A COMPARISON OF PHARMACOLOGICAL TREATMENT, KNOWLEDGE AND LIFE STYLE MODIFICATION AMONG DIABETIC PATIENTS WITH MICROALBUMINURIA IN FOUR HOSPITALS IN INDIA AND MALAYSIA

by

MIRZA RAFIULLAH BAIG

Thesis submitted in the fulfillment of the requirements
for the degree of
Doctor of Philosophy

UNIVERSITI SAINS MALAYSIA

December 2010

"Dreams and Dedications are the swiftest way to Success"

Dedication

This research work is dedicated to my beloved father
(Late) MIRZA JANI BAIG
who died of Diabetic Nephropathy

STATEMENT OF ORIGINALITY

I declared that the work presented in this thesis contains no material which has been accepted for the reward of any other degree or diploma in any university or other institution. To the best of my knowledge, the thesis contains no material previously published or written by another person, except where due reference is made in the text.

Mirza Rafiullah Baig

ACKNOWLEDGEMENT

It is a great pleasure to acknowledge those who inspire and encouraged me to perform this great task, without whom this work would not have been accomplished. A teacher is a person who immediately transfers his soul to student's soul and sees through his eyes and thinks through his mind. At the onset I place on records my sincere thanks to my Supervisor Dr. Syed Azhar Syed Sulaiman, Associate Professor and Dean, School of Pharmacy, USM for his excellent guidance, moral support and for providing all the facilities which are required for research purpose. I really appreciate his kindness and down to earth personality which makes him unique among others. In spite of his hectic schedule, he always spares his precious time for his research students.

A field supervisor is a perennial source of inspiration and guidance in all the activities throughout the research field. These words are only prologue to acknowledge whole heartedly my deep and sincere gratitude to my field supervisors Dr. Ong Loke Meng, Director, Clinical Research Centre, Malaysia, and Dr. D. R. Krishna, Dean, School Of Pharmacy, Kakatiya University, Warangal, India. I owe a great deal of appreciation and gratitude to Dr. Punithavathi, for designing the epidemiological studies. The nursing staff from out-patient clinic of general medicine and nephrology, Puan Khadija & Kak Norain deserves my true appreciation for providing co-operative and creative environment to work excellently.

I am thankful to Dr. JayaRaman, Professor, School of Management, USM, for his guidance in analyzing the data using SPSS software. I am thankful to all the teaching staff

and non-teaching staff of school of pharmacy, USM for their support and co-operation throughout my work. I am also thankful to librarian and other staff of library USM for their timely help in issuing me books and journals for course of my study.

I express my sincere thanks to Dr. Azmi Hassali, Mr. Ahmed Awaisu, Mr. Abdullah Dahbali, Mr. Ahmed Zakuan, Dr. Chong and Mr. Abdul Hadi for their help in assessing statistical analysis. Words are inadequate to express my heartfelt feelings to my seniors and all my friends Ejaz Ahmed, Ali Raza Shah, Amer Khan, Jawad Ahmed, Khurram, Hameed, Khurshid. This work would not have materialized without their timely help and co-operation.

I am also thankful to my wife for her overall support, timely help and constant innovations that help me to complete this work. I had no words to express my gratitude to my elder brother Mirza Rasheed Ahmed Baig for his moral & financial support and I thanks to all my brothers & bhabhis, sisters & brother-in-laws for the overall support provided by them and the prayers done by them for my welfare and studies.

Last but not least, I feel indebted to my mother for the confidence she had on me and the blessings she had offered me to get complete my course of study in a fruitful manner. Above all, all praises go to my LORD, who is always beneficent, merciful and kind, who always gives me hope and strength whenever I feel disappointed. Without His Will I would never be able to perform this task. May ALLAH bless all the people who helped and supported me directly or indirectly in any aspect to complete my task and fulfill my aim.

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LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitors
ADA	American Diabetes Association
AGEs	Advanced Glycosylation End products
ANOVA	Analysis of Variance
AODM	Adult Onset Diabetes Mellitus
ARB	Angiotensin II Receptor Blockers
BMI	Body Mass Index
CCB	Calcium Channel Blocker
CRC	Clinical Research Centre
DCCT	Diabetes Control & Complication Trial
DCDCP	Diabetes Care Data Collection Project
DM	Diabetes Mellitus
EOD	Early Onset Diabetes
ESRD	End Stage Renal Disease
FBG	Fasting Blood Glucose
FBS	Fasting Blood Sugar
FDA	Food and Drug Administration(United States of America)
FPG	Fasting Plasma Glucose
GFR	Glomerular Filtration Rate
GPs	General Practitioners
HDL	High-Density Lipoprotein
HRQOL	Health Related Quality Of Life

IDDM	Insulin Dependent Diabetes Mellitus
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
LDL	Low-Density Lipoprotein
LOD	Late Onset Diabetes
MDRD	Modification of Diet In Renal Disease
MOH	Ministry Of Health
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NSAID	Non-steroidal Anti-Inflammatory Drugs
OGTT	Oral Glucose Tolerance Test
PLBG	Post Lunch Blood Glucose
PLBS	Post Lunch Blood Sugar
RBG	Random Blood Glucose
SPSS	Statistical Package for the Social Sciences
TGF-β	Transforming Growth Factor- β
UAER	Urinary Albumin Excretion Rate
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization

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LIST OF PRESENTATIONS AND COMMUNICATIONS

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Mirza Rafiullah Baig, Syed Azhar Syed Sulaiman, Abdul Hadi, D. Radhakrishna, Narayan
Poster presentation in the 8th Asian Conference on Clinical Pharmacy (ACCP), July, 1st – 4th, 2008, Surabaya, Indonesia

Abstract 2 "Effect of Antidiabetic & Antihypertensive Drugs used in the treatment of Diabetic Nephropathy"
Mirza.R.Baig, Syed Azhar Syed suleiman, D.R.Krishna, K.Satyanarayan Rao
Oral Presentation in the 7th Continuing Professional Development (CPD) Series: 'DIABETES ASIA 2008' CONFERENCE, October 23rd – 26th, 2008, Kuala Lumpur, Malaysia

Abstract 3 "Use of sulphonylureas to delay the progression of nephropathy in type II diabetes mellitus"
Baig MR , Syed Azhar SS, Ong Loke Meng
Oral Presentation in the 10th Asian Conference on Clinical Pharmacy (ACCP), July, 9th – 12th, 2010, Singapore

Thesis Presentation

Pharmacoepidemiology of diabetic nephropathy- A comparison of treatment module, knowledge and health related quality of life in early complication status of diabetic patients in India and Malaysia
Mirza Rafiullah Baig
Pre Viva Presentation in School of pharmacy, Universiti Sains Malaysia on 14th Jan 2010.

SATU PERBANDINGAN RAWATAN FARMAKOLOGI, PENGETAHUAN DAN GAYA HIDUP DALAM KALANGAN PESAKIT-PESAKIT DIABETIK DENGAN MIKROALBUMINURIA DI EMPAT HOSPITAL DI INDIA DAN MALAYSIA

ABSTRAK

Nefropati diabetik adalah salah satu komplikasi mikrovaskular yang utama dalam kalangan pesakit diabetik. Ahli epidemiologi meramalkan bahawa individu yang mengalami diabetes dalam populasi dunia akan mencecah 300 juta menjelang tahun 2025 dan hampir separuh daripadanya adalah dari benua Asia. Malaysia dan India terletak di tangga teratas dalam senarai penularan diabetik dengan India digelar 'Ibu kota diabetik sedunia'. Pelbagai cara telah dikaji dalam pelbagai bidang yang berkaitan komplikasi diabetik namun keputusannya masih kurang jelas. Oleh yang demikian, suatu kajian terkumpul dan perbandingan telah direka untuk merumus rawatan farmakologi, pengetahuan dan gaya hidup pesakit diabetik dengan mikroalbuminuria dengan kaedah pengesanan awal status komplikasi bagi mengelak atau memperlahankan perkembangan nefropati diabetic.

Kajian prospektif diskriptif garis lintang dan kajian cohort telah dijalankan dengan menggunakan teknik persampelan mudah di empat buah hospital di India dan Malaysia. Bagi mengumpul maklumat, satu borang pengumpul data yang standard telah direka dan dibahagikan kepada dua bahagian. Bahagian pertama mengumpul informasi tentang modul sosio-demografik dan modul rawatan serta diagnosis daripada rekod-rekod perubatan pesakit. Bahagian kedua melibatkan soal selidik yang mengumpul maklumat tentang ilmu pesakit dan modifikasi gaya hidup dengan cara menemuramah para pesakit.

Hasil keputusan dianalisis secara statistik dengan menggunakan perisian Statistical Package for the Social Sciences (SPSS), versi 15.

Sejumlah 3358, pesakit diabetik telah dihampiri untuk kajian ini yang mana 1025 pesakit telah didiagnos dengan mikroalbuminuria. Oleh yang demikian mereka telah dipertimbangkan untuk kajian penuh di India dan Malaysia. Min umur pesakit diabetik dengan nefropati di hospital kerajaan dan swasta di India dan Malaysia adalah 46.32±9.36 tahun, 44.34±8.01 tahun and 57.26±11.38 tahun, 55.45±10.31 tahun masing-masing. Penularan nefropati dalam kalangan pesakit di India didapati bermula pada umur yang lebih muda jika dibandingkan pesakit di Malaysia. Faktor-faktor risiko pesakit nefropati diabetik di keempat-empat hospital adalah umur, jantina, bangsa ($p<0.05$), sejarah keluarga, kemiskinan, diet, indeks massa tubuh (BMI), merokok, pengambilan alkohol, senaman, pematuhan terhadap pengambilan ubatan. Kesan faktor bangsa yang diperolehi dalam kajian pesakit Malaysia menunjukkan bahawa dalam ketiga-tiga bangsa (Melayu, Cina dan India), orang Melayu lebih cenderung mendapat masalah mikrovaskular diikuti dengan orang Cina dan sangat rendah dalam kalangan orang India ($p=0.048$). Sulphonylureas and perencat ACE masing-masing digunakan secara meluas untuk rawatan nefropati diabetik di kedua-dua negara. Analisis mendedahkan bahawa pesakit dengan perencat ACE yang menerima sulphonylurea ($p<0.001$), pioglitazone ($p<0.05$), dan insulin ($p<0.05$) menunjukkan keputusan yang lebih baik dalam kesemua tiga parameter (glukos darah, tekanan darah dan mikroalbumin) apabila dibandingkan dengan ubat-ubat kelas lain. Kajian yang dibuat terhadap pengetahuan dan gaya hidup dalam populasi multietnik Malaysia yang berkongsi konteks sosio-budaya yang sama mendapati bahawa latar belakang etnik mempengaruhi kualiti gaya hidup secara signifikan. Daripada keempat-empat hospital, pesakit-pesakit dari hospital kerajaan India mendapat skor

terendah dalam pengetahuan dan modifikasi gaya hidup ($p<0.001$). Kemiskinan adalah faktor utama yang memberi kesan terhadap gaya hidup mereka.

Akhir sekali, kesimpulannya adalah, pesakit-pesakit diabetik di kedua-dua negara menerima jenis rawatan yang sama dan mempunyai pengetahuan yang secukupnya tentang penyakit tersebut tetapi tidak mempraktikkannya dalam kehidupan seharian mereka untuk meneruskan gaya hidup yang baik dan sihat.

A COMPARISON OF PHARMACOLOGICAL TREATMENT, KNOWLEDGE AND LIFE STYLE MODIFICATION AMONG DIABETIC PATIENTS WITH MICROALBUMINURIA IN FOUR HOSPITALS IN INDIA AND MALAYSIA

ABSTRACT

Diabetic nephropathy is one of the major microvascular complications in diabetic patients. Epidemiologist predicts that the world population of diabetic individuals will swell up to an astounding 300 million by the year 2025 and almost half of that will be in the Asian region alone. Malaysia and India are ranked top in the list for the high prevalence of diabetes with India being termed as the "diabetes capital of the world". Interventions have been extensively studied in different areas of diabetic complications, but still results remained unclear. Therefore a collective and comparative study is designed to resolute the pharmacological treatment, knowledge and life style among diabetic patients with microalbuminuria by early detection of the complication status to prevent or delay the progression of diabetic nephropathy.

A prospective, cross sectional descriptive and a cohort study was conducted by using convenience sampling technique in four hospitals in India and Malaysia. To collect the information, a standard data collection form was developed and was divided into two parts. The first part was to gather information on socio-demographic as well as treatment module and diagnosis from the patient medical records. The second part involved questionnaires which collected the information about the patient knowledge and life style modification by interviewing the patients. Results were analyzed statistically using Statistical Package for the Social Sciences (SPSS) software version 15.

A total of 3358 diabetic patients were approached for the study out of which 1025 patients were diagnosed with microalbuminuria, therefore were taken into consideration for the

complete study in India and Malaysia. The mean age of the diabetic patients with nephropathy in government, private hospital in India and Malaysia, was found to be 46.32±9.36 years, 44.34±8.01 years and 57.26±11.38 years, 55.45±10.31 years respectively. The progression of nephropathy in Indian patients was found to be in early ages compared to Malaysian patients. The risk factors of diabetic neprhopathy patients found in all the four hospitals were age, gender, family history, poverty, diet, BMI, smoking, alcohol intake, exercise, medicine compliance, and race ($p<0.05$). The effect of race was found in the Malaysian study, which shows that within the three different races (Malay, Chinese, and Indian) Malays are more prone to microvascular complications followed by Chinese and least found to be in Indians ($p=0.048$). Sulphonylureas and ACE inhibitors were used most widely for the treatment of diabetes and nephropathy respectively in both the countries. The analysis revealed that the patients with ACE inhibitors receiving sulphonylurea ($p<0.001$), pioglitazone ($p<0.05$), and insulin ($p<0.05$) showed better results on all three parameters (blood glucose, blood pressure and microalbuminuria) when compared to other class of drugs. The survey conducted on knowledge and life style in multiethnic Malaysian population sharing the same socio-cultural context, found that ethnicity significantly influenced quality of lifestyle. Among the four hospitals, the patients from government hospital in India had lowest scores in knowledge and life style modification ($p<0.001$). Poverty was the main impact which affected their life style.

Finally, it is concluded that the diabetic patients in both the countries received a similar kind of treatment and have sufficient knowledge on the disease but are not implementing it in their daily life to maintain a good and healthy life style.

Chapter-1: INTRODUCTION

1.1 An Overview on Renal Disease

Nephropathy is a medical term used to refer to disease or damage in the kidneys. The kidneys act as one of the filtration systems in the body, expressing undesirable substances and retaining useful ones in addition to maintaining normal blood pressure levels. They also produce urine, a fluid which is used to express substances which are not needed by the body. When the kidneys are damaged, the lack of filtration resulting from it can make people extremely sick. People may develop nephritis, an inflammation of the kidneys, and this can progress to a full-blown nephropathy (Goodman et al., 2004).

In some cases, nephropathy is congenital, caused by a genetic problem which interferes with kidney function. Many congenital forms of nephropathy involve enzyme deficiencies which make it difficult for the body to process certain compounds. People can also acquire disease or damage through the use of certain drugs or lead exposure (Stephanie S Taber & Deborah A Pasko, 2008). Nephropathy is a very common complication of diabetes, resulting from damage to the kidneys caused by high blood sugar, and people with high blood pressure can also develop nephropathy.

One common form of nephropathy is Berger's disease, also known as IgA nephropathy, (Melk A, 2003) in which an antibody known as IgA builds up in the kidneys, impairing kidney function and causing an inflammation of some of the structures inside the kidneys. These Conditions can be diagnosed through samples of blood and urine, along with

biopsies, ultrasounds, and other studies which are designed to determine the functions of the body (Lamb et al., 2003).

Treatments are usually focused on determining the cause of the nephropathy and treating it. If the kidneys are overloaded with something the body cannot process, some of the kidneys fuction could partly be performed by dialysis. In extreme cases, kidney transplant is a treatment option for people with damaged kidneys that independent recovery is unlikely.

Because of the crucial role of the kidney in filtering blood, a wide range of systemic diseases and disease of other organ systems may be manifested most prominently in the kidney. Thus, renal disease is a prominent presentation of long-standing diabetes mellitus, hypertension, and autoimmune disorders such as systemic lupus erythematosus (Julio Avila, et al., 2008).

Without treatment, renal disease may result in sufficient loss of kidney functions. However, not all renal disease has an inexorable downhill course and dismal outcome. The consequences of renal disease depend on the extent and nature of the injury and its natural history and time course. Some forms of renal disease are transient. Even when severe, they may be self-limited and reversible and, if managed properly, may have no permanent bad consequences (Lai et al., 2005). Other forms progress eventually to renal failure, either rapidly or slowly, with a host of metabolic and hemodynamic consequences along the way. When renal disease progresses, there can be loss of aspects of renal filtration capacity (eg, disordered regulation of body electrolyte and volume status) as well as loss of nonexcretory renal functions such as the production of erythropoietin (resulting in anemia). The anatomic unit of kidney function is the nephron, a structure

consisting of a tuft of capillaries termed the glomerulus, the site at which blood is filtered, and a renal tubule from which water and salts in the filtrate are reclaimed. Each human kidney has approximately 1 million nephrons.

A glomerulus consists of an afferent and an efferent arteriole and an intervening tuft of capillaries lined by endothelial cells and covered by epithelial cells that form a continuous layer with those of Bowman's capsule and the renal tubule. The space between capillaries in the glomerulus is called the mesangium. Material comprising a basement membrane is located between the capillary and the epithelial cells. (Klahr S, 2002). Closer examination of glomerular histology and cell biology reveals features not found in most peripheral capillaries. First, the glomerular capillary endothelium is fenestrated. However, because the endothelial cells have a coat of negatively charged glycoproteins and glycosaminoglycans, they normally exclude plasma proteins such as albumin. On the other side of the glomerular basement membrane are the epithelial cells. (Christensen CK & Mogensen CE, 1985; Tremblay R, 2004). The mesangium is an extension of the glomerular basement membrane but is less dense and contains two distinct cell types: intrinsic glomerular cells and tissue macrophages. Both cell types contribute to the development of immune-mediated glomerular disease by their production of, and response to, cytokines such as transforming growth factor-β (Melk A, 2003).

The complex organization of the glomerulus is crucial not only for renal function but also for explaining the differences observed in glomerular disease. Thus, in some conditions immune complexes may accumulate under the epithelial cells, whereas in others they accumulate under the endothelial cells. Likewise, because immune cells are not able to

cross the glomerular basement membrane, immune complex deposition under the epithelial cells is generally not accompanied by a cellular inflammatory reaction.

The renal tubule itself has a number of different structural regions: the proximal convoluted tubule, from which approximately 80% of the electrolytes and water are reclaimed; the loop of Henle; and a distal convoluted tubule and collecting duct, where the urine is concentrated and additional electrolyte and water changes are made in response to hormonal control (Lewis EJ et al., 1993).

1.1.1 Renal Regulation of Blood Pressure

The kidney plays an important role in blood pressure regulation by virtue of its effect on sodium ion (Na^+) balance, a major determinant of blood pressure. First, the Na^+ concentration in the proximal tubular fluid is sensed at the macula densa, part of the juxtaglomerular apparatus. The juxtaglomerular apparatus also assesses the perfusion pressure of the blood, an important indicator of intravascular volume status under normal circumstances. Through the action of these two sensors, either low Na^+ or low perfusion pressure acts as a stimulus to renin release. Renin, a protease made in the juxtaglomerular cells, cleaves angiotensinogen in the blood to generate angiotensin I, which is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II raises blood pressure by triggering vasoconstriction directly and by stimulating aldosterone secretion, resulting in Na^+ and water retention by the collecting duct. All of these effects expand the extracellular fluid (ECF) and hence renal perfusion pressure, completing a homeostatic negative feedback loop that alleviates the initial stimulus for renin release (Lai et al., 2005).

Intravascular volume depletion also triggers vasopressin release. Receptors in the carotid body and elsewhere sense a fall in blood pressure and activate autonomic neural pathways, including fibers that go to the hypothalamus, where vasopressin release is controlled. Vasopressin is released and travels via the bloodstream throughout the body. At the collecting duct renal tubular apical plasma membrane, vasopressin facilitates insertion of water channels, thereby increasing the number of water channels. This results in reabsorption of free water (Lewis EJ et al., 1993).

1.1.2 Regulation of Renal Function

There are a variety of physical, hormonal, and neural mechanisms by which the functions of the kidney are controlled. Vasopressin, together with the physics of the countercurrent multiplier in the loop of Henle and the hypertonic medullary interstitium, makes it possible to concentrate the urine under normal circumstances. This confers on the normal kidney the ability to maintain fluid homeostasis under widely diverse conditions by generating either concentrated or dilute urine, depending on whether the body needs to conserve or excrete salt and water (Ljungman et al., 1980).

Tubuloglomerular feedback refers to the ability of the kidney to regulate the glomerular filtration rate (GFR) in response to the solute concentration in the distal renal tubule. When an excessive concentration of Na^+ in the tubular fluid is sensed by the macula densa, afferent arteriolar vasoconstriction is triggered. This diminishes the GFR so that the renal tubule has a smaller solute load per unit time, allowing Na^+ to be more efficiently reclaimed from tubular fluid. A variety of vasoactive substances, including prostaglandins, nitric oxide, and peptides such as endothelin and bradykinin, contribute to

the humoral control of tubuloglomerular feedback (Pedersen EB and Mogensen CE.,1976).

Another important challenge for the kidney is regulation of renal cortical versus medullary blood flow. Renal cortical blood flow needs to be sufficient to maintain a GFR high enough to clear renally excreted wastes efficiently without exceeding the capacity of the renal tubules for solute reabsorption. Likewise, medullary blood flow must be closely regulated. Excessive medullary blood flow can disrupt the osmolar gradient achieved by the countercurrent exchange mechanism. Insufficient medullary blood flow can result in anoxic injury to the renal tubule. From the perspective of individual nephrons, redistribution of blood flow from cortex to medulla involves preferentially supplying blood (and, therefore, oxygen) to those nephrons with long Loops of Henle that dip down into the inner medulla. (Prakash J. et al., 2006)

Most medullary oxygen consumption goes to generate the adenosine triphosphate (ATP) that fuels the array of active transporters involved in reabsorption of solute in the loop of Henle. Thus, when oxygen demand exceeds available supply, regulatory mechanisms tend to limit the workload of the ATP-consuming transporters. These regulatory mechanisms diminish the solute delivered to the loop of Henle (ie, by decreasing GFR). Renal blood flow is also preferentially shunted to medullary nephrons. In times of excessive oxygen demand, mediators are released, resulting in vasoconstriction of some vascular beds and vasodilation of others. This serves to both decrease GFR and, at the same time, redistribute blood flow from cortex to medulla (Pedersen EB and Mogensen CE.,1976).

1.1.3 Mechanisms underlying the decline in kidney function

There is no clear-cut consensus about what mechanisms may underlie the structural and functional changes occurring in the kidney in the older population. It is fairly clear however that there are both predisposing genetic and environmental factors that play a role (Levey AS et al., 2005).

1.1.3 (a) Predisposing Factors

It has been well known for many years that several diseases predispose to kidney failure and will accelerate the progress of age-related glomerulosclerosis. By far the most frequent of these are hypertension and diabetes, both common disorders in the older population. There are however several other mechanisms that have been postulated to underlie the aging changes in the kidney (U.S. Department of Health and Human Services, 2000).

1.1.3 (b) Free radicals and lipid peroxides

One possible explanation for the profound effects of calorie restriction is a reduction in the generation of free radicals and lipid peroxides. There is a wide body of literature discussing the damaging effects of free radicals on cellular systems and the role that this plays in aging. The main consequence of free radical production is lipid peroxidation, which results in damage to cellular proteins, lipids, and nucleic acids. Increased calorie intake is believed to fuel increased free radical production with accelerated aging damage. This hypothesis has generated interest in the role of antioxidants in slowing the aging process (Perneger et al., 1995).

1.1.3 (c) Protein restriction

The benefits of calorie restriction have been attributed to concomitant reductions in dietary protein. Clearly, protein restriction does have some benefit in the prevention of age-related nephropathy, but that advantage is small compared to those achieved with caloric restriction. (Perneger et al., 1995)

1.1.3 (d) Lipids

There is a well-established link between lipids and cardiovascular disease, and restriction of fat intake accompanied by treatment of hyperlipidemia has been shown to be efficacious in preventing or slowing the progress of cardiovascular disease. Certainly protecting the integrity and function of the vascular supply to the kidney is important to maintaining normal function. Patients with established renal disease with or without diabetes have more rapid deterioration of kidney function in the presence of hyperlipidemia. The relevance of lipids to the age-related decline in kidney function remains to be established, but it would certainly be reasonable to recommend low-fat diet and lipid management in patients with declining renal function (Perneger et al., 1995).

1.2 Pharmacoepidemiology

1.2.1 Definition

Pharmacoepidemiology is the study of the use of and the effects of drugs in large number of people. The term pharmacoepidemiology obviously contains two components: “pharmaco” and “epidemiology”. Thus pharmacoepidemiology is a relatively new applied field, bridging between clinical pharmacology and epidemiology. From clinical pharmacology, pharmacoepidemiology borrows its focus of inquiry. From epidemiology, pharmacoepidemiology borrows its methods of inquiry. The field of pharmacoepidemiology uses the techniques of chronic disease epidemiology to study the use of and the effects of drugs. Pharmacoepidemiology has primarily been in context of post marketing drug surveillance (Brain L.Strom, 2005).

1.2.2 Contributions of Pharmacoepidemiology

The potential contributions of pharmacoepidemiology are only beginning to be realized, as the field is new. Premarketing studies of drug effects are necessarily limited in size. After marketing, non-experimental epidemiologic studies can be performed, evaluating the effects of drugs administered as part of ongoing medical care. As an academic or a clinician, one is most interested in the new information about drug effects and drug costs that can be gained from pharmacoepidemiology. In an era of product liability litigation, this is an important assurance for looking any undiscovered problems which may be there. Pharmacoepidemiology study designs the investigator does not control the therapy, but simply observes and evaluates the results of ongoing medical care. Certainly, these are the findings that receive the greatest public and political attention. Moreover the field is expanding its focus to include many issues other than adverse reactions (Fletcher et al., 1996).

1.2.3 Study designs

Epidemiological studies can be divided into two main types:

1. Descriptive epidemiology describes disease and/or exposure and may consist of calculating rates, e.g., incidence and prevalence. Such descriptive studies do not use control groups and can only generate hypotheses, not test them. Studies of drug utilization would generally fall under descriptive studies (Brain L.Strom, 2005; Collett JP & Boissel JP, 1991).

2. Analytic epidemiology includes two types of studies: observational studies, such as case-control and cohort studies, and experimental studies which would include clinical trials such as randomized clinical trials. The analytic studies compare an exposed group with a control group and are usually designed as hypothesis testing studies (Brain L.Strom, 2005; Collett JP & Boissel JP, 1991).

Pharmacoepidemiology benefits from the methodology developed in general epidemiology and may further develop them for applications of such methodology unique to pharmacoepidemiology. There are also some areas that are altogether unique to pharmacoepidemiology, e.g., pharmacovigilance. Pharmacovigilance is a type of continual monitoring for unwanted effects and other safety-related aspects of drugs that are already on the market. In practice, pharmacovigilance refers almost exclusively to the spontaneous reporting systems which allow health care professionals and others to report adverse drug reactions to a central agency (Fletcher et al., 1996).

1.2.4 Perspectives on Pharmacoepidemiology

As the programs of pharmacoepidemiology study are expanded and developed, it is important that their effects are rigorously evaluated. There are several obvious roles of pharmacoepidemiologists in this process. These include drug utilization studies as part of a program to improve the quality of use of medicines, designing interventions to improve prescribing, the conduct and evaluation of pharmacoeconomic studies, and identifying and quantifying adverse drug reactions. In developing countries, there is still a need for adverse reaction reporting as part of the process to identify failure in the quality of producing sound data.

The future of pharmacoepidemiology seems apparent in many ways, judging from the past trends and recent events. Interest in the field by the pharmaceutical industry, government agencies, new trainees, and the public is truly exploding, as is realization of what pharmacoepidemiology can contribute. Thus from the perspective of academia, the pharmaceutical industry, regulatory agencies, and then the law in the field, the future of pharmacoepidemiology looks remarkably bright, although many important challenges remain (Brain L.Strom, 2005).

1.3 Diabetes Mellitus

1.3.1 Definition

Diabetes Mellitus is a syndrome which is caused by relative absence or lack of insulin. Clinically it is defined as a group of metabolic diseases characterized by high blood sugar (glucose) levels, which result from defects in insulin secretion, or action, or both. Diabetes mellitus, commonly referred to as diabetes, was first identified as a disease associated with “sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine. Normally, blood glucose levels are tightly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates (for example, after eating food), insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts a lifetime (International Diabetes Federation, 1999; American Diabetes Association, 2007).

1.3.2 Types of Diabetes

Generally there are two major types of diabetes, called type 1 and type 2 diabetes. Type 1 diabetes (previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the body’s ineffective use of insulin. It often results from excess body weight and physical inactivity (American

Diabetes Association, 2007, Diagnosis and classification of diabetes mellitus). Gestational diabetes is hyperglycemia that is first recognized during pregnancy.

Type 1 diabetes was also called insulin dependent diabetes mellitus (IDDM), or juvenile onset diabetes mellitus. In type 1 diabetes, the pancreas undergoes an autoimmune attack by the body itself, and is rendered incapable of making insulin. Abnormal antibodies have been found in the majority of patients with type 1 diabetes. Antibodies are proteins in the blood that are part of the body's immune system. The patient with type 1 diabetes must rely on insulin medication for survival.

Type 2 diabetes was also referred to as non-insulin dependent diabetes mellitus (NIDDM), or adult onset diabetes mellitus (AODM). In type 2 diabetes, patients can still produce insulin, but do so relatively inadequately for their body's needs. In many cases this actually means the pancreas produces larger than normal quantities of insulin. A major feature of type 2 diabetes is a lack of sensitivity to insulin by the cells of the body (particularly fat and muscle cells). In addition to the problems with an increase in insulin resistance, the release of insulin by the pancreas may also be defective and suboptimal. In fact, there is a known steady decline in beta cell production of insulin in type 2 diabetes that contributes to worsening glucose control. This is a major factor for many patients with type 2 diabetes who ultimately require insulin therapy. Finally, the liver in these patients continues to produce glucose through a process called gluconeogenesis despite elevated glucose levels. The control of gluconeogenesis becomes compromised.

While that type 2 diabetes occurs mostly in individuals over 30 years old and the incidence increases with age, we are seeing an alarming number patients with type 2

diabetes who are barely in their teen years. In fact, for the first time in the history of humans, type 2 diabetes is now more common than type 1 diabetes in childhood. Most of these cases are a direct result of poor eating habits, higher body weight, and lack of exercise.

While there is a strong genetic component to developing this form of diabetes, there are other risk factors - the most significant of which is obesity. There is a direct relationship between the degree of obesity and the risk of developing type 2 diabetes, and this holds true in children as well as adults. It is estimated that the chance to develop diabetes doubles for every 20% increase over desirable body weight (Evans et al., 2000)

Regarding age, data shows that for each decade after 40 years of age regardless of weight there is an increase in incidence of diabetes. The prevalence of diabetes in persons 65 to 74 years of age is nearly 20%. Type 2 diabetes is also more common in certain ethnic groups. Finally, diabetes occurs much more frequently in women with a prior history of diabetes that develops during pregnancy.

Diabetes can occur temporarily during pregnancy. Significant hormonal changes during pregnancy can lead to blood sugar elevation in genetically predisposed individuals. Blood sugar elevation during pregnancy is called gestational diabetes. Gestational diabetes usually resolves once the baby is born. However, 25-50% of women with gestational diabetes will eventually develop Type 2 diabetes later in life, especially in those who require insulin during pregnancy and those who remain overweight after their delivery. Patients with gestational diabetes are usually asked to undergo an oral glucose tolerance test about 6 weeks after giving birth to determine if their diabetes has persisted beyond the

pregnancy, or if any evidence (such as impaired glucose tolerance) is present that may be a clue to the patient's future risk for developing diabetes (American Diabetes Association. Preconception care of women with diabetes, 2004).

"Secondary" diabetes refers to elevated blood sugar levels from another medical condition. Secondary diabetes may develop when the pancreatic tissue responsible for the production of insulin is destroyed by disease, such as chronic pancreatitis (inflammation of the pancreas by toxins like excessive alcohol), trauma, or surgical removal of the pancreas. Diabetes can also result from other hormonal disturbances, such as excessive growth hormone production (acromegaly) and Cushing's syndrome. In acromegaly, a pituitary gland tumor at the base of the brain causes excessive production of growth hormone, leading to hyperglycemia. In Cushing's syndrome, the adrenal glands produce an excess of cortisol, which promotes blood sugar elevation (AACE, 2007)

1.3.3 Symptoms of diabetes

The early symptoms of untreated diabetes are related to elevated blood sugar levels, and loss of glucose in the urine. High amounts of glucose in the urine can cause increased urine output and lead to dehydration. Dehydration causes increased thirst and water consumption. The inability of insulin to perform normally has effects on protein, fat and carbohydrate metabolism. Insulin is an anabolic hormone, that is, one that encourages storage of fat and protein. A relative or absolute insulin deficiency eventually leads to weight loss despite an increase in appetite. Some untreated diabetes patients also complain of fatigue, nausea and vomiting. Patients with diabetes are prone to developing infections of the bladder, skin, and vaginal areas. Fluctuations in blood glucose levels can lead to

blurred vision. Extremely elevated glucose levels can lead to lethargy and coma. (American Diabetes Association., Standards for medical care in diabetes, 2007)

1.3.4 Screening and diagnosis

Any person found to have symptoms of diabetes mellitus (tiredness, lethargy, polyuria, polydipsia, polyphagia, weight loss, pruritus vulvae, balanitis) must be screened (American Diabetes Association, ADA 2004).

Any person who presents to a primary care facility for any reason, without symptoms of diabetes, but has any ONE of the following risk factors should be screened:

- Age 35 years or older
- Pre-obese, BMI > 23 kg/m2
- History of Gestational Diabetes Mellitus
- History of big baby (birth weight ≥ 4.0kg)
- History of diabetes mellitus in first degree relatives (parents, siblings)
- Hypertension (140/90 mmHg)
- Hyperlipidaemia
- Dyslipidaemia either HDL-cholesterol < 0.9 or Triglyceride > 1.7 mmol/L

Pregnant women should be screened at least once at > 24 weeks of gestation.

Screening at an earlier stage of gestation depends on degree of suspicion and at the physician's / obstetrician's request (American Diabetes Association 2007, Diagnosis and classification of diabetes mellitus).

The fasting blood glucose (sugar) test is the preferred way to diagnose diabetes. It is easy to perform and convenient. After the person has fasted overnight (at least 8 hours), a single sample of blood is drawn and sent to the laboratory for analysis. This can also be done accurately in a doctor's office using a glucose meter.

Normal fasting plasma glucose levels are less than 100 milligrams per deciliter (mg/dl). Fasting plasma glucose levels of more than 126 mg/dl on two or more tests on different days indicate diabetes. A random blood glucose test can also be used to diagnose diabetes. A blood glucose level of 200 mg/dl or higher indicates diabetes.

When fasting blood glucose stays above 100mg/dl, but in the range of 100-126mg/dl, this is known as impaired fasting glucose (IFG). While patients with IFG do not have the diagnosis of diabetes, this condition carries with it its own risks and concerns, and is addressed elsewhere.

Though not routinely used anymore, the oral glucose tolerance test (OGTT) is a gold standard for making the diagnosis of type 2 diabetes. It is still commonly used for diagnosing gestational diabetes. With an oral glucose tolerance test, the person fasts overnight (at least eight but not more than 16 hours). Then first, the fasting plasma glucose is tested. After this test, the person receives 75 grams of glucose (100 grams for pregnant women). There are several methods employed by obstetricians to do this test, but the one described here is standard. Usually, the glucose is in a sweet-tasting liquid that the person drinks. Blood samples are taken at specific intervals to measure the blood glucose (AACE medical guidelines, 2007).

Glucose tolerance tests may lead to one of the following diagnoses:

A person is said to have a normal response when the 2-hour glucose level is less than 140 mg/dl or 7.7 mmol/L, and all values between 0 and 2 hours are less than 200 mg/dl or 11 mmol/L (Malaysian Clinical Practice Guidelines: Management of Diabetic Nephropathy, 2004).

A person is said to have impaired glucose tolerance when the fasting plasma glucose is less than 126 mg/dl or 6.9 mmol/L and the 2-hour glucose level is between 140 and 199 mg/dl or 7.7 and 11 mmol/L.

A person has diabetes when two diagnostic tests done on different days show that the blood glucose level is high. (ie when 2- hr glucose level is more than 140mg/dl or 7.7 mmol/L)

A woman has gestational diabetes when she has any two of the following: 100g OGTT, fasting plasma glucose of more than 95 mg/dl or 5.2 mmol/L, 1-hour glucose level of more than 180 mg/dl or 10 mmol/L, a 2-hour glucose level of more than 155 mg/dl or 8.6 mmol/L, or a 3-hour glucose level of more than 140 mg/dl or 7.7 mmol/L (American Diabetes Association 2007, Diagnosis and classification of diabetes mellitus).

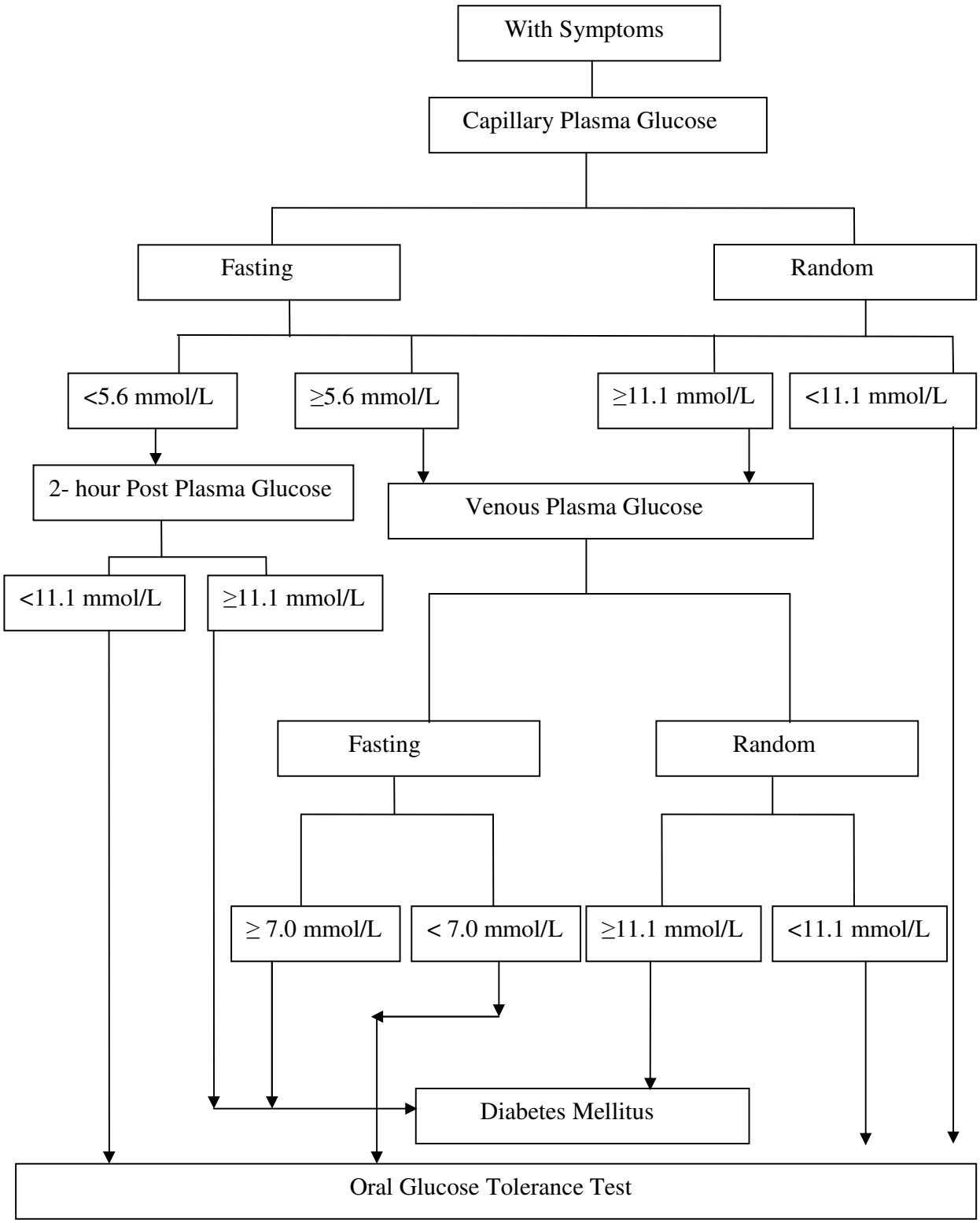

Figure 1.1: Screening for type 2 Diabetes Mellitus at Primary Care Level – with symptoms

(Source: Adapted from Appendix 1a, Clinical practice guidelines, Malaysia 2004)

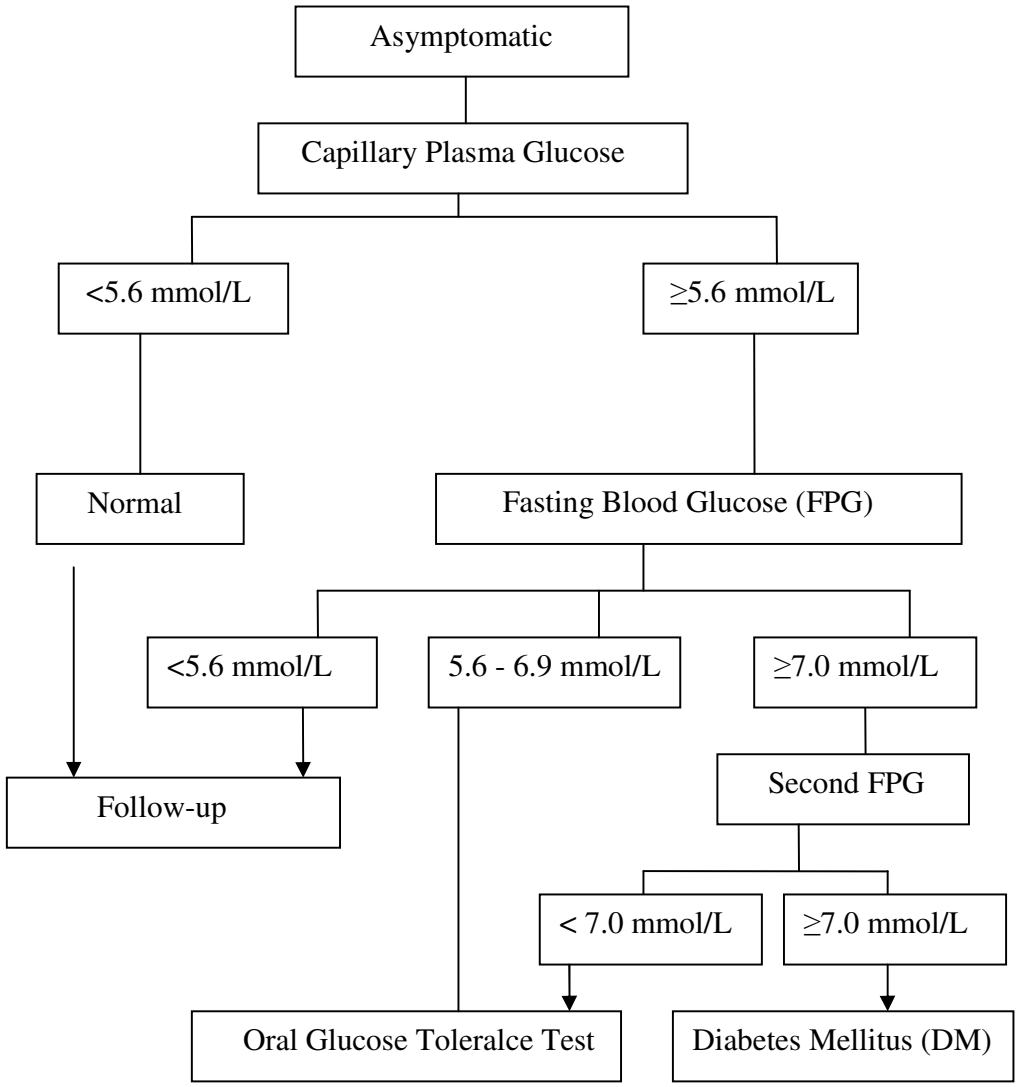

Figure 1.2: Screening for type 2 Diabetes Mellitus at Primary Care Level-without symptoms

(Source: Adapted from Appendix 1b, Clinical practice guidelines, Malaysia 2004)

1.3.5 Hemoglobin A1c (A1c)

In the blood stream there are red blood cells, which contain hemoglobin. Glucose sticks to the hemoglobin to make a 'glycosylated hemoglobin' molecule, called hemoglobin A1c. The more glucose in the blood, the more A1c will be present in the blood. The red blood cells that circulate in the body live for about three months before they die off. When sugar sticks to these cells, it gives us an idea of how much sugar is around for the preceding three months. In most labs, the normal range is 4-5.9 %. In poorly controlled diabetes, its 8.0% or above, and in well controlled patients it's less than 7.0% (optimal is <6.5%). The benefits of measuring A1c is that it gives a more reasonable and stable view of what's happening over the course of time (three months), and the value does not bounce as much as finger stick blood sugar measurements. There is a direct correlation between A1c levels and average blood sugar levels as follows (Engelgau MM, Thompson TJ, Herman WH, et al.,1997).

While there are no guidelines to use A1c as a screening tool, it gives a physician a good idea that someone is diabetic if the value is elevated. Right now, it is used as a standard tool to determine blood sugar control in patients known to have diabetes.

The American Diabetes Association currently recommends an A1c goal of less than 7.0%. Other Groups such as the American Association of Clinical Endocrinologists feel that an A1c of < 6.5% should be the goal (American Diabetes Association, 2007. Diagnosis and classification of diabetes mellitus).

Table-1.1: Correlation of HbA1c and Blood sugar levels

HbA1c (%)	Mean blood sugar	
	(mg/dl)	(mmol/L)
7	170	8
8	205	10
9	240	12
10	275	13
11	310	15
12	345	17

(Comparison of blood glucose and HbA1c,
http://medweb.bham.ac.uk/easdec/prevention/what_is_the_hba1c)

Of interest, studies have shown that there is about a 10% decrease in relative risk for microvascular disease for every 1 % reduction in HbA1c. So, if a patient starts off with an A1c of 10.7% and drops to 8.2%, though there are not yet at goal, they have managed to decrease their risk of microvascular complications by about 20%. The closer to normal the A1c, the lower the absolute risk for microvascular complications. Data also suggests that the risk of macrovascular disease decreases by about 24% for every 1% reduction in HbA1c values (American Diabetes Association, 2005).

It should be mentioned here that there are a number of conditions in which an A1c value may not be accurate. For example, with significant anemia, the red blood cell count is low, and thus the HbA1c is falsely low as is similarly in cases of sickle cell disease and other hemoglobinopathies (Engelgau MM et al.,1997).

1.3.6 Chronic Complications of Diabetes

These diabetes complications are related to blood vessel diseases and are generally classified into small vessel disease, such as those involving the eyes, kidneys and nerves (Redon J et al, 1994), and large vessel disease involving the heart and blood vessels (macrovascular disease,). Diabetes accelerates hardening of the arteries (atherosclerosis) of the larger blood vessels, leading to coronary heart disease (angina or heart attack), strokes, and pain in the lower extremities because of lack of blood supply (Diabetes Control and Complications Trial Research Group, 1993).

1.3.6(a) Eye Complications

The major eye complication of diabetes is called diabetic retinopathy. Diabetic retinopathy occurs in patients who have had diabetes for at least five years. Diseased small blood vessels in the back of the eye cause the leakage of protein and blood in the retina. Disease in these blood vessels also causes the formation of small aneurysms (microaneurysms), and new but brittle blood vessels (neovascularization). Spontaneous bleeding from the new and brittle blood vessels can lead to retinal scarring and retinal detachment, thus impairing vision (Diabetic retinopathy study, 1978).

To treat diabetic retinopathy a laser is used to destroy and prevent the recurrence of the development of these small aneurysms and brittle blood vessels. Approximately 50% of patients with diabetes will develop some degree of diabetic retinopathy after 10 years of diabetes, and 80% of diabetics have retinopathy after 15 years of the disease. Poor control of blood sugar and blood pressure further aggravates eye disease in diabetes (Ciulla TA et al., 2003).

Cataracts and glaucoma are also more common among diabetics. It is also important to note that since the lens of the eye lets water through, if blood sugar concentrations vary a lot, the lens of the eye will shrink and swell with fluid accordingly. As a result, blurry vision is very common in poorly controlled diabetes. Patients are usually discouraged from getting a new eyeglass prescription until their blood sugar is controlled. This allows for a more accurate assessment of what kind of glasses prescription is required.

1.3.6(b) Kidney damage

Kidney damage from diabetes is called diabetic nephropathy. The onset of kidney disease and its progression is extremely variable. Initially, diseased small blood vessels in the kidneys cause the leakage of protein in the urine. Later on, the kidneys lose their ability to cleanse and filter blood. The accumulation of toxic waste products in the blood leads to the need for dialysis. Dialysis involves using a machine that serves the function of the kidney by filtering and cleaning the blood. In patients who do not want to undergo chronic dialysis, kidney transplantation can be considered (The Diabetes Control and Complications Trial Research Group, 1995).

The progression of nephropathy in patients can be significantly slowed by controlling high blood pressure, and by aggressively treating high blood sugar levels. Angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) used in treating high blood pressure may also benefit kidney disease in diabetic patients.

1.3.6(c) Nerve damage

Nerve damage in diabetes is called diabetic neuropathy and is also caused by disease of small blood vessels. In essence, the blood flow to the nerves is limited, leaving the nerves without blood flow, and they get damaged or die as a result (a term known as ischemia). Symptoms of diabetic nerve damage include numbness, burning, and aching of the feet and lower extremities. When the nerve disease causes a complete loss of sensation in the feet, patients may not be aware of injuries to the feet, and fail to properly protect them. Shoes or other protection should be worn as much as possible. Seemingly minor skin injuries should be attended to promptly to avoid serious infections. Because of poor blood circulation, diabetic foot injuries may not heal. Sometimes, minor foot injuries can lead to serious infection, ulcers, and even gangrene, necessitating surgical amputation of toes, feet, and other infected parts (Obrosova IG, 2003).

Diabetic nerve damage can affect the nerves that are important for penile erection, causing erectile dysfunction (ED, impotence). Erectile dysfunction can also be caused by poor blood flow to the penis from diabetic blood vessel disease. Diabetic neuropathy can also affect nerves to the stomach and intestines, causing nausea, weight loss, diarrhea, and other symptoms of gastroparesis (delayed emptying of food contents from the stomach into the intestines, due to ineffective contraction of the stomach muscles).