

# QUARTERLY MEDICAL REVIEW

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Vol.55, No. 3

July - September 2003

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## DIABETES MELLITUS

(Part 1)

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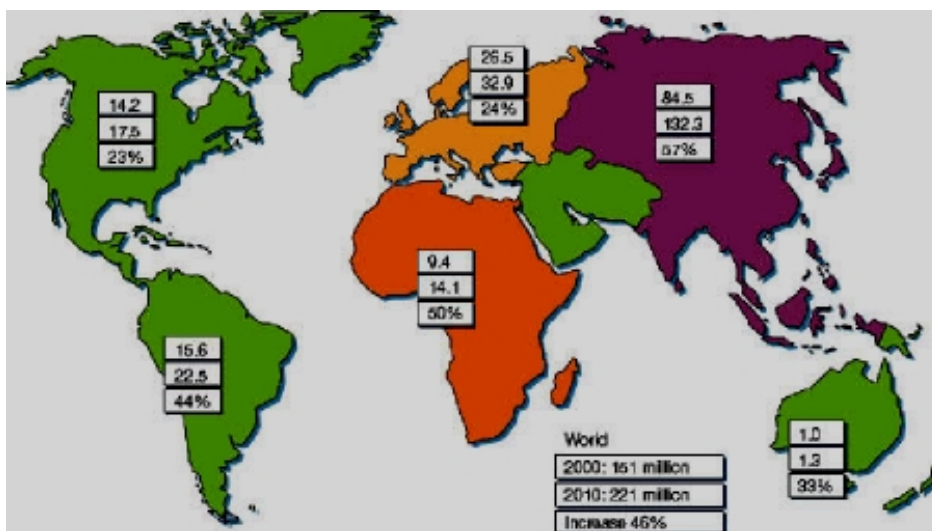
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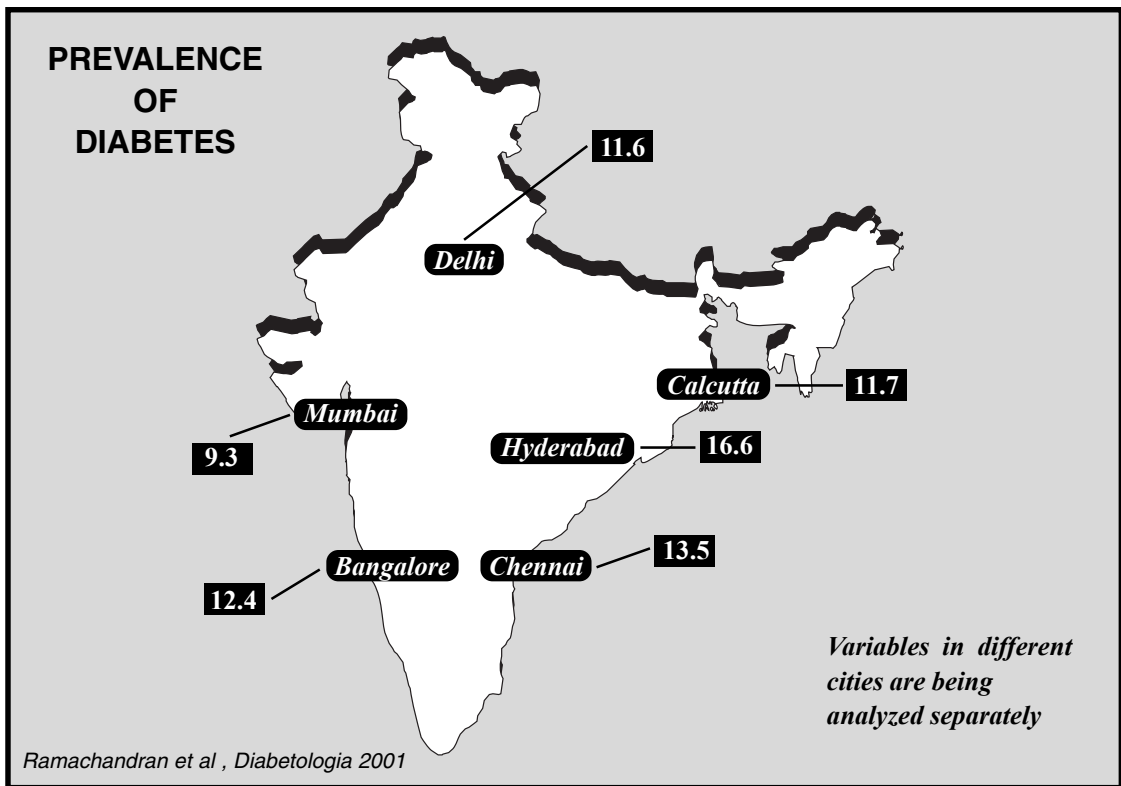
## INTRODUCTION & EPIDEMIOLOGY

According to WHO report the prevalence of diabetes in adults worldwide has risen and the number will rise from 135 million in 1995 to 300 million by the year 2025. Epidemiological data in India shows the same upward trend from 33 million diabetics in 2000 to 57 million in 2025. India has thus become the “Diabetic Capital of the World”. The factors for this steep rise include genetic predisposition, urbanization, ethnicity, insulin resistance and central obesity. Type 2 diabetes with early age onset carries higher risk of heart attacks, 4-5 times for stroke, 5 times for nephropathy and even higher for peripheral vascular disease. While hypertension is observed in 38% of type 2 DM the prevalence of retinopathy in 23.7%, coronary artery disease in 11.4%, peripheral neuropathy in 27.5% and nephropathy in 5.5% are observed by Ramchandran at Chennai. The WHO estimated that there were 19.4 million persons with diabetes in India in 1995 and that this number is likely to be 57.2 million in 2025. India has the distinction of having the largest number of diabetics in the world. Studies in 1980-90s showed higher prevalence rates of type 2 diabetes among migrant Indians in several countries, compared with their native populations and other migrant ethnic groups. Current prevalence rates are 10-18% in the urban Indian adult population and there is evidence that the prevalence of type 2 diabetes is increasing in rural population also. Hyperglycemia contributes to the increased incidence

### WORLDWIDE PREVALENCE OF DIABETES FOR 2000 AND 2010: AN EPIDEMIC



ZIMMET P, ALBERTI KGMM & SHAW J. Nature 414, 782 - 787 (2001)



of macrovascular disease but dyslipidemia, hypertension, central obesity, decreased physical activity and smoking play a major role in accelerated atherosclerosis seen in diabetics.

Therefore, the complete treatment of diabetic patients not only includes meticulous attention to achievement of normoglycemia, but also correction of hypertension and dyslipidemia, correction of body weight and increase in physical activity. It is desirable to have the fasting and post-prandial blood glucose concentration and HbA<sub>1C</sub> as well as BP, Lipids and Body weight as close to normal as possible. All the above goals are desirable and can be achieved without significant deterioration in quality of life. Patient education is also an essential goal of any treatment regimen. Patients who understand the importance of achieving these goals and their role in preserving health will be motivated to do so.

## DEFINITION

Diabetes mellitus is a metabolic syndrome characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from improper insulin secretion and/or inefficient insulin action. This chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vessels.

**TABLE 1 : Top ten countries for number of persons with diabetes**

Year 1995			Year 2025		
No.	Country	Numbers in million	No.	Country	Numbers in million
1.	India	19.4	1.	India	57.2
2.	China	16.0	2.	China	37.6
3.	USA	13.9	3.	USA	21.9
4.	Russian Fed	8.9	4.	Pakistan	14.5
5.	Japan	6.3	5.	Indonesia	12.4
6.	Brazil	4.9	6.	Russian Fed	12.2
7.	Indonesia	4.5	7.	Mexico	11.7
8.	Pakistan	4.3	8.	Brazil	11.6
9.	Mexico	3.8	9.	Egypt	8.8
10.	Ukraine	3.6	10.	Japan	8.5

## CLASSIFICATION

Several international bodies like American Diabetic Association (ADA), World Health Organisation (WHO), European Association for Study of Diabetes (EASD), International Diabetic Federation (IDF), have attempted to classify diabetes and by now there is a universal consensus on the common classification.

### 1) Type 1 Diabetes

**A. Immune Mediated Diabetes :** This form previously called insulin dependent diabetes, type 1 diabetes or juvenile onset diabetes results from a cellular mediated autoimmune destruction of the beta cells of the pancreas. Markers of the immune destruction of the beta cell include Islet Cell Antibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GAD 65) and autoantibodies to the tyrosine phosphates, IA-2A and IA-2B. The disease has strong HLA associations, wherein DR3, DR4 and DR 2 is protective. In this form of diabetes, the rate of beta cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults).



### Indian Criteria for Diagnosis of the Metabolic Syndrome

Abdominal Obesity (waist circumference)	
Men	>35 inch (>90 cm)
Women	>27 inch (>68.5 cm)
Triglycerides	>150 mg/dL
HDL-Cholesterol	
Men	<35 mg/dL
Women	<38 mg/dL
Blood Pressure	>130/>85 mm Hg
Fasting Glucose	>110 mg/dL

### 3) Other Forms of Diabetes

- a. Genetic defects in insulin action
- b. Diseases of the exocrine pancreas - Includes fibrocalculous pancreatopathy
- c. Endocrinopathies
- d. Drug or chemical induced
- e. Infection
- f. Uncommon forms of immune-mediated diabetes
- g. Other genetic syndromes associated with diabetes

### 4) Gestational Diabetes Mellitus (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Six weeks or more after pregnancy ends, the woman should be reclassified into one of the following categories:

1. Diabetes
2. Impaired fasting glucose
3. Impaired glucose tolerance
4. Normoglycemia

In majority of GDM cases, glucose regulation will return to normal after delivery.

Clinical recognition of GDM is important because therapy, including diet, exercise, insulin and antepartum fetal surveillance can reduce the associated perinatal morbidity and mortality. Although many patients diagnosed with GDM will not develop diabetes later in life, others will be diagnosed many years post-partum as having type 1 diabetes, type 2 diabetes, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

### Special types of diabetes in India

The WHO classification (1985) had malnutrition related diabetes as a separate class protein deficient diabetes mellitus (PDDM) and fibrocalculous pancreatic diabetes mellitus (FCPD). In the recent ADA classification, FCPD has been included in other specific types and PDDM has been deleted. However, this type of diabetes which is modulated by malnutrition is specially seen in India. It is characterized by younger age of onset, BMI < 18.5 kg/m<sup>2</sup>, no pancreatic calcification, relative insulin resistance, non-ketotic but requiring insulin for control of blood glucose.

Low body weight type 2 diabetes mellitus is also seen in our country and is characterized by BMI less than 19 kg/m<sup>2</sup> and may not require insulin for their glycemetic control for a variable period of time. This type of diabetes is not associated with malnutrition. The incidence of lean type 2 diabetes mellitus in India was observed to be varying from 11-25% at different centres.

## DIAGNOSIS

The criteria for the diagnosis of diabetes are as follows :

Symptoms of diabetes associated with

- a. Random \* plasma glucose concentration > 200 mg/dl
- b. Fasting \*\* plasma glucose > 126 mg/dl
- c. 2 hr plasma glucose > 200 mg/dl during a 75g OGTT.

For asymptomatic individuals with any one of the above values, a 75 g OGTT is required to confirm the diagnosis.

(\*Random is defined as any time of day without regard to time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia, polyphagia and unexplained weight loss, \*\*Fasting is defined as no caloric intake for at least eight hours. Plasma glucose should be estimated by glucose oxidase method)

### Oral Glucose Tolerance Test (OGTT) as Specified by WHO

#### Procedure

1. The test should be done after at least three days of unrestricted diet (more than 150 g carbohydrate daily) and normal physical activity.
2. It should be preceded by 10-16 hours of fasting, during which drinking plain water is permitted.
3. It should be carried out in the resting subject.
4. Smoking is not allowed on the morning of the test as well as during the test.

5. Factors that could influence the test's interpretation must be recorded.
6. Following collection of fasting blood sample, 75 g of glucose should be dissolved in 250-300 ml of water and should be drunk over the course of about five minutes.
7. The another sample is collected 2 hr after the glucose load.
8. The test results are interpreted as given in Table 4.

***Once diagnosed as diabetes, repetition of OGTT is not required***

**The diagnosis should not be based on urine sugar alone.**

**TABLE 4 : Diagnostic values for diabetes**

Glucose concentration in mg/dl			
	Plasma		Whole blood Venous
	Venous	Capillary	
Diabetes Fasting and/or 2 hr (75g glucose) post-glucose	> 126	> 126	> 108
	> 200	> 220	> 180

**Note :** Plasma glucose is 15% higher than the whole blood glucose. In fasting state, venous and capillary glucose are the same, but it differs in the post-prandial state.

An intermediate group of subjects, called impaired fasting glucose (IFG) is recognised as those with FPG levels > 110 mg/dl but < 126 mg/dl.

Impaired glucose tolerance (IGT) is defined as 2-hr post-glucose levels > 140 mg/dl but < 200 mg/dl. The IGT and IFG group of individuals are important since they have risk of becoming diabetic and are prone to develop macrovascular complications.

## SCREENING

In view of the rising trend in the prevalence of diabetes and associated morbidities, it is imperative to screen high risk groups (Table 5) and the population at large.

The population screening is usually done from Health check up schemes, Insurance screening, Employment check up schemes, Diabetic detection camps etc. Even though ideally fasting blood glucose should be performed, an abnormal random plasma glucose value would also indicate diabetes. However, such individuals should be retested at the next visit for establishing the diagnosis of diabetes as per the diagnostic criteria given in Table 4.

**TABLE 5 : High risk group**

- a. Family history of diabetes
- b. Overweight / Obese (BMI > 23kg/m<sup>2</sup>)
- c. Waist - Hip ratio (0.80 for females and 0.9 for males)
- d. History of gestational diabetes mellitus or baby born more than 3.5 kg or less than 2.5 kg
- e. Hypertension
- f. Dyslipidemia
- g. Impaired Glucose Tolerance (IGT)
- h. Impaired Fasting Glucose (IFG)
- i. Age above 30 years
- j. Vascular disease
- k. Recurrent infections, Tuberculosis, Non-healing wounds

## CLINICAL ASSESSMENT

Persistent hyperglycemia is the hallmark of all forms of diabetes mellitus. A detailed evaluation optimizes the care required to provide better quality of life for these patients.

The first visit : The very first visit of the patient is fully utilized for a detailed medical history and physical examination.

### I Medical History

- Symptoms of hyperglycemia : (polyuria, polydipsia, polyphagia)  
Weight loss, generalized weakness  
Periarthritis  
Delayed healing of ulcers  
Visual disturbances  
Balanitis, or vulvovaginitis/vaginitis
- Previous history of ketosis, hyperosmolar coma, hypoglycemia; cerebrovascular complications, coronary events, pancreatitis.
- Symptoms suggesting development and severity of complications : Facial puffiness, pedal edema, frequency, urgency, dysuria, angina, effort intolerance, Claudication (vascular / neurogenic), gangrene, amputation, Sensory impairment - pain, temperature, gait disturbance in dark, Foot ulcers - site, size, source, sepsis, associated cellulitis, Infections (prior or current) - skin, dental, genitourinary, pulmonary tuberculosis, bladder and gastrointestinal function; orthostatic hypotension, erectile dysfunction

- Evaluation for possible causes of secondary diabetes mellitus.
- Current nutritional status, eating pattern, adequacy of intake; weight history.
- Risk factors for atherosclerosis : smoking, hypertension, obesity, hyperlipidemia, alcohol use, atherosclerosis in family members.
- Lifestyle, cultural, psychosocial, educational, economic, activity status and exercise history.
- Gestational history : hyperglycaemia, delivery of baby > 3.5 kg, toxemia, stillbirth, polyhydramnios or other complications of pregnancy.
- Family history of diabetes and its complications and other disorders (Hypertension, hyperlipidemia, coronary artery disease)
- Previous treatment details and their outcomes.
- Current treatment and glycemic status : medications, compliance, other medications altering glycemic status, frequency of monitoring to achieve glycemic goal.

## **II Physical Examination**

- Measures for height, weight, waist and hip, (calculation of BMI and waist - hip ratio)
- Resting pulse, palpation of peripheral pulses including carotid pulses
- Blood pressure, (lying down, sitting up and standing). Ankle pressure measurement and calculation of ankle-brachial index wherever indicated
- Presence of pallor, pyrexia, dyspnoea, cyanosis, clubbing, dehydration
- Eye - examination including ophthalmoscopic evaluation reviewed by ophthalmologist
- Oral examination
- Thyroid palpation
- Systemic evaluation
  - \* Cardiac evaluation
  - \* Respiratory system examination
  - \* Abdominal examination
  - \* Neurological examination with special reference to ankle jerk and peripheral sensation by vibration, pain and touch.
- Foot examination particularly for callosities, inter-digital web deformities and ulcers, cracks of skin and foot pulses
- Skin examination

## LABORATORY ASSESSMENT

- ❑ Complete urinalysis : glucose, ketones, protein, sediments
- ❑ CBC (complete blood count) : hemoglobin, total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate (ESR)
- ❑ Fasting and 2 hr post-prandial plasma glucose
- ❑ Fasting lipid profile after blood glucose control.
- ❑ Electrocardiogram
- ❑ X-ray chest PA view to see for cardiac size and undetected pulmonary tuberculosis.
- ❑ Serum creatinine, blood urea
- ❑ Test for urinary albumin-creatinine ratio in all patients. 24 hr urinary protein if proteinuria present.
- ❑ These tests should be done where indicated.
  - HbA<sub>1c</sub> (if possible)
  - Sputum for AFB (Acid Fast Bacilli)
  - 2 D-Echocardiography
  - Urine culture if sediment is abnormal or symptoms are present
  - Microalbuminuria (if possible)
  - Serum electrolytes
  - SGOT/SGPT (if the patient is on glitazones)

## FOLLOW UP EVALUATION

Frequency of follow up visits is determined by the control achieved.

- 1) **First follow up visit** : First follow up visit should be scheduled at 2-4 weeks to evaluate blood glucose control and to reinforce diabetic education, diet, exercise and management plan.
- 2) **Subsequent visits** : Once the blood glucose is under control, the subsequent visits should be at three monthly interval to evaluate.
  - Improvement in symptoms
  - Compliance for diet, physical activity and drugs
  - Weight
  - Blood pressure
  - HbA<sub>1c</sub>
  - Lipid levels if initially abnormal

However plasma glucose (fasting and post-prandial) must be checked every month and if the blood glucose values are high, it must be reported to the physician.

### 3) Yearly investigations :

- Physical examination including, ophthalmoscopic evaluation and fundoscopy by ophthalmologist.
- Renal evaluation at first visit and microalbuminuria if possible
- Chest radiography, if required
- Electrocardiogram
- Rest of the investigations as in 3-4 monthly visits
- Evaluation of patient education and diabetes awareness

**Note :** Echocardiography, Doppler studies for foot pulses, cardiac stress test are to be done in appropriate situations and these need not be repeated without proper indications.

## GOALS OF THERAPY

The goals of management in a diabetic patient are to provide

- Relief from diabetic symptoms and improvement in quality of life
- Prevention of acute complications like diabetic ketoacidosis (DKA), hyperosmolar non-ketotic coma (HONK), hypoglycemia and lactic acidosis
- Prevention of infections
- Prevention of microvascular complications-nephropathy, retinopathy and neuropathy.
- Prevention of atherosclerotic vascular diseases : cardiovascular disease, cerebrovascular disease and peripheral vascular disease.
- Prevention of diabetic foot lesions.

Therefore the complete treatment of diabetic patients includes correction of body weight and increased physical activity, meticulous attention to achievement of normoglycemia, control of hypertension and correction of dyslipidemia.

The goals are mentioned in the Table 6. All these goals are desirable and can be achieved without significant deterioration in quality of life. Patient education is also an essential goal of any treatment regimen.

**TABLE 6 : Biochemical and Clinical endpoints of diabetes management**

<b>Parameter</b>	<b>Good</b>	<b>Fair</b>	<b>Poor</b>
Fasting plasma glucose (mg/dl)	< 110	< 126	> 126
Postprandial (2h) plasma glucose (mg/dl)	< 140	< 200	> 200
HbA <sub>1c</sub> (%)	< 6.0	< 7.0	> 7.0
Plasma total cholesterol (mg/dl)	< 180	< 200	> 200
Plasma LDL cholesterol (mg/dl)	< 100	< 130	> 130
Plasma triglyceride (mg/dl)	< 150	< 180	> 180
Plasma HDL cholesterol (mg/dl)	> 45	> 40	< 40
Blood pressure (mm Hg)	< 120/80	< 130/85	> 130/85
Microalbuminuria (mg/day)	< 30	< 300	> 300
Ideal body weight (%)	> 80-< 100	< 120	> 120

## **PRINCIPLES OF MANAGEMENT**

The approach to the management of diabetes has not changed significantly over the years. However, with the development of newer drugs and better understanding of the pathophysiology of type 2 diabetes, the outlook has improved considerably.

The initial step after the diagnosis is made, is life-style modification. The patient is advised an appropriate diet and suitable exercise programme, with cessation of smoking and alcohol. The response to diet and exercise should be assessed for two months in general. The importance of diet and exercise as a cost-effective measure in the management of diabetes should be understood and imparted to the patients. If adequate glycaemic control is achieved, the patient should be motivated to continue the diet and exercise, while monitoring the blood glucose levels at regular intervals.

If diet and exercise do not achieve the desired levels of glycaemic control, drugs have to be added. The choice of drug should be individualized based on the possible underlying pathogenic mechanism in each case. The anthropometric data - weight, height, body mass index (BMI = weight in kg/height in mts<sup>2</sup>), waist-hip ratio (WHR) should be the guiding factors. In obese patients, initiate the therapy with metformin and in non-obese patients, one can initiate the therapy with sulfonylureas, repaglinide or insulin, depending on the clinical presentation. When monotherapy fails to achieve adequate control, combination therapy is adopted.

**BMI chart**

	Weight (kg)			Height (cm)						
	145	150	155	160	165	170	175	180	185	190
50	24	22	21	20	18	17	16	15	15	14
52	25	23	22	20	19	18	17	16	15	14
54	26	24	22	21	20	19	18	17	16	15
56	27	25	23	22	21	19	18	17	16	16
58	28	26	24	23	21	20	19	18	17	16
60	29	27	25	23	22	21	20	19	18	17
62	29	28	26	24	23	21	20	19	18	17
64	30	28	27	25	24	22	21	20	19	18
66	31	29	27	26	24	23	22	20	19	18
68	32	30	28	27	25	24	22	21	20	19
70	33	31	29	27	26	24	23	22	20	19
72	34	32	30	28	26	25	24	22	21	20
74	35	33	31	29	27	26	24	23	22	20
76	36	34	32	30	28	26	25	23	22	21
78	37	35	32	30	29	27	25	24	23	22
80	38	36	33	31	29	28	26	25	23	22
82	39	36	34	32	30	28	27	25	24	23
84	40	37	35	33	31	29	27	26	25	23
86	41	38	36	34	32	30	28	27	25	24
88	42	39	37	34	32	30	29	27	26	24
90	43	40	37	35	33	31	29	28	26	25

**Waist/HIP ratio - An important marker for obese type 2 diabetic**

Waist measurement (cms)																Hip measurement (cms)			
50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	
1.00	1.10	1.20	1.30	1.40	1.50	1.60	1.70	1.80	1.90	2.00	2.10	2.20	2.30	2.40	2.50	2.60	2.70	2.80	50
0.91	1.00	1.09	1.18	1.27	1.36	1.45	1.55	1.64	1.73	1.82	1.91	2.00	2.09	2.18	2.27	2.36	2.45	2.55	55
0.83	0.92	1.00	1.08	1.17	1.25	1.33	1.42	1.50	1.58	1.67	1.75	1.83	1.92	2.00	2.08	2.17	2.25	2.33	60
0.77	0.85	0.92	1.00	1.08	1.15	1.23	1.31	1.38	1.46	1.54	1.62	1.69	1.77	1.85	1.92	2.00	2.08	2.15	65
0.71	0.79	0.86	0.93	1.00	1.07	1.14	1.21	1.29	1.36	1.43	1.50	1.57	1.67	1.71	1.79	1.86	1.93	2.00	70
0.67	0.73	0.80	0.87	0.93	1.00	1.07	1.13	1.20	1.27	1.33	1.40	1.47	1.53	1.60	1.67	1.73	1.80	1.87	75
0.63	0.69	0.75	0.81	0.88	0.94	1.00	1.06	1.13	1.19	1.25	1.31	1.38	1.44	1.50	1.56	1.63	1.69	1.75	80
0.59	0.65	0.71	0.76	0.82	0.88	0.94	1.00	1.06	1.12	1.18	1.24	1.29	1.35	1.41	1.47	1.53	1.59	1.65	85
0.56	0.61	0.67	0.72	0.78	0.83	0.89	0.94	1.00	1.06	1.11	1.17	1.22	1.28	1.33	1.39	1.44	1.50	1.56	90
0.53	0.58	0.63	0.68	0.74	0.79	0.84	0.89	0.95	1.00	1.05	1.11	1.16	1.21	1.26	1.32	1.37	1.42	1.47	95
0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20	1.25	1.30	1.35	1.40	100
0.48	0.52	0.57	0.62	0.67	0.71	0.76	0.81	0.86	0.90	0.95	1.00	1.05	1.10	1.14	1.19	1.24	1.29	1.33	105
0.45	0.50	0.55	0.59	0.64	0.68	0.73	0.77	0.82	0.86	0.91	0.95	1.00	10.05	1.09	1.14	1.18	1.23	1.27	110
0.43	0.48	0.52	0.57	0.61	0.65	0.70	0.74	0.78	0.83	0.87	0.91	0.96	1.00	1.04	1.09	1.13	1.17	1.22	115
0.42	0.48	0.50	0.54	0.58	0.63	0.67	0.71	0.75	0.79	0.83	0.88	0.92	0.96	1.00	1.04	1.08	1.13	1.17	120
0.40	0.44	0.48	0.52	0.56	0.60	0.64	0.68	0.72	0.76	0.80	0.84	0.88	0.92	0.96	1.00	1.04	1.08	1.12	125
0.38	0.42	0.46	0.50	0.54	0.58	0.62	0.65	0.69	0.73	0.77	0.81	0.85	0.88	0.92	0.96	1.00	1.04	1.08	130
0.37	0.41	0.44	0.48	0.52	0.56	0.59	0.63	0.67	0.70	0.74	0.78	0.81	0.85	0.89	0.93	0.96	1.00	1.04	135
0.36	0.39	0.43	0.46	0.50	0.54	0.57	0.61	0.64	0.68	0.71	0.75	0.79	0.82	0.88	0.89	0.93	0.96	1.00	140
0.34	0.38	0.41	0.45	0.48	0.52	0.56	0.59	0.62	0.68	0.69	0.72	0.76	0.79	0.83	0.86	0.90	0.93	0.97	145
0.30	0.37	0.40	0.43	0.47	0.50	0.53	0.55	0.60	0.63	0.67	0.70	0.73	0.77	0.80	0.83	0.87	0.90	0.93	150

However, in certain situations, drug therapy will have to be initiated soon after the diagnosis is made without giving a trial of diet/exercise.

These situations are :

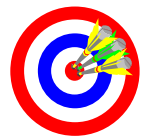
1. When there is an associated infection at the time of diagnosis
2. Myocardial infarction
3. Stroke
4. Ketoacidosis
5. Hyperosmolar coma or pregnancy and
6. When the patient has to undergo surgery.

In all these situations the initial therapy will be with insulin which can be changed after an appropriate time to oral drugs or non-drug therapy. Yet another subset of patients who require such an approach are patients with a high fasting plasma glucose level at onset i.e. greater than 250 mg/dl (> 200 mg/dl in lean patients) and patients with marked loss of weight (> 10 kg).

Monitoring is also an important component of management of diabetes. This should include not only the glycemic status but also risk factors for macrovascular and microvascular disease such as microalbuminuria, hypertension and dyslipidemia.

#### TARGETS FOR CONTROL

	<b>Good</b>	<b>Acceptable</b>	<b>Unacceptable</b>
<b>FPG</b>	80-120	121-140	> 140
<b>PP</b>	< 140	141-160	> 160
<b>HbA1c</b>	< 6.0	6.0-7.0	> 8.0



**General guidelines: First Visit**

- Complete physical examination with special emphasis on vibration testing, (monofilament), foot examination, pulses, bruits and fundus
- Complete History with special attention to complications (macro/microvascular i.e. Neuropathy, retinopathy, nephropathy, CAD, Carotid disease, PVD)
- *Complete lab tests (Diabetes Profile),*
  - Glycosylated Hb,
  - Blood glucose profile and meter correlation
  - Lipids
  - Liver Function Test (LFT Limited)
  - Blood urea, Serum Creatinine
  - Urine Routine. If negative for protein do urine microalbumin.
  - ECG (if above 30)
  - Refer to dietician and nurse educator.
  - Refer to Ophthalmologist if required  
(Every type 2 at diagnosis, type 1 DM - 5 years after diagnosis, then every year)
  - Refer to Podiatrist if available / required
  - Pharmacotherapy

**Management plan: Follow up visit**

- Review blood glucose profile
- Home blood glucose monitoring, if possible
- Reinforce diet, exercise
- Weight, BP, with foot exam every visit.
- Glyco-Hb every 3 months

<b>Staged diabetes management</b>	
<b>Stage 1</b> <ul style="list-style-type: none"> <li>• new diagnosis</li> <li>• RPG &lt; 250 \</li> <li>• FPG &lt; 200</li> <li>• no symptoms</li> </ul>	<b>Management</b> <ul style="list-style-type: none"> <li>• Diet</li> <li>• Exercise</li> </ul>
<b>Stage 2</b> <ul style="list-style-type: none"> <li>• Uncontrolled Stage 1 and / or</li> <li>• FPG 200-250</li> <li>• RPG 250-300</li> </ul>	<b>Management</b> <ul style="list-style-type: none"> <li>• Lean - sulfonylurea</li> <li>• Obese - metformin</li> </ul>
<b>Stage 3</b> Uncontrolled stage 2 and / or <ul style="list-style-type: none"> <li>• RPG&gt;300</li> <li>• FPG&gt;250</li> </ul>	<b>Management</b> <ul style="list-style-type: none"> <li>• Use combination therapy</li> <li>• SU + metformin</li> </ul>
<b>Stage 4 - uncontrolled stage 3</b> <ul style="list-style-type: none"> <li>• 4A: Symptomatic patient with FPG&gt;300</li> <li>• 4B: Patient only with PP hyperglycemia</li> </ul>	<b>Management</b> <ul style="list-style-type: none"> <li>• Insulin either bid or bedtime insulin</li> <li>• Bedtime insulin with day time OHA</li> <li>• Triple combination. (SU + Metformin + Glitazones.) for patient who does not want insulin</li> <li>• Add Acarbose as triple therapy.</li> </ul>
<b>Stage 5</b> <ul style="list-style-type: none"> <li>• Uncontrolled stage 4</li> </ul>	<b>Management</b> <ul style="list-style-type: none"> <li>• Intensive insulin therapy 3-4 doses of insulin daily</li> </ul>

## **NON-PHARMACOLOGICAL MANAGEMENT**

### **DIET**

Modification of diet is the most important aspect in the therapeutic plan for patients with diabetes mellitus. Diet therapy consists of the following :

1. Maintenance of proper nutrition
2. Total number of calories ingested
3. Individual food sources that make up these calories
4. Distribution of calories throughout the day

**Lifestyle Modification, Diet & Exercise**

- Balance food intake with drug therapy
- 5-20 % calories from proteins
- < 7 % calories from saturated fats
- < or equal to 7 % calories from polyunsaturated fats
- 55-60 % calories from carbohydrate
- < 300mg cholesterol per day

**Principles of “Healthy”Diet**

- Low fat
- No simple sugars
- High fibre
- Small frequent meals
- No fasting, no feasting
- No fried, fast foods
- No white food: Maida, Sugar, Salt

Selection, moderation and restriction are the key words in planning. The entire success of dietary modification in a diabetic subject depends on the judicious selection of carbohydrates, adequate protein intake and a determined restriction of total fat intake.

Attainment of optimal body weight results in marked reduction of hyperglycemia and increase in target cell response to insulin. Ideal body weight (IBW) of a person can be calculated by the formula.

IBW (in Kg) = [Height in cm - 100 (for men) - 105 (for women)]

The obese and the overweight must be encouraged to reduce weight. An energy deficit of 500 Kcal daily, will help the patient to reduce 500 gm of weight every week. The next step is to calculate the optimal calories.

**TABLE 7 : Calorie intake based on weight**

Category	Calorie requirement
Overweight	20 Kcal/kg/day
Ideal weight	25-30 Kcal/kg/day
Underweight	35-40 Kcal/kg/day

**TABLE 8 : Calorie intake based on activity**

Lifestyle	Daily calorie requirement
Sedentary	20 Kcal/kg of IBW
Moderately active	25-30 Kcal/kg of IBW
Strenuous	30-35 Kcal/kg of IBW

Any person above 50 years may require 10% less calories for each decade. Children need baseline calories of 1000 plus 100 calories for girls and 125 calories for boys, per year of age up to 12 years.

General guidelines for diet planning in diabetes mellitus is given in Table 9.

**TABLE 9 : Guidelines for diet in diabetes mellitus**

<p><b>1. Energy (calories)</b> 25-30 kal/kg IBW - reduce in obese and increase in underweight</p> <p><b>2. Carbohydrates</b> 55-60% of total calories. Encourage complex carbohydrates i.e. mainly grains, cereals, pulses, beans, vegetables and salads. Avoid simple and refined carbohydrates like sugar, honey, maida and jaggery. Avoid bakery products or deep fried items.</p> <p><b>3. Protein</b> 0.8 g/kg body weight. Supplement for pregnancy, lactation and growth. Include a small quota of animal proteins - fish, chicken, milk and yoghurt. Avoid cattle meat (red) and egg yolk.</p> <p><b>4. Fats</b> 20-25% of total calories Saturated : 6-7% of total calories PUFA : 6-7% of total calories MUFA : 10% of total calories N6/N3 ratio : 4:1 Cooking oil : 750gms /month/person* Total fat intake in the form of cholesterol per day &lt; 300 mg. <b>Note :</b> When prescribing fat in the diet one should take into account the invisible fat in the diet which nearly contributes to 50% of the required fat. None of the available oils are ideal, therefore blending is recommended. The choice of cooking oil should be as follows. a) Use an oil which has a moderate quantity of linoleic acid like groundnut oil, Rice Bran or Sesame. b) Use any of the above oils with alpha linoleic acid containing oil like mustard and soya bean oil.  (* See later for content of saturated and unsaturated fatty acids, omega 3:6 content in oils and spices).</p>
--

**5. Fruits**

Consume one fresh fruit per day. Avoid juices. Ideal fruits are citrus fruits, orange, sweet lime, guava, apple, papaya and watermelon. They provide vitamins, fibre. One portion contains about 40-50 unit calories.

**6. Dietary fibres**

30-40 g/day preferably from natural sources. Avoid loss from refining and processing. Indian diet is rich in fibre and generally does not require addition of fiber supplements However most modern diets are deficient in fibre due to westernisation. (See below).

**7. Common Salt**

Upto 6 g/day. Reduce intake to 4 g/day in the presence of hypertension, renal failure and heart problems.

**8. Condiments and spices**

Include in diet plan. Provide antioxidants, trace elements, minerals and omega-3 fatty acids.

**9. Artificial sweeteners**

Use of aspartame in limited quantity is acceptable. The maximum permitted consumption range from 2-4 mg/kg/day. Avoid in pregnancy and lactation.

**10. Alcohol**

Avoid if possible. If not, drastically restricted. It is utilized as carbohydrates. 1 gm of alcohol provides seven calories. Alcohol may exacerbate neuropathy, dyslipidemia, obesity and may worsen the control of diabetes and cause hyperglycemia.

**11. Tobacco/Smoking**

Avoid smoking and use of tobacco in any form.

**Fatty Acid Composition of Commonly Used Oils**

	Fatty Acid%		
	<i>Saturated</i>	MUFA	PUFA
Groundnut Oil	18	48	34
Sunflower Oil	11	20	69
Safflower Oil	9.1	12.1	74.5
Mustard Oil	6.8	55.5	33.3
Coconut Oil	86.5	5.8	1.8
Palm Oil	49.5	37	9.3

**Omega 6:Omega 3 Content of the Commonly used Edible Oils**

<b>Oil</b>	<b>Omega 6</b>	<b>Omega 3</b>	<b>Omega6 : Omega3</b>
Corn	57	0.8	71
Groundnut	28	0.8	35
Coconut	1.8	–	–
Ghee (Buffalo)	2	0.9	2.2
Mustard Oil	13	8.6	1.5
Safflower	73	0.5	146
Sunflower	49	0.3	163

**Rich Sources of Alpha Linolenic Acid**

Cereals and millets	Wheat, bajra
Pulses and legumes	Black gram, cow pea, rajmah, soya
Vegetables	Green leafy
Spices	Fenugreek, mustard
Oils	Mustard, soya bean
Animal foods	Fish

**Total Fibre Content of Common Foods (g/100 g)**

<b>High (&gt;10)</b>	<b>Medium (1-10)</b>	<b>Low (&lt;1)</b>	<b>Nil</b>
Wheat	Rice	Refined and	Sugar
Jowar	Most vegetables	processed foods	Fats/oils
Bajra	Most fruits		Milk
Ragi	Coconut		All types of Meat
Maize sesame			
Legumes			
Dals			
Fenugreek			

## **EXERCISE & YOGA**

- Start slow, 10 min a day, and do minimum of 3 times a week for 30 minutes
- Carry sweets/sugar
- Leg or chest pain during exercise-stop exercise

Regular exercises form an important component of therapy in patients with type 2 diabetes. However a careful assessment of the expected benefits and associated risks of exercise in individual patients should be made while incorporating an exercise program in the treatment. Appropriate monitoring should be done to avoid complications.

### **I. General Principles for Exercise in Diabetics**

To be effective, exercise must be done regularly. An exercise schedule should be one that the individual enjoys and which suits his/her needs. Daily exercise is preferable; however for the desired metabolic effects it should be undertaken for at least five days per week. The patient must be told that well fitting canvas/sports shoes should be worn while walking. The duration of exercise should be 30-60 minutes. The ideal time is on an empty stomach in the morning or evening (taking into consideration the risk of hypoglycemia). Any exercise should have a warming up and cooling down period of 5-10 min. Most diabetics may need to reduce the dose of insulin and oral drugs when they exercise regularly. Before an exercise programme is initiated, a fair control of diabetes is to be ensured and a thorough clinical evaluation of the patient should be made particularly with regard to complications of diabetes, hypertension, coronary artery disease, peripheral vascular disease, retinopathy and nephropathy. The drugs that a patient is receiving should be ascertained and their possible interaction with exercise should be assessed. It is advisable to individualize the exercise prescription.

### **II. Evaluation of the Patient Before Exercise**

Before beginning an exercise program, the individual with diabetes mellitus should undergo detailed medical evaluation with appropriate diagnostic studies.

#### **Cardiovascular system**

Before embarking on a moderate to high intensity exercise program, an assessment of the cardiovascular risk status of the individual should be performed.

Any individual with any of the cardiovascular risk factors will need to undergo a graded exercise test.

#### **Retinopathy**

For patients who have proliferative diabetic retinopathy, strenuous activity may precipitate vitreous hemorrhages or traction retinal detachment.

These individuals should avoid exercises that involve straining and jarring.

### **Nephropathy**

Patients with overt nephropathy often have a reduced capacity for exercise. High intensity of strenuous exercises should therefore be avoided.

### **Peripheral neuropathy**

Peripheral neuropathy results in loss of protective sensation in the feet.

Significant peripheral neuropathy is an indication to limit weight-bearing exercise.

Repetitive exercises in an insensitive feet can lead to ulceration and fractures.

It is necessary to advise proper footwear to these patients. Patients should be taught to monitor for blisters and other potential damage to the feet before and after an exercise session.

### **Autonomic neuropathy**

Presence of autonomic neuropathy may limit an individual's exercise capacity and increase the risk of an adverse cardiovascular event during an exercise.

Hypotension and hypertension are more likely to develop in exercising patients with autonomic neuropathy.

These patients also have difficulties in thermoregulation and should be advised to avoid exercises in extremely hot or cold environments and to be careful about their hydration.

## **III. Type of Exercises for Diabetic Patients**

The best form of exercise recommended to a diabetic is a stepwise increase of aerobic exercises. Plain brisk walking is the simplest and safest of all exercises. It can be started by anyone. All the aerobic (isometric) exercises like badminton, tennis and basketball improve the cardio-respiratory functions and utilize a large portion of muscle mass. On the other hand isometric exercises like weight lifting, sustained handgrip are to be avoided in diabetics as they increase the arterial pressure and/or precipitable angina.

## **IV. Exercise in Special Populations**

**Elderly:** Many of the elderly patients tend to avoid physical exercise. There is a progressive decline in insulin sensitivity, muscle mass and strength and loss of mineral from the bones with increasing age. Regular physical exercise can prevent and reverse these changes. With exercise a better quality of life is attained in this population with reduction in the burden of chronic vascular disease.

**Arthritic patients:** To recommend upper body exercises.

**Pregnant ladies:** To recommend walking and if not feasible to recommend upper body exercises.

**V. Benefits of Exercise**

Several benefits accrue from a regular exercise schedule. These include: Improvement in insulin sensitivity. Reduction of hypertension. Reduction in weight. Improvement in lipid profile : reduces serum triglycerides and increases HDL particularly HDL2 cholesterol. Improvement in cardiovascular function. Improvement in the sense of physical and mental well being. Minimizing calcium loss. Improvement in quality of life. Improving lipid profile and reducing BP is a major benefit of exercise on the cardiovascular risk factors.

**VI. Risks of Exercise**

There are several potential risks of exercise for patients with diabetes. Careful screening for underlying cardiac disease is important in all patients with diabetes before starting any exercise. Exercise may aggravate several complications of diabetes and hence all patients should be screened thoroughly before initiating exercise. Patients with proliferative retinopathy may develop vitreous hemorrhages. Heavy weight lifting and Valsalva maneuver are particularly dangerous.

**VII. Special Precautions**

- Feet should be inspected daily (before and after exercise) for cuts, blisters and infections.
- Exercise should be avoided in extreme hot and cold weather conditions.
- Exercise should be avoided during periods of poor metabolic control.
- An exercise program for obese patients with type 2 diabetes should start slowly, build up gradually and include exercises that are familiar to the patient and least likely to cause injuries or worsening of long term diabetic complications.
- Diabetic patients who exercise regularly should always carry quick acting carbohydrate and visible diabetes identification cards to be used in the event of hypoglycemia.

**VIII. Role of Yoga**

Several well-planned studies have demonstrated the beneficial effects of yogic practices in diabetics. Table 11 lists the beneficial effects of yogic practices in patients with diabetes. Some of the asanas that were found to produce these benefits are Dhanurasana, Ardhamatsayendrasana, Bhujangasana, Naukasana, Halasana, Paschimotasana, and Shavasana pranayam. However, the patient should be thoroughly evaluated by a physician before undertaking any yogic practices.

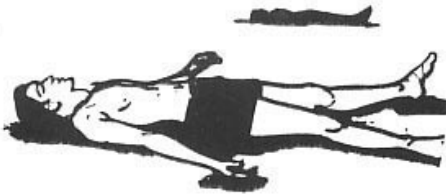
## Yogic Asanas



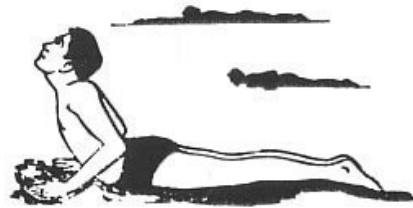
**ARDHA-MATSYENDRA**



**SHASHANKASANA**



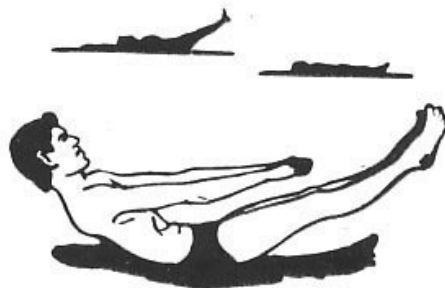
**SHAVASANA**



**BHUJANGASANA**



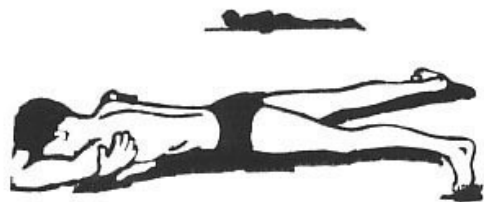
**LANGALASANA**



**VICHITRAKARANA**



**DHANURASANA**



**MAKARASANA**

**TABLE 10 : Summary of exercise recommendations**

<p>Screening : Search for vascular and neurological complications including silent is chemic heart disease.</p> <p>An electrocardiogram is recommended in patients.</p> <ul style="list-style-type: none"> <li>• Age &gt; 35 years</li> <li>• Type 2 diabetes of &gt; 10 years duration.</li> <li>• Presence of an additional risk factor for coronary artery disease</li> <li>• Presence of microvascular disease (retinopathy or nephropathy, including microalbuminuria)</li> <li>• Peripheral vascular disease.</li> <li>• Autonomic neuropathy</li> </ul> <p>Exercise program and type</p> <ul style="list-style-type: none"> <li>• Aerobic</li> </ul> <p>Duration</p> <ul style="list-style-type: none"> <li>• 30-60 minutes</li> </ul> <p>Frequency</p> <ul style="list-style-type: none"> <li>• Five days a week</li> </ul> <p>Avoid complications</p> <ul style="list-style-type: none"> <li>• Warm up and cool down</li> <li>• Carefully select the type of exercise and its intensity</li> <li>• Patient education</li> <li>• Monitoring of plasma glucose by patient and overall program by medical personnel</li> </ul> <p>Compliance</p> <ul style="list-style-type: none"> <li>• Making exercise enjoyable</li> <li>• Convenient location</li> <li>• Positive feedback from involved medical personnel and family</li> </ul>
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**TABLE 11 : Beneficial effects of yogic practices**

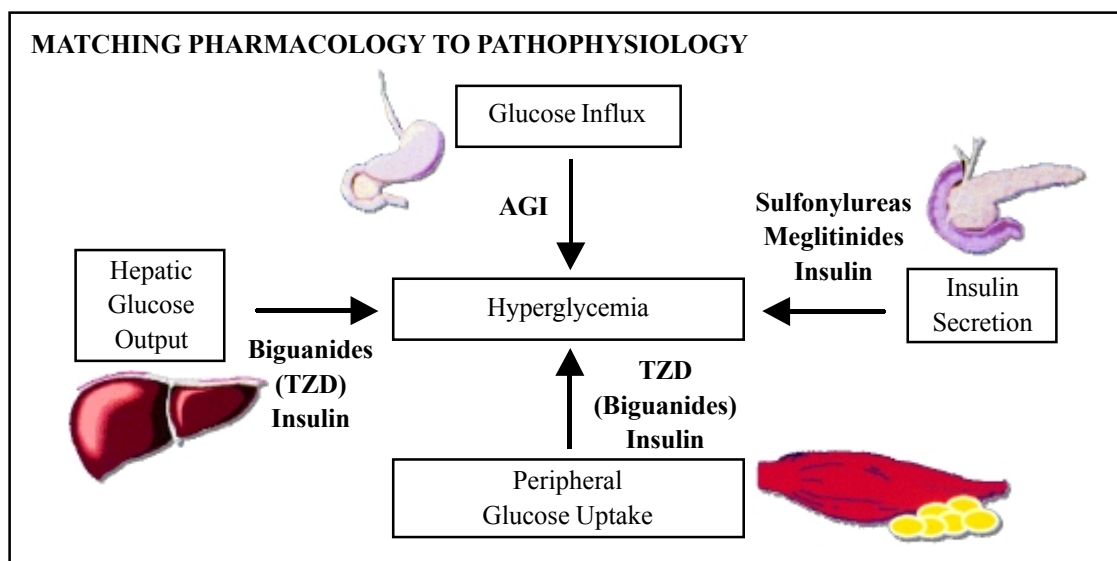
<ul style="list-style-type: none"> <li>• Reduction of blood pressure</li> <li>• Correction of dyslipidemia</li> <li>• Reduction of insulin resistance and correction of hyperinsulinemia</li> <li>• Elimination of stress</li> </ul>
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## PHARMACOLOGICAL MANAGEMENT

### 1. Oral Hypoglycemic Agents

Blood glucose levels are mainly determined by absorption of glucose from gut, uptake of glucose by peripheral tissues (muscle, adipose tissue, liver, etc.), hepatic glucose output, and the insulin secretion from pancreas (Fig. 1). In diabetics various oral agents act to modify these factors, aiding in the control of hyperglycemia. (Fig. 2, Table 12).

SITE & MODE OF ACTION OF ORAL ANTI-HYPERGLYCEMIC MEDICATIONS		
Site of action	MOA	Agents
	↑ Insulin secretion	Sulfonylureas Other insulin secretagogues
	↓ Glucose production	Biguanides Thiazolidinediones
	Slow Carbohydrate Digestion	Alphaglucosidase inhibitors
	↑ Peripheral insulin sensitivity	Thiazolidinediones (TZD) Biguanides



**TABLE 12 : Mode of action of various oral antidiabetic agents**

Mode of action	Drug
Increasing insulin secretion	Sulfonylureas, Meglitinides
Reduction of insulin resistance	Glitazones, Biguanides
Decreased hepatic glucose output	Biguanide, Glitazones
Reduced carbohydrate absorption	Alpha glucosidase inhibitors

**TABLE 13 : Types of oral antidiabetic agents**

dosage	Daily per day	Frequency of action	Duration of excretion	Mode
<b>I. Sulphonylureas (SU)</b>				
A. First generation				
Chlorpropamide	100-500 mg	1	60 hrs.	Kidney
Tolbutamide	500-2500 mg	2-3	6-12 hrs	Kidney
B. Second generation				
Glibenclamide	2.5-20 mg	1-2	16-24 hrs	Kidney (50%), bile (50%)
Glipizide	2.5-20 mg	1-3	12-24 hrs	Kidney (80%), bile (20%)
Gliclazide	80-320 mg	1-2	12-18 hrs	Kidney (80%), bile (20%)
Glimepiride	1-8 mg	1	16-24 hrs	Kidney (60%), bile (40%)
Glipizide XL	5-20 mg	1	24 hrs	Kidney (80%), bile (20%)
Gliclazide MR	30-120 mg	1	24 hrs	Kidney (80%), bile (20%)
<b>II. Non-Sulphonylurea Agents</b>				
A. Meglitinide analogs				
Repaglinide	1.5-10 mg	3	2-4 hrs	Bile
B. Biguanides				
Metformin	250-2500 mg	2-3	8-12 hrs	Kidney (50%), feces (27%)
Phenformin	25-150 mg	3-4	4-6 hrs	Kidneys
Phenformin TD		2-3	8-14 hrs	
C. Alpha glucosidase inhibitors				
Acarbose	25-300 mg	3	4 hrs.	–
D. Thiazolidinediones				
Rosiglitazone	2-8 mg	1-2	12-24 hrs	Kidney
Pioglitazone	15-45 mg	1	24 hrs	Kidney

## SULPHONYLUREAS

### Sulfonylureas



Increase insulin release from pancreatic beta cells

Bind to specific receptor on beta cell

ATP-dependent potassium channel closes reducing outward flux of potassium ions

Cell depolarizes triggering opening of calcium channels

Calcium influx triggers insulin release into bloodstream

Insulin in portal vein decreases hepatic glucose production

Higher circulating levels of insulin cause greater glucose uptake in muscle tissue

- The sulphonylureas bind to specific sulphonylurea receptors on  $\beta$  - cell and increase insulin secretion. All sulphonylureas bind to the 140 kDa subunit of sulphonylurea receptor whereas gliclazide binds to the 65 kDa subunit of the sulphonylurea receptor.
- They are most effective in recently diagnosed type 2 diabetics with good  $\beta$  - cell function and FPG < 250 m/dl.
- Therapy should be initiated with lowest effective doses and titrated upwards every one to two weeks until desired control or maximal dosage is reached.
- If no hypoglycemic effect is observed with half the maximal effective dose, then the drug is not likely to be effective.
- Sulfonylureas are preferably given 15-30 min before meals.
- Sulfonylureas can be combined with metformin, acarbose, thiazolidinediones and insulin to give synergistic effect. However, they should not be combined with another sulphonylurea since they act similarly and there is no potentiation of action. In fact there is an increase in side effects.
- About 10 to 20% patients fail to respond to sulphonylureas (primary failure).
- Every year about 5% stop responding (secondary failure).  
Secondary failure may be due to insulin deficiency, but various other factors need to be excluded before it is labelled as secondary failure.
- Factors to be considered before labeling as secondary failure are given in Table 14. In these cases, the failure may be reversible.

**TABLE 14 : Factors to be considered before labeling as secondary failure**

- Weight gain
- Lack of exercise
- Non-compliance to drugs
- Inadequate dosages
- Impaired absorption
- Co-existing medical disorders
- Concomitant medication such as steroids, etc.
- Infection, stress
- Non compliance to diet and exercise

Various clinical trials have failed to conclusively demonstrate superiority of one sulphonylurea over the other, when used in optimal doses. In special clinical situations one may decide in favour of one sulphonylurea over other. Gliclazide has been shown to possess antioxidant properties, which is thought to be separate from its hypoglycaemic properties. Thus when an individual patient requires this activity, it may be preferred. Glibenclamide is toxic to beta cells while Gliclazide, Glipizide and Glimeperide are safe for the beta cells. In addition, switching over from one sulphonylurea to another may show some benefit but this may not be long lasting.

### **Side effects**

Hypoglycemia is the commonest side effect. Side effects are mild (nausea, vomiting) and generally reversible on discontinuation of treatment. Rarely, skin rashes, leucopenia, anaemia, thrombocytopenia, cholestatic jaundice, Stenvens-Johnson syndrome, granulomatous hepatitis may occur. Weight gain may be seen in patients on sulphonylureas. Hypoglycemia is more likely, prolonged and profound with long acting sulphonylureas i.e. chlorpropamide and glibenclamide. Hyponatremia may develop in patients on chlorpropamide, apparently due to its ability to enhance the action of antidiuretic hormone (ADH). Photosensitivity reaction to sulfonylureas (hyperpigmentation of exposed parts) may occur.

### **Contraindications**

Renal failure, Hepatic failure, Hepatitis, Type 1 diabetes, Pregnancy, Ketosis, Major surgery, Severe infections, Stress or trauma, Disseminated tuberculosis, History of severe adverse reaction to sulfonylureas.

### Drug interactions

- **Agents that augment the sulfonylurea action**

Salicylates or NSAIDs, Sulfonamides, Trimethoprim, Fibrates, MAO inhibitors, H<sub>2</sub> blockers, Anticoagulants.

- **Agents that attenuate sulfonylurea action**

Alcohol (chronic, moderate use), Barbiturates, Rifampicin, Beta blockers, Thiazides  
Corticosteroids, Estrogens, Isoniazid, Nicotinic acid

In elderly patients (> 60 years) short acting sulphonylureas are preferred. Chlorpropamide should not be used in elderly patient and glibenclamide should be used with caution.

## NON-SULFONYLUREA AGENTS

### MEGLITINIDE ANALOGUES

#### Meglitinides



Repaglinide is the only meglitinide approved for type 2 diabetes  
Increases insulin release in response to glucose  
Acts on ATP-dependent potassium channel  
Closure of potassium channel allows calcium influx  
Calcium influx stimulates insulin release from beta cell  
Increased insulin level reduces blood glucose

- Meglitinide analogues are non-sulphonylurea insulin secretagogues which act on separate non-sulphonylurea receptor binding sites on a-cell and enhance insulin secretion.
- These agents are as efficacious as sulphonylureas when used as monotherapy for treatment of type 2 diabetes.

#### Repaglinide

- Repaglinide is absorbed rapidly (0.5-1 hr) and has a short half life (< 1 hr). Thus it results in a rapid but brief release of insulin.
- The starting dose is 0.5 mg, with each meal, increased weekly to a maximum of 10 mg/day.
- It produces fewer and milder hypoglycemic episodes as compared to sulphonylureas.
- 90% of it is excreted in feces. It can be used in patients with moderate renal insufficiency but is not recommended for severe renal impairment.
- Weight gain is mild when used in newly diagnosed type 2 diabetics.

### Nateglinide

- Better than Repaglinide
- Usual dose is 60-120 mg.
- Useful for erratic meal pattern
- Ideal for fasting, feasting, special situations

## BIGUANIDES

### Biguanides



Metformin is the only biguanide approved in the U.S for type 2 diabetes

Reduces gluconeogenesis and glycogenolysis

Lower hepatic glucose production leads to lower nocturnal, fasting, and premeal plasma glucose

Action requires circulating insulin

- Metformin is the most commonly used biguanide.
- It mediates its effect by enhancing sensitivity of the hepatic and peripheral tissues to circulating insulin as well as decreasing hepatic glucose output. It inhibits the intestinal absorption of glucose and demonstrates anorexic effect.
- The starting dose can be 250 mg twice a day which is increased by 500 mg every two weeks until desired therapeutic goals are achieved or maximum daily doses (2500 mg) are reached.
- It can be used in an effective combination with sulphonylurea and other oral hypoglycemic agents.
- Metformin, being an antihyperglycemic agent, does not produce hypoglycemia when used as monotherapy. The UKPDS has demonstrated that use of metformin reduces the risk of macrovascular complications. Metformin is now recommended as the first line treatment in obese type 2 diabetics as monotherapy.

### Side effects

Gastrointestinal side effects like abdominal discomfort and diarrhoea occur in 20-30% of patients. These can be minimized if metformin is administered after meals and with slow titration of doses. Lactic acidosis is an uncommon side effect and is reported in the frequency of three to nine cases per 100,000 patient 1 years. It is rare in the absence of other serious hypoxic medical disorders.

**Contraindications**

Patients with renal disease (serum creatinine level more than 1.4 mg/dl in females and 1.5 mg/dl in males). Hepatic disease, Respiratory insufficiency, Hypoxemic conditions, Acute myocardial infarction, Congestive cardiac failure, Alcohol abuse, Patients undergoing contrast study should have a serum creatinine checked within two days to ensure that metformin can be continued, Ketosis prone diabetes, Pregnancy, Acute complications; Severe infections, Major operations and trauma, Deficiency of vitamin B<sub>12</sub>, Folic acid and iron, Bad general condition (e.g. malnutrition, dehydration), Metformin should be stopped at least three days before elective surgery.

**Other effects**

Metformin has a favourable effect on lipids, decreasing triglycerides and LDL cholesterol by 10-15%. Weight loss of 2-5 kg in first six months of treatment has been observed in some studies, whereas in other studies, it has been found to provide a weight stabilizing effect.

Phenformin the other biguanide is now a part of WHO list of banned drugs.

 **$\alpha$ -GLUCOSIDASE INHIBITORS****ACARBOSE**

Acarbose acts by competitively inhibiting  $\alpha$ -glucosidase, the enzyme in the small intestine brush border which breaks down oligosaccharides and disaccharides into monosaccharides. Thus the conversion of carbohydrates (starch and sugar) to glucose is delayed. It is especially useful in decreasing post-prandial glucose levels (to the extent of 40-50 mg%). It is beneficial in new onset type 2 diabetics when fasting hyperglycemia is mild. It can be combined with sulphonylureas and biguanides but its hypoglycemic potency is much less in comparison. The dosage is 25-50 mg once daily increased to 50-100 mg two to three times in a day. It must be ingested with the first bite of food, as the drug must be present in the small bowel with the food for proper effect. Hypoglycemia does not occur if used as monotherapy. If hypoglycemia results from combination therapy with sulphonylurea, treatment should be with oral glucose rather than sucrose.

**Side effects**

Bloating, abdominal discomfort, diarrhoea and flatulence. These side effects are more pronounced in patients on high carbohydrate diet.

**Contraindications**

Inflammatory bowel disease, Cirrhosis, Serum creatinine more than 2.0 mg/dl, Malabsorption, Intestinal obstruction.

## THIAZOLIDINEDIONES (GLITAZONES)

### Thiazolidinediones



Work in nuclei to modulate expression of genes important in glucose and lipid metabolism and insulin action

Alter fat metabolism, shifting distribution of adipose tissue and reducing free fatty acid levels

Lower hepatic glucose production

Activate PPAR- $\gamma$  in nuclei of muscle cells increasing glucose uptake and utilization

- These agents act by inhibition of gluconeogenesis in hepatocytes and by improving insulin sensitivity in adipose tissue and skeletal muscles. This effect is brought about by binding to nuclear peroxisome proliferator activated receptor-gamma (PPAR $\gamma$ ) leading to increased glucose transporter expression. The action on adipocytes reduces the plasma free fatty acids. This is a major mechanism for restoring insulin sensitivity.
- Pioglitazone has partial PPAR alpha agonist activity unlike rosiglitazone which accounts for its beneficial effects on lipid profile.
- Pioglitazone has a favourable effect on serum triglyceride and HDL cholesterol levels.
- The dosage of rosiglitazone is 2-8 mg in one to two divided doses while that of pioglitazone is 15 to 45 mg per day.
- Combination with sulphonylurea is as effective as the combination of metformin and sulphonylurea.
- Obese and hyperinsulinemic patients are good candidates for glitazone therapy.
- Some patients show no response to this class of agents; 'non-responders' account for 20-50% of individuals. Patients with low insulin levels are less likely to show significant response.
- The onset of action starts from 2-4 weeks of therapy and the maximum effect is observed after 11 weeks.
- Combination of glitazones with insulin should be used with caution.

**Side effects**

Mild to moderate hypoglycemia has been reported in patients undergoing therapy with glitazone in combination with a sulphonylurea or insulin in clinical studies. Edema was reported in about 4.8% of patients. Edema was reported most frequently in the study in which glitazone was combined with insulin. Elevated (= 3 times upper limit of normal range) serum levels of ALT after glitazone treatment was reported in 0.26% patients. Adverse events of glitazone when used with metformin are anaemia, weight gain, headache, visual disturbance, arthralgia, hematuria, impotence and edema. Adverse events of glitazone when used with sulfonylurea therapy are weight gain, dizziness, flatulence and edema.

**Precautions**

As a monotherapy, glitazone does not produce hypoglycemia. However in combination, it does so and thus the dose of the other agent must be reduced. Treatment with glitazone may lead to resumption of irregular ovulation. Patients may be at a risk of pregnancy. Glitazones cause a decrease in hemoglobin and hemotocrit. Mean Hb values decline by 2-4%. The changes occurred in the first 4-12 weeks of therapy. It should be used with caution in patients with edema. Body weight must be monitored. In preclinical trials, they have been reported to cause plasma volume expansion and preload induced cardiac hypertrophy. It should be used with caution in patients with reduced cardiac reserve. Patients on glitazone must undergo serum ALT level evaluation prior to initiation of therapy; every two months for the first year of therapy and periodically thereafter. Therapy with glitazone should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. If ALT levels remain > 3 times the upper limit of normal or if the patient has developed jaundice, glitazone therapy should be discontinued.

**Contraindications**

Type 1 diabetes, Hypersensitivity to glitazones, Pregnancy, Lactation, Pediatric age group, Dialysis, Hepatic impairment, Severe anaemia, Cardiac failure or history of cardiac failure.

**Combination Therapy**

The better understanding of the pathophysiology of type 2 diabetes as well as the development of new drugs with different modes of action has led to the understanding of the rationale for combination therapy.

Type 2 diabetes is caused due to insulin resistance and insulin secretory defects. In any given patient with type 2 diabetes, while one of these two abnormalities may play a

predominant role, the other is also frequently present. For an effective management of this disorder both these defects have to be corrected. The drugs available now act at the various sites and overcomes both these primary defects. While metformin and the glitazones improve insulin sensitivity and overcome insulin resistance, the sulfonylureas and meglitinide derivatives stimulate the  $\beta$  cells to increase the insulin output.

Hence there is a role for a combination of both group of drugs, the insulin sensitizers and the insulin secretagogues. The common practice is to start with monotherapy with either of the two and resort to a combination therapy with the addition of a drug from the other group when adequate glycemic control is not achieved. The usual combinations are SU + metformin, SU + glitazone, SU + insulin, insulin + metformin.

Acarbose can be combined with SU, metformin or insulin to correct post-prandial hyperglycemia.

When fixed dose combination of SU and metformin is used, it should be preferably given before the meals.

In patients with secondary sulfonylurea failure, when there is an inadequate response to the addition of metformin, the options would be either to add insulin to the above combination once at bedtime or to stop the oral drugs and add two doses of split mix insulin.

When insulin is added to the SU, a single dose of intermediate acting insulin (usually in a dose of 10-12 units) is given at bedtime to provide for basal insulin supplementation. The small dose required at bedtime prevents weight gain and prevents hyperinsulinemia. It corrects the hepatic glucose output and brings down the fasting glucose and glucotoxicity, thereby making the oral preparation effective.

### **Role of Indigenous Drugs**

Many patients in our country are motivated to use several alternative systems of medicine like ayurveda, homeopathy, unani or some indigenous drugs. These drugs by themselves singly or in combination have inadequate hypoglycemic effects, their exact mode of action is not clear. However, most of these are rich in fibre content and may be effective by interfering and delaying carbohydrate absorption from the intestines. There is ample scope for research and careful evaluation of these in the management of diabetes. Till then their role in the treatment of diabetes will remain inconclusive.

## INSULIN THERAPY

### a. Indications of Insulin in Type 2 Diabetes

At onset, if FBG is > 250 mg/dl and/or ketonuria. In stressful situations (acute myocardial infarction, stroke, fulminant infections, trauma). During pregnancy. Peri-operative state. Hepatic and renal decompensation. Diabetic coma Idiosyncrasies to oral anti-diabetic agents. Secondary failure to OHA. Diabetics on steroids

### b. Types of Insulin Preparations

Different types and species of insulins are available. They have different pharmacokinetic properties. Different insulin preparations can be divided based on the species, duration of action and impurities present (Table 15). Insulin type, species, injection technique, insulin antibodies, site of injection and individual patient response differences can affect the onset, degree, and duration of insulin activity. Changing insulin species may affect blood glucose control and should only be done under the supervision of a health professional with expertise in diabetes.<sup>8</sup>

**TABLE 15 : Insulin preparations**

<b>A. Based on insulin source</b>	
Bovine	
Porcine	
Semisynthetic human insulin (enzyme modified pork insulin)	
Recombinant human insulin or biosynthetic human insulin	
<b>B. Based on pharmacokinetic properties</b>	
Short acting (bovine, porcine, human)	
Intermediate acting (bovine, porcine, human)	
Long acting (bovine, porcine, human); not available in our country	
<b>C. Based on purity</b>	
Impurities (pro-insulin in ppm)	
Conventional (porcine, bovine)	10,000-30,000
Single peak (chromatographically purified insulin)	300-3000
Improved single peak (purified)	< 50
Highly purified	< 10
Monocomponent	< 1
<b>D. Insulin analogues</b>	
Short acting (Lispro) : It is useful in children and in situations where other methods have failed to control post-prandial hyperglycemia	
Long acting (Glargine): It is not yet available in India but may be used in situations where other methods have failed to control the blood glucose	

### b. i. Species of Insulin

Insulin of bovine or porcine origin were the only commercially available preparations for the first half-century of the insulin era. The aminoacid sequence of the animal insulin differs from that of human insulin by one (porcine) or three (bovine) amino acid residues as follows:

Species	A8	A10	B30
Human	Threonine	Isoleucine	Threonine
Porcine	Threonine	Isoleucine	Alanine
Bovine	Alanine	Valine	Alanine

### ii. Duration of Action of Insulin Preparations

Insulin is available in short, intermediate and long-acting forms that may be injected separately or mixed in the same syringe (Table 16).

### iii. Purity of Insulins

Purification of insulin reduces the level of antibodies. Immunological reactions to insulin are rare for purified preparations irrespective of species.

**TABLE 16 : Duration of action of currently available insulin following subcutaneous administration**

Preparation	Onset of action	Peak action	Duration of action (hrs)
<b>Short acting/soluble</b>			
Regular (bovine, porcine)	30 minutes	2-4 hrs	4-8
Human	20 minutes		4-8
Lispro	05 minutes	1 hour	3-4
<b>Intermediate acting</b>			
NPH	2-4 hrs	6-8 hrs	20-24
Lente	2-4 hrs	6-8 hrs	
<b>Biphasic</b>			
Premixed (NPH + Regular) (30/70,25/75,50/50)	30 minutes	2-10 hrs	18-24
<b>Long acting</b>			
Ultra lente	3-4 hrs	6-12 hrs	12-28
Insulin glargine	3-4 hrs	Peakless	24

**c. Indications for Human Insulin**

Insulin allergy, Immunological insulin resistance, Insulin lipodystrophy. Human insulin may also be used in the following conditions; however, animal insulin is not contraindicated in these situations.

Pregnant diabetics, Diabetics requiring temporary insulin like those under stress or undergoing surgery, Diabetics with angiopathies and renal damage

In developing countries like India, highly purified (proinsulin < 2 ppm) bovine and monocomponent (proinsulin < 1 ppm) porcine insulin offer cost-effective modes of insulin therapy for those who cannot afford human insulin.

**d. Storage**

Vials of insulin not in use should be refrigerated. They should not be kept in the freezer compartment. Insulin should not be exposed to direct sunlight. Excess agitation should be avoided to prevent loss of potency, clumping, frosting, or precipitation. Insulin in use may be kept at room temperature to limit local irritation at the injection site, which may occur when cold insulin is used. Once the vial is opened, it should be used for a period of 30 days. If refrigeration is not available, insulin should be stored in closed cabinets or under the clothes. If regular insulin shows haziness, it indicates bacterial growth and should not be used.

**e. Mixing Insulin**

Administration of mixtures of rapid or short and intermediate or long-acting insulin will produce better glycemic control in some patients than use of a single insulin. It is recommended that insulin of the same species should be used for mixing. Regular and lente insulin can be mixed but must be injected immediately.

**f. Use of Syringes**

- Conventional insulin administration involves subcutaneous injection with syringes marked in insulin units.
- There may be differences in the way units are indicated (U-40, U-100), and in India both are available in 1-ml vial.
- It is important to make sure that there is no syringe-vial mismatch as far as insulin concentration is concerned e.g. U-40 syringe must be used only for U-40 vials.
- Syringes must never be shared with another person
- Some individuals prefer to reuse a syringe until its needle becomes dull.
- If reuse is planned, the needle must be recapped after each use.
- Most insulin preparations have bacteriostatic additives that inhibit growth of bacteria commonly found on the skin.

## **g. Insulin Administration**

### **i. Dose Preparation**

Before each injection, the hands and the injection site should be cleaned. The top of the insulin vial should be wiped with 70% isopropyl alcohol. For all insulin preparations except rapid and short acting, the vial should be gently rolled in the palms of the hands (not shaken) to resuspend the insulin. An amount of air equal to the dose of insulin required should first be drawn up and injected into the vial to avoid creating a vacuum. For a mixed dose, putting sufficient air into both bottles before drawing up the dose is important. When mixing rapid or short-acting insulin with intermediate or long-acting insulin, the clear rapid or short acting insulin should be drawn into the syringe first.

### **ii. Injection Procedures**

Injections are given into the subcutaneous tissue. Most individuals are able to lightly grip a fold of skin and inject at a 90° angle. Thin individuals or children may need to pinch the skin and inject at a 45° angle to avoid intramuscular injection, especially in the thigh area.

### **iii. Injection Site**

Insulin may be injected into the subcutaneous tissue of the upper arm, the anterior and lateral aspects of the thigh, the buttocks, and the abdomen. Rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Rotating within one area is recommended (e.g. rotating injections systematically within the abdomen) rather than rotating to a different area with each injection. This practice may decrease variability in absorption from day to day. Site selection should take into consideration the variable absorption between sites. The abdomen has the fastest rate of absorption, followed by the arms, thighs, and buttocks. Exercise increases the rate of absorption from the injection sites, probably by increasing blood flow to the skin and perhaps also by local actions. The most commonly recommended interval between injection of short-acting (regular) insulin and a meal is 30 min.

## **h. Adverse Effects**

The main problems associated with insulin use are hypoglycemia and weight gain. Weight gain can be substantial, and the amount is generally well correlated with the total daily dose of insulin.

### **i. Insulin Pens**

Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle. They are easy to use.

**j. Initiating Insulin Therapy**

For initiating insulin it is not necessary to hospitalize the patient, it can be done at their home. The dosing has to be individualized depending upon the blood glucose profile and clinical setting. It is better to start with small doses and modify accordingly every three days. Generally the initial starting dose of insulin should be 0.2 units/kg/day.

**k. Adding Insulin to Oral Agents**

When combinations of oral agents no longer maintain the level of control desired, insulin is needed. Less dose of insulin is needed and less hyperinsulinemia and weight gain occur when one insulin injection is combined with oral agents than with multiple insulin injections.

**l. Multiple Insulin Injections**

Insulin allergy. For less obese patients (BMI < 30), a bedtime injection of NPH insulin safely controls fasting hyperglycemia. When a single insulin injection plus one or more oral agents no longer maintains good glucose control, two or more injections are needed. In contrast to type 1 diabetes, who nearly always requires three or four injections for good control, long duration type 2 diabetes is usually treated with two injections. Older persons need careful monitoring to avoid hypoglycemia. A regimen of equal amounts of insulin, either NPH and regular insulin mixed by the patients or premixed, taken before breakfast and dinner is a reasonable way to start multiple injections. When glitazones are added to insulin regimen, insulin requirements may come down and thus such subjects need to be carefully watched for hypoglycemia.

The alternate routes of delivery under evaluation include intranasal and intrapulmonary.

(Other remaining topics such as Monitoring of Diabetes & Complications, diabetes in special situations along with recent advances would be included in Part-II of the issue to be published in next quarter)

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