1. Introduction

Diabetes mellitus is not a single disease but a syndrome consisting of different sub types of diabetes with hyperglycemia due to insulin deficiency, either absolute or relative, as a common factor. Its prevalence is increasing rapidly and has already reached an epidemic proportion in urban India. Hence every Family Physician and General Duty Medical Officer should be proficient in managing diabetic patients. If one's basics are strong, it is very easy to take correct decisions regarding ordering precise investigations, advising about diet and exercise and selecting appropriate Oral Antidiabetic Drugs (OAD's), Non insulin injectable anti diabetic agents [incretin based therapy]; and Insulin in correct dosages.

The aim of this book is to provide concise information required by a Family Physician or General Duty Medical Officer, to let him confidently handle his diabetic patients on his own and manage them successfully over a period of time. It will also be useful to the General Physician and Residents in medicine. This handbook's focus is Type 2 diabetes, (previously known as Non Insulin Dependent Diabetes or Maturity Onset Diabetes), and its management in an out patient/dispensary set up. It may be noted that more than 96% of diabetics in our country haveType 2 DM.

2. Classification and Clinical Manifestations

Diabetes mellitus has been classified in the following categories:

I) Type 1 DM, previously known as Insulin Dependent Diabetes Mellitus, (IDDM) or Juvenile diabetes.

Less than 2% of diabetics in our country belong to this class. Onset of Type 1 DM is usually very acute and in childhood. These patients depend on insulin for their survival and withdrawal of insulin leads to keto acidosis. Type 1 DM occurs due to auto-immune or idiopathic destruction of insulin producing beta cells in Islets of Langerhans in the pancreas resulting in inability to produce endogenous insulin which is vital for control of blood glucose and other metabolic functions. These patients usually require at least two shots of short-acting and intermediate-acting insulin every day. Some of the Type 1 DM patients require more intensive insulin therapy such as multiple subcutaneous insulin injections or continuous subcutaneous insulin injections through an external insulin pump. One must note that not all young diabetics on insulin are necessarily type 1 diabetics. Many young diabetics in our country require large doses of insulin for adequate blood glucose control. [E.g. those who have diabetes secondary to pancreatic destruction following fibro calculus pancreatitis or those type 2 diabetics who had severe malnutrition in intrauterine or infantile period. These patients are very often wrongly labeled as “insulin dependant” just because they are young and they are on insulin. Some of these patients stop insulin when they go to native place for a vacation and report back after few weeks in poor metabolic state but the fact that they are still surviving, is a confirmation that they are not type 1 or “insulin dependant” for life but insulin requiring diabetics. Initial presentation of type 1 diabetic patients is usually dramatic.

Type 1 diabetics present with severe symptoms such as polyurea, polydepsia, polyphagia, weight loss, and in some cases superadded with symptoms of diabetic keto acidosis

such as vomiting, deep rapid breathing characteristic of acidosis and deteriorating level of consciousness. If there is an underlying cause which has triggered metabolic deterioration, its symptoms are also superadded. E.g. cough and fever in case of pneumonia or tuberculosis. Type 1 diabetes usually presents in childhood or in young adults. Occasionally it strikes middle aged patients. In some middle aged patients initial presentation of type 1 diabetes is similar to type 2 DM, which is several times more common in that age group. They may show response to oral agents initially thus they are wrongly labeled as type 2 patients. However they become insulin dependant over a shorter period as compared to average type 2 diabetics and they are positive for GAD antibodies which confirm Type 1 DM. These patients are labeled as **LADA [Latent Autoimmune Diabetes in Adults].**

As far as initial management of type 1 diabetics and decision making is concerned, it requires experience. Hence Family Physicians should consult Diabetologists as regards policy decisions.

Type 1 diabetics require insulin for lifetime. Those who are severely symptomatic or in keto acidosis should be admitted. Severe hyperglycemia, recurrent vomiting, unpredictable food intake are indications for intravenous insulin infusion while others can be put on multiple subcutaneous insulin injections. Besides insulin, fluid and electrolyte replacement should be carried out. A search for the underlying precipitating cause should be made and if found, should be appropriately treated. [e.g. appropriate parenteral antibiotic for pneumonia]. Before discharge, patient should be trained for insulin injection technique and educated on various aspects of diabetes with a focus on importance of persistent tight blood glucose control, weight maintenance, control of blood pressure and cholesterol. He should be also trained on prevention and treatment of hypoglycemia, meal planning and appropriate physical exercise. At least one additional member of the

family should be trained along with the patient. Common sense should be used while selecting the family member for training. Those not requiring hospitalization should be trained on all the above mentioned aspects on out patient basis in phased manner. In our country many doctors particularly family physicians are unlikely to have services of trainers and dietitians on the daily basis. In such situations, it is prudent to reserve once a week two hours slot for 'diabetes clinic'. It is convenient to call diabetic patients for training and follow up during this slot. It is very important to know that unless and until the diabetic patient is well educated and trained, he will not be motivated to aim for and achieve persistent tight metabolic control. Dr. Joslin, a pioneer American diabetologist who had devoted a large part of working time to education of diabetic patients had stated in nineteen thirties: "The diabetic who knows most, will live the longest".

II) Type 2 DM previously known as Non-insulin Dependent Diabetes mellitus (NIDDM), or Maturity onset Diabetes mellitus

This sub type of diabetes is the commonest type of diabetes all over the world, more so, in our country. More than 96% of diabetics in India belong to this sub class. In the nineties, it was labeled as non insulin dependant diabetes because unlike Type 1 patients, these patients are not dependant on insulin for survival, even though many require insulin for adequate control of blood glucose a few years after maintaining good control on oral pills. Till eighties, Type 2 DM was called maturity onset diabetes because it is usually diagnosed in the middle age. Unless associated with acute stressful conditions such as severe infection, these patients are asymptomatic for a long period and onset of symptoms is very gradual. Very often diagnosis is made accidentally during periodic health check up, pre insurance check up, pre employment or pre operative check up. If one bypasses all

these check ups, he may present with severe symptoms of diabetes such as weakness, weight loss, polyurea, polydypsia, polyphagia, itching etc. It takes up to five years after the beginning of diabetes to reach this state. Rarely type 2 patients present with symptoms typical of diabetic keto acidosis, i.e., deep rapid breathing, deteriorating level of consciousness, vomiting, etc, in addition to above mentioned symptoms.

In type 2 DM, there is interplay between environmental and genetic factors leading to a chain of events, ultimately leading to diabetes. Most of the patients have varying degrees of dual defects, **beta cell dysfunction and Insulin resistance.** Both these pathogenic factors have contributions from genetic and acquired factors. For example, many type 2 diabetics have inherited beta cell defect to which acquired dysfunction of beta cells due to infantile or intrauterine malnutrition and transient dysfunction due to toxic effect of severe hyperglycemia are superadded. Insulin resistance has genetic as well as acquired components. Obesity is associated with insulin resistance and has acquired as well as genetic components.

Acquired insulin resistance can be multi factorial. Stress, drugs, sedentary life style, are some of the factors leading to acquired insulin resistance.

Type 2 DM is more common in obese people because of insulin resistance which is associated with obesity. If obese people have absolutely healthy beta cells, they never become diabetic because their beta cells have the capacity to produce extra insulin to override insulin resistance. Thus all the obese people do not become diabetic. In USA, 25% of the non diabetic adults are insulin resistant. They do not become diabetic because their beta cells do not have any genetic defect and thus are able to respond to increased demand of insulin by producing more insulin to counteract insulin resistance. However, in those who have inherited beta cell defect, their capacity to override insulin resistance by producing additional

insulin is limited thus they can not cope up with body's demand for extra insulin and become diabetic.

It is now accepted that T2DM is a multi hormonal and multi locational disease. In addition to insulin resistance and beta cell dysfunction, there are many other patho physiological alterations in type 2 diabetic patients.

Some of the patho physiological defects are mentioned below:

1] Alpha cell defect: There is an inappropriate post prandial hyperglucogonaemia in type 2 diabetic patients due to inability of alpha cells to suppress glucagon release in response to rising blood glucose in post prandial period. This leads to excessive hepatic glucose production in post prandial period.

2] Reduced GLP1 levels : The physiological role of GLP1 is to combine with its receptors on beta cells and facilitate release of insulin from the beta cells. Type 2 diabetic patients have impaired post prandial rise in GLP1 in response to food. This defect contributes towards hyperglycemia, particularly post prandial hyperglycemia.

3] Those with T2DM, obesity and other insulin resistant states have reduced dopaminergic tone in supra chaismatic hypothalamic region in early morning, thus disturbing the physiological circadian rhythm. This is associated with excessive release of neuro transmitters such as nor adrenaline, which in turn leads to inadequate suppression of hepatic glucose production and inadequate suppression of adipose tissue lypolysis.

Type 2 DM in children and adolescents

Recently increasing prevalence of type 2 diabetes has been reported in children and adolescents from all over the world including India. These patients are overweight, have significant insulin resistance and unlike type 1 diabetic, are ketosis resistance. They respond well to diet, exercise and metformin.

Thus, even tough type 2 DM presents most commonly in adults, it can present in childhood, similarly not all type 1 patients present in childhood, occasionally they can present in middle age.

Please refer to next chapter on Type 2 diabetes in children and adolescents for details.

III] Other specific types of diabetes

There are many rare conditions which are associated with or which lead to diabetes. The list is given below.

Genetic defects of beta cell function [e. g. glucokinase gene mutation].

Genetic defects in insulin action [e.g. leprechaunism].

Diseases of exocrine pancreas [e.g. pancreatitis, fibro calculus pancreatic disease].

Endocrine disorders [e.g. Cushing's syndrome, acromegaly and thyrotoxicosis].

Drug or chemical induced diabetes [e.g. thiazide, corticosteroids].

Infections [e.g. congenital rubella].

Immune mediated diabetes [e. g. due to anti insulin antibodies].

Other genetic syndromes associated with diabetes [e.g. Down's syndrome].

IV] Gestational diabetes

Diabetes first diagnosed during pregnancy is called gestational diabetes. It occurs in about 4% of pregnancies in western countries. In a study done in Chennai and nearby rural area in 2003, a prevalence of 16.7% and 10.7% was reported respectively. GDM results from insulin resistance of pregnancy interacting with beta cell defects. Usually blood glucose is normalized after the delivery. Since significant insulin resistance of pregnancy develops only in third trimester, gestational diabetes sets in only in this period. Presence of glucose intolerance in early pregnancy indicates pre existing type 1 or type 2 DM. Women having gestational diabetes are at higher risk to develop type 2 DM during later part of their life.

A note on older classification of diabetes

The above mentioned classification of diabetes was initially put up by American Diabetes Association in 1997 and subsequently adopted by WHO in 1998. The earlier classification of diabetes which was in use till 1997 had a sub type called Malnutrition Related Diabetes Mellitus [Pancreatic Diabetes].

The patients who were earlier classified in this type of diabetes are seen in many of the developing countries including India, particularly in Southern and Eastern states. Usually young adults are affected in their second or third decades. They are usually malnourished and they require relatively large doses of insulin for metabolic control. With few exceptions, all of them require insulin for control but at the same time discontinuation of insulin does not lead to diabetic keto acidosis unless severe stressful conditions co-exist.

Hence these patients are insulin-requiring but not insulin dependent. Pancreatic diabetes was further divided in two sub-types,

a) Fibro calculus Pancreatic Diabetes (FCPD)

In this condition, diabetes develops following recurrent and chronic pancreatitis associated with destruction and stone formation in the pancreatic duct. Symptoms of diabetes are associated with recurrent severe upper abdominal pain and in some cases, symptoms of malabsorption, due to associated deficiency of digestive enzymes produced in exocrine part of

the pancreas. Plain X-Ray of the abdomen and USG of abdomen reveal pancreatic stones and calcification. In addition, in many patients ultrasonography shows pancreatic ductal dilatation.

FCPD is now reclassified under "other specific types of diabetes" because according to current thinking it is secondary to pancreatic destruction.

b) Protein Deficient Diabetes Mellitus (PDDM)

Many of these patients have suffered from severe protein deficiency in their intra uterine period, infancy; or early childhood, leading to damage of Beta cells in the pancreas. Many of PDDM patients have current or old signs of under nutrition.

According to current classification of diabetes, PDDM does not warrant a separate class and is included in type 2 diabetes.

Hormonal and clinical profiles in these two sub-types of pancreatic diabetes are slightly different. However, further details are beyond the scope of this book. These patients usually require twice a day insulin administration.

Peculiarities of diabetics in India

1. India has second largest number of diabetics.
2. Percentage of type 2 diabetics among the diabetic population is higher than the developed countries, except Asian developed countries such as Japan. [Incidence of Type 1 diabetes increases as one travels from South Pole to North Pole, and is highest in Nordic countries such as Finland. Even in Europe, as one travels from north to southern European countries, such as Portugal, Spain, incidence of type 1 diabetes is reduced].
3. Type 2 diabetes presents at least 10-15 years earlier than western countries.

4. Obesity, as defined by BMI Criteria, is not as commonly associated with Indian type 2 diabetics as compared to west however central obesity with BMI in normal range is very common, so is insulin resistance.
5. Hereditary component in pathogenesis of type 2 DM is strong, particularly in south India.
6. Secondary diabetes following destruction of pancreas due to fibro calculus pancreatic disease is seen in a small percentage of patients. This variety of secondary diabetes is restricted to developing countries such as India.
7. Prevalence of type 2 diabetes in children and adolescents is increasing very rapidly in India.

3. Type 2 Diabetes in Children and Adolescents

Till a decade back type 2 diabetes was considered as an exclusive disease of adults, mostly middle aged people. In fact till nineties it was officially known as maturity onset diabetes. It was known since long that average age at the diagnosis of type 2 diabetes in India was 10 years younger. [in 4 th and 5 th decade and occasionally in 3 rd decade instead of 5 th and 6th decade as in western population] however over last decade, more and more cases of type 2 diabetes are seen in children and adolescent. Such cases were first described from the western countries and soon they started appearing in India. In USA, less than 3% of diabetics in children had type 2 diabetes barely a decade back. At present 45% of children having diabetes have type 2 diabetes in USA. In Japan, 80% of children with diabetes have type 2 diabetes. Precise figures are not available from our country even though our incidence and prevalence figures are closely following the advanced countries. The increased prevalence of type 2 diabetes in children and adolescents is mainly due to rapidly increasing prevalence of obesity in this age group.

Over entire last century, the prevalence of obesity was gradually increasing and over last two decades the rate of increase has tremendously accelerated. In addition to increase in prevalence in middle aged persons, the prevalence in children and adolescents has also increased considerably. In a recent survey done in Chennai, about 15% of children and adolescents were overweight. In India, socio economic changes are occurring at very rapid speed. Urbanization, industrialization; and westernization have become unstoppable. While industrialization is good and urbanization inevitable with industrialization, blindly following western habits is detrimental and hence should be avoided. Our food habits are changing rapidly. The frequency of eating in restaurants has increased. We are eating more refined, energy dense fast food. The portion sizes of various dishes and ready made fast food items have increased as a result of aggressive marketing of "jumbo sized" food items and multi unit packs at so called discounted prices

inducing the consumers to buy and consume more than required. Even while eating at home, the food our children eat has undergone dramatic changes. Maida based preparations such as biscuits and bread have replaced rough cereal based freshly cooked preparations such as rotis and bhakris. The ready made items contain refined raw material deficient in fiber and thus are energy dense. [A unit volume contains more calories than home made fresh preparations based on whole cereal flour and fresh vegetables and fruits]. TV, internet and computers take up whatever little free time children could use for physical activity on the playground. All these factors are responsible for rapidly increasing prevalence of obesity and diabetes.

Clinical features :

The common age of onset is during adolescence and teens. The clinical features are similar to those of type 2 diabetes in adults. Most of the patients are obese, even morbid obesity is not rare in these patients. Signs of insulin resistance such as acanthosis nigricans are usually present. Strong family history of type 2 diabetes is often present. Like their adult counterparts, symptoms are usually gradual in onset. Weight loss, lethargy, tiredness, polyurea, polydypsia and itching are some of the common symptoms. Sometimes type 2 diabetes in children presents with acute symptoms which resemble classical symptoms of type 1 diabetes. During the initial presentation, patients may be dehydrated and extremely weak and occasionally urine can be weakly positive for ketones. Under such circumstances clinical differentiation between the two types of diabetes is difficult. These patients are initially treated with insulin and fluid and electrolyte replacement. After swift control of glucotoxicity with insulin, their insulin requirement is rapidly reduced. This serves as a clue for possibility of type 2 diabetes and absence of markers such as GAD and other antibodies in blood clinches the diagnosis. These patients can be subsequently maintained on lifestyle management and OADs.

Management of type 2 diabetes in children:

The basic principles of management are same as those of type 2 diabetes in adults. Appropriate diet and exercise form the basic foundations of management. If and when these measures are not sufficient to reach glycemic goals, OAD's are added. Since insulin resistance is predominant underlying patho physiology in most of these patients, Metformin, the time tested insulin sensitizer is usually the agent of first choice. Since it is a new entity, large scale randomized double blind trials with metformin or any other OAD have not yet been performed in type 2 diabetic children. The general principles of subsequent management are same as in the adult counterpart. Early diagnosis and prompt management to reach the glycemic and BMI targets is vital, more so than even the adult counterpart because of the long life ahead of the patients who are struck with type 2 diabetes in childhood. If the targets are not reached and maintained the vascular complications strike these patients in their youth affecting their productivity at the prime of their lives and in the long run having adverse effects on the socio economic aspects of the family. Thus besides diet, exercise and medications, patient education has vital central role. Patient must understand as early as possible that there is no alternative to tight metabolic control.

4. Epidemiology of Diabetes

A study of prevalence pattern of a disease in a community is known as epidemiology.

Prevalence of a particular disease in any given community at any given time is expressed in percent and it represents percent of total population suffering from that disease. **Incidence** gives information on the number of new cases developing a particular disease in a community during a specified period, usually a calendar year.

During the past 50 years, many countries in the world including India have experienced dramatic improvement in life expectancy due to improved nutrition, better hygiene and control over many communicable diseases. However prevalence of non communicable diseases such as diabetes has dramatically increased, leading to increasing burden and cost to the society. The term **epidemiological transition** is applied to describe these changes in disease pattern. This transition has catapulted diabetes from its former status as a rare disease at the beginning of last century, to its current position is a major global disease responsible for considerable mortality and morbidity.

The prevalence of diabetes has increased by leaps and bounds in India and has already reached epidemic proportions. India has more than 62 million diabetic patients. Thus it is vital to collect epidemiological data on diabetes from all over the country so that it can be used to evolve prudent preventive and therapeutic strategies best suited for our socio economic situation.

Till early seventies, properly collected epidemiological data on diabetes from India was conspicuous by its absence. There were few studies from different parts of India, most of them were spot surveys done during social gatherings and also hospital or practice based studies. Such a data does not represent the prevalence rates in the community as only healthy people attend social gatherings while hospital and

practice based data totally misses out on asymptomatic, undiagnosed patients. Even in an advanced country such as USA, it is estimated that for every known diabetic, there is one unknown [undiagnosed] diabetic. If this is a state of affairs in USA, one can imagine the situation in our country. The era of community based, scientific epidemiological studies on diabetes in our country were unfolded in early seventies, when Indian Council of Medical Research conducted multicentric urban as well as rural studies from six different parts of our country. Subsequently, many more scientific studies have been conducted.

Epidemiology of Type 1 DM

Definitive data from population based studies on prevalence of Type 1 DM is not available from India. However, it is relatively rare in our country and less than 2% of the diabetics in India are having Type 1 DM. Asian continent has lowest incidence rate of Type 1 DM, approximately 0.5 cases per annum per 100,000 populations. However recently it has been postulated that some patients who have onset of diabetes in the middle age and whose symptoms develop gradually and who develop either primary failure or early secondary failure to sulfonylureas, are actually suffering from late onset and slowly progressive subtype of Type 1 DM. Immunological markers for Type 1 DM are positive in these patients. There are a few studies on these patients from south India, but epidemiological studies are lacking.

Prevalence of Type 1 DM increases as one travels from southern to northern hemisphere. About 15-20% of diabetics in northern European countries are having Type 1 DM. Among the countries in the European continent, there are significant north-south differences as regards incidence. Incidence rate of Type 1 DM in Finland is 28 per 100,000 as against 6 per 100,000 in France. In addition to geographical variation, there is a seasonal variation in incidence rates. More cases are diagnosed in winter. This is attributed to seasonal variation for viral infections which

trigger autoimmune destruction of beta cells in pancreas leading to acute onset diabetes. An interesting finding about incidence is that in USA, incidence is much higher in white population as compared to blacks in the same area. Since the environmental factors are same for both the ethnic groups, the difference in incidence is probably based on genetic factors. Offspring of Type 1 DM father are three times more likely to develop it by the age of 20 years as compared to those of Type 1 DM mother, [6% vs. 2%]. It is postulated that exposure to diabetic environment in utero offers protection, perhaps by inducing immunological tolerance to the antigen involved in autoimmune destruction of pancreatic beta cells. However genetic factors are less important in pathogenesis of Type 1 DM as compared to Type 2 DM. This has been amply proved by the studies done in twins.

Relationship between Type 1 DM occurrence and certain HLA antigens: In the early seventies, certain HLA antigens were shown to be positively associated with Type 1 DM but not with Type 2 DM. Although, initially certain HLA B antigens were identified for association with Type 1 DM, DR antigens have since been shown to have stronger association with the disease. In all the populations studied, Type 1 DM has been confined largely to the individuals who carry HLA DR 3 or HLA DR 4 antigens.

Epidemiology of Type 2 DM

As against incidence studies in Type 1 DM, prevalence studies are more commonly done in Type 2 DM. It has become epidemic in many developing and rapidly industrializing countries including India. In our country, more than 96% of the diabetics have Type 2 DM. Prevalence of Type 2 DM which was about 2% in early seventies has sharply risen to more than 8% in late nineties and more than 14% in recent surveys in urban areas of our country. As per the latest prevalence study done by ICMR in 2011, India has 62.4 million diabetics and 72.2 million pre

diabetics. Prevalence rates of Type 2 DM correlate with the degree of modernization, and many societies which are rapidly undergoing a transformation from traditional to modern lifestyles are experiencing some of the highest rates of diabetes. Noted diabetologist and epidemiologist Dr. Paul Zimmet has termed the process leading to the epidemic of diabetes in developing countries as "Coca Cola-ization". Thus globalization may be good for economy but it is a threat to civilization. "Westernization, industrialization and Coca-Colization have ruined civilization". Over the years, epidemiological studies done in different parts of the globe have shown that the Indian migrants settled abroad have a higher prevalence as compared to the local host population living in identical environment, as well as the population native in India. This has been reported from countries with long established Indian populations such as Singapore, Fiji islands, South Africa, Tanzania, Uganda, Trinidad and UK. Data generated over last two decades from our country have proved that the prevalence of Type 2 DM is rapidly rising among urban population and is approaching the prevalence rates seen in the migrant Indian population. The following table gives various prevalence surveys done in urban India over last two and half decades.

Year	CITY	Author	Prevalance %
1972	New Delhi	Ahuja et al	2.3
1988	Kudremukh	Ramchandran et al	5.0
1989	New Delhi	Ahuja et al	6.7
1992	Madras	Ramchandran et al	8.2
1997	Madras	Ramchandran et al	11.6
2000	Kashmir	Zarger	12.1
2001	Chennai	Mohan	12.1

While there is a drastic increase in prevalence rate in urban India the prevalence in rural India has increased at slower rate. Consumption of traditional diet and relative absence of mechanization have protected the rural population.

However as per recent survey done is Tamilnadu, prevalence or diabetes is rapidly rising even in rural areas. In PODIS Study by Mohan and his group, prevalence of T2DM was 4.26% in rural areas. Another very worrisome finding is reduction in prevalence rate of IGT (Pre diabetes). It means faster conversion of these people to diabetes and thus more rapid rise is the prevalence of diabetes.

The following chart gives future global and Indian prevalence Rates for Diabetes

Estimated numbers of people with diabetes in India and China for 2000 and 2030 and summary of population changes (Figures in millions)

	Number of people with diabetes in 2000	Number of people with diabetes in 2030	Percentage of change in number of people with diabetes	Percentage of change in total population	Percentage of change in population > 65 years of age	Percentage of change in urban population
India	31.705	79.441	151	40	168	101
China	20.757	42.321	104	16	168	115
World	171.228	366.212	114	37	134	61

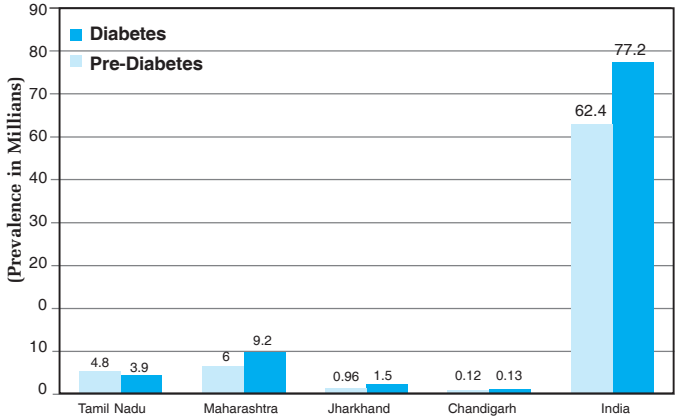
These estimations and projections were made by international authorities a few years back.

However, as per recent study done by ICMR in 2011 in the states of Tamilnadu, Maharashtra and Jharkhand and in the city of Chandigarh , India already has 62.4 million people having diabetes, thus we are likely to surpass the figure of 79.4 million much before the year of 2030.

The following table gives prevalence of diabetes and pre diabetes as per the latest study done by ICMR in 2011.

Prevalence of Diabetes and Pre-Diabetes in India : ICMR-India B Study

No. of people with Diabetes & Pre-Diabetes in India - 2011

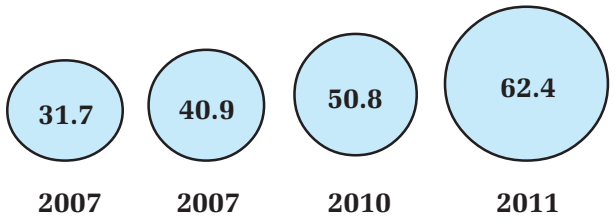


Source : Diabetologia 2011

The following table gives information on increasing prevalence of diabetes in India.

Increasing Prevalence of Diabetes : India

Persons with Diabetes (Millions)



Source : MDRS

There is a large variation in prevalence of Type 2 DM between the communities. The highest rates are found in some native American tribes such as Pima Indians [over 50%], while low prevalence rates are found in least developed rural communities in many Afro Asian countries. [3%].

Epidemiology of GDM

GDM occurs in about 4% of the pregnancies in the western world. In a Study done in Chennai is 2003 the prevalence of GDM was 10.7% in rural and 16.7 is urban areas. In the majority of cases, blood glucose returns to normal in post partum period but the lifetime risk for future diabetes is substantially increased in women who develop GDM. About 40% develop diabetes in next 10 years.

Conclusion

The epidemics of inter related lifestyle disorders have struck the globe like tsunami with its epicenter in rapidly developing and industrializing Asian continental India and China. A global epidemic of Type 2 DM is occurring, particularly affecting developing countries and migrant population from these countries to more industrialized and westernized societies. This epidemic has closely followed the epidemic of obesity. The epidemic of T2DM itself is being closely followed by that of cardiovascular disorders particularly coronary artery disease. Until recently, based on the available epidemiological data, which was outdated to some extent, it was believed that India had the dubious distinction of having more diabetic patients than any other country including China. However, **India is probably not the country with highest number of diabetics, anymore!** Recently [March 2010], a large scale epidemiological survey was done across China to study the prevalence of diabetes in that country. Instead of using fasting plasma glucose as a sole test, as done in the earlier epidemiological studies, the survey also did post 75 g. glucose blood glucose levels in all the people who were included in the survey. It was found out that there are about 93 million diabetic patients in China. Based on the earlier surveys, it was estimated that China has about 39 million diabetic people, a figure lower than the estimated figure for prevalence of diabetes in India. However with 2011

data from ICMR study, we now know that the difference between the Chinese diabetic population based on the recent data and Indian diabetic population is smaller.

As estimation of post glucose load blood glucose level is cumbersome and time consuming, most of the epidemiological studies use fasting plasma glucose, which is a bit less sensitive as compared to post 75 gm glucose load plasma glucose level. However, if a scientific national survey is done in our country by using same methods of diagnosis of diabetes as used in a recent study in China, the prevalence of diabetes is likely to be much higher. How much higher? And whether it will be higher than China? These are the "million dollars questions" and thus not possible to precisely answer.

5. Diagnosis & Laboratory Investigations

It goes without saying that a pre-requisite for proper management of diabetes is precise diagnosis. However, in practice, in mild or borderline cases, many times a wrong diagnosis is made due to various factors such as misconception, use of non-specific tests (e.g. Folin & Wu or Somogi Nelson methods of blood sugar estimation), too much reliance on urine sugar reports, etc. Misconception in the minds of pathologists adds to the problems instead of solving them! For example, it is not uncommon to get a report from pathologists in a seventy five year old patient with post prandial blood glucose of 145 mg% with a red underline below 145 mg% or the values are mentioned in red. Unfortunately, sometimes these patients are straightaway put on Oral Antidiabetic Drugs (OAD) leading to severe hypoglycemia.

Remember; a positive Benedict's test in urine does not necessarily mean diabetes, as it is a non-specific test which shows positive results with many reducing substances including various sugars and medicines. In pregnancy, it is physiological to pass lactose in the urine and hence a Benedict's test is positive. However, occasionally pregnant women have been treated for "diabetes". These are just two of many pitfalls in diagnosis of diabetes. Just as over diagnosis of diabetes leads to over enthusiastic treatment, more often, the late diagnosis is the cause of worry. The time gap between the onset or T2DM and development of symptoms can be as long as 5 years. During this period, vascular complications set in. Thus it is not uncommon to come across a patient having diabetic retinopathy on the day of diagnosis of DM. In short, early and correct diagnosis of DM, as well as avoidance of over diagnosis, both are vitally important.

CRITERIA FOR DIAGNOSIS OF DIABETES

For non pregnant persons:

A) In a person with classical symptoms of diabetes, one reading of unequivocal hyperglycemia, i.e. random venous plasma glucose > 200 mg% is sufficient to make diagnosis of diabetes. For example, if a person has polyurea, polydipsia, weight loss and random blood glucose of 315 mg%, he is diabetic and no other test is required to confirm the diagnosis. In such a situation, full GTT is a definite waste of time and money and hence need not be done.

B) Fasting venous plasma glucose of 126 mg% on more than one occasion is sufficient for diagnosis of diabetes even in the absence of symptoms.

C) A two-hour venous plasma glucose of 200 mg% or more after oral glucose load of 75 g on more than one occasion.

In non diabetic persons, fasting and 2 hours post oral 75 g glucose values of venous plasma glucose are lower than 100 mg% and 140 mg% respectively.

If fasting venous plasma glucose level is between 100 to 126 mg% and if two hours post 75 g glucose venous plasma glucose level is below 140 mg% the condition is called ***Impaired fasting glucose [IFG]*** and if two hour post 75 Gm oral glucose challange values are between 140 to 200 mg%, the condition is known as ***Impaired glucose tolerance [IGT].*** These two conditions represent an intermediary state between normal on one side and diabetes on the other side **(Pre diabetes).** Some people have isolated IFG/IGT, while others have combined IFG and IGT. As regards micro vascular complications of diabetes, people in IFG and IGT are not at significant risk and in this respect, both the conditions are equivalent. However as regards macro vascular diseases associated with diabetes, people in IGT are at a higher risk as

compared to those in IFG. With control of weight with prudent diet and physical exercise, approximately 50% of people with IGT revert back to normal. Some remain in IGT range while others slip into clear diabetic range over a course of time. On an average, every year 5% of people with IGT become diabetic. It should be remembered that in IGT group, there is no urgency to put them on OAD. However, they need proper diet control, exercise and six monthly follow up with blood glucose estimation. Those who are unlikely to follow diet and exercise regimen can be put on metformin or acarbose. It is not uncommon to see an IGT patient, recently and wrongly diagnosed as a diabetic and put on a stiff dose of Sulphonylurea, to present with OAD induced repeated hypoglycemia as the presenting symptom.

While interpreting results of laboratory tests, remember to verify the following:

i) Is it true glucose estimation or sugar estimation (Folin & Wu)? The latter method gives 10-15% higher values.

ii) Is it a plasma value or whole blood value? Whole blood glucose values are lower by about 20%.

iii) Is it capillary glucose value or venous glucose value? While there is no difference in the fasting state between the two methods, post prandial values are higher in capillary blood as compared to venous blood.

All values mentioned under diagnostic criteria are venous, plasma true glucose values.

Diagnostic glucose concentrations for diabetes, IFG and IGT in Mg%

	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Diabetes mellitus				
Fasting	≥ 110	≥ 110	≥ 126	≥ 126
Two hrs post glucose load	≥ 180	≥ 200	≥ 200	≥ 220
IGT				
Two hrs post	≥ 120 &	≥ 140 &	≥ 140 &	≥ 160 &
glucose load	< 180	< 200	< 200	< 220
IFG				
Fasting	≥ 90- < 113	≥ 90- < 126	≥ 100- < 126	≥ 100- < 126

Diagnosis of Gestational Diabetes mellitus [GDM]:

Historically, criteria for the diagnosis of GDM have always been intensely debated and more than one school of thoughts has always existed. We will bypass the details of these debates and rationales put forward by the various schools of thoughts and follow the 2010 recommendations of International Association of Diabetes and Pregnancy Study Groups, which were adopted by American Diabetes Association in 2011. These are:

Diagnosis of GDM in Pregnancy-Threshold values

Glucose value	Mg%
FPG	92
1 hr OGT-PG [75 g]	180
2 hr OGT-PG [75 g]	153

GDM = one or more values ≥ threshold [all are venous plasma glucose values]

In addition to the abovementioned method of diagnosis of GDM, WHO definition is also commonly followed in our country. As per WHO, GDM is diagnosed when 2 hours post 75 g glucose challenge plasma glucose equals or exceeds 140 mg %.

Limitations of urine glucose estimation:

As regards urine glucose estimation, it should never be solely relied upon for diagnosis of diabetes. It can only be used for getting a very rough idea of control on a day to day basis, provided the patient or his physician interpreting the results is thoroughly conversant with limitations and pitfalls.

While doing urine tests, observe the following:

a) Use the dry strip method (e.g. Diasticks) which is specific for glucose instead of Benedict's test which gives many false positive results.

In order to reduce the cost by 50%, cut the test strip vertically in two equal halves.

b) Ask the patient to completely empty the bladder 15 minutes before the time of urine estimation so that when the second sample is collected for estimation, freshly formed urine is obtained. Such urine glucose estimation will give a more realistic idea about the spot blood glucose value.

In many diabetics, glucose is invariably spilled over in urine during the post prandial period but they can still have a normal fasting blood glucose and absence of urine glucose in fasting state. However, in such patients, urine voided first thing in the morning is actually a mixture of urine formed over several hours overnight and hence it can show glycosuria even though urine actually formed in the morning does not contain glucose. Hence it is important to always collect freshly voided urine for glucose-estimation.

c) Every time you order blood glucose, insist for a glucose test on freshly voided urine so that you get some idea of the patient's renal threshold (i.e. blood glucose level beyond which glucose starts spilling in urine). Normally the threshold for glucose is 180 mg%. However, many diabetics have a low renal threshold in the initial stages i.e. glucose appears in their urine at blood glucose levels lower than 180 mg%. Hence one should be careful while increasing the dosage of OADs in such patients solely on estimation of the urine glucose value. On the other hand many long standing diabetics have a high renal threshold for glucose. In other words, glucose in urine is absent even when blood glucose is higher than 180 mg%.

In short, urine glucose tests should be used by patients for day to day self monitoring in-between his visits to the doctor for getting a rough idea about control and he should report back to the doctor prior to his next appointment date if there is a persistent change in the pattern of urine glucose.

In addition to the various points mentioned above, it may be worthwhile to remember the following:

1) Absence of glucose in the urine does not rule out diabetes as in many mild diabetics, fasting urine could be negative for glucose but post prandial urine is more likely to be positive for glucose.

2) Presence of sugar in the urine in the Benedict's test does not necessarily mean that the person is a diabetic.

3) Even if you have a reasonably good idea of a given patient's urine threshold for glucose, urine glucose estimation still cannot differentiate between normoglycemia and hypoglycemia. Hence it cannot replace a blood glucose test (Absence of glucose in the urine does not mean the patient is “well controlled”; he could be “over controlled”).

4) Do not rule out hypoglycemia in a patient in whom a spot urine test is positive for glucose, if the patient had not voided urine for several hours.

Considering several limitations of urine glucose estimation and easy availability of glucometers and laboratory tests, urine glucose estimation has extremely limited utility in the current scenario and should be used only if glucometers are not available or affordable.

Urine examination for ketones:

It is very important to examine urine for ketones in certain specific situations such as:

1] When patient has excessive thirst, hunger and urination.

2] Whenever there is vomiting with or without deterioration in general condition.

3] Whenever a diabetic is drowsy and urine is loaded with glucose and blood glucose is above 250 Mg% [in such a case close relative should perform urine ketone examination].

In above mentioned situations, presence of ketones in urine indicates diabetic ketosis and the patient should be instructed to seek immediate medical attention.

Method for examination of ketones in urine is simple and essentially same as that for glucose estimation. Many companies market dry strips for urine ketone examination.[e.g. Keto diastick, which is designed to simultaneously examine glucose and ketones in urine.

Investigations in diabetics and suspected diabetics:

For the diagnosis of diabetes, one should order Fasting and Post 75 gm glucose challange, venous plasma glucose. GTT is usually not required. One should order fasting and post glucose challenge blood glucose tests in the following situations:

a) Those having symptoms of diabetes.

b) Those having tuberculosis, peripheral neuropathy, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, eczema, premature cataract, etc.

c) As a pre-operative check-up.

d) Those above 40 years, as part of a routine medical checkup (above 30 years in case of those with a very strong e.g. family history of type 2 DM).

e) These tests should be done every six months in those who have pre diabetes, and every 3 months in those who are known diabetics provided they are well controlled. In known diabetics, instead of post glucose blood glucose, post meal blood glucose should be ordered. In the initial period and in those who have unstable control, blood glucose tests should be repeated more frequently whereas in emergencies, such as diabetic keto acidosis, hypoglycemic coma, etc. blood glucose should be done several times a day.

In a newly detected diabetic patient, the following additional baseline investigations should be ordered:

a) Lipid profile (at first follow up)

b) Serum creatinine

c) Full urine examination and test for micro albuminurea, if routine urine exam. Shows absence of albuminurea.

d) Electrocardiogram

e) Detailed Ophthalmic check-up. (5 years after the diagnosis in type 1 patients)

Subsequently, Serum creatinine, ophthalmic check-up and urine for microalbuminuria should be repeated every year. If the patient develops proliferate retinopathy, it should be further evaluated with Flouroscein Angiography and treated with Laser photocoagulation to prevent blindness.

If a patient develops diabetic nephropathy, his OAD should be reassessed, and use of nephrotoxic drugs e.g. Aminoglycoside antibiotics (Gentamycin, Amikacin, etc.) and NSAIDs should be avoided. Whenever a diabetic patient loses control and in those who are difficult to control from the beginning, a thorough search should be made for occult tuberculosis and other infections and X ray chest and other appropriate investigations should be ordered. Whenever a long-standing diabetic gradually requires lesser dosage of OAD or Insulin or he goes into hypoglycemia with the same dosage, suspect diabetic nephropathy.

Glycosylated Hemoglobin Estimation [HbAlc]

This blood test is useful to estimate the average control of blood glucose in the previous 90 days.

The blood can be drawn any time of the day. If done by a reliable laboratory, it provides important information which blood glucose estimation cannot provide. Ideally, it should be done at every three monthly follow up visit, in addition to blood glucose estimation. The two values together give vital information.

For example :

1) Normal HbA1c, high FBS- interpretation: overall control over the last 90 days was okay and it is possible that either control was lost recently or the patient did not take the previous evening's medication. One should verify before increasing the dosage of medication under such circumstances.

2] High HbA1c, normal fasting and post lunch blood glucose: Other post prandial values need to be checked. Some people take small working lunch but a large dinner, their post dinner blood glucose values are much higher than post lunch blood glucose values.

3) High HbA1c but normal blood glucose. Interpretation: overall control over the last 90 days was poor and control was achieved in the last few days. If such results are obtained in pre-employment check-up, one should suspect the possibility of a diabetic person hastily achieving control through treatment from a private doctor so as to pass the pre-employment medical examination.

Estimation of HbA1c has become an integral part of routine laboratory tests in a day to day management of diabetes in economically advanced countries and also in many centers in our country. HbA1c has very good co relation with micro vascular complications of diabetes. However, it has certain limitations which precludes it's widespread use in our country, such as cost of estimation and non availability of standardization.

Principles of HbAlc test :

In circulating blood, glucose is constantly getting attached to hemoglobin through non enzymatic process. This attachment is irreversible and percentage of hemoglobin in glycated form out of total hemoglobin in circulation depends upon blood glucose level. Thus in a diabetic patient, depending on the degree of hyperglycemia over previous 90 days, higher percentage of hemoglobin is glycated as compared to normal persons in whom around 4% to 6% of hemoglobin is glycated. In other words HbA1c levels are in the range of 4% to 6% in non diabetic, normal persons. Thus a diabetic with persistent poor control will have very high level of HbA1c while a diabetic with persistent tight blood glucose control will have his HbA1c values near those for normal persons. **All diabetics should aim to keep their HbAlc constantly between 6.5% to 7%.**

Haemoglobin A1c [HbA1c], as a diagnostic test for diabetes mellitus, Are we ready for it?

Diabetes mellitus is a metabolic and vascular disease with hyperglycemia and specific micro vascular complications in those who are poorly controlled over a long term period as its characteristic features. However, there is no well defined threshold level of blood glucose beyond which micro vascular complications develop and below which there is a complete immunity from complications. Thus fasting venous plasma glucose value of 126 mg% and two hours post 75 g oral glucose load value of 200 mg% are somewhat arbitrary diagnostic values for diabetes mellitus. At present, for the want of better diagnostic test, blood glucose values are used as the only criteria for the diagnosis of diabetes, however these have certain limitations.

Among the micro vascular complications of diabetes, diabetic retinopathy is the most extensively studied complication as regards its co relationship with fasting and post glucose load blood glucose values. Till 1997, fasting venous plasma glucose and two hours post 75 g oral glucose load cut off point for diagnosis of diabetes were 140 mg% and 200 mg% respectively. These points were based on symptoms of diabetes and not on risk for development of micro vascular complications. Even tough there is no clear cut threshold blood glucose value for retinopathy, some people with fasting blood glucose values between 126-140 mg% have evidence of early non proliferative diabetic retinopathy, however retinopathy is very rare in those having fasting venous plasma glucose value below 126 mg%. Thus, in 1997 criteria for diagnosis of diabetes based on fasting blood glucose were lowered from 140 to 126 mg.[venous plasma glucose] Moreover fasting value of 126 mg% has better co relation with post glucose load value of 200 mg% as regards micro vascular complications. Even though, lowering of diagnostic fasting blood glucose value was seen as a definite improvement, using

blood glucose values for diagnosis of diabetes still have some limitations such as 1) poor reproducibility due to analytical variance, 2) need to remain in fasting state for 8 hours, 3) false lower values if the blood sample is not analyzed with in 1 hour due to glycolysis. Laboratory methods for estimation of Haemoglobin A1c and instruments used for estimation have been standardized in the advance countries by National Glycohamoglobin standardization programme, (NGSP, of USA). 99% of the laboratories estimating HbA1c are NSGP certified in USA. HbA1c values are reproducible. Storage of collected blood for few hours does not lead to faulty estimation. In addition HbA1c has a better co relationship with micro vascular complications as compared to blood glucose values. While the former is an indicator of average glycemic control over preceding 12 weeks, the later gives information about glycemic control at the precise point of time of drawing glucose from the body. Thus HbA1c is relatively unaffected by acute stressful conditions. Moreover blood for its estimation can be drawn at any time of the day.

Considering above listed advantages of using HbA1c test, some diabetologists in advanced countries are of the opinion that it should be used as an additional option for the diagnosis of diabetes in non pregnant persons. In 2008, The American Diabetes Association along with International Diabetes Federation and European Society for Study of Diabetes had jointly set up a committee of experts to study the current and future means of diagnosing diabetes in non pregnant adults. The international committee's report was discussed in a symposium held during American Diabetes Association's annual Congress in June 2009 and published in July 2009 issue of Diabetes Care.

Recommendations and conclusions of International Committee:

1) At present there is no single "gold standard" test for the diagnosis of diabetes.

2) The measure to capture chronic exposure to glucose is more likely to be informative regarding presence of diabetes than single measure of glucose.

3) HbA1c is a reliable measure of chronic hyperglycaemia and has a better co relationship with chronic micro vascular complications.

3) HbA1c estimation done by the method certified by NSGP has several advantages over blood glucose estimation.

4) Properly performed HbA1c is a better test for diagnosis of diabetes than blood glucose estimation.

5) Diagnosis of diabetes is made if HbA1c is equal to or greater than 6.5%.

6) Diagnosis of diabetes should be confirmed by repeat HbA1c estimation unless there are gross symptoms of diabetes and random blood glucose is above 200 mg%.

7) In those suffering from haemoglobinopathies and anemia interfering with HbA1c estimation and interpretation, and if HbA1c estimation is not available, current conventional tests should be used for the diagnosis of diabetes.

8) In pregnancy, blood glucose estimation should be continued to be used for the diagnosis of diabetes as changes accruing in red cell turnover rate during the pregnancy can affect HbA1c estimation.

9] Individuals with HbA1c values between 6.0 to 6.5% are likely to have higher risk for progression to diabetes and thus should be kept on follow up and screened for other risk factors .

Subsequently, in January 2010, American Diabetes Association ratified the recommendations of the International committee as regards the use of HbA1c for the diagnosis of diabetes mellitus in its position statement issued in supplement to Diabetes Care (January 2010).

Are we in India ready for adaptation of HbA1c as a diagnostic test for diabetes in non pregnant persons? In many places and situations, we are not yet ready, because of the following reasons.

1) Properly done HbA1c test is available at very limited laboratories in big cities.
2) The cost of doing HbA1c is eight times more than that of blood glucose test, thus it would be out of reach of majority of Indians.
3) Many doctors are not conversant with the interpretation of HbA1c report.

However clinicians should be aware of this latest addition to the diagnostic criteria for diabetes and wherever possible, this new criterion can be used.

Following table gives average blood glucose levels over last 90 days for a range ofHbA1c values.

HbA1c in %	Mean blood glucose in mg%
4	60
5	90
6	120
7	150
8	180
9	210
10	240
11	270
12	300
13	330

Fructosamine Test

Like HbA1c, it is a blood test in which glycated plasma proteins are measured and expressed as percentage of total plasma proteins. It gives information on average metabolic

control over the previous two weeks. It is not yet regularly done in our country. It is more useful than HbA1c to access metabolic control during pregnancy.

HbA1c derived average glucose [eAG], a new patient friendly concept of expressing metabolic control:

Glycosylated haemoglobin, HbA1c, a gold standard in assessing metabolic control, is expressed in % value. Even though it is an indicator of average blood glucose control, since the unit of expression is not in mg%, and since the values are at variance with blood glucose values, the expression is not patient friendly, but is confusing to the patient. (HbA1c of 7% indicates average blood glucose of 150 mg %).

In order to express average blood glucose in patient friendly and meaningful manner, a large multi centric, multi national work was carried out in 700 persons. (300 each had type 1 and 2 diabetes and 100 were normal controls. Originally 11 centers spread across North America, Europe, Africa; and Asia were included. One centre dropped out due to technical reasons. Those having conditions such as anemia, haemoglobinopathies, and renal impairment were excluded from the study. A large amount of data on glycemic control was generated in these people by studying them for 4 months. In this period, all were subjected to continuous interstitial fluid glucose monitoring for 48 hours every month for 4 months. In addition, they were subjected to HbA1c estimation 5 times at a central laboratory in Europe. Participants also underwent self capillary glucose monitoring seven times a day, three times a week for 4 months. From this data, (2400 interstitial fluid measurements, 300 capillary measurements and 5 HbA1c measurements per patient), average glucose value was calculated and it's correlation with HbA1c was worked out and a mathematical formula to convert HbA1c in to average glucose value was developed. Interstitial fluid

values were scaled up by 5% to derive capillary glucose values. 507 participants completed the entire study.

Estimated average glucose in Mg%, eAG = 28.7 X HbA1c - 46.7.

Estimated average glucose in m. mol\L = 159 X HbA1c - 2.59

The entire work was a joint effort of ADA, EASD, IDF; and IFCC (International Federation of Clinical Chemists)

It is proposed that in future IFCC will standardize and cal liberate all the equipment used for estimation of HbA1c and also officially release the mathematical formula. Subsequently, the laboratories will give report in HbA1c format expressed in %, as currently done, in m.mol\L. format, as well as in eAG in mg% format.

In other words, HbA1c will not be done away with but will be standardized and calliberated by IFCC method [[instead of less accurate NGSP method as it is done at present]. In addition, eAG in mg% will be calculated by mathematical formula and given along with HbA1c report as an additional value. 7% HbA1c will be equivalent to 154 mg% of glucose instead of 150 mg% as at present. Hence in future, indicators of long term glycemic control and spot or point of time glycemic control will be expressed in same units. This move will be very much patient friendly and will be welcome by all.

6. Use of Glucometer in Family Practice

In a day to day practice of a family physician or a general duty medical officer, he commonly has to deal with routine management including dosage adjustments and also handle emergencies in a diabetic patient. Thus a properly functioning glucometer with all the accessories is a must for him both in the clinic and in emergency bag. ***Glucometer is as essential to a clinician as a stethoscope, blood pressure apparatus and a torch.***

Applications of glucometer in family physician's clinic:

1] When a patient walks in with symptoms suggestive of diabetes. Even though one should not solely rely on glucometer readings when hyperglycemia is detected for the first time, availability of on the spot blood glucose value will definitely help in planning of further line of action including the investigations.

2] When a known diabetic visits the clinic for routine check up on the eve of his departure from the city and thus does not have a time for formal laboratory tests in near future.

3] When a known diabetic attends the clinic with symptoms which may or may not be related to diabetes and does not have a recent laboratory blood glucose report.

4] On emergency visit. On the spot blood glucose estimation is a must at every emergency.

Symptoms such as hunger, palpitations, sudden sweating, giddiness etc. could be due to hypoglycemia. Random blood glucose on the spots helps to detect or rule out hypoglycemia. In case of hypoglycemia, one should immediately correct the low blood glucose level by serving a carbohydrate snack like biscuits or refined sugar containing liquids and subsequently reduce dosage of his anti diabetic medications if required. In case the patient is semi conscious or unconscious, 50 ml of 25% glucose should be injected intravenously. Hypoglycemia

in patients on alpha glucosidase inhibitors [acarbose, miglitol, voglibose] should be treated by administering oral or intravenous glucose as it does not respond to carbohydrate snacks or table sugar. [Alpha glucosidase inhibitors slow down the digestion of carbohydrates to glucose]. On the spot blood glucose estimation with glucometer also helps to rule out hypoglycemia and think of alternative condition. Sudden sweating could be a symptom of acute myocardial infarction. Since hypoglycemia is more common, there is a tendency in patients to assume that they are having hypoglycemia and to consume two teaspoons of sugar every 10 minutes. In case of heart attack, it leads to late diagnosis and loss of vital time before the patient is admitted in intensive care unit. Thus timely on the spot blood glucose estimation can save precious time and life as well as lots of money by avoiding delay in hospitalization in case of serious condition such as acute myocardial infarction or other cardiac emergencies, or by avoiding unnecessary hospitalization in case of simple hypoglycemic episode. Prompt use of glucometer and swift appropriate action in only one episode will more than compensate for the entire investment cost of glucometer.

Equipment required for home blood glucose monitoring

1] Reliable glucometer

2] Chemically treated strips compatible with the meter

3] Lancets or fine needles to prick the finger for a drop of blood

4] Cotton swabs

5] Methyl alcohol or medicated spirit.

Glucometer: It is a small electronic instrument which analyzes the concentration of glucose in a drop of blood transferred on chemically treated plastic stick from patient's finger. The strip is inserted in a slot on the meter. Glucometer runs on batteries. Several brands are available in our country.

The cost of the meter varies from Rs. 850/- to Rs. 3000/-.For those with high consumption of strips, many companies offer free glucometers. The high end meters have additional features such as varying memory capacity to store previous readings along with date and time, automatic calculation and display of mean blood glucose value of last 15 days, warning beep and message if the values are out of range on either side, facility to download the readings to computer, coding free operations, etc.

Once a drop of blood from finger, after a prick with the lancet or needle is deposited on the designated area on the plastic strip which is inserted in the slot on the meter, the blood glucose value is digitally displayed on the meter screen in five to fifteen seconds. One plastic stick is required for each test. The cost of strip works out to be in the range of Rs. 14 - 25/- depending upon the meter and the number of strips purchased at a time. These strips are available in vials; usually each vial contains 25 strips. They have unopened expiry period of about 18 months and six months after the seal is opened. The disposable lancets and needles cost approximately Rs. 1 - 4/-. The pain following finger prick, particularly when spring loaded lancet device is used is minimal and easily bearable. All meters come with a spring loaded lancet device at no extra cost.

Reliability of glucometer:

More than twenty five years have elapsed since the introduction of glucometers. During this period, technology has been continuously updated and deficiencies found in earlier meters have been gradually overcome. The modern meters are reliable provided one understands and follows the instructions mentioned in the manual, stores the strips properly and avoids using outdated strips. [Expiry dates of unopened and opened vials are mentioned on the vial]. It must be noted that with glucometer, capillary whole blood is

tested for glucose, while during laboratory test; venous plasma component of blood is tested for glucose. While in fasting state, glucose levels in capillary whole blood and venous plasma are more or less equal, in the fed state, level in former is about 20 mg% higher than later. Even after accounting for the above mentioned difference, up to 15% difference between capillary whole blood values and laboratory test are acceptable. Thus one need not doubt reliability of glucometer if the values of laboratory test and glucometer reading done at the same time are not identical. However, glucometer requires periodic calliberation. This can be done every two to three months by simultaneous testing of blood glucose in laboratory and with glucometer. One should also remember that Hypo perfusion and anemia affect capillary blood glucose. Former give false low values while later results in to false high values. Family physicians should also strongly recommend glucometer to all the diabetic patients for self monitoring of blood glucose [SMBG].

Training the patients using glucometers.

1] Frequency of self monitoring of blood glucose [SMBG]:

The frequency of SMBG depends on several factors such as sub type of diabetes, degree of stability of blood glucose, presence of special situations [pregnancy, peri operative period, emergency situations, etc.]. In stable and well controlled type 2 diabetics, SMBG is required once or twice a week while in type 1 diabetics, those diabetics on insulin, those with brittle blood glucose control, and in pregnant diabetic woman, at least three tests per day are required. These are rough guidelines which will require modifications in an individual case.

2] Timing of blood glucose examination:

Routine tests:

The timing of blood glucose will depend on individual case.

The usual test timings are pre meals, [before breakfast, lunch; and dinner], and post meals, [2 hours after breakfast, lunch; and dinner]. Usually initially emphasis is on pre meal monitoring and adjustment of dosages of anti diabetic medications based on pre meal blood glucose values. Once these are stabilized, attention is shifted to post meal monitoring. One also has a choice of estimating pre meal and post meal values on the same day. One can plan to test the blood glucose at different times in a rotating manner, e.g. on Monday pre breakfast, post lunch and pre dinner, on Tuesdays, pre breakfast, pre lunch; and post dinner blood glucose estimation. In addition to pre and post meal estimation, occasionally, particularly in those on insulin, [once a week in those on multiple insulin injections and once a month in those on one injection], one should test at 3 am. These values give more precise idea about the level of overnight control and help in taking correct decision regarding adjustment of pre dinner and bedtime insulin dosage. In some patients particularly with relatively large dose of pre dinner intermediate acting insulin, early morning [around 3 am], blood glucose dips in hypoglycemic range and reactive hyperglycemia occurs in morning [around 8 am], as a result of early morning hypoglycemia. This vicious cycle can be broken by detecting early morning hypoglycemia and making appropriate changes in insulin dosage.

SOS tests:

In addition to the test timings mentioned above, patients should be advised to do random blood glucose estimation in following circumstances.

1] During symptoms such as hunger, palpitations, sudden sweating, giddiness etc. These symptoms could be due to hypoglycemia which needs to be confirmed or ruled out on the spot. However anxiety related non specific symptoms are also common in the community including in diabetic patients. Anxious diabetic patients, who do

not have glucometer or don't use it during sudden symptom, are likely to be caught in a trap if they interpret their anxiety related symptoms as those due to hypoglycemia and reduce the dose of their anti diabetic medications without consulting their doctor and avoid doing a lab blood glucose test. They also eat snacks every time they get these symptoms. Symptoms disappear on their own, however since they have taken a snack, they assume that they really had hypoglycemia. These two uncalled for actions lead to hyperglycemia and exposes them to the complications of diabetes.

Thus timely SMBG can save precious time and life as well as lots of money by avoiding delay in hospitalization in case of serious condition such as heart attack, or by avoiding unnecessary hospitalization in case of simple hypoglycemic episode. Prompt use of glucometer and SMBG and swift appropriate action in only one episode will more than compensate for the entire investment cost of glucometer.

Recording of SMBG data:

It is important to enter each blood glucose value along with date, time and appropriate comments neatly in tabular form and take the data at every consultation visit. This data along with the periodic laboratory blood glucose tests helps the treating doctor for fine tuning of anti diabetic medication dosage. Patients should be advised to contact you if two successive readings are out of range so that you can take timely action. This is the precise purpose of doing periodic SMBG. Those who do not do periodic SMBG miss the opportunity to correct blood glucose fluctuations in mid course. Their blood glucose values remain out of range till they do laboratory blood glucose test. Every day of abnormal blood glucose increases the chances of developing complications of diabetes.

Conclusion:

Every family physician and general duty medical officer must have his own properly calliberated and functioning glucometer all the time with him in the clinic as well as on the emergency visits. He should also encourage self monitoring of blood glucose [SMBG] by the patients.

7. Management of Diabetes

Why control diabetes?

It has now been proved beyond doubt that dreaded micro vascular complications of diabetes can definitely be prevented or at least considerably postponed if persistent metabolic control is maintained. Micro vascular complications are specific for diabetes and are responsible for considerable morbidity and mortality. For example, affliction of the capillaries in the retina (Diabetic Retinopathy), can ultimately lead to blindness (commonest cause of blindness in the developed world and well off patients in our country), thus making the affected patient dependent. Affection of capillaries in the Kidneys (Diabetic nephropathy) ultimately leads to end stage renal failure, the commonest cause of renal failure, needing either renal transplantation or permanent thrice-a-week haemodialysis. Both are extremely expensive and beyond the reach of an average Indian.

Diabetic neuropathy leads to

a) Unbearable pain and paraesthesia in the legs which interfere with the day to day activities and sleep, and can be totally incapacitating. Moreover, impaired sensations over the legs are one of the major underlying factors responsible for 'diabetic foot' lesions which can lead to gangrene and amputations.

If blood glucose is kept under control persistently, one can also prevent infections such as tuberculosis, pneumonia, skin and soft tissue infections, fungal infections, etc. which can affect morbidity.

Macro vascular diseases [cerebro vascular disease leading to stroke, coronary artery disease leading to myocardial infarction, cardiac failure and peripheral vascular disease leading to gangrene], are commonly associated with diabetes, due to accelerated atherosclerosis. This process can be slowed down with prudent management of diabetes.

Moreover, the mortality and morbidity is definitely less in those diabetics who are metabolically well controlled as compared to those who are uncontrolled, when they develop macro vascular emergencies.

The only way to prevent all these complications is to meticulously and persistently manage diabetes.

Till the mid nineties, we did not have concrete proof based on properly designed long term clinical research as regards beneficial effects of persistent tight blood glucose control. Diabetologists used to debate a lot on pros and cons of tight blood glucose control. However the scenario has totally changed since the publication of **Diabetes Control and Complication Trial, [DCCT] in 1993.** This trial was done in USA and Canada on Type 1 diabetic patients. DCCT was a prospective, randomized trial that assessed the effect of intensive versus conventional insulin therapy on the incidence of micro vascular complications of diabetes [retinopathy, nephropathy and neuropathy] in 1441 patients over a mean follow up period of 6.5 years. Intensive therapy consisted of at least three insulin injections daily and at least four capillary blood glucose examinations daily with frequent communications with the investigators. Conventional therapy consisted of one to two insulin injections and one capillary blood glucose estimation daily with less frequent communication with the investigators. At the end of the trial it was found that the relative risk reduction as regards development of retinopathy, nephropathy and neuropathy, or progression of these micro vascular lesions in those who had mild involvement at the beginning of trial, was more than 50% in those type 1 diabetics on intensive treatment as compared to those on conventional treatment. This difference was highly significant statistically. Subsequent to publication of DCCT trial, which was a very major milestone in the field of diabetes research, **United Kingdom Prospective Diabetes Study [UKPDS]** was published. This was the biggest clinical

research ever undertaken in the field of diabetes till that time and it proved that better blood glucose control through intensive management of diabetes led to statistically significant relative risk reductions as regards all the three diabetic micro angiopathies as compared to conventional treatment. The relative risk reduction was 24% for all the micro angiopathies taken together. More than 5000 newly diagnosed type 2 diabetic patients participated and were followed up for a mean of seven years. In another side study in the UKPDS, it was proved that in those diabetics who also had hypertension, intensive therapy with antihypertensive medications led to significant reductions in mortality and morbidity as compared to conventional anti hypertensive therapy. 1148 patients participated in this sub study. Mean BP achieved in intensive and conventional treatment groups was 144\82 and 154\87 mm of mercury respectively. Atenelol and captopril were the anti hypertensive drugs used in intensive arm. Both fared equally.

Metabolic memory [Legacy Effect]]

In last 15 years, several large well planned long term longitudinal studies comparing aggressive management for glycemic control as well as for blood pressure and lipid control with conventional management were completed. [DCCT, UKPDS, Steno 2]. In DCCT, aggressive insulin therapy was compared with conventional insulin therapy, in main UKPDS, aggressive therapy for blood glucose control was compared to conventional therapy, while in Steno 2 study, simultaneous aggressive management of hyperglycemia, hypertension; and hyper lipidemia was compared with conventional management of above mentioned risk factors. As expected and as is well known, aggressively managed patients in DCCT and UKPDS had better glycemic control and fewer micro vascular complications at the end of study period. Similarly, aggressively treated patients in Steno 2 study had better control of blood glucose, blood pressure and lipids and all

these factors resulted in lesser cardio vascular events. The differences in two groups in all the studies were statistically significant. At the end of these studies, patients were given a choice to continue same treatment or cross over. [The second part of DCCT study was called 'EDICT" study.] Both the groups were closely observed till the end of further pre determined long term period. Over the period of time the differences in their values gradually reduced. [Difference in HbA1c in DCCT and UKPDS studies and in HbA1c, blood pressure and lipid levels in Steno 2 study.] This occurred because majority of patients in conventional arm in the original studies opted for aggressive treatment after they received the briefing about study results, while there was some slackening as regards life style changes as well as drug compliance in those who were originally in aggressive arm. However patients, who were in aggressive arm in the first half of the respective studies, continued to receive the benefits of tighter controls and achievements of target values in first half of the respective studies. Thus at the end of second half of the study, the difference in the rate of developing micro vascular complications was maintained in spite of similar HbA1c values in the DCCT and UKPDS studies, while cardio vascular mortality was further reduced as compared to at the end of first half of the steno 2 study in those who received aggressive management in first half of the study. Similar findings were also observed in **Hope study**. This was a large study which ran for four and half years in its first part. People with risk factors for cardio vascular disease or having type 2 diabetes were divided in two groups. One group was put on 10 mg. of ramipril daily in addition to their routine medications for diabetes, hypertension, hypercholesterolemia and anti platelet medications This group was compared with a group on placebo [for ramipril], OAD's, anti hypertensives, anti platelet medications, and statins were given as required. The group on ramipril had statistically significant reduction in macro vascular and micro vascular events. At the end of four and

half years, those on placebo were given an option of taking ramipril while those on ramipril in the first half were given the option of discontinuation. Majority in placebo group started ramipril while some in ramipril group discontinued it. At the end of second half of the study [Hope Two study], those originally on ramipril continued to get vascular protection and the gap between relative rate of reduction of vascular complications between the two groups widened. This phenomenon of extension of metabolic and vascular benefits is coined as "**Legacy effect or metabolic memory effect.**"

The implications of these studies are very important. There is a strong case for early diagnosis of diabetes and aggressive management of blood glucose without wasting time immediately after diagnosis of diabetes. Similarly associated risk factors should be promptly identified and quickly brought under control. This will help in our endeavor for primary or secondary prevention of vascular complications of diabetes.

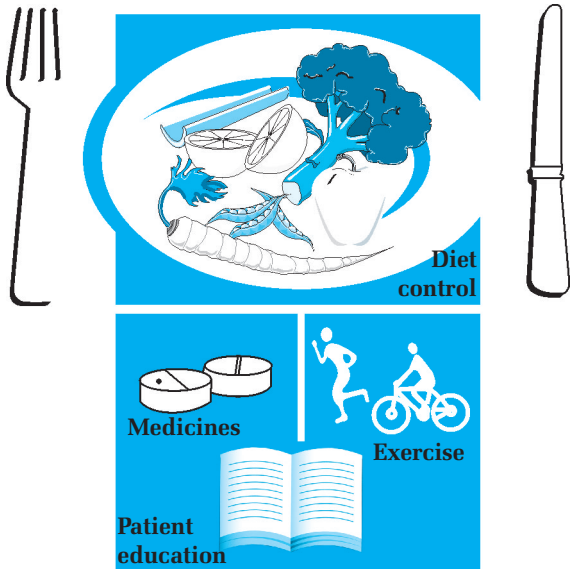
In 1935 the pioneer American diabetologist Dr. Elliot Joslin made a statement "Aim of therapy in diabetes is to bring down blood sugars to as near normal as possible." Most diabetologists disagreed with him at that time. We now understand far sightedness and vision of Dr Joslin!

Thus Clinicians should devote a lot of time explaining the importance of persistent tight blood glucose control to the patients and their relatives in order to motivate them to follow the advice and come for regular follow-up. If they understand "A stitch in time saves nine" and also the fact that there is absolutely no alternative to persistent tight blood glucose control, they will do a regular follow- up which will lead to better glycemic control and also better control of other risk factors such as hypertension, hyperlipaedemia and obesity.

Even in a general practice set-up you can reserve a separate time slot away from peak hours to manage your diabetic patients, say for example, you can hold once a week Diabetic Clinics in your own dispensary. Such a practice is common in advanced countries like the U.K.

Management of diabetes

Management of diabetes revolves around four cornerstones as shown in the following diagram:



All the four modalities of management are equally important and to be successful, all the modalities should be implemented simultaneously. Addition of insulin in the prescription in hitherto OAD controlled patient does not mean that now he can relax diet and exercise.

8. Role of Exercise in the Management of Diabetes Mellitus

Along with diet, medicines (insulin and other injectables or OAD) and education, exercise forms the four corner stones in the management of diabetes mellitus. However, it is the most neglected aspect of management. If undertaken properly, diabetics are immensely benefited from exercise. Some of the beneficial effects are as follows:

Benefits of Exercise.

Appropriate exercise leads to improvement in metabolic control because during the exercise, glucose is spent up to provide energy. Moreover long term regular exercise leads to reduction in insulin resistance, which is often significant contributor in the pathogenesis of diabetes. Reduction in degree of insulin resistance leads to better utilization of endogenous and\or exogenously administered insulin and thus better blood glucose control, often with reduction of insulin \OAD dosage.

Other benefits:

- Exercise helps in weight reduction.
- Appropriate exercise and diet control together are sufficient to control blood glucose levels in many mild Type 2 DM patients, thus avoiding drug treatment.
- Exercise leads to lowering of blood pressure, which is commonly elevated in diabetes.
- Exercise helps in reducing blood levels of VLDL & LDL and increase the blood level of HDL cholesterol.
- Exercise improves blood circulation in the legs (many longstanding diabetics suffer from poor blood circulation in the legs).
- Exercise leads to improved physical fitness and stamina.
- Last but not the least, exercise imparts a sense of well being and Improves psychological status.

What are the precautions to be observed before starting exercise?

Inappropriate exercise can be hazardous. Hence before prescribing exercise, you should carry out a detailed physical examination and certain laboratory investigations including Electro-cardiogram to verify the following:

1. The blood glucose level is reasonably controlled.
   Starting vigorous exercise in very poorly controlled diabetes, particularly in Type I diabetes, could worsen blood glucose control and precipitate an emergency as insulin is required to facilitate entry of glucose into the cells where it is burned down as fuel. In severe insulin deficiency, glucose is unable to enter the cells and hence can accumulate in the blood to dangerous levels.
2. The condition of Cardio vascular system is stable
   Ischemic heart disease is more common in diabetes and may remain silent or have atypical symptoms thus remaining undetected. Sudden vigorous exercise in such patients could precipitate serious problems such as acute myocardial infarction or left ventricular failure.
3. Absence of advanced proliferative retinopathy
   This complication is present in some long-standing diabetics particularly those who are poorly controlled. If sudden vigorous exercise is performed by diabetics having proliferative retinopathy, vitreous hemorrhage and retinal detachment can occur. Hence fundoscopy is essential, particularly in long-standing diabetics having diminished vision, before they embark on an exercise programme.
4. Prevention of Hypoglycemia
   Ask your patient to observe the following don'ts and do's to prevent hypoglycemia.

a) DON'T exercise during peak insulin time i.e. around three hours and seven hours after plain and intermediate acting insulin respectively.

b) DON'T inject insulin in the exercising arm as exercise hastens absorption of insulin and may precipitate hypoglycemia.

c) DO remember that occasionally hypoglycemia unexpectedly occurs very late, for example, late at nights, following morning exercise. Hence assess your patient's blood glucose at different hours with the help of glucometer so that dietary supplements can be taken at proper time or the dosage of drugs (i.e. insulin or oral pills) can be adjusted. Such elaborate monitoring is only required initially to study the individual response pattern.

The ideal time to perform exercise is in the morning after a light snack. This will prevent hypoglycemic reactions.

5. Feet are healthy and there are no open wounds.
6. Ensure that the patient is using properly fitting footwear while exercising.

Which type of exercise ?

Various exercises are basically divided into two types:

1) Dynamic or aerobic.
2) Static or anaerobic

In the former, the major muscle groups are stretched in a rhythmic pattern and the entire body is in motion while in the latter, muscles contract against the fixed objects and the body is static. Walking, jogging, cycling, swimming etc., are examples of the former while pressing palms against the walls or weight lifting are examples of the latter. Dynamic exercise in which a large amount of energy is gradually spent, over a period of time is ideal for diabetic patients. Depending upon the patient's age, sex, physical condition and cardiovascular status, you should prescribe one of the dynamic exercises.

For older diabetics, brisk walking is safe, easy to perform and an inexpensive exercise. All that they have to do is to invest in time and a pair of properly fitting and comfortable footwear. Younger and fitter diabetics can choose from the following exercises - Running, swimming, cycling, a game of tennis, etc.

All the above mentioned exercises are equally beneficial as compared to fancy or trendy things such as a work-up in a Gymnasium and Health Club; and Yog. The latter is not an exercise in its correct sense and helps in an indirect manner. Of course, there is no harm performing yog in addition to exercise.

The following Table gives various dynamic exercises and approximate calories spent per minute while doing the given exercise.

Type of exercise	Calories spent / minute
Brisk Walking	3.6
Cycling	4.5
Jogging	4.5
Running	5.0
Swimming	6.0
Tennis (Singles)	7 .0

How Long?

Ideally 30-45 minutes of sustained dynamic exercise should be done without breaks. However, one should start gradually with 10 minutes daily in the first week and gradually go to 30-45 minutes daily in the next 2-4 weeks.

Remember, sustained exercise is important. The exercise should be strenuous enough to raise heart rate to 75% of Maximal Heart Rate (MHR), for 10-15 minutes in the middle third of exercise period.

To calculate, use the following formula: subtract age of the patient in years from 220. For example: A man of 50 years should raise his heart rate to about 125 beats per min. during peak exercise time, which should be one third of the total duration of exercise. [220 minus 50 = 170, 75% of 170 is 127.5 or aprox. 125 beats\min.]Many housewives tell me they spend two hours shopping and do a lot of walking during this time but still it does not help them in achieving their goal. They obviously forget the several halts they make while shopping and the long casual talks with friends! If occasionally, your patient has to cancel the exercise programme, ask him to make up during the course of the day by:

i) Avoiding lifts.

ii) Purposely parking the car away from the place of work.

iii) Getting down a bus stop or Railway station earlier than the one nearest to the place of work/residence.

How Often?

If one wants to derive real benefit, exercise must be done at least 5 times a week.

Conclusion

Remember, proper exercise is very useful, safe, inexpensive, pleasant, and an integral mode of management of diabetes, and should never be bypassed.

9. Meal Planning In Diabetes

Meal planning or judicious selection of food items as regards the type of foodstuff and the quantities is an essential and primary step in the management of diabetes and by itself, along with prudent exercise, is sufficient to control blood glucose in many of those who have pre diabetes and mild type 2 diabetes. Those who require insulin or oral pills to control blood glucose should never neglect meal planning, just because they are on blood glucose lowering medicines.

I have purposely avoided the term "diet", because it carries different meanings to different people and is usually interpreted as restriction in quantity of foodstuff across the board. It has negative, restrictive or unfriendly connotation. In fact people with diabetes and normal body weight need not reduce the calories consumed in 24 hours. What they need to do is to take small frequent meals, to avoid foodstuff containing refined sugar and reduce fatty food and red meat and to consume sufficient quantities of rough cereals and vegetables to provide for adequate fiber and feeling of satisfaction from eating adequate food.

If a diabetic patient understands the basic principles of sensible eating, he can consume food which is very near to his family's daily food and which does not require any special or separate preparation.

All of us, including those having diabetes, require consuming well balanced food for promotion of growth in our formative years as well as for maintenance of our body functions and repair of wear and tear of our tissues. While charting daily meal plan the objectives should be : 1] to provide the required calories to create energy and to attain and maintain ideal bodyweight. 2] To plan a well balanced menu containing proteins, carbohydrates, fats, vitamins, minerals and fiber in optimum quantities. Overweight people should purposely consume fewer calories than their daily requirement, so that extra deposits of visceral and subcutaneous fat are mobilized

to bridge the gap between the required energy and that provided by the foodstuff. In this way the patient is able to shed extra weight and this helps in improving insulin sensitivity of his tissues. In other words, insulin resistance is corrected. In this way tissues get "extra mileage" out of insulin, externally administered as well as endogenous insulin. About 90 % of type 2 diabetic patients and 24 % of adult population have Insulin Resistance.

What is a balanced food?

Well balanced food contains all the constituents of food in ideal proportion. Now let us gather some basic information on various food constituents.

Carbohydrates

Carbohydrates should provide the main source of energy. About 60-65 % of energy should be supplied by carbohydrates, mainly complex carbohydrates, while simple sugar or items containing it should be avoided or very sparingly consumed. Cereals and cereal based foods supply complex carbohydrates, while sugar, honey, jam etc. provide simple carbohydrates. Cereal based foodstuff such as chapatti, roti, rice, bajara roti, etc form the bulk of the food in our country and is ideally suited for diabetic patients. Complex carbohydrates in these foodstuffs are slowly digested and converted in to glucose in a gradual manner and hence their consumption is not associated with quick and sharp rise in blood glucose level. However simple carbohydrates such as table sugar [sucrose], honey etc are rapidly converted in to glucose.

Proteins

Proteins are essential for growth as well as for repair of wear and tear. Milk and milk products, egg white, meat, fish, and daIs are rich sources of proteins. About 15-20 % of daily calories should come from proteins. Diabetics should

consume 0.8 gm. of proteins per kg of their ideal body weight. Patients with diabetic nephropathy should restrict protein consumption.

Fats

Fats are important constituents of cell membrane and are storage centers for energy. 20 % of daily energy requirement should be provided by fats. Fats consist of fatty acids and glycerides. Depending upon the type of fatty acid it contains, fat is classified in to following types:

1] Saturated fat

Animal fat, including fat in milk and milk products and vanaspati are rich in saturated fat. Animal fats are also rich in cholesterol. Among the oils, coconut oil is a rich source of saturated fats. Excessive consumption of saturated fats leads to rise in serum cholesterol level which accelerates atherosclerosis. However animal fats are also a source of vital omega 3 fatty acids and thus should be consumed in moderation. One third of the energy from fat should be derived from saturated fats. Thus a small amount of ghee, half to one teaspoonful per day is recommended particularly for vegetarians.

2] Mono unsaturated fats

Ground nut oil, mustard oil, and palm oil provide mono unsaturated fats. One third of the energy derived from fat should come from mono unsaturated fat.

3] Poly unsaturated fats

Safflower oil, sunflower oil, corn oil, soy bean oil, cotton seed oil etc are some of the rich sources of poly unsaturated fats. Remaining one third of the energy provided by fats should be derived from poly unsaturated fats.

Essential fatty acids

These are vital fatty acids which can not be made by the body hence should be derived from food. Omega 6 [w6] and Omega 3 [w3] fatty acids belong to this class. Each source of fatty food has different w6 and w3 fatty acids in different proportions. The ideal w6\w3 ratio should be 4: 1. It should be noted that certain oils rich in poly unsaturated fats, such as sunflower oil and safflower oil are very aggressively marketed as safe oils because their consumption does not lead to rise in serum cholesterol. The advertisements even make an indirect claim that one can consume large quantities of these oils. However these oils contain very unhealthy w6\w3 ratio thus should never be used as sole source of cooking medium. Moreover all oils provide same calories, 9 per gram. Thus excessive consumption of poly unsaturated oils is unhealthy.

In order to provide a better w6\w3 ratio one should not solely depend upon poly unsaturated oils but use a judicious mixture of these oils with mustard oil, coconut oil, and ghee. However ghee and coconut oil are rich in saturated fats thus should not be used as sole cooking medium. Fish oil is very rich source of w3 fatty acids and it has been amply demonstrated that in countries where fish is a staple food, incidence of coronary heart disease is low. Thus fish consumption is encouraged. Those who are vegetarians may consume 1 to 3 capsules of fish oil daily. However it has not yet been proved that capsulated fish oil is as good as consumption of natural fish. The normal weight diabetic should consume four teaspoonful of cooking oil daily. [0.5 litter per month]. Besides, he should consume half teaspoonful of ghee. Over weight diabetics should consume less.

Other constituents of food

Fiber

Fiber is provided by indigestible plant cell components in our food. There are two types of fiber,

1] Water insoluble fiber: It is present in skin of fruits and peel of husks. It is good laxative. One should not peel off the skin of fruits before eating.

2] Water soluble fiber; It has a property of holding or adsorbing water and getting swollen. Many vegetables and cereals particularly fenugreek, oats, beans, carrots, barley etc are rich in water soluble fiber.

Traditional Indian vegetarian food rich in vegetables and cereals provide adequate fiber and hence supplementary medicated fiber preparations are usually not required. Moreover such branded preparations are expensive. One can provide adequate fiber rich, natural food to entire family at the same cost. [Provided of course the family has a reasonable size] Fiber rich food provide following advantages;

1] Digestion of carbohydrates to glucose and its absorption is delayed., thus a sharp post meal rise in blood glucose is avoided.

2] High fiber intake helps to reduce serum cholesterol and triglycerides.

3] Due to bulk formation after water holding in the fiber, one gets a feeling of fullness in abdomen thus limiting food intake.

4] By preventing chronic constipation, risk for cancer of large intestine is reduced.

Water

Water is an important constituent of food and is absolutely essential for survival. Sufficient amount of water is required for maintenance of blood volume and digestion of food:

Vitamins and minerals

Persons with diabetes require vitamins and minerals in adequate quantities just as a normal person needs them. There is no difference in daily requirement. Well balanced food provides all the vitamins and minerals in adequate quantities and regular life long vitamin supplements are not required for all the diabetics. However those on low calorie diet should take one tablet or capsule of B complex or Multi vitamin preparation.

Average diabetic, particularly the one who has it for several years usually requires several medications such as, for example, two or three oral anti diabetic pills, two anti hypertensive pills, a statin to reduce his cholesterol or prevent heart disease even if cholesterol is normal; and aspirin. All these medicines are absolutely necessary, thus make the matters less complicated for the patient by avoiding vitamins and anti oxidant pills. Remember lesser the number of pills, higher are the chances of compliance.

Thus you may avoid prescribing a B1,B6,B12 preparation or a preparation containing methycobalamin in each and every diabetic.

Now let us plan daily menu in a stepwise manner

Step I Calculate desirable body weight

Take height in centimeters and subtract 100 or 109 in men and women respectively. For example, if height is 170 centimeter, ideal body weight should be around 70 kg for men and 61 kg for women. Please note that height- weight charts which are used in many clinics are based on Life Insurance Corporation of India's [LIC] guidelines and are out dated. You may add about 10 kgs to the weight figure mentioned in LIC's charts. The above mentioned simple mathematical formula gives a rough idea about ideal body weight. If one wants to be more specific, he should calculate patient's Body Mass Index [BMI] by using following formula.

BMI = weight in kg ÷[Height in meters]2

The normal range is 18-23 for men and 19-25 for women. One should keep his BMI in normal range. If it is high, he needs to shed weight.

Step II calculate the calorie requirement.

Refer to Table I to decide about the calories required.

Table I Calories\Kg of desirable body weight based on physical activity

	Sedentary	Moderate	Heavy
Over weight	20	30	35
Normal weight	30	35	40
Under weight	35	40	40-50
Bedridden Patient	25	-	-

Growing children and pregnant and lactating women require extra calories.

Physical activities carried out by following groups are classified as sedentary activity: Teacher, doctor, nurse, tailor, peon, housewife, and retired people.

Physical activities carried out by following groups are classified as moderate activity:

Fisherman, agricultural labor, electrician, carpenter, welder, turner, industrial labor, automobile driver, etc.

Physical activities carried out by following groups are classified as heavy activity:

Stone cutter, mine worker, wood cutter, porter, etc.

Step III Convert required calories in to a meal plan

To make a meal plan, one requires knowing the composition of foodstuffs we eat and the calories provided by each gram of protein, carbohydrate, and fat, and also have some information on food exchange system.

Cereals [rice, wheat etc] are rich in carbohydrates which form about 70% of their weight, but poor in proteins, while pulses [various dals] are comparatively richer in proteins.
Vegetables are a good source of carbohydrates, fiber, vitamins, and micronutrients but are a poor source of proteins. All these foodstuffs provide a small quantity of fat which is known as " invisible fat". Meat and fish are rich in proteins while former, particularly red meat is also rich in fat. Meat and fish do not provide carbohydrates. Milk provides all the three proximate principles with quantity of fat varying depending upon the animal source and also whether it is processed to make it "low fat" milk. Cow's milk contains less fat as compared to buffalo's milk. Each gram of protein and carbohydrate provides 4 calories while each gram of fat provides 9 calories.

The food exchanges:

A person with diabetes can and should make frequent changes in his menu, so that the monotony of eating same food is broken and he can actually enjoy his meals. While making changes, he should know that the total calories consumed in a day and the proportions of calories provided by proteins, carbohydrates, and fats should remain same.
In other words, he must know the various alternatives he can consume in place of each food item on his menu. For example, if one does not want to consume a cup of cow's milk at breakfast, what are the various alternatives which he can consume instead of milk? This information is provided by a list of food exchanges, which is given below.

Cereal exchange:

Each exchange provides:
Carbohydrates -15 gm
Proteins -2 gm
Calories 70
One exchange is = any one of the following;

Cooked rice	75 gm [3 tablespoons]
Chapatti	20 gm atta [1 small chapatti]
Roti	20 gm atta of Jowar\Bajra\Corn\Ragi
Idli	1 medium
Bread	30 gm [1 large size\one and half average size]
Cornflakes	20 gm [3 tablespoons]
Dosa	1 medium
Porridge	3\4 cup
Marie\Cream Kraker biscuits	3 pieces

Pulses and Dal exchange :

Each exchange provides:
Carbohydrates - 15 gm
Proteins - 6 gm
Fat - 1 gm
Calories - 90
One exchange is = any one of the following [in raw weight]

Rajmah	25 gm
Bengal Gram	25 gm
Black Gram	30 gm
Chawli	25 gm
Mung	25 gm
Kesari dal	25 gm
Red gram	25 gm
Masur dal	25 gm

Milk exchange:

Each exchange provides
Carbohydrates - 7.5 gm
Proteins - 4.5 gm
Fats - 6 gm
Calories - 110
One exchange = any one of the following

Cow's milk	150 ml
Buffalo's milk	90 ml
Skimmed milk	350 ml
Skimmed milk powder	30 gm (3 table spoons)
Butter milk	750 ml
Cheese	30 gm
Curds (cow's milk)	150 ml

Fruits exchange

Each exchange provides
Carbohydrates- 10 gm
Calories- 40

Orange	100 gm[l medium]
Pear	90 gm [1 medium]
Apple	90 gm [1 medium]
Banana	40 gm [1\2 small]
Mango	60 gm [1\2 small]
Water melon	300 gm [3 slices]
Papaya	120 gm [2 slices]
Grapes	75 gm [12 numbers]
Figs	100 gm [3 medium]
Pineapple	90 gm [5-6 thin round slices]
Coconut water	200 ml [1 glass]
Guava	100 gm [1 medium]

Vegetables A group

All leafy and green vegetables except those mentioned in group B. They provide negligible calories

Vegetables B group

100 gm = 1 exchange = 1 katori provides
Carbohydrates - 7 gm
Proteins - 2 gm
Fats - nil
Calories - 35

Examples : Carrot, Beetroot, Green mango, Beans, Green peas, Onion, Lotus stem.

Roots and Tubers:

100 gm = 1 exchange = 1 katori provides
Carbohydrates - 25 gm
Proteins - nil
Calories - 100

Examples: Potato, Sweat potato [ratala], Yam [Suran], Colocasia [Arwi], tapioca [Simla Aloo].

Note: Roots and tubers should be avoided or taken in very small quantity only.

Fat \Oil exchange:
Each exchange provides
Fat- 5gm
Calories- 45

Examples : One teaspoonful [5 gm] of any cooking oils: e.g. safflower, Sunflower, Soya, Mustard, Ground nut, Til, Vanaspati; or 2 teaspoonfuls [10 gm] of Cream.

Now refer to meal planning chart at the end of this chapter and plan a menu.

General Guidelines:

Foods to be consumed in very limited quantity.

Fried snacks like shev, chivda, farsan, papad, bhajiya, wafers, chips, batata wada, etc.

Saturated fats like butter, ghee, cream, fatty meat[beef, lamb, organ meat, ham, and pork], coconut oil, and hydrogenated oil [vanaspati], Yellow of egg, Fatty gravies, Nuts and oil seeds such as cashew nut, pista, walnut, groundnut etc.

Beer, wines, whisky and other alcoholic drinks are best avoided as far as possible. If total abstinence is not possible, intake should be limited to one peg per day and 5 pegs per week of hard drinks or one bottle per day and 5 bottles per week of mild bear and one small glass of wine per day. Sweat wines such as port wine should be avoided. Calories provided by alcohol should be accounted in the meal plan. One gm of alcohol provides 7 calories. Avoid excess of salt as this can lead to hypertension, which as such is extremely common in diabetic patients. Both diabetes and hypertension are independent risk factors for coronary heart disease and when present together, the risk is compounded. Foods high in salt are papad, pickles, chutney, baking soda containing eatables, dried fish, processed food, preserved and canned food, cured meat, Chinese food etc. There is no difference between rock salt and common salt. Salt intake should not exceed 5 gm per day in diabetics who have concomitant hypertension and \or cardiac failure

Food items to be totally avoided.

Simple sugars such as glucose, sucrose[table sugar], dextrose, honey, jaggery, jam, jelly, syrups, marmalade, cakes, pastries, pies, puddings, ice cream, sweat biscuits, sweat meats, chocolates, condensed milk, fruit juices, aerated soft drinks such as coca cola, limca, thums up, pepsi, gold spot, tinned juices, sweat pickles etc.

Diet coke or diet pepsi can be consumed.

Food items allowed in unlimited quantities.

Condiments and spices, lime water[without sugar], tea and coffee [without sugar and using milk from the milk quota], thin butter milk, raw and green vegetables etc.

The 1800 calories readymade menu which is suitable for persons 60 Kg. ideal body weight and sedentary life is given in a table below.

Menu for 1800 calories diet

Time	Food item
On getting up	1 cup tea\coffee [milk-50 ml]
Breakfast	2 pieces of any of the following: phulkas\bread slices\ medium size idli. 1 cup cow's milk\ 1 egg. 1 tsp ghee\ I tsp oil\ 1 1\2 tsp butter.
Mid morning snack	2 cream craker biscuits\1 idli\1 fistfull kurmura
Lunch	3 phulkas\2 thick roties\2 phulkas+1 katori rice. 1 1\2 katori dal. 1 katori curds \ 1 glass butter milk. 1 to 2 katories green vegetables. 1 katori vegetables from group B. Cooking oil: 1 tsp.
Aternoon snack	1 cup tea \ coffee. 2 slices bread.
Evening snack	1 orange \ sweat lime \apple.
Dinner	Same as lunch
Bed time	1 cup milk. 2 Marie or Cream Kraker biscuits.

Notes: 1] Non vegetarians can consume 60 gm. fish \50 gm. chicken \30 gm. mutton instead of curds\butter milk.

Those who would like to plan their own menu and keep it flexible should refer to table depicting calories chart, printed

above in this chapter and calculate calories required. Subsequently they should refer to meal planning chart given below and also to food exchange lists to formulate their own menu.

Meal planning chart

Calories	1200	1600	1800	2000	2200	2400
Bed tea\ coffee	1cup	1cp	1cup	1cup	1cup	1cup
Breakfast						
Cereal exchange	2	2	2	3	3	4
Milk exchange	1	1	1	1	1	1
Fat exchange	-	1	1	1	1	1
Mid morning snack						
Cereal exchange	1\2	1\2	1\2	1\2	1\2	1\2
Milk exchange	-	-	-	-	1	1
Lunch						
Cereal exchange	2	2	3	4	4	5
Pulse exchange	1	1	1.5	1.5	1.5	1.5
Curds	50ml	100 ml	100ml	100ml	100 ml	100 ml
A Gr.Vegetables	unlimited	unlimited	unlimited	unlimited	unlimited	unlimited
B Gr.Vegetables exchange	1	1	1	1	1	1
Fat exchange	Nil	Nil	1	1	1	1
Afternoon snack						
Tea\coffee	1 cup	1 cup	1 cup	1 cup	1 cup	1 cup
Cereal exchange	1	2	2	2	2	2
Fat exchange	1	1	1	1	1	1
Evening snack						
Fruit exchange	1	1	1	1	1	1
Milk exchange	-	-	-	-	1	1
Dinner	Same as lunch	Same as lunch	Same as lunch	Same as lunch	Same as lunch	Same as lunch
Bedtime						
Milk exchange	1	1	1	1	1	1
Fruit exchange	-	1	1	1	1	1

Notes:
1] 1 egg can be exchanged for 1 milk exchange.
2] Half cereal exchange can be exchanged with 1 fruit exchange at evening and at bed time.

10. ORAL ANTI DIABETIC AGENTS [OAD'S] AND INJECTABLE INCRETIN MIMETICS

Introduction

The ease of administration, low cost[With the exception of DPP4 inhibitors], ability to control blood glucose levels in about 60% of type 2 diabetic patients at any given point of time in a clinic setting, and apprehensions to use insulin due to several misconceptions; have made oral blood glucose lowering agents immensely popular among the patients.

More than 96% of 62 million diabetics in our country have type 2 diabetes. As in any other type of diabetes, the primary aim of treatment in type 2 DM is to achieve persistent tight blood glucose control. As long as the oral pills are effective to achieve this goal and if they are well tolerated and if there are no contraindications to their use in a given patient, OADs can be used without any hesitation. However one should also know their limitations. Hence it is very important for an average General Practitioner as well as a Physician to have in-depth knowledge of OADs available in our country so that he can choose the appropriate agent in the correct dosage, depending upon the clinical situation.

History of Development of OADs

The history of oral anti diabetic agent therapy long antedates insulin, the first validated report being by Muller in 1877 on the effect of sodium salicylate on urinary glucose. In 1918, the blood sugar lowering influence of guanidine was described but the use of a series of somewhat toxic guanidine derivatives ceased a few years later as insulin became more rapidly available.

The modern oral anti diabetic drugs era began with the accidental discovery of the hypoglycemic activity of the sulphonamide, sulphonyl thiadizoles in 1942, and with the systematic study of their structure-activity relationships two years later by Loubatieres. The clinical introduction of sulphonylurea therapy followed in 1955 and after a

reexamination of the chemistry and pharmacology of the guanidines, effective biguanide therapy became available two years later. OADs are in use for almost six decades. Till mid nineties only two pharmacological classes of OAD's were available namely Suphonylureas and Biguanides. Subsequently in mid nineties, Acarbose, which acts at small intestinal brush borders and delays digestion of complex carbohydrates, was launched. In late nineties, Repaglinide, first non sulphonylurea insulin secretogogue was made available and around the turn of century thiazolindindiones, namely Rosiglitazone and Pioglitazone were on the market. In 2008, Sitagliptin, the first DPP4 inhibitor was launched, soon followed by vildagliptin and saxagliptin. In 2010, bromocriptine, which acts by resetting the reduced tone in hypothalamus, was introduced in clinical practice. Thus opened a totally new era in oral anti diabetic therapy. These recently introduced molecules are not merely "me too" molecules but they represent totally different pharmacological classes of anti diabetic medications having a mechanism of action distinct from the older classes of OADs. These new agents have mechanisms of action which are complementary to traditional agents with which they can be judiciously combined. In the meantime while existing new molecules were being rapidly introduced in clinical practice, rosiglitazone was withdrawn from global market due to its cardiac toxicity. We still have 15 agents from 6 broad classes of OADs. Thus we have mind boggling alternatives sometimes confusing a generalist. Let us look at how they act, how they differ with each other, complement each other; and what are the specific slots\niches of an individual OADs.

Pharmacology

The currently available agents fall into six main groups i.e.

1] Insulin secretogogues subdivided in to Sulphonylureas and non sulphonylureas.

2] Biguanides.

3] Thiazolindindiones, also known as Glitazones.

4] Alpha Glucosidase inhibitors.

5] DPP4 Inhibitors also known as Gliptins.

6] Dopamine Agonists [bromocriptine].

Based on sites of action, the above mentioned agents are grouped in following manner.

1] Centrally acting agents: acting at pancreas to stimulate release of insulin from beta cells (Sulphonylureas and non sulphonylurea insulin secretogogues.)

2] Peripherally acting agents: which increase the tissue sensitivity towards insulin. These agents are also known as Insulin sensitizers. They are sub divided in to Biguanides acting mainly at liver and Thiazolindindiones acting mainly at striated muscles and adipose tissues.

3] Agents acting at intestinal mucosa: These agents slow down digestion of carbohydrates and thus the absorption of glucose: (Alpha Glucosidase Inhibitors.)

4] Agents acting through incretin axis: DPP4 inhibitors increase the blood levels of GLP1, a natural incretin secreted by small intestinal cells in response to food intake. GLP1 reduces blood glucose through multiple actions. These agents act by inhibiting DPP4, an enzyme secreted in small intestinal mucosa in close proximity to site of secretion of GLP1.

5] Agent acting on supra chaismatic nuclei in hypothalamus: Bromocriptine, the only member of this class acts by resetting the lowered dopaminergic tone in type 2 diabetic patients.

Sulphonylureas and other insulin secretogogues

Glibenclamide, Glipizide, Gliclazide; and Glimepiride are the four members of Sulphonylurea [SU], family available

in our country. Besides SU, Repaglinide and Nateglinide, which have similar mechanism of action but chemically distinct structure, are also available in our country. They are rapidly absorbed from the gastrointestinal tract and transported in blood as protein bound complexes. The free ions, which are gradually released, diffuse in the tissues and reach the site of the action.

Mechanism of action:

The main action of Secretogogues is through acute induction of insulin release from Beta cells of islets of Langerhans. When these drugs combine with a specific receptor on the cell membrane of beta cells in pancreas, a chain of events is triggered ultimately leading to release of insulin in circulation. When used for a long term, it is claimed that Sulphonylureas also act through increasing insulin sensitivity. However, this hypothesis is not yet proved conclusively even though there is some experimental evidence particularly in favor of Glimepiride in this regard. These drugs are ineffective in the absence of functional beta cells. Thus they should not be used in type I diabetics. On an average, these agents are effective in controlling blood glucose for about five years, during which period their effect gradually diminishes and ultimately a stage is reached when they are ineffective in controlling blood glucose even at the highest dose. This stage is popularly described as Secondary SU failure. However it is actually due to failure of beta cells in pancreas to respond. It is estimated that usually at the time of diagnosis of type 2 diabetes, only about 50% of the beta cells are functional and these respond to insulin secretogogues. As the time passes the mass of functionally active beta cells gradually diminishes and in about five years time a stage of Secondary failure is reached. The rate at which beta cell mass decreases varies from patient to patient.

The rate and degree of absorption, degree of protein binding, rate of metabolism and renal excretion, and hypoglycemic properties of individual members of this group vary from each other **(TABLE 1).**

Compound	Half Life Hr	Duration of effect Hr.	Daily Dosages Mg
Glibenclamide	2-4	20-24	2.5-20
Glipizide	1-5	12-24	2.5-20
Gliclazide	6-15	10-15	40-320
Glimepiride	2-3	20-24	0.5-6

Contraindications:

All Insulin seceretogogues are contraindicated in pregnancy and lactation, severe liver disorders and in type1 diabetics. The additional contraindications of individual agents are mentioned separately.

Glibenclamide: It was introduced in our country about 30 years back. It is a long acting and potent SUs It should be administered once or twice a day, thirty minutes before meals. Usual daily dose range is 2.5 to 20 mg. Among all the SUs it is least expensive thus very suitable for economically average patients. It is contraindicated in renal impairment in addition to common contraindications of the class mentioned above.

It does not cross placental barrier. Even though officially contraindicated, it has undergone significant evaluation in the management of gestational diabetes mellitus,[GDM] and some centers have been using in GDM.

Indications:

1] It is used as a first line drug in type 2 diabetic patients who do not tolerate metformin.

2] In type 2 patients not controlled on metformin and or Glitazones, glibenclamide can be added as a first add on agent or second add on agent.

3] In those type 2 diabetics who require insulin for blood glucose control but who still have some functional beta cells; glibenclamide can be added to insulin. If beta cells respond to glibenclamide, the dose and frequency of insulin can be reduced. However very severe and long standing type 2 diabetics who are in severe hyperglycemia, [fasting plasma glucose > 200 Mg%] in spite of taking 4 or more tablets of glibenclamide, are unlikely to be benefited from addition of glibenclamide to insulin therapy because they are likely to be in 'end stage' failure of beta cells.

Glipizide: It is a shorter acting agent as compared to glibenclamide and thus is administered two or three times a day 30 minutes before meals. It is a better SU to control post prandial blood glucose. Modified release once a day preparations are also available. The average daily dose range is 2.5 to 20 mg%. A few years back price of glipizide formulations was drastically reduced by a government directive. Thus, like glibenclamide, it is very inexpensive.

Prevalence and severity of hypoglycemia induced by glipizide is a bit lesser than glibenclamide. It is contraindicated in severe renal insufficiency, in addition to other common contraindications of the class mentioned above.

Indications: In principle the indications are same as glibenclamide but in those with mild renal impairment [serum creatinine 1.5-2 mg%], and in those who are prone to hypoglycemia, particularly elderly, it may be preferred to glibenclamide.

Gliclazide: It is similar to glipizide and has same indications as glipizide. It is usually administered twice a day 30 minutes before meals. Usual daily dose is 40-320 mg. However

modified release once a day preparations, recently launched in market provide better bio availability and thus their average daily dose is 30 to 120 mg taken once a day. The claim that "It works beyond blood sugar control" by reducing micro vascular complications of diabetes is not adequately substantiated. As compared to glibenclamide, weight gain is not significant. It is more expensive than glipizide.

Glimepiride: This is the latest SU introduced in our country about a decade back. It has a long duration of action and is thus is recommended once a day, however in some patients it produces a much smoother blood glucose control if administered twice a day. Unlike other SUs, even if administered just before meals, it still gives similar post prandial control as compared to 30 minutes before meals administration. The usual daily dose is 0.5 to 6 mg. It has a short half-life but still has a long duration of action. It is claimed that stronger extra pancreatic action as compared to other SUs, is responsible for long duration of action in spite of short half life. Prevalence and severity of hypoglycemia is less as compared to glibenclamide. SU induced weight gain is also less as compared to glibenclamide. Comparative studies with glipizide and gliclazide as regards hypoglycemia and weight gain are not available. Unlike glibenclamide and glipizide, glimepiride acts mainly on receptors on the beta cells in pancreas and has insignificant action on cardiac and vascular receptors. Theoretically, this gives an edge to glimepiride in patients having coronary artery disease. However practical significance of this is not yet known.

Indications: The general indications of glimepiride are same as those of any other SUs. The main indications are:

1] as first line drug when metformin is not tolerated or is contraindicated in type 2 diabetic patients.

2] In type 2 diabetic patients not controlled on metformin and\or glitazones, glimepiride can be added.

3] In type 2 diabetics requiring insulin, it can be co prescribed with insulin.

Advantages such as once a day dosage, lesser chances of hypoglycemia, and lower weight gain, relative safety in renally impaired patients and in elderly, have made glimepiride a popular SU.

It has no specific contraindication in addition to the group contraindications mentioned above. It can be used in mild to moderate renal insufficiency.

Sulphonylureas and Hypoglycemia

It should be noted that if given indiscriminately, all Sulphonylureas can lead to dangerous episodes of hypoglycemia which can be occasionally fatal. In older diabetics, symptoms of sympathetic over activity such as palpitations, tremors, sweating etc., which serve as a warning are often absent, and hence they could land up straight away in hypoglycemic coma or other types of neurological deficits of acute onset such as hemiplegia or acute delirious state. Renal and hepatic insufficiency, alcohol consumption, infrequent follow-ups and failure to review the dosage of OAD from time to time are some of the common predisposing factors, and inadequate carbohydrate intake is a common precipitating factor.

Unlike insulin, hypoglycemia induced by Sulphonylureas could be very prolonged or recurrent, even with drugs like Glibenclamide which has a short biological half-life. Hence all patients with Sulphonylurea induced severe hypoglycemia should be hospitalized and maintained on continuous IV. 5 % Glucose drip and observed upto 48-72 hours.

In order to avoid Sulphonylurea induced hypoglycemia the following precautions should be taken.

I) Do not use Sulphonylureas in patients with hepatic and / or renal insufficiency.

ii) Ask the patients to avoid alcohol and take small frequent

feeds as per time-table drawn. He/she should not miss the food.

iii) Periodically monitor Blood Glucose (every 3 months), and if it is well controlled, try to reduce the dosage of Sulphonylureas.

iv) Stress on persistent diet control and regular exercise so that the dosage of OAD could be kept to the minimum.

v) If the patients are on a combination of Sulphonylurea plus Biguanides, DPP4 inhibitors or incretin mimetics, the upward increment in dosage of either drug should be more gradual.

vi) In older diabetics, (above 70 years), do not insist on a very tight control of blood glucose and use Glimepiride.

NON SU Insulin Secretogogues:

Repaglinide:

This is the first insulin secretogogue which was not a sulphonylurea derivative but a benzoic acid derivative. Its mechanism of action is same as that of SU. However the main differences are:

1] Its onset of action is much quicker and duration of action, much shorter than SUs.

2] It can be given in renal impairment.

Repaglinide is a better agent than most SUs to control post prandial hyperglycemia, but at the same time, much weaker agent to control fasting hyperglycemia. It needs to be given before each meal and the usual dose is 0.5 to 2 mg three times a day. Prevalence of hypoglycemia is much lower than SUs.

Indications:

The general indications are same as those of SUs but it can be used as a agent of choice in those who have predominantly post prandial hyperglycemia, tendency for repeated hypoglycemia, irregular life style, elderly diabetics etc.

Multiple doses and higher daily cost are the relative disadvantages.

Contraindications: Hepatic impairment, pregnancy and lactation

Nataglinide:

Like Repaglinide, it has a quick onset and a short duration of action. Onset, slightly quicker and duration, slightly shorter as compared to the former. Thus, it has a slight edge. The usual daily dose is 30 to 120 mg before each meal. Its slot in the management for type 2 diabetic patients and relative advantages and disadvantages over SUs as well as indications and contraindications are same as Repaglinide.

Biguanides:

Metformin is the only biguanide now available in our country as phenformin was banned in December 2003. However for historical perspective, some comparative information on phenformin is retained in this book. After absorption from the upper G.I. tract, Phenformin is concentrated predominantly in the liver while Metformin in the intestinal mucosa. The former is metabolized in the liver while the latter is excreted unchanged.

Biguanides do not stimulate release of insulin from pancreas; they act at peripheral sites and improve tissue response to available insulin. Thus when given as monotherapy or along with other peripherally acting drugs, they are not liable to cause hypoglycemia. Biguanides mainly act at liver and suppress neoglucogenesis, i.e. formation of glucose from non glucose sources. In addition, Biguanides also have some action on striated muscles where they improve insulin mediated glucose disposal.

Among the biguanides, Metformin is the agent of choice. In fact Phenformin was either banned or voluntarily withdrawn

from most of the developed countries between 1978 to 1980. It took exactly quarter of century for Indian regulatory authorities to order its withdrawal from the market.

Metformin is usually administered twice or thrice a day while it's slow release preparations can be given once a day. The usual daily dose is 500 to 2550 mg. It is available in a wide range of formulations to enable the prescriber to titrate the dosage as per the exact requirement of an individual patient. [conventional form of metformin is available in 4 strengths, 250 mg, 500 mg, 850 mg; and 1000 mg. In addition, extended release metformin is available in 500 mg 1000mg strengths].

Indications:

1] Metformin is indicated as an agent of first choice in all type 2 diabetic patients, unless it is contraindicated. It should be started along with diet and exercise soon after the diagnosis is confirmed. Universally, metformin is considered as the foundation agent to initiate the treatment of type 2 diabetes. Subsequently, if and when required, the agents from other classes of OADs can be added around it. Proved efficacy, safety from hypoglycemia, a track record of more than 5 decades, absence of cardio vascular side effects; and weight neutrality are some of the main assets of metformin leading to its pivotal status in the management of type 2 diabetes.

In those type 2 diabetics who do not adequately respond to metformin or who do not tolerate full dose of metformin, it can be combined with glitazones, SUs or gliptins. Younger patients with severe insulin resistance [clinical markers: central obesity, hypertension, hypertriglyceridaemia etc] are suitable for metformin - glitazone combination, while others can be prescribed metformin - SU combinations. Affording patients have a choice of metformin - gliptin combination, which has a

strong synergy and safety from side effects such as weight gain and hypoglycemia.

2] In those diabetics on insulin and requiring large doses of insulin due to insulin resistance overlapping on insulin deficiency, metformin can be added as an adjuvant to insulin.

3] Metformin has multiple additional indications such as prevention of diabetes, polycystic ovary syndrome, non alcoholic hepatic steatosis, prevention and treatment of certain malignancies. Further details are beyond the scope of this book.

Contraindications:

Metformin is contraindicated in hepatic and renal insufficiency and in cardiac failure or those with severe bronchial asthma and chronic bronchitis. It is also contraindicated in diabetic keto acidosis, pregnancy and lactation; type I diabetics.

Biguanides and Lactic Acidosis

Among the two biguanides, Metformin is now universally considered as the drug of choice because of its relative safety as regards occurrence of lactic acidosis, which is extremely rare but a life threatening complication of biguanide therapy having 50 % mortality rate even after prompt diagnosis and treatment in well equipped ICU with dialysis facilities. This is precisely the reason for withdrawing phenformin from the most of the advanced countries in 1978-80 and continuing with metformin.

Most of the patients who developed biguanide induced lactic acidosis had hepatic, renal, or circulatory impairment, and in fact, they should never have received a biguanide. However, there are a few case reports of phenformin associated lactic acidosis in patients who did not have any contraindications for use of Phenformin which was prescribed in correct dose.

A noteworthy feature about Metformin induced lactic acidosis is that in all patients, Metformin was consumed in spite of a contraindication or in very large doses, hence lactic acidosis was avoidable. The lesser incidence of Metformin associated lactic acidosis can be explained by the fact that Metformin is less lipophilic than Phenformin, and it is not concentrated and metabolized in the liver thus hepatic insufficiency does not increase the probability of metformin induced lactic acidosis.

It was generally believed by Indian Diabetologists that lactic acidosis is rare in our patients as compared to western countries. It is well known that our patients consume complex carbohydrates containing higher amounts of fiber content, in large amounts. Alcohol consumption is also much less as compared to western countries and possibly because of these reasons; our patients are controlled with comparatively smaller doses of biguanides leading to lesser incidence of lactic acidosis.

However, considering the lack of laboratory facilities required for estimation of blood lactic acid and blood pH and lack of awareness about lactic acidosis in some clinicians, one can assume that lactic acidosis is not as rare as it appears and possibly many cases are missed. A few cases of biguanide associated lactic acidosis have already been reported from our country.

In order to avoid biguanide induced lactic acidosis, the following precautions should be taken.

i) Do not use biguanides in hepatic or renal insufficiency and in patients with severely impaired left ventricular function and severe bronchial asthma or COPD or any condition which can lead to severe hypoxia.

ii) Monitor serum creatinine yearly and discontinue biguanides when S. creatinine touches higher limit of normal range.

iii) Advise the patients not to consume alcohol.

iv) Use minimal effective doses of biguanides and try to reduce it from time to time.

v) Avoid biguanides in patients suffering from diabetic proliferate retinopathy even if S. creatinine is within normal limits because usually proliferate retinopathy and nephropathy are associated in a diabetic and also because serum creatinine is an insensitive test to detect early nephropathy.

Note : Of late, a consensus has developed among diabetologists that metformin need not be stopped when serum creatinine touches higher normal limit. Metformin can be continued under careful surveillance in mild renal impairement. (till creatinine clearance is reduced to < 60 mL/min).

vi) Keep the possibility of biguanide induced lactic acidosis in mind whenever you come across a diabetic on biguanides having symptoms suggestive of lactic acidosis such as deep, rapid breathing, dyspnoea, upper abdominal discomfort, drowsiness, unexpected deterioration in health etc, when other common causes are excluded. Under such circumstances, promptly withdraw biguanides and hospitalize the patient for further management.

Thiazolindindione, [also known as Glitazones]:

Glitazones work as insulin sensitizers. Like metformin, they act only on peripheral tissues, mainly muscle and fat cells, and increase their sensitivity to insulin. They do not increase pancreatic insulin secretion, thus when given alone or in combination with metformin, they do not cause hypoglycemia.

Their action is mediated through activation of Ppar gamma activated intra nuclear receptors. The cellular site of action

is predominantly adipocytes and muscle cells with some action on hepatocytes. Glitazones sensitize tissues towards insulin and reduce circulating free fatty acid levels.

Rosiglitazone and Pioglitazone were the two glitazones available in our country till recently. In September 2010, the regulatory authorities of Govt. of India banned rosiglitazone following its ban in advanced countries. Both have identical mechanism of action and indications. Water retention leading increased volume of fluid in intra vascular compartment is liable to occur with both the compounds. Precipitation of incipient cardiac failure has occurred with both the glitazones, thus they are contraindicated in those in cardiac failure or those who have history of cardiac failure. In addition, a meta analysis published in 2007 associated rosiglitazone with higher prevalence of myocardial infarction and sudden cardiac death. Pioglitazone has a favorable influence on plasma lipids and was not associated with increased prevalence of myocardial infarction or sudden cardiac deaths in any of the clinical trials or meta analysis. The usual daily dose of pioglitazone is 15 to 45 mg. in a single dose. Most of the Indian authorities do not prescribe it beyond 30 mg\day. Both the agents produce weight gain which can be as much as ten kgs in some patients. The weight gain is mainly due to water retention with some contributions from adipogenesis and weight regain due to better metabolic control. In those with significant edema or weight gain, glitazones need to be discontinued.

Indications:

1] In predominantly insulin resistant type 2 diabetic patients, pioglitazone is used as an alternative to metformin particularly if the latter is not tolerated or contra indicated. It can also be combined with metformin when monotherapy with metformin fails to achieve glycemic targets.

2] In combination with SUs or other insulin secretogogues when latter agents alone are not sufficient to control blood glucose level.

3] In triple drug combination along with any two from SU, metformin and gliptin groups, when two drug therapy fails to meet glycemic targets and the patient is still some distance away from end stage beta cell failure. Experienced clinicians can make such a judgment.

Contra indications:

Glitazones are contra indicated in hepatic insufficiency and in cardiac failure. They are ineffective in type 1 diabetics..

Glitazones for prevention of diabetes

DREAM trial has demonstrated that use of Rosiglitazone in the dose of 16 mg daily by those having IGT led to 60% relative risk reduction as regards conversion to diabetes. However, henceforth, rosiglitazone will not be available due to its withdrawal from the market.

ACT NOW Trial: In recently concluded prevention trial, administration of 45 mg. of pioglitazone led to 72% relative risk reduction of diabetes as compared to placebo in those with impaired glucose tolerance. However there was weight gain in patients on pioglitazone.

The following table gives relative efficacies of various OAD's in prevention of diabetes in those having IGT

OADs	Risk reduction%	TRIAL
Pioglitazone	72	**Act Now**
Rosiglitazone	60	**Dream**
Metformin	33	**DPP**
Acarbose	25	**STOP NIDDM**
Agressive Diet + Exercise	56	**DPP**

Precautions:

Liver functions [SGOT and SGPT] should be monitored, before starting the therapy and at periodic intervals. Those with values less than higher limit of normal can initiate therapy and continue it. Those with values more than twice the upper limit of normal should not use glitazones or discontinue if already on therapy. Physicians should use their discretion for those with values in between.

Note: By now, glitazones are in clinical practice for more than a decade. During this period, cases developing hepato toxicity were very rare and thus formal guidelines about pre treatment and subsequent periodic monitoring of SGOT and SGPT have been relaxed and the prescriber should his discretion to advise liver function tests depending upon individual case.

Alpha Glucosidase Inhibitors:

Acarbose, miglitol, and voglibose are available in India. They act locally on the surface of small intestine. By inhibiting enzymes which convert complex carbohydrates in to disaccharides, they delay digestion of carbohydrates and convert them in to glucose gradually thus its absorption in circulation is slowed down and post prandial peaks are blunted. These agents are not very effective in controlling fasting blood glucose and thus are usually used as an adjuvant to other anti diabetic agents. They tend to produce abdominal distention, borbigmy and diarrhea in many patients, particularly when given in higher doses. These side effects are more common in Indians as compared with western people because we take a lot of fiber in our diet. Usual dose is one to two tablets three times a day with meals, the pill to be taken with first bite of food. In west, many patients are prescribed higher dosages but these are not tolerated by Indians.

Indications:

1] As a monotherapy in patients with mild and predominantly post prandial hyperglycemia, if metformin is contra indicated or not tolerated.

2] As an adjuvant to insulin, metformin, glitazones and insulin secretogogues for improvement in post prandial glucose control.

Contraindications :

Alpha glucosidase inhibitors are contraindicated in inflammatory bowel disorders and in pregnancy and lactation.

Precautions:

If a patient develops hypoglycemia, he should be treated by administering glucose, even if hypoglycemia is mild because, in patients on these agents, complex carbohydrates take longer time for conversion to glucose.

Incretin Mimetics and Incretin Enhancers:

Recently, two new classes of anti diabetic agents with novel and totally different mechanism of action, as compared to insulin and traditional OADs, have been introduced in clinical practice. Incretin mimetics [GLP1 Agonists] are injectable agents while incretin enhancers, which are also known as DPP IV inhibitors or gliptins, are oral agents. Their mechanisms of action partially overlap each other. Before looking in to these agents, let us review incretin physiology.

Incretin physiology: Incretins are hormones secreted by small intestine in response to food intake. The two important incretins are; 1] GLIP 1 [Glucagon like peptide 1] and 2] GIP [Glucose dependent insulinotropic peptide]. Circulating levels of these hormones, particularly GLP I are reduced in type 2 diabetics. They respond to iv infusion of GLP1 but are resistant to action of GIP, Thus it has no therapeutic value.

Thus let us now concentrate on GLP I. Its four important physiological actions are:

1] Glucose dependant enhancement of insulin secretion by beta cells.

2] Glucose dependant suppression of post prandial glucagon secretion by alpha cells

3] Delaying gastric emptying

4] Stimulation of satietary centre in hypothalamus, leading to reduction in appetite.

All these actions lead to control of post prandial blood glucose in normal persons. In type 2 diabetics, reduced levels of GLP I is one of the contributing patho physiological factors responsible for hyperglycemia. GLP I has very short biological half life because immediately after its formation and secretion in ileum, it is degraded by DPP IV enzymes locally secreted in small intestine. Thus in order to be therapeutically effective, it has to be given in continuous iv infusion, which is not practicable.

Incretin mimetics:

Extenatide, which is a synthetic derivative of extendin found in saliva of Zila monster has a biological half life of 2 hours and remains effective for about 12 hours after sc administration in human beings. It is available in our country as Byetta since 2007. It shares all the physiological actions of GLP I and is not degraded by DPP IV enzymes. It's administration in the dosage of 5 to 10 mcg in sc injection twice a day 30-60 minutes before meals in those type 2 diabetics with viable beta cells leads to significant reduction in post prandial blood glucose, about 1% reduction in Hba1c, and some reduction in fasting plasma glucose. Its main advantages over SU are weight reduction and absence of hypoglycemic episodes since it acts only in presence of hyperglycemia. These two properties have led to its vast

popularity in western countries. It is a good alternative to SU's in the management of type 2 diabetes, particularly those who are overweigh and can afford to spend around 8000 Rs. per month. The main side effects seen in about 10% patients are nausea and vomiting. Starting with the dose of 5 mcg for four weeks, and then increasing to 10 mcg. if required helps to reduce g i. side effects.

Liraglutide : It is a GLP1 agonist having longer biological half life and needs to be given once a day thus is more patient friendly. As compared to exenatide, it's other subtle differences are: 1] Less pronounced effect on gastric emptying leading to lesser reduction of post prandial blood glucose and also lesser gastro intestinal side effects. 2] It reduces fasting blood glucose as well as Hba1c by a greater extent. 3] It has greater homology with glucagon like polypeptide 1. Liraglutide been recently introduced in India. Its dose is 1.2 to 1.8 mg sc once a day. The starting dose is 0.6 mg and if well tolerated, the dose should be stepped up to 1.2 mg after 1 week.

Indications of Exenatide and liraglutide:

Both the agents are suitable in affording overweight type 2 diabetics, particularly if they are not responding to combination therapy with OADs and they still have some surviving beta cell mass.

Long acting Extenatide: A longer acting version of extenatide, with effective duration of action up to one week is being developed. In recently concluded clinical trial, long acting extenatide in the dose of 2 mg sc once a week has been able to reduce HbA1c by 1.6% in 20 weeks.

Incretin enhancers [DPP IV Inhibitors\ Gliptins]:

As mentioned above, DPP IV is an enzyme secreted by small intestinal mucosa in areas next to incretin secreting cells. It degrades incretins including GLP I immediately after

formation thus making it ineffective as a therapeutic agent. However, now orally active agents which inhibit DPP IV enzyme are available. This action leads to sustained availability of physiological amounts of incretins including GLP I. If given to diabetic patients, these agents effectively reduce blood glucose level by working through GLP I.

Sitagliptin; [Januvia] is first agent from this class, which is available for day to day practice. It is given in once a day in 100 mg. dosage by mouth, just before breakfast. It is a bit less potent than extenatide because it does not have equally potent actions on gastro intestinal motility and satietary centre. Unlike extenatide its use does not lead to significant weight reduction. It is weight neutral. When used alone or in combination with insulin sensitizers, it does not lead to significant hypoglycemia because of its glucose dependant action on beta cells. Availability in oral form is its main advantage over extenatide. It has been in clinical use for 3 years while extenatide is in use for 4 years.

It can be a good alternative for SU's both as monotherapy if metformin is unsuitable, or in combination with metformin and\ or glitazones. In mild renal impairment, the dose need not be changed. In moderate and severe renal impairment the dose is 50 mg. and 25 mg. once a day respectively. Tablets in 50\25 mg. strengths are available but the cost of both is same as 100 mg. tablets.

Vildagliptin [Jalara \ Galvus] is another agent from this class which has been introduced recently in India. It's usual dose is 50 mg. twice a day and has a profile similar to that of sitagliptin. It is not cleared for use in renally impaired patients. Both sitagliptin and vildagliptin are available in fixed dose combinations with metformin in our country.

Another DPP4 inhibitor, **Saxagliptin [Onglyza],** has been recently introduced in India . It is available as a formulation containing 5 mg. tablet and is administered once daily.

Its indications and contraindications are same as those of other DPP4 inhibitors.

Linagliptin:

In May 2011, a new DPP4 inhibitor, 4th in series, linagliptin was launched in USA. It has a long biological half life as well as ability to maintain raised GLP1 level for about 24 hrs. Thus it is true once a day agent. It is safe in all grades of renal insufficiency and is administered in same full therapeutic dose as in those with normal renal functions, thus frequent monitoring of renal functions is not required for those on linagliptin.

The main advantages of extenatide and gliptins over SU's are: 1] Lack of weight gain and hypoglycemic episodes. In addition, in experimental animals, long term exposure of these agents has led to some degree of beta cell preservation. Beta cell regeneration, replication as well as reduced apoptosis have been postulated. SU's do not have this property. Thus SU's are expected to be gradually replaced by these agents particularly in rich countries. Due to economic limitations, only a small fraction of diabetics can afford these expensive agents, thus time tested SUs will continue to remain one of the mainstay of oral anti diabetic therapy in our country for a long time to come. However, it should be noted that while SUs have withstood the test of time, these new agents are in clinical use for very short time. Thus, it is a bit early to write obituary of SUs and hail incretin mimetics and DPP4 inhibitors as great discoveries and wonder drugs.

Quick Release Bromocriptine Tablets:

Conventional Bromocriptine has been in clinical practice for more than two decades for the management of Parkinsonism and galactorhoea. Quick release preparation of Bromocriptine has been introduced in India in mid 2010 and in USA in November 2010. It is indicated in the management of type 2 diabetes.

In type 2 diabetes, dopaminergic tone in hypothalamic area is reduced. This is associated with increased secretion of noradrenalin in hypothalamic hypophysial axis, which in turn leads to insulin resistance, obesity and hyperglycemia. Bromocriptine is dopamine agonist. Administration of quick release version leads to rapid build up of its blood levels and resetting of dopaminergic tone. This is associated with reduction in insulin resistance and improvement in glycemic status, particularly post prandial hyperglycemia.

Quick release bromocriptine has better bio availability than its conventional version. It is available in tablet form; each tablet contains 0.8 mg. of bromocriptine in special quick release formulation. The therapeutic dosage is 1.6 to 4.8 mg once daily two hours after getting up in morning, preferably after food. In order to avoid gastro intestinal side effects, treatment should be started with 0.8 mg and dosage should be stepped up at weakly interval.

Quick release bromocriptin is the first and so far only anti diabetic medication which has successfully undergone elaborate pre marketing cardio vascular safety studies in USA. After the publication of report of excess cardio vascular mortality with rosiglitazone in The New England Journal of Medicine in June 2007, The US FDA has made these tests mandatory for any new anti diabetic agent before its introduction in the market.

Quick release bromocriptin can be used as one of the add on agents, particularly in those with manifestations of insulin resistance.

Clinical applications of OADs

OADs are indicated in type 2 DM patients when diet fails to control hyperglycemia. Stressful conditions such as severe infections, pregnancy, and major surgery, renal and hepatic insufficiency are contra-indications to the use of OADs. These drugs do not work in the absence of insulin, hence should not be used alone in Type 1 DM.

CRITERIA FOR CONTROL

One should aim at total freedom form glycosuria and steady near normal blood glucose. TABLE-2 gives Criteria for control.

Table 2 : Criteria for metabolic control - blood glucose values

Time	Good	Fair	Poor
Fasting*	<110 mg%	110-130 mg%	>130 mg%
2 hrs post meal*	<140 mg%	140-180 mg%	>180 mg%
HbA1c	6.5-7%	7-7.5%	>7.5%

***venous plasma true glucose values**

Note : Criteria for control need to be modified as per the individual patient's situation.

In elderly people, in those who do not have warning adrenergic symptoms; and in those with significant cardiovascular affection with long standing diabetes, less stringent criteria should be applied.

During pregnancy, fasting and 2 hours post prandial plasma glucose values should be < 100 and 125 mg% respectively. In young and recently diagnosed diabetic patients, generally aggressive criteria should be applied. [Their all the three glycemic values, i.e. fasting and post prandial plasma glucose values and HbA1c should be at or very near lower limit of the range mentioned above.

FAILURE OF CONTROL

A common cause of failure is inadequate dietary regulations. Some diabetics are under the wrong impression that since they are taking OAD, they are at liberty to eat anything. In addition to review of diet in patients failing to respond to OAD, a systematic search for occult infection (e.g. Tuberculosis, Urinary Tract infection, etc.) should be made.

It is also advisable to thoroughly analyze all the medicines he/she is taking. In addition to medicines prescribed by you, he/she may be taking, say for example, steroids for asthma (some powders dispensed by quacks for "asthma" and 'jaundice" contain steroids) strong potassium wasting diuretics like Fursemide; and Diphenylhydantoin can also interfere with the action of OAD. If a failure occurs even after proper dietary regulations and maximal dose of OAD, drugs from other groups (i.e. SU in those taking metformin and vice versa) should be added and the dosage gradually increased, until optimal control is achieved. After a prolonged use for several years, OAD gradually start losing their effect and ultimately a stage is reached in many patients where a maximum dosage of combined agents is also unable to control hyperglycemia and (secondary failure). At this stage OAD should be replaced by insulin.

Side Effects

Sulphonylureas: A number of non-specific gastrointestinal symptoms ranging from dyspepsia to diarrhea occur with the sulphonylureas in a small number of patients (3 to 5%). A variety of skin reactions also occur. These are mostly of minor significance and resolve on drug cessation; however, an occasional severe complication may arise such as exfoliative dermatitis or Stevens-Johnson syndrome. A cholestatic type of jaundice is rarely seen, as is bone marrow depression. Water retention giving rise to dilutional hyponatraemia (similar to that seen in the inappropriate ADH syndrome) was first described with Chlorpropamide but has also been reported with other sulphonylureas. Hypoglycemia should be regarded as a consequence of excessive dosage rather than as a side effect, unless due to drug interaction.

Biguanides: Gastro-intestinal side effects including anorexia, nausea and diarrhea, occur in 10-15% of patients, and being dose-dependent, these may limit the opportunity to employ

maximum dosage. Vitamin B12 deficiency may result from the effect of biguanides on the bowel. In contrast to the sulphonylureas, hypoglycemia is rare and usually is only reported with suicidal drug use. We have already discussed lactic acidosis.

Glitazones: Weight gain, swelling of feet due to edema; and cardiac failure when used in patients with left ventricular dysfunction are main side effects. Mild anemia is also seen. This is due to dilution of blood following increased blood volume due to water retention.

Alpha Glucosidase Inhibitors: Abdominal distention, borbigmy and diarrhea are main side effects.

DPP4 Inhibitors: A variety of skin reactions are occasionally reported. These are mostly of minor significance and resolve on drug cessation; however, an occasional severe complication such as exfoliative dermatitis or Stevens-Johnson syndrome, has been reported in those on sitagliptin. Rare cases of pancreatitis in those on sitagliptin and incretin mimetics have been reported, however cause and effect has not been proved. As such, pancreatitis is more common in diabetics as compared to others.

Incretin mimetics: main side effects are gastro intestinal intolerance. These can be reduced by starting the therapy with smaller dose and subsequently stepping up. Pancreatitis has been reported in rare cases.

Bromocrptine: Gastro intestinal intolerance is not uncommon. The prevalence and severity is reduced by starting with lower dose and stepping up after one week. Giddiness and postural hypotension is seen in some patients. Bromocriptine should be avoided in those on other ergot agents, antipsychotic agents and dopamine antagonists.

Drug Interactions

These occur mainly with Sulphonylureas. Alcohol intolerance occurs in a number of patients particularly those on Chlorpropamide. Many drugs potentiate hypoglycemic effects of Sulphonylureas. These include Clofibrate, Dicumarol, large doses of Salicylates, Beta blockers, NSAIDs and Biguanides. In those taking Biguanides, the risk of lactic acidosis increases if they consume alcohol.

Synopsis of actions of oral anti diabetic agents.

	Insulin	SU & Glinides	Metformin	Alpha glucosidase Inhibitors	Glitazones	DPP4 inhibitors	Incr. Mim
Fasting glucose	↓↓	↓	↓	-or ↓	↓	↓	↓
Post prandial glucose	↓↓	↓	↓	↓	↓	↓↓	↓↓
Insulin concentration	↑↑	↑	-or ↓	-or ↓	-or ↓	↑	↑
Body weight	↑	↑	-or ↓	–	↑	–	↓↓
Free fatty add,	↓	-or ↓	-or ↓	–	↓	–	↑
Triglycerides	–	–	- or ↓	–	-or ↓	–	–
Total cholesterol	–	–	- or ↓	–	-or ↑	–	–
Safety	Hypo	Hypo	Lactic Acidosis	–	?	–	–
Tolerability	Inject		GI disturb	GI disturb	–	–	GI disturb
Exclude\ caution	–	Llver\ kidney impairment	Liver kidney impairment, hypoxia	Inflammatory bowel dis	liver impairment		
Monitor	–	Creat	Creat	LFT	LFT Cardiac function	–	–

↑ = increased, ↓ = decreased, – = no change.