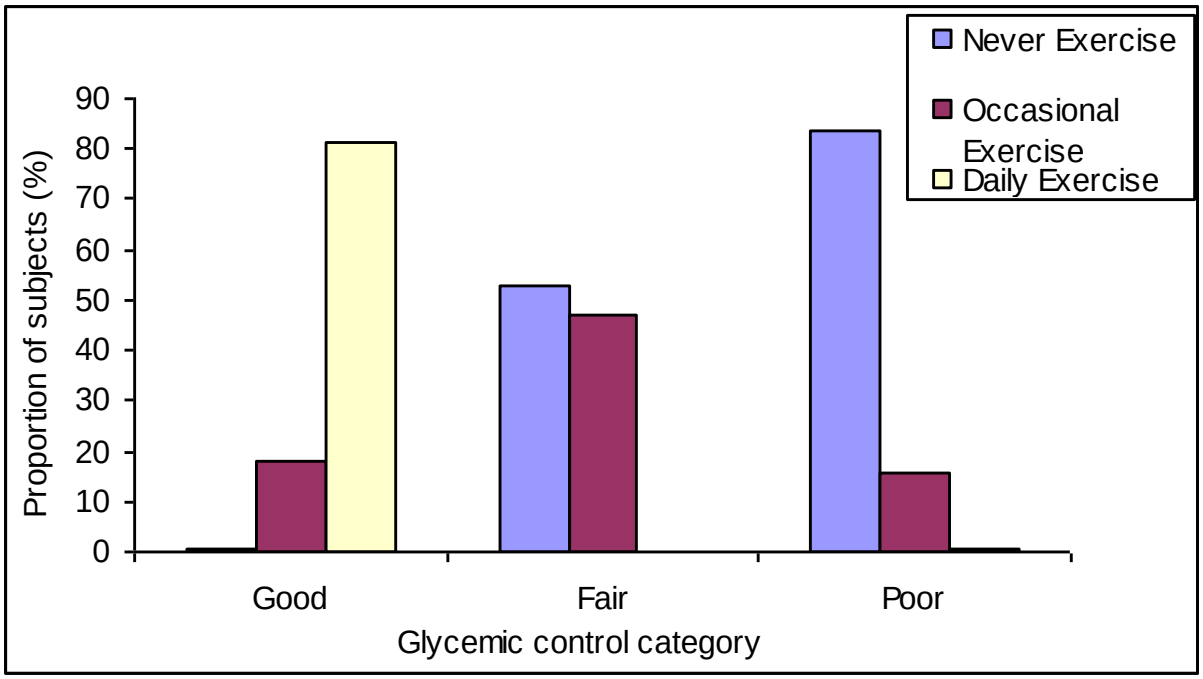
*(χ^2 =1135.0; df=6; p = 0.000)

Figure 19: Relationship between Degree of Subjects' Alcohol Intake and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.7.3 Relationship between Degree of Subjects' Exercise and Glycemic Control (Outcome of Anti-Diabetic Therapy).

Three Hundred and Twenty Eight (81.4%) out of 403 and 436 (83.5%) out of 522 subjects who had good and poor glycemic control were those who exercised daily and those who never exercised respectively. There was an association between degree of exercise and glycemic control*.

Overall, there was an association between practice of lifestyle modification and glycemic control (outcome of anti-diabetic therapy).



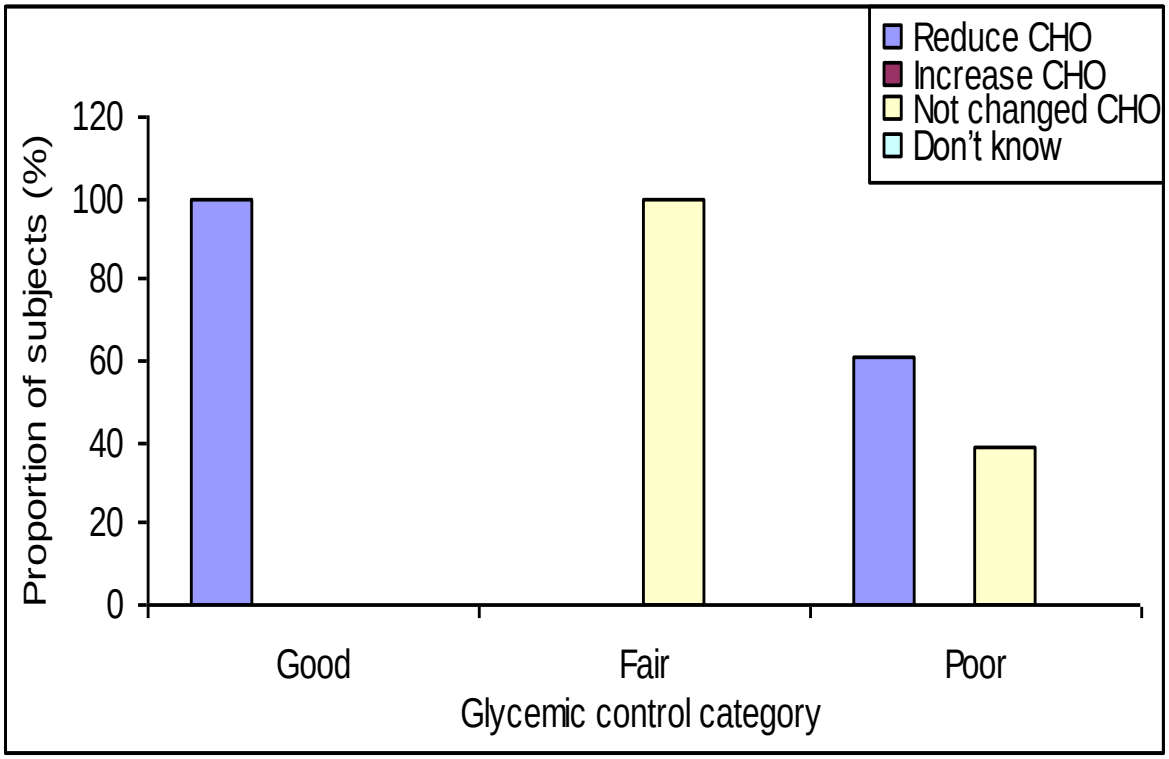
*(χ^2 =1040.7; df=4; p = 0.00)

Figure 20: Relationship between Degree of Subjects' Exercise and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.8 Relationship between Practice of Dietary Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.8.1 Relationship between Modification of Carbohydrate Intake and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Four Hundred and Three (100.0%) out of 403 and 275 (100.0%) out of 275 subjects who had good and fair glycemic control were those who reduced and those who did not change their carbohydrate intake respectively. There was an association between carbohydrate intake modification and glycemic control*.



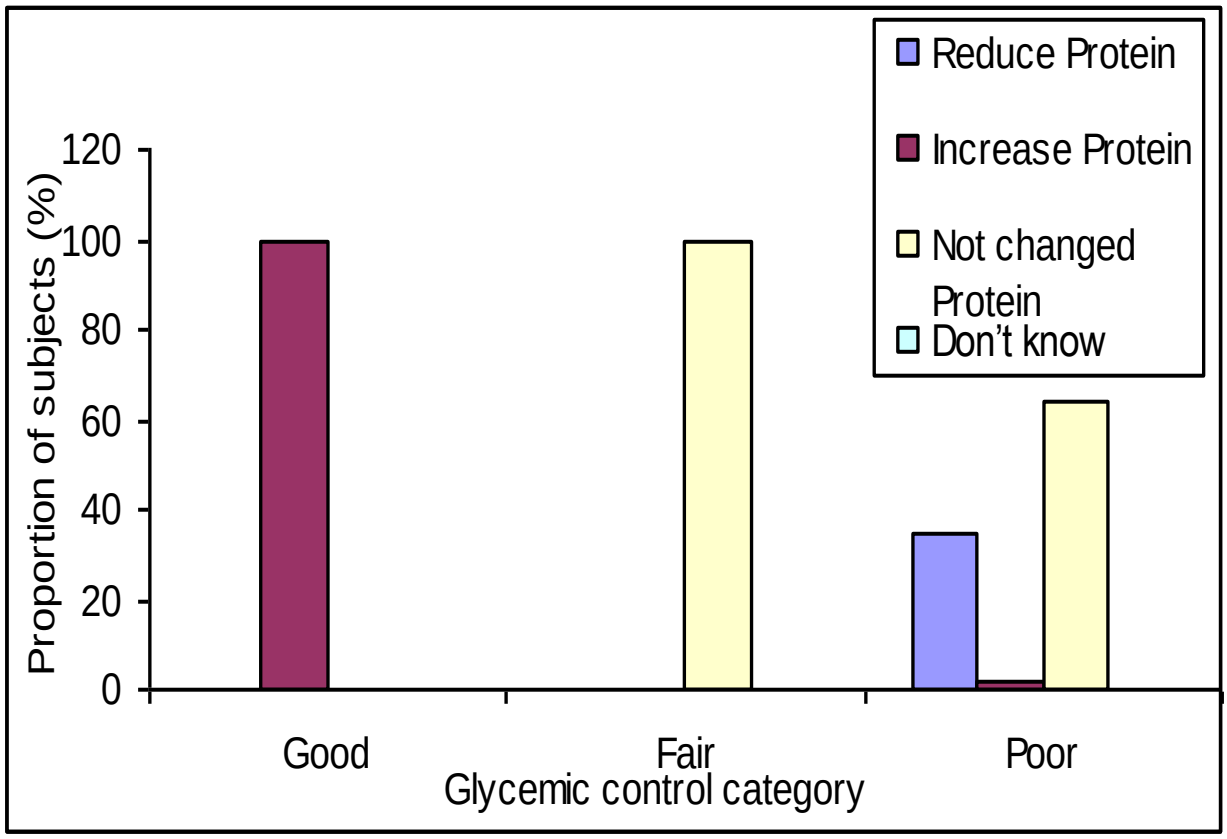
*(χ^2=682.9; df=2; p = 0.00)

Figure 21: Relationship between Carbohydrate Intake Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

CHO = Carbohydrate

4.6.8.2 Relationship between Modification of Protein Intake and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Four Hundred and Three (100%) out 403 and 275 (100%) out of 275 subjects who had good and fair glycemic control were those who increased and those who did not change their protein intake after diagnosis of their diabetes mellitus respectively. There was an association between protein intake modification and glycemic control*.



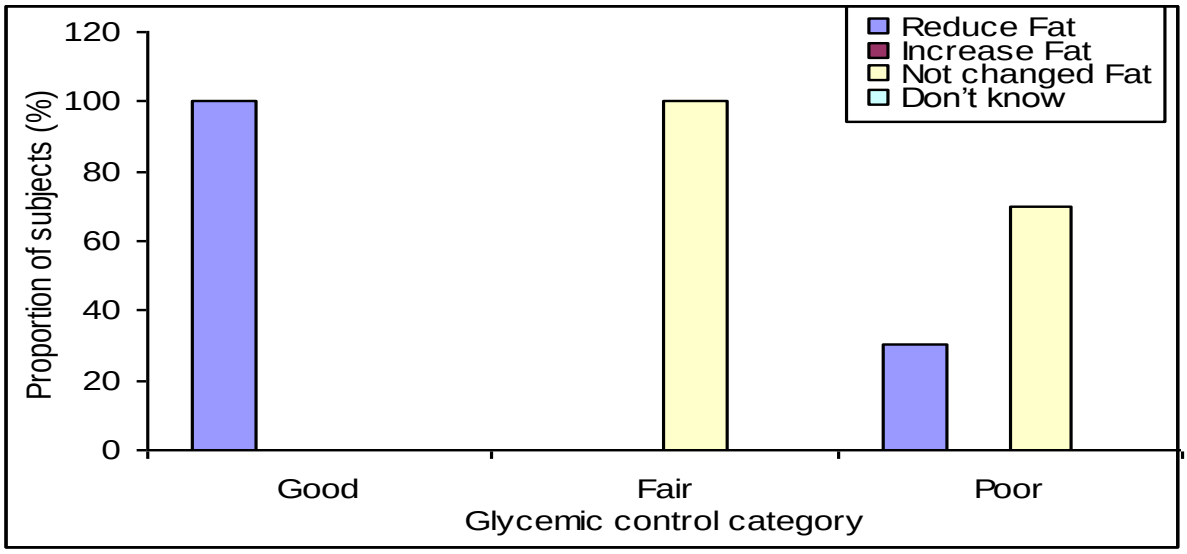
*(χ^2 =1355.1; df=4; p = 0.00).

Figure 22: Relationship between Modification of Protein Intake and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.6.8.3 Relationship between Modification of Fat Intake and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Four Hundred and Three (100.0%) out of 403 and 365 (69.9%) out of 522 subjects who had good and poor glycemic control were those who reduced and those who did not change their fat intake after diagnosis of their diabetes mellitus respectively. There was an association between fat intake modification and glycemic control*.

Overall, there was an association between practice of dietary modification and glycemic control.



*(χ^2 =758.9; df=2; p=0.00)

Figure 23: Relationship between Modification of Fat Intake and Glycemic Control (Outcome of Anti-Diabetic Therapy)

4.7 Quality Control Parameters of Branded and Generic Anti-Diabetic Drugs

Samples (A, B, C, D, E and F) used in University of Maiduguri Teaching Hospital

A = Branded Glibenclamide Tablet 5mg Daonil®

D = Generic Glibenclamide Tablet 5mg

B = Branded Metformin Tablet 500mg Glucophage®

E = Generic Metformin Tablet 500mg

C = Branded Chlopropamide Tablet 250mg Diabenese®

F = Generic Chlopropamide Tablet 250mg

4.7.1 Identification Tests for Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

All the branded and generic anti-diabetic drugs passed their respective identification test, using B.P. (2004) methods of colour reaction.

Table 39: Identification Tests for Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

Anti-Diabetic Drug Sample	Observation	Remark
A	Solution showed absorption maximum at 300 nm and a less intense absorption maximum at 275 mm	Passed
D	Solution showed absorption maximum at 300 nm and a less intense absorption maximum at 275 mm	Passed
B	Pink colour observed	Passed
E	Pink colour observed	Passed
C	Curdy white precipitate observed	Passed
F	Curdy white precipitate observed	Passed

4.7.2 Tablet Hardness Characteristics of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

All branded and generic anti-diabetic drugs passed tablet hardness characteristics test, using B.P. (2004) specification of mean hardness of between 5-7 kgf inclusive.

Table 40: Tablet Hardness Characteristics of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

n=5 for each drug sample

Anti-Diabetic Drug Sample	Mean Hardness (kgf) $\pm$ S. E. M	Standard Deviation	Coefficient of Variation	Remark
A	5.4 $\pm$ 0.42	0.84	15.56	Passed
D	5.35 $\pm$1.32	2.64	49.35	Passed
B	6.75 $\pm$ 0.16	0.32	4.74	Passed
E	6.90 $\pm$ 0.01	0.02	0.29	Passed
C	5.88 $\pm$ 0.09	0.18	3.06	Passed
F	5.90 $\pm$ 0.10	0.20	3.39	Passed

4.7.3 Weight Uniformity Characteristics of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

All branded and generic anti-diabetic drugs passed the weight uniformity characteristics test, using B.P. (2008) specification of percentage deviation of not more than 10% for glibenclamide tablet and not more than 5% for chlorpropamide and metformin tablets.

Table 41: Weight Uniformity Characteristics of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

n=20 for each drug sample

Anti-Diabetic Drug Sample	Mean Weight (mg) ± S. E. M	Standard Deviation	Percentage Deviation	Remark
A	172 .7 ± 1.62	7.25	4.2	Passed
D	173 ± 1.55	6.92	4.0	Passed
B	754.9 ± 5.23	23.40	3.1	Passed
E	755.5 ± 3.89	17.38	2.3	Passed
C	474.5 ± 4.35	19.45	4.1	Passed
F	474.3 ± 3.71	16.60	3.5	Passed

4.7.4 Friability Characteristics of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

All branded and generic anti-diabetic drugs passed friability characteristics test, using B.P. (2008) specification of percentage weight variation of not more than 1%.

Table 42: Friability Characteristics of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

n=10 for each drug sample

Anti-Diabetic Drug Sample	Initial Weight (mg)	Final Weight(mg)	% Average Weight Variation (% wt loss)	Remark
A	170.9	170.5	0.234	Passed
D	171.0	170.5	0.234	Passed
B	769.7	769.7	0	Passed
E	769.8	769.7	0.013	Passed
C	477.0	475.0	0.419	Passed
F	479.5	478.5	0.209	Passed

4.7.5 Disintegration Time (seconds) of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

All branded and generic anti-diabetic drugs passed disintegration time test, using B.P. (2008) specification of mean disintegration time of not more than 15 minutes.

Table 43: Disintegration Time (seconds) of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

n=6 for each drug sample

Anti-Diabetic Drug Sample	Mean Disintegration Time (seconds)	Disintegration Range (seconds)	Remark
A	24	23 – 26	Passed
D	25	23 – 26	Passed
B	23	20 – 25	Passed
E	22	20 – 25	Passed
C	46	35 – 51	Passed
F	45	39 – 50	Passed

4.7.6 Average Absolute Drug Content of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

All branded and generic anti-diabetic drugs samples passed their respective assay test for average absolute drug content, using B.P. (2008) specification of range of 95%-105% for glibenclamide and metformin, and 92.5% - 107.5% for chlorpropamide.

Table 44: Average Absolute Drug Content of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

n=20 for each drug sample

Anti-Diabetic Drug Sample	Average Absolute Drug Content (mg)	% Average Absolute Drug Content	Remarks
A	4.75	95.0	Passed
D	4.80	96.0	Passed
B	475.0	95.0	Passed
E	484.0	96.8	Passed
C	232.5	93.0	Passed
F	235.0	94.0	Passed

4.7.7 Average Absolute Dissolution Rate (%) of Branded and Generic Anti-Diabetic Drugs used in University of Maiduguri Teaching Hospital

All the branded and generic anti-diabetic drugs passed the dissolution rate test, using B.P. (2008) specification of average percentage dissolution rate of not less than 70%.

Table 45: Average Absolute Dissolution Rate (%) of Branded and Generic Anti-Diabetic Drugs Sampled in University of Maiduguri Teaching Hospital

n=5 for each drug sample

Anti-Diabetic Drug Sample	% Average Dissolution	Remark
A	88.89	Passed
D	88.90	Passed
B	96.28	Passed
E	96.35	Passed
C	79.10	Passed
F	79.30	Passed

5. DISCUSSION

5.1 Relationship between Socio-economic Status, Affordability and Outcome of Anti-Diabetic Therapy (Glycemic Control)

The distribution of one thousand two hundred Type II diabetes mellitus Subject according to socio-economic status showed that there seems to be a causal relationship between poverty and diabetes mellitus. Use of anti-diabetic drugs in the management of diabetes mellitus is for the lifetime of the patients from time of diagnosis and this translates into a substantial cost in drug therapy to the patients and government (Cantrill, 1999). Upon consideration of the depressed nature of Nigerian Economy and the fact that majority of the subjects were poor, efforts designed to reduce public and private expenditure on anti-diabetic therapy as well as to use anti-diabetic drugs in a more cost-effective manner would be advantageous.

Poor and non-poor subjects significantly differ in affordability of anti-diabetic drugs. The fact that people may be ill or require medical services and drugs but not have enough money to pay for them (non-affordability) because of low economic status have been reported by Kara *et al*. (1997). This is a matter of great concern which needs urgent attention as it can erode the credibility of our health care system. There is therefore a need for feedback system to prescriber about patients that could not afford prescribed drugs to be institutionalized.

The high proportion of subjects with poor glycemic control which was due to irregularity on medication as remarked by the physician in case-notes could be due to lack of affordability by the poor subjects. This is in agreement with a fact that non-affordability of medicines due to cost/poverty has negatively affected therapeutic outcome because people may not have enough money to pay for adequate medical services (Kara *et al*. 1997). This is also

consistent with Winslow (1951) report of unholy alliance of poverty, sickness and medicines resulting into vicious circle of poverty and sickness, a situation he described as "Men and Women were sick because they were poor. They become poorer because they were sick and sicker because they were poorer". This implies that poverty is a hindrance to good health in terms of drug purchase (non-affordability). This is a strong justification to consider adoption of pharmaco-economic principles in our national health policy, hence its application at all levels of our healthcare delivery system in taking therapeutic and other healthcare intervention decisions as already proposed by Bootman *et al*. (1996).

5.2 Cost of Illness Analysis

The annual average cost of illness, N47, 924.36 (319.50), represent about 88% of annual per capital income in the country (Nigeria), using ADA (2003) and FMOH (2006) report of per capita income of less than 1USD per day. This average COI takes into account only the direct costs of therapy: the procurement cost of drugs, transport cost, cost of diagnostic/monitoring test(s) and personnel cost. Spending 88% of per capital income on diabetes management alone is a great burden.

The total cost of drugs was N4, 492, 822.95 (78.1%) of total cost of illness. This is enormous. Therefore, any measure taken to promote more rational drug selection such as economic evaluation of therapy (CMA and CEA), provision of regularly up-dated formulary and evidence-based standard treatment guidelines will be invaluable in promoting efficient use of limited resources.

About 77% of the patient had hypertension as concurrent illness and were placed on antihypertensive drugs as well, which form part of the drug cost (N1, 876, 542.05; 41.8%). Out of this amount, the cost of lisinopril alone was N1, 249, 830 (66.6% of antihypertensive

drug cost; 27.8 % of total drug cost). Lisinopril has a cost per /DDD of between N30 (2.5mg o.d.) to N180 (15mg o.d.) and was prescribed for 92 patients.

The fact that lisinopril has been shown to stabilize renal function in hypertensive diabetics might be responsible for its high degree of usage (BNF, 1998; ADA, 2003). Screening of patients for those at risk of nephropathy might be beneficial as well as subsequent regular monitoring of their renal function (BNF, 1998; ADA, 2003). High cost of therapy may lead to poor compliance by some patient, leading to other complication in addition to renal problems, which will adversely affect their quality of life. Affordability by patient may be the determinant of choice of therapy for core poor patient even if it is only moderately efficacious.

The total cost of anti-diabetic agents was N2, 605, 268.95 (57.99% of total drug cost and 45.30% of total diabetes cost) out of which insulin (for 24 patients; 20%) was N1, 636, 000 (36.41% of total drug cost). Insulin has a cost/DDD of between N230.00 (10 unit o.d.) to N700.00 (30 units o.d.).

Measures such as diabetic compatible life style, improved compliance to medication and dietary modification need to be taken in order to prevent complications of diabetes. Other modalities include possible home visits by social workers and pharmaceutical care by neighborhood registered pharmacy. These are not without costs, and should be weighed against the benefits as well as affordability by patients. It can equally be restricted to selected patients. Enlightenment of patients on grave implications of non-compliance is important. Patients and public enlightenment patient on dietary habits is of absolute necessity.

Aspirin was prescribed in 85% of the patients and cost just N11, 011.95. This is in order as it prevents/minimizes incidence of cardiovascular disease such as thrombo-embolic disorders (Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension, 2003).

With an annual average cost of N47, 924.36, the cost of treating 1000 cases will be N47, 924,360. Given a prevalence rate of about 3% in the country, with a projected 2010 population of 158, 689, 093 from 2006 census (NPC, 2006), About 4, 760, 672 people or more may be suffering from diabetes mellitus. The annual national cost of illness for diabetes may be about N226,152,196,630.00 ($1,521,014.644) i.e. over N226 billion annually. In North-Eastern Nigeria alone, with 2010 projected population of 21,647,800, The annual cost of illness for diabetes may be N31,123,708,812.00 ($207,491,392). This may be an under estimated, because of prevalence rate of 3% used and the non inclusion indirect cost (cost due to morbidity, disability, premature mortality and loss of productive output etc) is a lot. Indirect costs are difficult to evaluate, but gray *et al.* (1995) has shown that it may be as high as the direct cost.

Bakari and Onyemelukwe (2004) reported impaired glucose tolerance (IGT) of 7.7% rate among Hausa-Fulani in North-Eastern Nigeria who has no history of diabetes mellitus. They opined that this would increase incidence of diabetes mellitus, as one in three individual with IGT will develop Type II diabetes mellitus. Although, WHO (2007) accorded priority status to diabetes mellitus, many public health planners remain largely unaware of its magnitude and the seriousness of its complications. Of equal consequence, is the increasing prevalence of the disease and the long-term cost of therapy for both patients and the health

sector, and its cost to nations in economic terms, due to the fact that use of anti-diabetic drugs in the management of diabetes mellitus is for lifetime of the patients from time of diagnosis. This translates into a substantial cost in drug therapy to the patients and government (Cantrill, 1999).

Government need to do something urgently such as massive, intensive and sustainable public enlightenment, improved policy on diabetes care and feeding habits among others, not only because of the enormous cost associated with its therapy but also because of skyrocketing prevalence rate as reported by WHO (1998), which will further compound the cost problems and affect productivity.

The fact that poverty is on the increase is no longer new and is another reason to be more proactive. The percentage of core poor, rising from 6.2% in 1980 to as high as 29.3% in 1997 and reaching 58.2% in 1999 is a cause for concern (Federal Office of Statistics, 1999). In UNDP (2004) report, about 70.18% (93.2 million) Nigerians live below the poverty line, earning less than 1US$ (about N149.00) per day. This is worrisome.

Diabetes is widely known to be on increase world wide and Africa will be the most affected (WHO, 1998). More so, low income, uneducated and poor people are more effected (Robinson, 1998; Nilsson *et al*., 1998), hence, instituted therapy should be as cost-effective as possible. Effective policy, adequate information education and communication (IEC) strategy must be put in-place to safe guard the health of the nation from ruin by diabetes mellitus among other chronic illnesses. Currie *et al*. (1997) reported 8.7% of acute sector fund for diabetes mellitus in the UK with an average of £2,101 cost per year for resident with diabetes mellitus compared with £308 per year for resident without diabetes mellitus.

With increasing HIV/AIDS epidemics, hypertension, tuberculosis, malaria and their

attendant costs, increase cost of therapy for other chronic condition like diabetes can further cripple the depressed economy, hence limited resources must be use more wisely through economic evaluation of therapeutic options among others.

5.3 Cost Minimization Analysis

Anti-Diabetic drugs utilization studies for cost minimization analysis in UMTH shows that branded products were more frequently prescribed for all categories of oral hypoglycemic agents used than their generic equivalents. This is in agreement with a previous study that reported that branded anti-microbial drugs were more frequently prescribed even when generic equivalents were available in hospitals (Suleiman and Tayo, 2003). It, however, conflicts with the National Drug Formulary and essential drugs decree (1989) the National Drug policy (2005) that specifically stipulate that generic products should be prescribed. Lack of assurance in efficacy/effectiveness of some

Generics may be a factor for this trend due to chaotic drug distribution system in Nigeria which facilitates faking and counterfeit products (Suleiman and Tayo, 2003). There was no rational for branded drug to be used if generic equivalent is available and there is guarantee of its effectiveness (outcome). Due to assumed identical outcome of the two options, it is important that generic products are properly analyzed to ensure their bioequivalence with acceptable standards. Branded Products can be substituted when generic products are not available, but they must also be of acceptable standards.

The use of generic names for drug purchasing as well as prescribing carries considerations of clarity, quality and price. Proponents of drug purchasing and prescribing point out that generic names are more informative than branded names, facilitate purchasing of products from multiple suppliers (competitive bidding) and facilitates products substitution whenever

appropriate (reduce inventory). In addition, generic drug products are often cheaper than branded products (Swift and Ryan, 1975). Generic substitution has long been applied in formulary system. It has the benefit of discouraging the use of less than optimal drug therapy, encourages competitive bidding and reduce inventory. These benefits have in some cases been quantified as direct drug and inventory saving (Rubin and Kellar, 1983). Generic drug programme are today probably the most relevant economic strategy for drug supply (WHO, 1996).

If generic substitution does not exist, price competition will not exist either and price of drugs will swell (WHO, 1996). Generic substitution which applied CMA stimulates bioequivalence comparisons and help to prevent the stocking of less than optimal products. The result of this study is evidence-based information that can be used to influence prescription practice: irrational prescription of branded anti-diabetic drugs which are used for lifetime from diagnosis of a patient than cheaper generic equivalents, by using the information for educational intervention at prescribers' and managerial level.

This work can form the basis for educational and managerial interventions on prescribing habit to conform to the requirements of the Nigeria essential drug policy of 2005. This can be facilitated in collaboration with drug regulatory agency such as National Agency for Food, Drug Administration and Control (NAFDAC).

A mechanism for comparing costs, such as CMA can lead to more rational prescribing and limit the number of drug products included in each therapeutic class. Cost of drug would be reduced as well as patients drop out of treatment because of cost. This is an established fact (La-Ruche *et al*., 1995; Gomo, 1995).

Brand name drugs are often dispensed when generic alternatives are available resulting in an estimated $8.8 billion in excess expenditure per year in the U.S (Haas *et al.,* 2005). This irrational use of brand name drugs may reflect physician and patient beliefs that brand name drugs are superior to their generic counterparts (Banahan *et al.*, 1997).

Habitual use of brand name terminology may also play an important role in the dispensing of brand name products, as the name recorded on a prescription can impact on whether a drug is dispensed in brand or generic form even when the physician would accept the generic version and the pharmacy is empowered to provide it (Suh, 1999; Mott *et al.*, 2002). However, generic substitution is not mandated in most states, can be overridden by the prescribing physician and does not universally occur when allowed by the physician (Suh, 1999; Mott *et al.,* 2002).

The use of brand names also has consequences for communication between physicians and patients. Confusion over drug terminology can result in adverse drug events. For example, a patient may inadvertently be given a second formulation of a drug because the prescribing physician fails to recognize that the patient was already taking the medication under a different name (Anton *et al.,* 2002; Schwab *et al.,* 2002). In addition, use of brand names in communication by physicians can undermine efforts to minimize commercial influence on medical practice.

The use of branded rather than generic names for medications can increase health care costs. Physicians refer to most medications by their brand names, including drugs with generic formulations. This however, leads to higher healthcare costs (Steinman *et al.*, 2007).

All prescribed branded and generic equivalent oral hypoglycemic agents were available in all cases. This trend would be profitable to the health care institution, relatively reduce cost

of drugs to patients with respect to retail pharmaceutical premises and enhance public confidence in government hospitals.

In the present study, subjects could not buy 28.4% of available oral hypoglycemic agents because of cost. This is in agreement with results of a similar study which found that patients could not afford 35% of available prescribed medicines in a tertiary healthcare institution in Nigeria due to cost/poverty (Giwa, 2001).

Subjects were able to afford more prescribed generic anti-diabetic drugs compared with branded. They were unable to afford more branded compared with generics. The difference was statistically significant. Millennium development goal 7 emphasized equitable access to essential drugs. One third of world population (1.7-2.1 billion) lacked access to essential drugs (WHO, 2004). A major obstacle to achieving equitable access to drugs is price/affordability (WHO, 2008), especially in countries where drugs are paid for out of pocket. Drug financing in Nigeria, for example, is generally out of pocket, with 70.2% people living below poverty line of less than 1USD per day (FMOH, 2006). Strategies which would contain and moderate drugs' prices are needed to improve access to drugs. One of such strategies is the efficient use of generic drugs to foster competition in drugs market and therefore provide lower priced drugs that can be afforded in the health system (De Joncheere *et al.*, 2002; WHO, 2004).

Cost Minimization Analysis revealed that the mean cost/ DDD of branded anti-diabetic drugs were significantly higher than that of their generic equivalents in use in UMTH. This was so for all the anti-diabetic drugs analyzed. This is evidence that generic

anti-diabetic drugs are cheaper than branded ones. This is consistent with a finding that use of branded anti-microbial drugs was common in hospitals despite the more expensive nature of branded over generic anti-microbial drugs (Suleiman and Tayo, 2003).

The cost implication is more important for anti-diabetic drugs which are used for lifetime from period of diagnosis of a patient.

Generic medicines are available in all medicine outlets in Nigeria but branded products were found to cost 2 to 7 times the lowest priced generic equivalent (FMOH, 2006).

Savings generated by generic drugs in the last ten years was USDS 734 billion in the USA (GPhA, 2009). Generic drugs generate savings of 25 billion pounds each year for EU healthcare (EGA, 2007).

5.4 Cost Effectiveness Analysis

There was no statistically significant difference in the effectiveness (outcome) of glibenclamide and chlopropamide. This is in line with their documented comparable efficacy, bioavailability, safety and frequency of administration applied as criteria of their effectiveness rating (Cantrill, 1999; Bernard and Kesth, 2001). Cost Effectiveness Analysis, however, revealed that glibenclamide which was more frequently prescribed, was more cost-effective than chlopropamide. This is in agreement with Cantrill (1999) that reported glibenclamide as the drug of choice in the monotherapy of moderate hyperglycemia in non-obese Type II diabetes mellitus. Indeed, BNF (2010) recommended glibenclamide as the drug of choice in the management of Type II diabetes mellitus and discouraged the use of chlopropamide due to its exaggerated hypoglycemic and other side effects when compared with other drugs in the same class. These effects are due to its relatively longer half life

(35hours) compared with 24 hours for glibenclamide in the same class. It is also the only drug in its class that exhibit disulfiram like reactions (BNF, 2010).

There was no significant difference in the effectiveness (outcome) measure of metformin + chlopropamide and metformin + Glibenclamide. This result is in agreement with Benard and Kesth (2001) that there is no evidence to justify benefit of a combination of hypoglycemic agents over another, especially on a long term basis. This result is in line with their documented comparable/apparently equal efficacy, bioavailability, safety and frequency of administration (Cantrill, 1999; Bernard and Kesth, 2001). Cost Effectiveness Analysis which indicated that metformin + glibenclamide combination which was more frequently used was not necessarily more cost-effective than metformin + chlopropamide after sensitivity analysis, is also in support of the same report that there is no evidence to justify benefit of a combination of hypoglycemic agents over another, especially on a long term basis.

Effectiveness Measure (outcome) of soluble insulin + insulin zinc and biphasic isophane insulin revealed no statistically significant difference. This finding agrees with their documented comparable, efficacy, tolerability, bioavailability, safety and frequency of administration (Cantrill, 1999; Bernard and Kesth, 2001). Biphasic isophane insulin which was less frequently prescribed was more cost-effective than soluble insulin + insulin zinc. This result may be probably due to the fact that biphasic isophane insulin is a ready mixed combination of 30% soluble insulin and 70% insulin zinc, long acting with a duration of action of 16-18hours extending to 24 hours in some individuals, eliminates mixing errors and of lower cost than soluble insulin + Insulin zinc combination which may introduce mixing errors as reported by Cantrill (1999).

For the same reasons, effectiveness measure (outcome) of soluble insulin + insulin zinc + metformin combination and biphasic isophane insulin + metformin combination in the management of severe hyperglycemia in obese Type II diabetes mellitus revealed that there was no statistically significant difference in their effectiveness.

Biphasic Isophane Insulin + Metformin combination was more cost-effective than soluble insulin + insulin zinc + metformin combination, which is more frequently used at present in the management of severe hyperglycemia in obese Type II diabetes mellitus. There is no justification for this utilization trend from cost effectiveness point of view.

The results of this study support the report of Kara *et al*. (1997). They reported that cost effectiveness analysis could help to make decisions about whether new drugs should be included in a drug formulary list where decisions are made. These decisions are made based on the principle that if a drug is not better than a comparable product, it should not cost more, if it is superior to existing therapies but more expensive (a common situation) and funds are available, any extra expenditure should represent "value for money".

The present finding is significant because it has given a guide to institutional treatment and formulary system development for anti-diabetic therapy based on cost effectiveness.

Ray (1979), Mc Ghan (1993) and Bootman *et al.* (1996) reported that the use of valid economic evaluation methods to measure the value and impact of new services can increase acceptance of such programs by the medical profession, third party payers and consumers.

5.5 Relationship between Degree of Subjects' Knowledge/Practice of Lifestyle/Dietary Modification and Glycemic Control (Outcome of Anti-Diabetic)

The observed association between degree of subjects' knowledge about dietary modification and glycemic control, and the association between degree of subjects' knowledge about

lifestyle modification and glycemic control are significant because they imply that when diabetes patients acquires knowledge about benefits and practice of lifestyle/dietary modification through a comprehensive educational programme,

they would most likely adopt positive behavioral changes that would show clinically significant improvement in glycemic control, coronary heart diseases risk factors and quality of life measures as reported by Toobert *et al.* (2003). They opined that behavioural change, although difficult to obtain, is possible with regular support. They reported a smoking cessation rate of 36% in diabetes patients undergoing lifestyle modification educational programme compared with only 8% in the usual care group. There was an association between degree of cigarette smoking and glycemic control in the present study. Cigarette Smoking markedly increased the risk of coronary heart diseases (CHD) in diabetes while its cessation is effective in CHD risk reduction in diabetic patients (Baskaki, 2005). In one study, compared to those who never smoked, the relative risk (RR) for CHD across categories of smoking was 1.21 for past smokers, 1.66 for current smokers of 1-14 cigarette/day and 1.66 for current smokers with more than 15 cigarette/day (Al-Delaimy *et al.*, 2002). Smokers with diabetes have an increased risk of death, nerve damage, kidney diseases and foot infection. As such, smoking should be avoided in diabetics (Al-Delaimy et *al.*, 2002).

In the same trend, there was an association between practice of alcohol intake and glycemic control (outcome of anti-diabetic therapy). In diabetics, alcohol consumption should be avoided in those suffering from hypertriglyceridaemia, in those that are overweight and in those with hypertension (Christiansen *et al.*, 1993; Koivisto *et al.*, 1993). In general, alcohol use is discouraged in diabetes patients, but individual diabetic should be assessed to

determine if the advantages of alcohol consumption (e.g. reducing emotional tension, anxiety e.t.c) out-weigh the potential effects on blood glucose control (Eric and Gurley, 1993).

One of the major risks of alcohol consumption among individuals with diabetes is the potential danger of hypoglycemia, especially among those who use sulphonyl ureas (Bastaki, 2005).

An association between practice of exercise and glycemic control was observed in this study. Tayo (1975) reported improved insulin sensitivity and insulin induced glucose metabolism (glycolysis, glycogenesis and conversion of glucose to fats) with exercise. Exercise improves circulatory function, an important factor in diabetes management.

It helps maintain normal body weight, aids in breathing, digestion and metabolism (Eric and Gourley, 1993). Exercise contributes positively to well-being physically and mentally. It also increases glucose utilization. Diabetics should participate in some form of regular exercise as it will enhance stable blood glucose.

Overall, this study revealed an association between practice of lifestyle modification and glycemic control (outcome of anti-diabetic therapy). A comprehensive lifestyle programme has been reported by Toobert *et al*. (2003) to improve glycemic control, lower the risk of cardiovascular diseases which are potential complications of Type II diabetes mellitus and improves quality of life outcomes. Research showed that intensive lifestyle changes may prevent and even reverse CHD (Ornish *et al.,* 1998), which occur 2.5 times more in diabetics than in non-diabetics (Haffner *et al.,* 1998).

Furthermore, there is evidence of effectiveness of lifestyle and behavioral changes, including diabetes self-management training, in Type II diabetes mellitus patients (Wing *et al.*, 2001).

Lifestyle changes that focus on healthy eating, physical activity, weight control and diabetes care can prevent or delay the complications associated with Type II diabetes mellitus. Infact, the Diabetes Control and Complications Trial (1993) confirmed that people with Type II diabetes mellitus who improve their metabolic control through an intensive self-care regimen significantly decreased the onset and progression of micro-vascular complications.

There was an association between carbohydrate intake modification and glycemic control (outcome of anti-diabetic therapy). Carbohydrate consumption is acceptable, provided that it is rich in soluble fiber and is of low glycemic index (Bastaki, 2005). The American Diabetes Association in 2009 recommended that 60-70% of caloric intake should be in the form of carbohydrate. Dietary carbohydrate from cereal, bread, other grain products and sugars should provide 50-60% of the individual energy requirement (Health and welfare Canada, 1990). Current guideline on carbohydrate consumption still emphasizes the importance of total carbohydrate intake but it focuses on selecting carbohydrate with a low glycemic index (Walker and Whittlesea, 2008).

Similarly, there was an association between protein intake modification and glycemic control. Current evidence indicates that people with diabetes has similar protein requirement with those of the general population, about 0.8g/kg/day (Health and welfare Canada, 1990).

An association between saturated fat intake modification and glycemic control was also found in this study. Fat is the most energy rich of all nutrients and reduction of fat intake

helps to reduce total energy intake which is important for many people with Type II diabetes mellitus.

75% occurrence of good glycemic control with 25% and 0% occurrence of fairly and poorly controlled glycemia based on monitoring tests in 24 subjects on diet only respectively in the present study is an evidence that dietary modification enhanced glycemic control.

Overall, this study showed that there was an association between practice of dietary modification and glycemic control. This agrees with Trichopoulou *et al*. (2003) who found that adherence to dietary modification caused a 25% reduction in overall mortality due to poor glycemic control and a 33% reduction in death from cardiovascular diseases. The results of this study is an evidence to support the use of dietary modification (low fat, low carbohydrate, moderately high protein) and lifestyle modification (exercise and maintenance of ideal body weight) as the mainstay of management of Type II diabetes mellitus (ADA, 2009). Use of hypoglycemic agents in Type II diabetes mellitus is not to replace dietary and lifestyle modification, but to compliment it (Benard and Kesth, 2001).

Outcome Indicators of effective anti-diabetic therapy are obvious from the report of American Diabetes Association (2009) as fasting blood glucose (FBG) < 7.0 mmole/litre, glycosylated haemoglobin (HbAlc) < 7% and absence of signs/symptoms and complications of diabetes mellitus. The present study revealed that following indicators could rationalize the effectiveness of anti-diabetic therapy to ensure optimum economic, clinical and humanistic outcomes (ECHO): Drug Selection based on cost effectiveness (value for money), drug prescription based on cost minimization (use of generic name), drug supply and quality based on quality control parameters, patient counselling and patient education (to impact knowledge) about signs and symptoms of hyperglycemia/hypoglycemia,

beneficial effect of exercise, complications associated with diabetes mellitus, treatment and self monitoring.

Others are degree of practice of exercise, degree of knowledge/practice of dietary/lifestyle modification, evidence from medication record/case-notes of treatment compliance monitoring by pharmacist, physician, patient relations and self monitoring.

The findings from this study has addressed the concern of Cantrill (1999) that it is essential to consider individual and societal costs of diabetes and to search for reliable indicators for effectiveness of care for the disease.

5.6 Comparative Quality Control Parameters of Branded and Generic Anti-Diabetic Drugs

All branded and corresponding generic anti-diabetic drugs sampled passed their respective identification test, using B.P. (2004) chemical test methods. This imply that all samples tested contain genuine active ingredients.

The Hardness test results showed that all branded and corresponding generic anti- diabetic drugs were within the acceptable limit of mean hardness of 5-7 kgf inclusive (B.P., 2004). The observed similarity in hardness could be adduced to similarity in formulations excipients, techniques and compression forces employed by different manufacturers.

The results of weight uniformity test showed that all branded and corresponding generic anti-diabetic drugs sampled could be considered acceptable. These fell within acceptable limit of percentage deviation of not more than 10% for glibenclamide (Sample A and D) and not more than 5% for chlopropamide (Sample C and F) and Metformin (Sample B and E) (B.P., 2008). For pharmaceutical products, uniformity in weight may be due to even feeding

of granules into the die or regular movement of the lower punch producing a die space of varying capacity.

Considering the friability test results, all the three branded and corresponding generic anti-diabetic drugs had percentage average weight variation within acceptable limit of not more than 1% (B.P., 2008). Friability is a measure of the resistance of tablet and granules formulations of pharmaceutical products to abrasion.

The results of disintegration time test showed that all the branded and generic products have mean disintegration time within acceptable limit of not more than 900 seconds (15 minutes) (B.P., 2008), and could therefore be considered as satisfactory. Disintegration time determination is one of the two official tests for measuring *in vitro,* the ability of the incorporated active ingredient to be released from the tablet.

The results of the content of active ingredient (absolute drug content), assay, revealed that all branded and corresponding generic anti-diabetic drugs sampled were within the B.P. (2008) acceptable limit of 95%-105% for glibenclamide and metformin, and 92.5%-107.5% for chlopropamide. All tested samples could be considered as conforming to dosage on administration as purported in their label claim.

The results of dissolution rate test showed that all branded and corresponding generic products passed the dissolution rate test, using B.P. (2008) specification of average percentage dissolution rate of not less than 70%. Dissolution rate test is the second official test for measuring *in vitro,* the ability of the incorporated active ingredient to be released from the tablet.

Clinically, the desired goal of any drug is to achieve a therapeutic effect on administration. It is therefore imperative that the quality of the drug or drug product must be assured. With the

current trend of globalization, regulation of the entry of drug products into a nation's market becomes a necessity. This will check the influx of fake, sub-standard or adulterated drugs into the market and their attendant clinical problems especially in developing economy like Nigeria.

A drug is said to be fake if does not contain what it purports to be in the label claim (WHO, 2006). Existence of fake or substandard brand of any drug product impairs interchangeability among its different brands (e.g. branded and generic equivalent products). Interchangeability is the process of dispensing a different brand of a drug product in place of the prescribed drug. Interchangeable drugs must contain the same amount of the active principle, and must exhibit similar biological activity and bioavailability profile on administration. However, because of variation in excipient type, concentration and method of incorporation in drug formulation by different pharmaceutical companies, the possibility of differential bioavailability of branded and generic equivalent product cannot be ruled out. To determine the possibility of interchangeability of drug products therefore, requires that quality control parameters like identification, tablet hardness, weight uniformity, friability, disintegration time, absolute drug content and dissolution rate among others must be checked in other to assess its quality and efficacy.

Lack of assurance in efficacy/effectiveness due to chaotic drug distribution system in Nigeria which facilitate faking and counterfeit products has been reported as a possible reason for rampant prescription of branded over generic equivalent products (Suleiman and Tayo 2003). There was no rational for the observed frequent prescription of more expensive branded anti-diabetic drugs over cheaper generic equivalents when available and there is guarantee of it's effectiveness (outcome), using quality control parameters. The result of this

study has substantiated the reported identical outcome of branded and generic equivalent products by Suleiman and Tayo (2003) and has demonstrated the recommendation in the same report that branded and generic equivalent products be properly analyzed to ensure their bioequivalence with acceptable standards. Branded products can be substituted when generic products are not available, but they must also be of acceptable standards.

The use of generic names for drug purchasing as well as prescribing carries considerations of clarity, quality and price. Proponents of drug purchasing and prescribing point out that generic names are more informative than branded names, facilitate purchasing of products from multiple suppliers (competitive bidding) and facilitates products substitution whenever appropriate (reduce inventory). Generic drug products are often cheaper than branded products (Swift and Ryan, 1975; Rubin and Kellar, 1983). Generic substitution has long been applied in formulary system. It has the benefits of discouraging the use of less than optimal drug therapy, encourages competitive bidding and reduce inventory. These benefits have is some cases been quantified as direct drug and inventory saving.

Generic drug programme are today probably the most relevant economic strategy for drug supply (WHO, 1996). If generic substitution does not exist, price competition will not exist either and price of drugs will swell (WHO, 1996). Generic substitution stimulates bioequivalence comparisons and help to prevent the stocking of less than optimal products.

6. CONCLUSION AND RECOMMENDATION

6.1 CONCLUSION

6.1.1 Relationship between Socio-economic Status, Affordability and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Poor and non-poor subjects significantly differ in glycemic control (outcome of anti-diabetic therapy). Subjects that could afford all their drugs and those who could not, significantly differ in glycemic control (outcome of anti-diabetic therapy). Poverty could be said to be a hindrance to glycemic control (good health) in terms of drug purchase (non-affordability).

6.1.2 Cost of Illness Analysis

Annual average cost of illness of diabetes mellitus was N47, 924.95 ($319.50), representing 88% of annual per capita income.

6.1.3 Cost Minimization Analysis

There was a statistically significant difference in the frequency of anti-diabetic drugs prescription with dranded anti-diabetic drugs more frequently prescribed in all cases. Patients were able to afford more generics than branded despite the fact that the latter were prescribed more often.

There was a statistically significant difference in the mean cost per DDD of branded and generic equivalent products, with generic products being lower cost options to branded equivalents for all anti-diabetic drugs applicable for cost minimization analysis.

6.1.4 Cost Effectiveness Analysis (CEA)

There was no statistically significant difference in the effectiveness of chlopropamide and glibenclamide tablet. Glibenclamide which was more frequently prescribed was more cost-

effective than chlopropamide in the management of moderate hyperglycemia in non-obese Type II diabetes mellitus patients.

There was no statistically significant difference in the effectiveness of metformin + chlopropamide and metformin + glibenclamide. Metformin + Glibenclamide appeared to be more cost effective than Metformin + Chlopropamide in the management of moderate hyperglycemia in obese Type II diabetes mellitus patients. Sensitivity analysis indicated that the decision becomes invalid, showing that Metformin + Glibenclamide which was more frequently prescribed combination was not necessarily more cost effective than Metformin + Chlopropamide.

There was no statistically significant difference in the effectiveness of soluble insulin + insulin zinc and biphasic isophane insulin. Biphasic Isophane Insulin was more cost-effective than soluble insulin + insulin zinc which was more frequently prescribed in the management of severe hyperglycemia in non-obese Type II diabetes mellitus patients.

There was no statistically significant difference in the effectiveness of soluble insulin + insulin zinc + metformin and biphasic isophane insulin + metformin. Biphasic Isophane Insulin + Metformin was more cost-effective than Soluble Insulin + Insulin Zinc + Metformin which was more frequently prescribed in the management of severe hyperglycemia in obese Type II diabetes mellitus patients.

6.1.5 Relationship between Degree of Knowledge/Practice of Lifestyle/Dietary Modification and Glycemic Control (Outcome of Anti-Diabetic Therapy)

Subjects significantly differ in degree of knowledge about signs and symptoms of hyperglycemia/hypoglycemia, beneficial effect of exercise, dietary modification, lifestyle modification, complications associated with diabetes mellitus, treatment and practice of self

monitoring, with majority having poor knowledge in all cases and poor practice of self monitoring.

There was an association between degree of subjects' knowledge about signs and symptoms of hyperglycemia/hypoglycemia, beneficial effects of exercise, dietary modification, lifestyle modification, complications of diabetes mellitus, treatment, practice of self monitoring respectively and glycemic control**.**

There was an association between degree of subjects' knowledge about lifestyle modification and practice of lifestyle modification. There was also an association between degree of knowledge about dietary modification and practice of dietary modifications.

There was an association between practice of lifestyle modification and glycemic control. There was also an association between practice of dietary modification and glycemic control.

The process indicators that could rationalize efficiency of anti-diabetic therapy to ensure optimum economic, clinical and humanistic outcomes, from this study are: Drug Selection based on cost-effectiveness (value for money), drug prescription based on cost-minimization (use of generic name), drug supply and quality, patient counseling, patient education, exercise, dietary modifications, lifestyle modifications, complications associated with diabetes mellitus, treatment /compliance, evidence from medication record/case-notes of treatment compliance monitoring by pharmacist, physician, patient relations and self monitoring.

6.1.6 Comparative Quality Control Parameters of Branded and Generic Anti-Diabetic Drugs

All the branded and generic equivalents of chlopropamide, glibenclamide and metformin sampled from UMTH passed identification test, tablet hardness test, weight uniformity test, friability test, disintegration time test, absolute drug content test and dissolution rate test, using official books specifications.

6.2 RECOMMENDATIONS

- Feedback system to prescribers by dispensing pharmacists on patients that could not afford prescribed drugs should be established in our public and private pharmacies.
- Pharmaco-Economic principles should be adopted in our National Health Policy, hence its application at all levels of our healthcare delivery system in taking therapeutic and other healthcare intervention decisions.
- The result of this study is evidence-based, and be used to change prescription practice through educational intervention at prescribers and managerial leels. These two should be used to enhance and/or support regulatory intervention.
- Institutional Treatment Guideline for anti-diabetic therapy and Hospital Drug Formulary based on cost-effectiveness should be developed using this and/or similar research methodology.
- The process indicators, identified in this study should be adopted, developed into appropriate checklist and enforced in anti-diabetic therapy.

- Functional quality control laboratories should be established in our health care institutions for independent assessment of quality control parameters of procured drugs.

7. CONTRIBUTION TO KNOWLEDGE

The study on pharmaco-economic evaluation of anti-diabetic therapy in North-Eastern Nigeria has contributed to knowledge in the following ways:

- Established the basis for pharmacist-physician feedback system to be institutionalized in our public and private pharmacies, especially about patients that could not afford prescribed drugs which could lead to therapeutic failure (e.g. poor glycemic control) and waste of limited health care resources. The institutionalization will bring about effectiveness and significant cost savings in drug therapy.
- Highlights average cost of illness, North-Eastern Nigeria cost of illness and Nigerian National cost of illness of diabetes mellitus.
- Provides evidence-based information that could be used to change prescription practice: irrational prescription of more expensive branded anti-diabetic drugs which are used for lifetime from diagnosis of a patient than cheaper generic equivalents, by using the information for educational intervention at prescribers' and managerial levels. The resultant effect will be cost savings drug therapy.
- Indicates cost-effectiveness of various anti-diabetic therapy options: a guide to rational institutional treatment and formulary system development.
- Highlights process indicators for effectiveness of anti-diabetic therapy.

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