Companion to Clinical Diabetology

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Preface

This is the Third and updated edition of the course material that can be used as a standalone practical guide to management of diabetes or as a course material for educating health professionals in delivering high quality of care to the patients. Diabetes Mellitus is one the most serious challenges and one of the most neglected conditions in this country. While revising the material after a gap of six years we have come to realize how much has changed with new evidence, new developments in testing as well as treatment. In this revised version, changes have been made according to the ADA Guidelines for Standards of Medical Care in Diabetes – 2015. Information has been updated in line with the rapid advancement of the knowledge on the pathogenesis and treatment of diabetes.

NPS & GNS

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Epidemiology of Diabetes

Diabetes Mellitus has become a major health burden worldwide with rapid rise of prevalence of diabetes across societies. It is particularly a problem in the populations of South Asia. 25% of the world's population with diabetes lives in South Asia. Sri Lanka too has shown an alarming increase in the number of diabetes patients in both rural and populations. Epidemiological data available for Sri Lanka is depicted in Table 1.

Table 1. Prevalence of Diabetes Mellitus in Sri Lanka

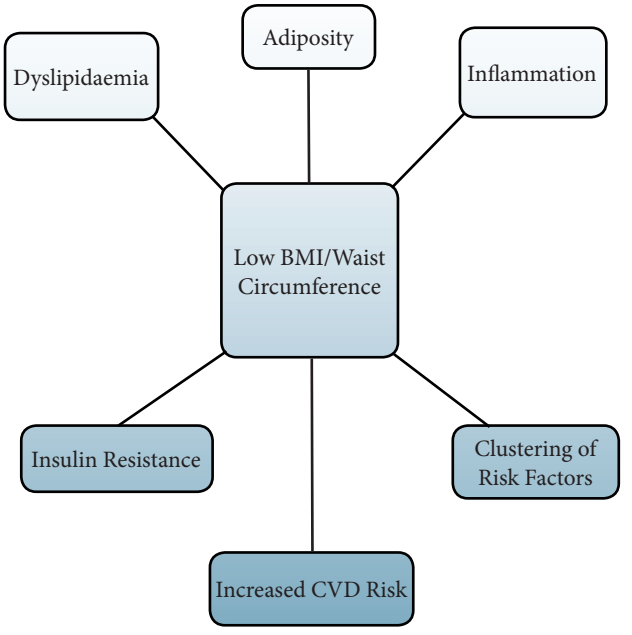
Year	Setting	Prevalence (%)
1988	Rural	2
1990	Rural	2.5
1994	Suburban	5
1995	Rural	7.7
	Urban	12.1
2000	Suburban	6.5
2002	Suburban	6.6
2004	Rural	8.5
2005	Mixed Urban and Rural	13.9
2005	Rural	8.7
	Urban	16.4
2012	Urban	20
2014	Colombo Urban	27

Factors Responsible for the Epidemic of Diabetes

South Asian Paradox

South Asians (SA) demonstrate insulin resistance and declining insulin production at much lower BMI than for the Caucasian populations. At a BMI of 23 kg/m^2 South Asians have a higher body and visceral fat resulting in inflammation, Insulin resistance, emergence of Cardiovascular risk factors and atherosclerosis. Changing lifestyle with higher refined carbohydrate consumption and fatty food resulting in higher calorie intake coupled with decreased levels of activity and increasing physical inactivity make the South Asian phenotype worse (Figure 1). South Asians metabolize slower than Caucasians.

Figure 1. South Asian Phenotype



Genetic Factors

Several Gene mutations that increase the risk of diabetes have been identified. The key Single nucleotide polymorphisms (SNPs) that have been identified are TCF7L2 and KCNQ1. Inheritance of any one of these SNPs confers a 30% increased risk of diabetes in South Asians as well as Caucasians. A gene mutation that accounts for the South Asian phenotype has not been identified.

Thrifty Genotype

In an era of scarcity certain genetic changes that cause fat storage and decreased metabolism of energy would have conferred a survival advantage. This seems to be a factor that plays a key role in the increased risk of diabetes and cardiovascular events that are seen in the SA populations. The thrifty Genotype is probably an epigenetic mechanism resulting in gene activation or suppression and can be inherited by the descendants.

Thrifty Phenotype

The environment during the embryonic life can also cause major long-standing changes in the fetus. Maternal malnutrition or obesity as well exposure to adverse factors such as hypergly-

cemia and endocrine disruptor chemicals can result in adverse fetal programming. The thrifty phenotype is probably inherited as an epigenetic mechanism: changes and modifications to the structure of the gene that can result in either increased or decreased expression of the affected genes.

Classification of Diabetes

Type 1 Diabetes

Immune mediated
Due to pancreatic islet β-cell destruction leading to absolute insulin deficiency

Usually but not invariably presents in young

Clinical features

- Weight loss (may be severe)
- Marked symptoms of thirst, polyuria
- Glycosuria usually with significant ketonuria
- Age usually but not invariably < 40 years

Investigations

Autoantibody (GAD or Islet cell Antibody) +ve (absent auto antibody does not exclude type 1)
C-peptide & Insulin levels - low

Type 2 Diabetes

Due to a progressive insulin secretory defect on the background of insulin resistance

Clinical features

- Age of onset usually > 40 years but obese children also may develop T2DM
- May have acanthosis nigricans
- Often (not invariably) obese
- Polyuria without ketosis(occasionally may present with ketoacidosis)
- May have established micro vascular and macro vascular complications at diagnosis

Other Specific Types

- Monogenic defects of β-cell function- MODY-Maturity onset Diabetes of the Young) & Neo natal diabetes
- Genetic defects in insulin action
- Endocrinopathies-(Cushing syndrome, Acromegaly, Thyrotoxicosis)
- Genetic syndromes associated with diabetes
- Infections
- Drugs or chemical induced
- Diseases of exocrine pancreas
- Uncommon forms of immune mediated diabetes

Gestational Diabetes

Diabetes diagnosed during the 2nd or 3rd trimester of pregnancy that is clearly not overt diabetes.
Usually disappears after the delivery.

Diagnosis of Diabetes Mellitus

Table 2: ADA Diagnostic Criteria for the diagnosis of Diabetes Mellitus

	Fasting plasma glucose (no caloric intake for at least 8h)		2 hour post 75g glucose plasma glucose	HbA1C (performed using UKDS-aligned methods)	Random plasma Glucose (in a patient with classic symptoms)
Diabetes mellitus	≥7.0 mmol/l (126mg/dl)	or	≥11.1mmol/l (200mg/dl)	≥6.5%	≥11.1 mmol/l (200mg/dl)
Prediabetes	6.1-6.9 mmol/l (100-125mg/dl)	or	7.8-11.0 mmol/l (140-199mg/dl)	5.7-6.4%	

Ideally diabetes should only be diagnosed on the basis of two abnormal glucose results if the patient has no symptoms.

One abnormal glucose result is sufficient if the patient has symptoms of diabetes. These levels apply to plasma glucose, not to capillary glucose (finger prick).

Testing for Diabetes in Asymptomatic Adults

For all persons, routine screening should begin at 40 years.

The following patients should be considered for testing even <40 years of age:

Over weight or obese BMI >23 kg/m^2

- Strong family history of diabetes (first degree relatives)
- Central obesity- Waist circumference men>90cm, women>80cm
- Evidence of insulin resistance- acanthosis nigricans, PCOS
- Previous history of gestational diabetes/foetal loss/large baby (>3.5kg)
- Sedentary life style/physical inactivity
- Hypertension BP>140/90 mm Hg or on treatment
- Dyslipidaemia (TG 250 mg/dl, LDL ≥100 mg/dl, Low HDL<35mg/dl in men, <50 mg/dl in women)
- Ethnicity: Ideally all Sri Lankans above the age of 30 years should be screened for diabetes.
- HbA1C ≥5.7% , IGT or IFG on previous testing
- History of cardio vascular disease (CVD)
- Children >10 years who have two or more risk factors

If results are normal, tests should be repeated at a minimum 3 year interval
Those with prediabetes should be tested yearly.

Evaluation of a Diabetic Patient

First Visit
History

- Symptoms of diabetes- polyuria, nocturia, polyphagia, polydipsia, sudden weight loss or weight gain, tingling, numbness or pain in the hands and or feet.
- Diabetes history- Age at which diabetes was detected, duration of disease, family history, previous and current treatment, history of diabetes related complications, hypoglycemia, DKA
- Comorbid conditions- Hypertension, Hyperlipidaemia, Ischemic heart disease, stroke, PVD, liver disease, bronchial asthma, allergies, depression, obstructive sleep apnoea, any major illness, erectile dysfunction.
- Smoking, alcohol history
- Eating pattern, physical activity, weight history
- Growth and development in children and adolescents

Check All Anthropometric Measures

- Height
- Weight
- Body mass index- Weight in kg/(Height in m)^2
- Waist circumference

Detailed Examination

- Including signs of insulin resistance like acanthosis nigricans, skin tags
- Signs of hyperlipidaemia e.g.: xanthelasma, xanthomas.
- Check injection sites for lipoatrophy or hypertrophy.
- Pay particular attention to cardiovascular system, check blood pressure
- Thyroid palpation

Foot Examination

- Is a must in every diabetic patient. Look for thick skin, calluses, cracks, ulcers and skin infection and interdigital candidiasis. Check for peripheral pulses (dorsalis pedis, posterior tibial), ankle jerks, vibration, proprioception and Monofilament test

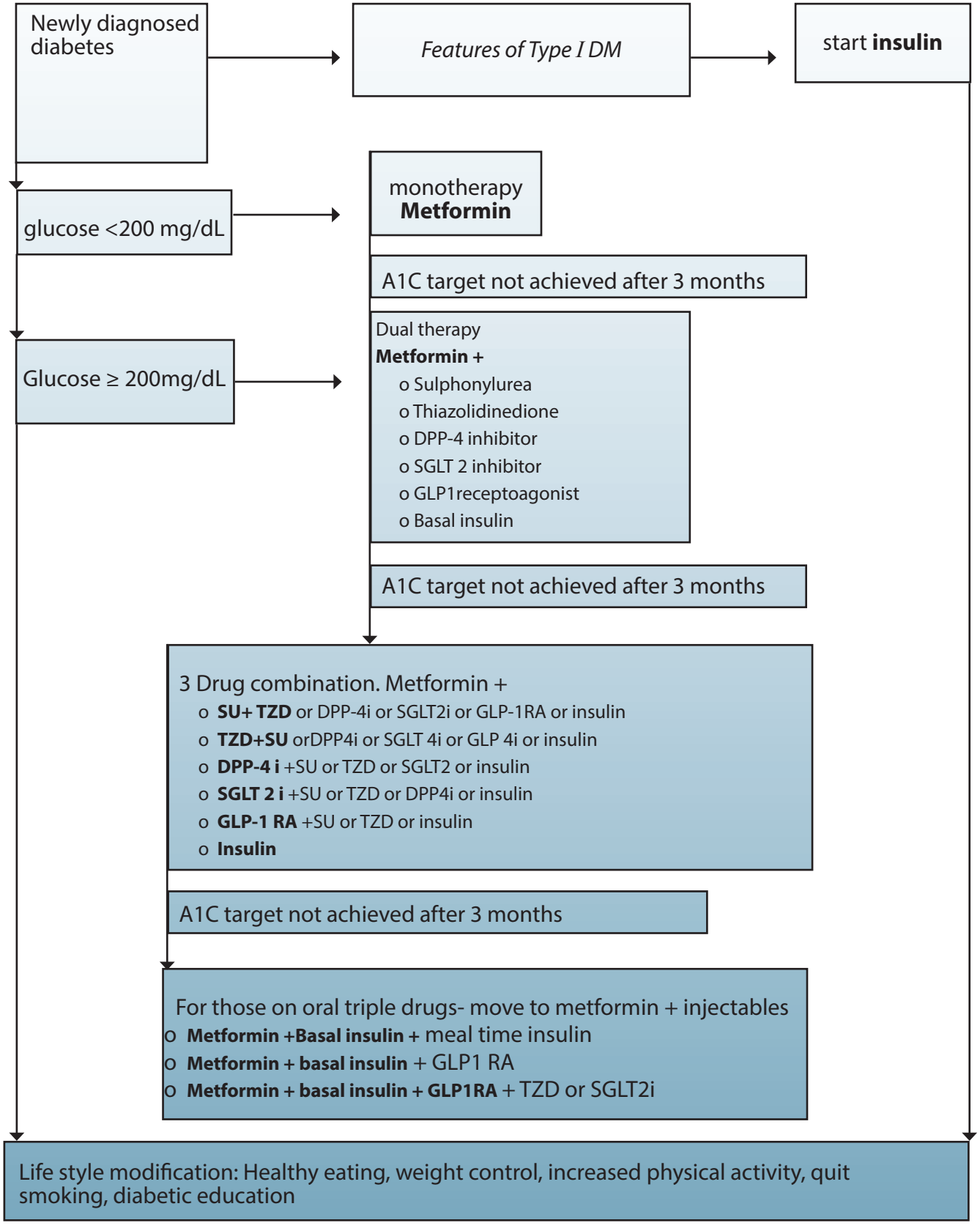
Dilated Fundoscopy

Investigations

- Urine analysis: Ketones, protein, glucose
- FPG and PPG
- HbA1C
- Fasting lipid profile
- S. creatinine. eGFR and electrolytes
- Spot urine albumin to creatinine ratio- in type 2 diabetes; after hyperglycemia is under control
- ALT, AST, ALP
- ECG
- TSH in Type 1 DM, dyslipidaemia and women over 50 years
- Islet cell antibody/GAD antibody if considering type 1 diabetes

Approach To Glucose Control of Newly Diagnosed Patient

Figure 2. Flow chart for management of glucose in a newly diagnosed diabetes patient



Review of Diabetic Patient

In addition to the regular reviews, every patient should ideally have a detailed annual review.

History

- Patient concerns
- Events-medical and life
- Check investigation reports, glucose diary
- Current treatment
- Hypoglycemia
- Pregnancy/contraception in women
- Impotence
- Symptoms of CHD/PVD
- Smoking?

Examination

- Weight/BMI
- Blood pressure- erect and supine
- Injection sites
- Urine analysis
- Eye examination
- Foot examination

Investigations

- HbA1C- every 3 months
- Lipid profile- every 6-12 months
- Urea and electrolytes- yearly and when the patient is on ACEI/ARB
- Serum creatinine- if normal, yearly
- Urine Microalbumin- if normal, yearly

Common comorbid conditions

Consider assessing for and addressing common comorbid conditions

- **Depression**- highly prevalent and associated with worse outcome
- **Obstructive Sleep Apnoea**- In obese and centrally obese patients
- **Fatty Liver Disease**- unexplained elevation of ALT/AST
- **Cancer**- Type 2 diabetes is associated with increased risk of cancers of liver, pancreas, endometrium, colon, rectum, breast and bladder
- **Fractures**- osteoporosis leading to hip fracture. Assess risk factors and BMD if appropriate.
- **Cognitive impairment**- all forms of dementia
- **Low testosterone in men**-
- **Periodontal disease**- adversely affects diabetes outcomes
- **Hearing impairment**-both high and low frequency impairments due to neuropathy + / vascular disease

Referrals

- Eye care professional; for annual dialated eye examination
- Family planning: for women of reproductive age
- Dietician: for medical nutrition therapy
- Dentist: for periodontal examination
- Mental health professional: if needed

Glycemic Targets in Management

Assessment of glycemic control

Two techniques available for health providers and patients to assess the effectiveness of glycemic control strategy are:

- Self monitoring of blood glucose and
- HbA1C.

Self Monitoring of Blood Glucose (SMBG):

- SMBG results may help guide treatment decisions / self-management for patients using insulin or non-insulin therapy.
- When using SMBG, patients should receive regular instructions, evaluation of SMBG technique, SMBG results and ability to use SMBG data to adjust therapy.

Continuous Glucose Monitoring (CGM)

- Useful in intensive insulin therapy in adults (≥25 years) with Type 1 Diabetes.
- May be useful in children and young adults if adherence to ongoing use of the device is ensured.
- CGM is useful; in addition to SMBG in those who get frequent hypoglycemic episodes and those with hypoglycemic unawareness.

HbA1C

- Can be done twice a year in those who have stable glycemic control.
- Should be done every3 monthly in those with poor glycemic control and when changing therapy.
- HbA1C may confirm the accuracy of patient's glucometer and adequacy of SMBG schedule.

Limitations of HbA1C: conditions that affect the red cell turnover (haemolysis, blood loss); and haemoglobin variants must be considered when HbA1C does not correlate with patient's blood sugar level.
HbA1C does not provide a measure of glycemic variability or hypoglycemia.

Fructosamine

Measures chronic glycaemia, but the linkage to average glucose and the prognostic significance are not clear.

Glycemic Targets

Many aspects must be considered when setting glycemic targets.Targets must be individualized to the needs of the patients and their disease factors.

E.g.

- Duration of diabetes
- Age/lifestyle expectancy
- Co morbid conditions
- Known CVD
- Micro vascular complications
- Hypoglycemic unawareness
- Individual patient consideration

Table 3. Targets for glucose control in Diabetes

Glycemic recommendations for adults with diabetes	
HbA1C	<7%
Pre-prandial capillary plasma glucose	80-130mg/dL(4.4-7.2 mmol/L)
Post prandial capillary plasma glucose	<180mg/dL (<10 mmol/L)

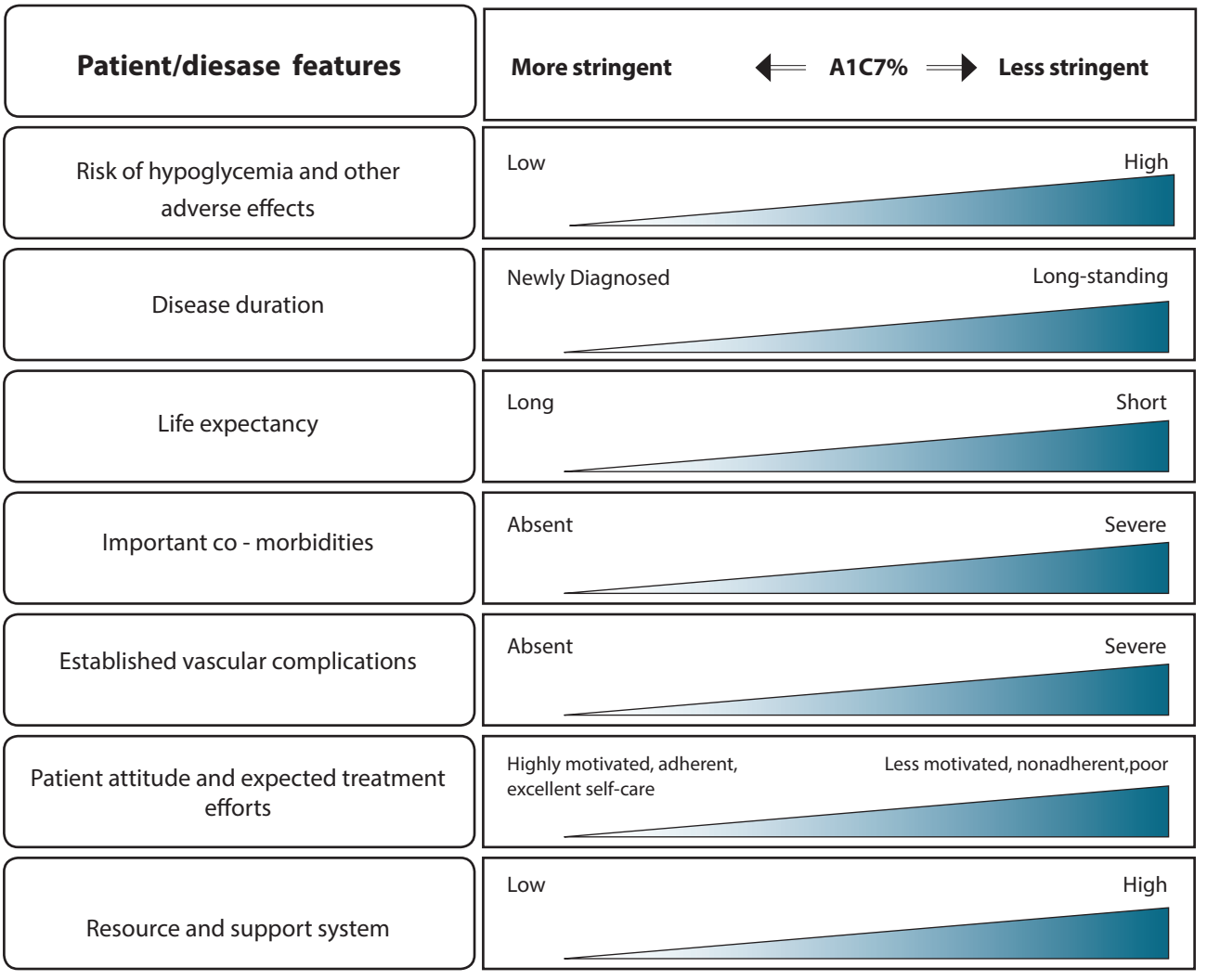
The above capillary glucose levels correlate with the achievement of HbA1C of <7%. Both post-prandial hyperglycemia, and preprandial hyperglycemia contribute to elevated HbA1C. Post-prandial hyperglycemia is associated with cardio vascular disease, independent of fasting glucose.

HbA1C goals for adults

- Reducing HbA1C to≤ 7 reduces micro vascular complications.
- If established early in the disease process, it is associated with long-term reduction in macro vascular disease.
- HbA1C<6.5% can be achieved in selected patients without causing significant hypoglycemia. A1C<6.5 is suitable for those with:
  - o Short duration of diabetes
  - o Type 2 diabetes treated with lifestyle or no hypoglycemia causing drug combinations
  - o Long life expectancy
  - o No significant cardiovascular disease.
- Less stringent HbA1C of <8 is appropriate for those with:
  - o History of severe hypoglycemia,
  - o Limited life expectancy,
  - o Advanced micro / macro vascular complictions,
  - o Extensive co - morbid conditions,
  - o Long standing diabetes in whom it is difficult to attain the goal despite self management education, glucose monitoring, effective doses of multiple agents including insulin.

Individualized Approach to the Management of Hyperglycemia

Figure 3. Recommended individualized targets based on other factors



Diabetes and Diet

A diabetic diet need not be a complete deviation from the normal diet. However the diet can be tailor made for the individual for his or her age, BMI, physical activity, physiological needs, co-morbid conditions and personal preferences.

Goals of Medical Nutrition Therapy

- To promote and support healthy eating patterns to
  - o Achieve glycemic, blood pressure and lipid goals
  - o Achieve and maintain body weight goals
  - o Prevent/ delay complications of diabetes
- To address individual nutritional needs based on
  - o Personal, cultural preferences,
  - o Health literacy
  - o Access to healthy food
  - o Barriers, wishes and willingness to change
- To maintain the pleasure of eating
  - o By providing positive messages about food-choices
  - o Limiting food choices only when indicated by scientific evidence
- To provide tools for day today meal planning, without focusing on single foods or macro/micro nutrients

Weight Loss

- Reducing energy intake to promote weight loss is recommended for overweight and obese
- Modest weight loss of 2-8 kg especially early in the disease process may provide clinical benefit such as
  - o Improvement of glucose, lipids and BP parameters
  - o Improvement of NASH

Macronutrients

Evidence suggest thst there is not an ideal % of calories from each macronutrient for all people with diabetes. Macronutrient distribution should be individualized, based on metabolic goals.

Carbohydrate

- In Type1 diabetes education on carbohydrate counting for intensive insulin therapy will be useful.
- For those on fixd dose insulin, consistent carbohydrate intake (amount and time) will improve glycemic control and reduce risk of hypoglycemia.
- Portion control and healthy food choices is required for all.
- Adjusting insulin dose based on carbohydrate intake will improve postprandial glucose control.
- Consumption of whole grains was not shown to be improving glycemic control but studies show that it may reduce mortality and cardiovascular disease.

Glycemic index

Different carbohydrates raise the blood sugar to a variable extent. The glycaemic index indicates the extent of rise in blood sugar in response to food in comparison with the response to equivalent amount of glucose and is expressed as a percentage. Although carbohydrates do have differing glycaemic responses, no clear trend in outcome benefits has been shown in clinical trials.

Table 4. Weight that gives 50g of available Carbohydrate & Glycemic index

Starch	Weight that gives 50g CHO	Glycemic index
White bread	101g	100%
White rice	58g	81%
Brown rice	60g	81%
Cornflakes	59g	92%
Potato	240g	80%
Lentils	94g	38%

Proteins

- For diabetics amount of protein should be individualized based on nutritional status
- In Chronic kidney disease protein intake recommended is 0.8 g/Kg/daily eating less than this is not useful as it does not alter decline in GFR.
- Food rich in protein should not be given to treat hypoglycemia as ingested protein may increase insulin response.

Fats

- 20 – 35% of total energy intake can be from fat intake
- The type of fatty acids consumed is more important than the total amount of fat
  - o Diet rich in monosaturated fatty acids, like a Mediterranean diet improves glycemic and lipid control
- Omega 3 fatty acids do not improve glycemic control
- Omega 3 FA supplementation is not recommended for prevention of CVD.
- Consumption of (fatty) fish at least 2 times a week and other foods rich in long chain omega 3 fatty acids and omega 3 linoleic acid (ALA) is recommended

Sodium

- Reducing sodium intake reduces blood pressure
- Less than 1500 mg/day of sodium is recommended

Alcohol

- Alcohol intake should be in moderation
- No more than one drink / day for adult women and no more than two drinks / day for adult men
- Alcohol may lead to delayed hypoglycemia in those who take insulin / insulin secretagogues

Micronutrients

- There is no clear evidence of benefit from vitamin /mineral supplementation with:
  - o Antioxidants
  - o Chromium. Magnesium or Vitamin D do not improve glycemic control.
- There is insufficient evidence to support cinnamon, or other herbal products.
- Optimize the food choices to meet the recom mended dietary allowance of all micronutrients.

Sweeteners

The following non-nutritive sweeteners are approved by the FDA (USA):

- Saccharin
- Aspartame
- Acesulfame potassium, and
- Sucralose.

Table 5: **Sample Menu: 1800 kcal**

Tea
2 tablespoon non fat milk

B'fast
Bread 2 slices / chickpea 1 cup
Curry / polsambol 1 tbs (tablespoons)

Mid morning
Fruit 1 (one serving of fruit is a small Banana or slice of larger fruit)

Lunch
Rice 2 cups
Vegetables 6 tbs
Green leaves ½ cup
Fish 1 piece
Fruit 1 serving

Mid afternoon *Milk non fat*

Dinner
Rice 1 cup
Vegetable 3 tbs
Dhal 3 tbs
Fruit 1 serving

Physical Activity

- Children are encouraged to engage in physical activity for at least 60 min a day.
- For adults 150 minutes / week of exercise is advised
  - o Activities:
    - *Moderate intensity aerobic exercise at least 3 days a week.*
    - *No more than 2 consecutive days without physical activity.*
    - *Resistance training at least twice / week (exercise with free weights or weight mechines)*
  - o Sedentary time:
    - *Break up extended time spent sitting (>90 min)*
- Use clinical judgement for cardiac fitness before recommending exercise.
  - o High risk individuals should start with short periods of low intensity exercise and slowly increase intensity and duration.
- Conditions that might contraindicate certain type of exercises:
  - o Uncontrolled hypertension
  - o Severe autonomic neuropathy
  - o Severe peripheral neuropathy
  - o History of foot lesion
  - o Unstable proliferative retinopathy

Smoking Cessation

- Advise and motivate patients not to smoke or use tobacco products.
- For patients motivated to quit:
  - o Offer pharmacological therapy (bupropion, nicotine patches or chewing gum)
  - o Provide counselling
  - o Combination of both of these is more effective than either treatment alone.
- Some patients may gain weight in the period shortly after smoking cessation; the CVD benefit gained by quitting smoking outweighs the risk by weight gain.

- There is no evidence that e-cigarettes are healthier alternative to smoking or e- cigarette can facilitate smoking cessation.

Psycological Assessment and Care

- Assessing psychological and social situation is part of on going medical management of diabetes.
- Screen for attitude about illness; expectation for medical management and outcome; mood, general and diabetes- related quality of life; financial, social and emotional resources; psychiatric history.
- Routine screening for psychological problems. eg: depression, diabetes- related stress, anxiety, eating disorders; cognitive impairment.
- Refer to mental health specialist when indicated,

Immunisation

Special vaccines recommended for patients with diabetes:

- Annual influenza vaccine for all patients with diabetes
- Pneumococcal polysaccharide vaccine 23 (PSSV23)
- Adults ≥ 65 years of age, pneumococcal conjugate vaccine (PCV 13) and 6-12 months later PPSV23
- Hepatitis B vaccine

Drugs Used in the Treatment of Type 2 Diabetes

Oral Therapy

Biguanides: Metformin

Mechanism of action

Primary

Decreases hepatic glucose production by improving insulin action at the liver

Secondary

Enhances glucose uptake and utilization in muscle cells

Improves insulin sensitivity by increasing peripheral glucose uptake and utilization

Metformin is the only available Biguanide

- Effective in obese and non-obese patients with type 2 diabetes
- Promotes modest weight reduction or at least weight stabilization
- Lowers fasting blood glucose concentrations by approximately 20%
- May be used as monotherapy or in combination with other medications or insulin
- Given in combination with a sulfonylurea lowers blood glucose concentrations more than either drug alone
- Less likely to cause hypoglycemia

Side effects

The most common side effects of metformin are gastrointestinal

- Metallic taste in the mouth
- Anorexia, nausea, abdominal discomfort
- Diarrhoea
- These symptoms are usually mild, transient, and reversible after dose reduction or discontinuation of the drug

Lactic acidosis is extremely rare. Predisposing factors:

- Renal insufficiency (creatinine >1.4 mg/dL in women & 1.5 mg/dL in men)
- Concurrent liver disease or alcohol abuse
- Heart failure
- P/H/O lactic acidosis
- Severe infection with poor tissue perfusion
- Hypoxic states
- Serious acute illness
- Haemodynamic instability

Stop metformin:

- If any of the predisposing factors are present
- Prior to receiving IV iodinated contrast material to avoid the potential for high plasma metformin concentrations (and lactic acidosis) if the patient develops contrast-induced acute renal failure

Sulfonylureas

Usually lower fasting blood glucose by about 20%

Effective as monotherapy or in combination with other glucose lowering therapies and insulin

Factors in choice of Sulphonylureas

Age

- Long acting sulphanylurea (glibenclamide) are associated with greater risk of hypoglycaemia
- These should be avoided in elderly

Coexisting Diseases

- Avoid in severe renal or liver failure and use insulin instead

Weight

- Most sulphonylureas particularly Glibenclamide cause weight gain. Use Metformin as monotherapy instead.
- Tolbutamide, gliclazide or Glimepiride can be used as add on therapy in obese

Cost

- All SUs are similar in efficacy. The newer sulfonylureas have lower hypoglycemia risk and evidence of cardiovascular safety (particularly gliclazide). Tailor the cost to the patients requirements

Compliance

- Once daily drugs e.g. Glibenclamide, Gliclazide MR, Glimepiride can be useful to avoid multiple doses

DPP-4 Inhibitors

They prevent degradation of incretin hormones, Glucagon-like-peptide by inhibiting the enzyme DPP 4 that proteolyses GLP1. The GLP 1:

- Enhances glucose dependent insulin secretion
- Inhibits glucose dependent glucagon secretion
- Inhibits gastric emptying and acid secretion

Advantages

DPP4i can be used as:

- Monotherapy
- Combination with metformin
- Part of triple therapy.
- Combination with insulin to reduce the dose requirement

No hypoglycemia when used as monotherapy Can be taken with or without food.

Adverse effects

- Reduce dosage in renal failure (Linagliptin is not cleared by kidney and requires no dose adjustment).
- Predisposition to nasopharygitis and upper respiratory infection.
- Severe allergic reaction including angioedema., anaphylaxis, and Stevens-Johnson syndrome can occur
- Incidence of pancreatitis including hemorrhagic necrotizing pancreatitis have been reported. But these are thought to be not related to DPP4i.

SGLT 2 Inhibitors

Under normal physiological conditions, approximately 180 g of glucose is filtered by the kidney daily. Almost all of this is reabsorbed into the circulation by Sodium Glucose co Transporters (SGLTs). SGLT 2, in the proximal tubules reabsorbs 90% of the filtered glucose. SGLT 2 inhibitors prevent glucose re-absortption form the glomerular filtrate resulting in a reduced renal threshold for glucose, glycosuria and calorie loss.

Advantages

- Can be use as monotherapy or in combination with other treatments including insulin
- Results in modest weight loss of 2-5 kg.
- Efficacy is reduced in chronic renal failure

Adverse effects

- Increased incidence of genital and urinary infections.
- Glycosuriya can cause intravascular volume depletion and hypotension.
- Canagliflozin can cause modest increase in LDL cholesterol level.

- In clinical trials patients taking Dapagliflozin had higher rates of bladder and breast cancer. This has not been substantiated as a significant association.

α-Glucosidase Inhibitors

Inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert carbohydrates into monosaccharides in a dose-dependent fashion. Slow absorption of glucose & rise in postprandial blood glucose. They may also increase insulin sensitivity.

Advantages

Appear beneficial in both type 1 and type 2 diabetes: decreases the amplitude of postprandial glycemic excursions and lowers hemoglobin HbA1C values.

Can be given alone or in combination with insulin, SU or metformin

Taken with the first bite of food

Acarbose may also have beneficial effects on serum lipid concentrations (decreases LDL, increases HDL)

Adverse effects

- o Flatulence and diarrhea, Symptoms are usually mild. Slow titration in dosage minimize these adverse effects
- o High serum aminotransferase concentrations have been reported with acarbose

Thiazolidinediones

They bind to and activate a transcription factor called peroxisome proliferator-activated receptor-gamma (PPAR-γ) PPAR-γ is involved in the transcription of insulin-responsive genes. Increase insulin sensitivity by acting on muscle and liver to increase glucose utilization and decrease glucose production. Increase insulin secretion in response to glucose

Adverse effects

They have a long list of significant side effects and should be initiated only it absolutely indicated.

- All of the thiazolidinediones cause weight gain. It is both dose-dependent and time-dependent. Weight gain is caused by both the proliferation of new adipocytes and redistribution of fat stores
- Fluid retention, which is more prominent with concomitant insulin therapy, can occur with all the thiazolidinediones
- Peripheral edema occurs in 2 to 5%. Precipitation or worsening of heart failure and, in some cases, the development of pulmonary edema may occur (Rare reports of macular oedema with high doses of rosiglitazone has been noted)
- Fluid retention induced by thiazolidinediones appears to be relatively resistant to loop diuretics but responds promptly to withdrawal of therapy (spironolactone may be effective)
- Should not be given to patients with New York Heart Association (NYHA) class III or IV HF
- Dose should be low in patients with risk factors for HF (left ventricular dysfunction, NYHA class I or II HF)
- Atypical fractures in men and women can occur
- Some association with bladder cancer has been shown, however metaanalysis does not support this.

Table 6: Oral glucose lowering agents

Drug	Dose range	Primary action	Advantages	Disadvantages
Biguanides Metformin	500 mg-2500 mg start at low dose with meals	↓hepatic glucose production	Extensive experience, No hypoglycemia, ↓CVD events, Low cost	Diarrhea,Dyspepsia, Bloating,Vitamin B12 deficiency Contra indicated in: CKD, Severe heart, Liver failure, Acidosis, dehydration, hypoxia
Sulphonylurea Gliclazide Gliclazide MR Glimepiride Glibenclamide Tolbutamide Glipizide	In divided doses 40-320mg 30-120mg 1-6 mg 2.5-15 mg 500-3000mg 2.5-20 mg	↑insulin secretion	Extensive experience, ↓microvascular risk, Low cost	Hypoglycemia, ↑weight gain, ?blunts myocardial ischemic preconditioning
TZD Pioglitazone	7.5-30mg	↑insulin sensitivity	No hypoglycemia, ↑HDL,↓Triglycerides,	Weight gain Oedema Worsening of cardiac failure Bone fractures
α-glucosidase inhibitors Acarbose	50-300mg divided doses with meals	Slows intestinal carbohydrate digestion/ absorption	No hypoglycemia, ↓postprandial glucose excursions, non systemic	Diarrhea Abdominal bloating Flatulence
Meglitanides Repaglinide Nateglinide	0.5-4mg with meals 60-180mg with meals	↑insulin secretion	Taken with meals no meal, no tablet Controls postprandial hyperglycemia Less weight gain in obese	Hypoglycemia, Frequent dosing
DPP4i Sitagliptin Vildagliptin Saxagliptin Linagliptin alogliptin	regardless of meals 25-100 mg 50-100 mg 2.5-5mg 2.5-5 mg 6.25-25mg	Glucose dependent: ↑insulin & ↓glucagon secretion	No hypoglycemia Well tolerated	Mild nausea, vomiting, abdominal pain Angioedema / urticaria and other immune mediated skin effects Acute pancreatitis ?↑heart failure hospitalizationLower dosage in renal impairment
SGLT 2 i Canagliflozin Dapagliflozin empagliflozin	Once daily 100-300mg 5-10mg 10-25mg	Blocks glucose re absorption by the kidney & Increase glucosuria	No hypoglycemia ↓weight ↓blood pressure Effective at all stages of T2DM	Genito-urinary infections, Polyuria Volume depletion/ hypotension ↑LDL-C ↑creatinine transiently

Subcutaneous Injections: GLP-1 Receptor Agonists

Oral glucose causes release of gut hormones , principally glucagon- like peptide-1(GLP-1) that amplify glucose induced insulin release. GLP-1 suppresses glucagon secretion and improvers glucagonaemia usually present in type 2 diabetes, thus improvig postprandial hyperglycemia. Delays gastric emptying. In animal studies GLP-1 has been shown to preserve islet cell integrity and reduces apoptotic cell death of islet cells.

- GLP 1 Agonists are metabolically stable analogs or dervatives of native GLP-1.
- Given as subcutaneous injection to patients with type 2diabetes taking metformin and / or sulfonylurea.
- Causes sustained weight loss.
- Main side effect is nausea which is dose dependent and decline with time.
- Cases of pancreatitis including haemorrhagic necrotizing pancreatitis have been reported. Many of these patients had other risk factors for pancreatitis.
- Cases of renal impairment and acute kidney injury have been reported. This could be due to volume depletion due to nausea, vomiting and diarrhea.
- Delayed gastric emptying can cause delay in absorption of other medications.
- High titre antibodies can develop and can result in attenuation of glycemic response.
- Liraglutide at a very high dose has been shown to stimulate T cell tumour in rodents. Therefore it is contraindicated in patients with a personal or family history of medullary

Table 7: GLP1 RA that are FDA approved

Duration	Drug	Dosage subcutaneous injection	Primary physiological action	Advantage	Disadvantage
Short Acting (Twice Daily)	Excenetide	5-10mcg (injected 60min before breakfast & dinner)	Glucose dependent: ↑insulin & ↓glucagon secretion Slows gastric emptying ↑satiety	Weight reduction No hypoglycemia(can occur in combination with SU/insulin) ↓postprandial glucose excursions ↓some cardiovascular risk factors	Nausea, vomiting, diarrhea. ↑heart rate Should not be used in end stage renal failure, patients with pancreatitis. Thyroid C cell tumors in animals: Contra indicated in patients with MEN2, and personal or family history of medullary thyroid ca.
Long Acting (Once Daily)	Liraglutide Lixisenatide	0.6-1.8mg 10-20 mcg			
Long Acting (Once Weekly)	Exenatide XR Albiglutide Dulaglutide	2 mg 30-50 mg 0.75-1.5 mg		Imporves HbA1C better than short acting.	

Insulin Treatment

Objectives of Insulin Therapy:

To use a variety of alternative insulin regimens to achieve optimal blood glucose control in patients with Type 1 and Type 2 diabetes.

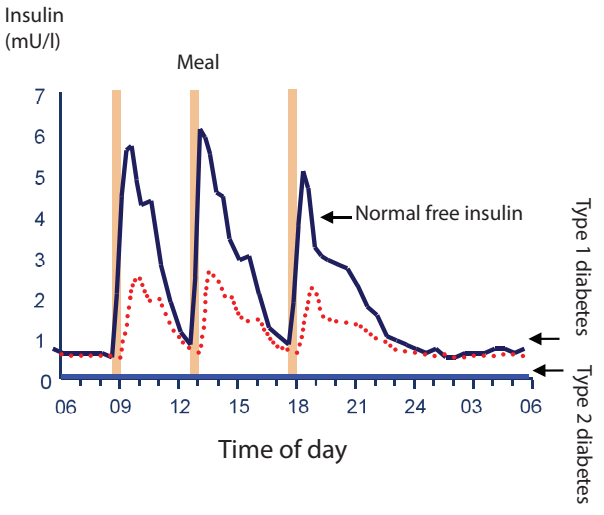
Type 1 Diabetes

The β-cells of Type I diabetics do not produce insulin and patients require insulin for survival.

Type 2 diabetes

In type 2 diabetes 50 % of the β-cell function is lost at diagnosis. The β-cell function declines over time and insulin is typically required 7–12 years after diagnosis.

Figure 4: Profile of Insulin synthesis



Types of Insulin

- o Human insulin – chemical methods & genetic engineering
- o Extended acting insulin – NPH (Hagedorn)
- o Rapid acting insulin analogues
- o Long acting insulin analogues

Rapid-Acting Insulin analogues

These are used as bolus (mealtime) insulin. Available preparations

- o Lispro (Humalog®)
- o Insulin Aspart (Novorapid®)
- o Glulisine (Apidra®)

Table 8. Types and properties of insulin preparations

Type	Description	Onset (hours)	Peak (hours)
Analogue	Ultra short acting	0.2-0.5	1-2
Regular	Short acting	0.5-1	2-4
NPH	Intermediate	2-4	6-16
Analogue	Long Acting	2-4	Peakless 24hrs

Short-Acting Insulin

Short-acting. Onset of action is delayed by 30-60 minutes. Duration of action 5-8 hours. To be taken 30-60 minutes before meals. Available preparations

- o Regular / soluble insulin (Actrapid® /Humlin R®)

Intermediate-Acting Insulin

The Hagedorn retards the release of insulin into the blood. Their onset of action is about 2 hours after injection. Their peak effect is from 6-10 hours. Appearance is cloudy

- o Human NPH Also called isophane (Insulatard®/ Humulin N®)

Long-Acting Insulin

The side chain causes slow dissolution at the site of injection resulting in a peakless delivery over 24 hours. Clear in solution Usually used as a single dose. The risk of hypoglycemia is lower.

- o Glargine (Lantus®)
- o Detemir (levemir®)
- o Degludec(Tresiba®)

Pre-Mixed Insulin

Usually mixtures of short acting insulin with NPH insulin or rapid acting analogues with NPH analogue insulin. This is more physiological than short acting or intermediate acting insulin alone.

Available products.

- 30/70 mixture: 30% Regular and 70% NPH (Mixtard 30/70®), Humulin 70/30®))
  - 25/75 mixture (Insuman 25®)
- Analogue insulins in premixed form:
  - Lispro + protamine lispro (Humalog 25®, Humalog 50®)
  - Aspart + Protamine aspart (Novomix 30®)

Basal Bolus Regime

Basal Insulin

Basal of background insulin is the amount of insulin required in the post-absorptive state to cover the glucose that the liver is releasing into the blood (endogenous glucose). Basal insulin suppresses hepatic gluconeogenesis and lipolysis and release of FFA into the blood.

Bolus Insulin

In normal individuals as plasma glucose rises after meal nsulin concentration increases rapidly, peak in 30-60 minutes and return to basal concentrations within 2-3 hours. To mimic that action rapid-acting or short-acting insulin before meals (bolus or mealtime insulin) is used. Mealtime insulin doses can be adjusted based on the amount of carbohydrate in the meal. Decisions are based on the insulin-CHO ratio for that individual.

Figure 5. Insulin regimes for Type 2 Diabetes:

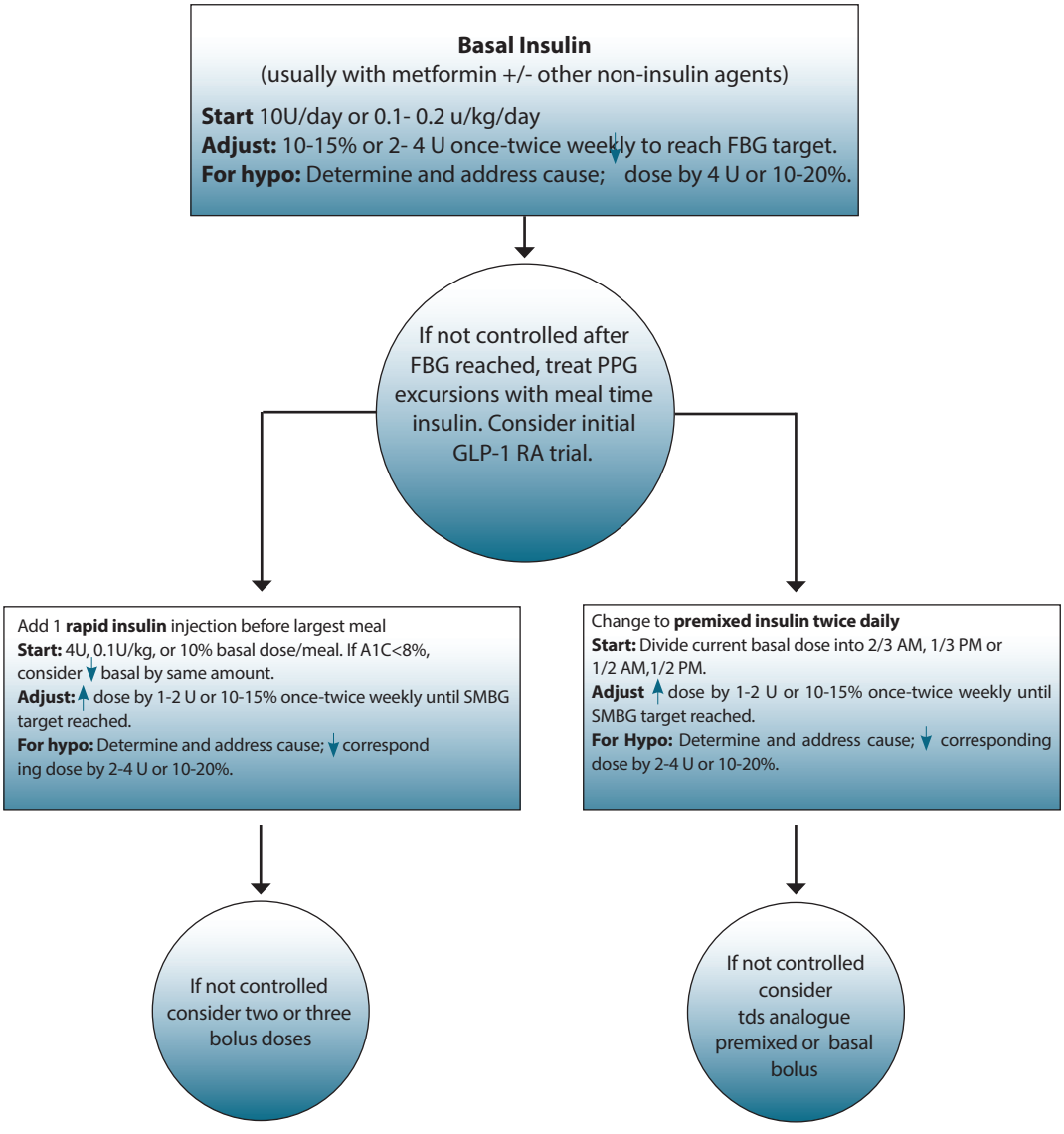
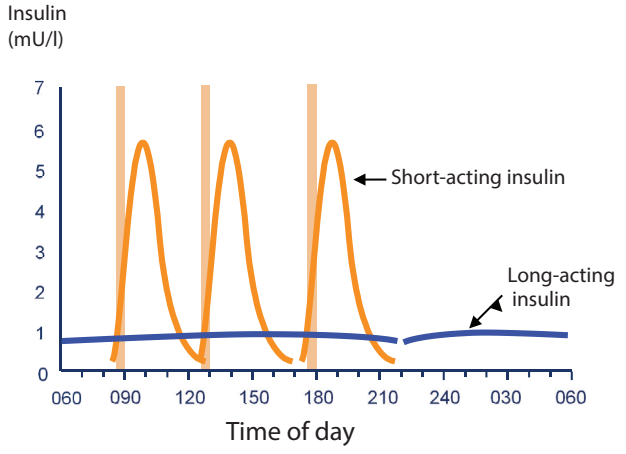


Figure 6: Basal bolus Insulin dosing to match normal physiology



Basal bolus regime

- 3 doses of regular/rapid acting insulin with meals and intermediate/long acting insulin at bed time.
- Basal bolus regimen is the ideal for a patient with type 1 diabetes.
- It provides flexibility of insulin dosage according to the meal time and the activity.
- About 50% of daily insulin for basal and about 50% of daily insulin divided among the three meals with usually about 1.0 -1.5 U insulin /10 grams of CHO.

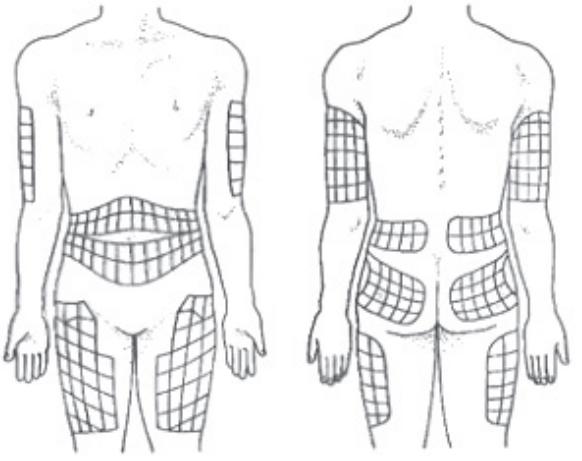
Biphasic: twice or thrice daily fixed mixture

- 20 minutes before breakfast and dinner. E.g.: Biphasic: Regular insulin is first drawn in to the syringe and then the intermediate acting insulin in a proportion of 30/70 or 50/50;
- Fixed mixture: Human Mixtard 30/70®, Humulin 70/30® or Insuman 25®
- Fixed mixture with analog: administered with the meal rather than 20 min before meal. Less incidence of hypoglycemia. Novomix 30®, Humalog mix 25®, Humalog mix 50®. These can be used as twice or thrice daily dosing.

Insulin administration

Insulin injection should be given in to a pinched-up skin fold, and the needle should penetrate no more than 3-5 mm, needle at 45° angles to avoid intramuscular injection, which accelerates absorption.

Figure 7. Insulin Injection sites



- Insulin absorption is faster in the abdominal area, slower in the arms, and more so in the thighs.
- Therefore fast acting (soluble and rapid acting analogs) insulin must be injected in the abdomen and longer acting insulin can be injected in the thighs.
- Movement of the limbs increases absorption. Abdomen should be used for injections before physical activity.
- Injections should be rotated within the same region to avoid lipohypertrophy. E.g.: by moving from top to bottom of one thigh and to the other side.
- To reduce variability, injections should be rotated with in the anatomical regions in a regular pattern.

Problems of Insulin Therapy

- Benefits of advances of insulin therapy are unavailable to a great majority of patients who need insulin because of cost, doctors and patient's reluctance
- Hypoglycaemia
- Weight gain – 2kg per 1% reduction of HBA1C
- Lipo atrophy, Lipo hypertrophy at injection sites
- Insulin allergy – very rare & not related to the presence of antibodies

In-Hospital Management of Diabetic Patients

Diabetic patients stay in hospital on average 1 - 3 days longer than patients without diabetes. Regardless of whether the patient has a known history of diabetes, hyperglycaemia in the hospital is associated with increased mortality and morbidity.

Hyperglycaemia (FBS >126 mg/dL [7.0 mmol/L], RBS >200 mg/dL [11.1 mmol/L]) on general medical and surgical units was associated with 18-fold increase in in-hospital mortality, a longer length of stay (9 vs. 4.5 days), more subsequent nursing home care, and a greater risk of infection.

In patients with acute MI, the risk of death is significantly higher if the blood glucose concentration at admission is >109.8 mg/dL. Meticulous glycaemic control can improve clinical outcomes. Insulin, given either IV or as a continuous infusion or subcutaneously, is the most effective agent for achieving glycemic control in hospitalized patients.

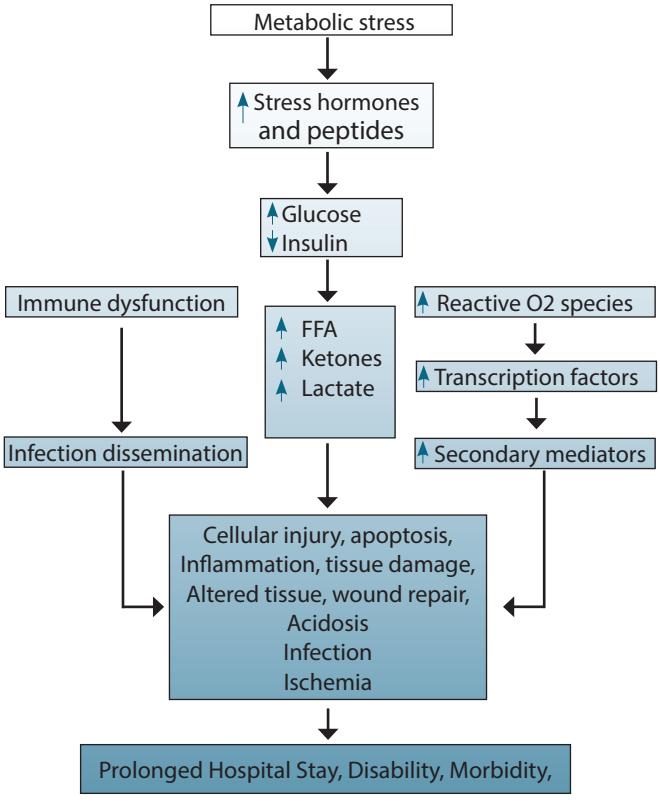
Factors Influencing Glucose Control In Hospitalized Patients With A High Glucose Level

- Increased counter-regulatory hormones
  - Usually in the perioperative period with increased insulin resistance due to increased catecholamines, cortisol, growth hormone and glucagon
- Unpredictable eating
  - From illness
  - Fasting for tests
  - Changing meal times
- Changing IV glucose rates
- Lack of exercise
- Unusual timing of insulin injections
  - Injection may be ordered on a timed basis, not having any relationship to meal
  - Insulin often given after meal is eaten
- Use of medications such as glucocorticoids and inotropes

Indications for Insulin Therapy

- In type 1 DM
- Prolonged fasting (> 12 hrs)
- Critical illness
- Before major surgical procedures
- After organ transplantation
- DKA
- Total parenteral nutrition therapy
- Labour and delivery
- Myocardial infarction
- Other illnesses requiring prompt glucose control.

Figure 8. Link between High Blood Glucose and Poor Outcomes: Potential Mechanisms



Critically Ill Patients

- Insulin therapy should be initiated if persistent glycaemia of > 180 mg/dL. (10mmol/L)
- Blood glucose range of 140-180 mg/dL is recommended for majority of critically ill patients.
- More stringent goals (110-140 mg/dL) may be appropriate for selected patients without causing significant hypoglycaemia.
- Ideal management will be with intravenous insulin infusion protocol

Continuous insulin therapy

A number of protocols for continuous insulin infusion have been published. No large studies have compared the effectiveness and safety of different protocols.

- Enough glucose must be provided to avoid starvation ketosis and prevent hypoglycaemia: most authors suggest 5 to 10 g/hour of glucose
- The blood glucose level must be checked frequently: ideally every hour until it is stable
- The protocol should include some mechanism for changing the infusion rate to reach glucose targets and to avoid hypoglycaemia.

Table 8. IV insulin protocol

	Insulin infusion (Unit/hour)			
BG(mgdl)	**A1**	**A2**	**A3**	**A4**
< 70 Hypoglycaemia	0	0	0	0
70–109	0	0	0.5	1
110–119	0.5	1	2	3
120–149	1	1.5	3	5
150–179	1.5	2	4	7
180–209	2	3	5	9
210–239	2	4	6	12
240–269	3	5	8	16
270–299	3	6	10	20
300–329	4	7	12	24
330–359	4	8	14	28
> 360	6	12	16	28

- **Move up to the next higher algorithm** if the BG is above the goal range & does not change by at least 60 mg/dL within 1hour
- **Move down an algorithm** when BG is < 110 mg/dL for 2 hours.
- Standard drip: 100 units/100 mL 0.9% NaCl via an infusion device (1 unit/1 mL)
- Surgical patients who have received an OHG within 24 hrs should start when BG >130 mg/dL.
- Others can start when BG ≥ 120 mg/dL
- Infusions should be discontinued when a patient is eating AND has received first dose of S/C insulin
- Give a dose of short-acting or rapid-acting insulin subcutaneously 1 to 2 hrs before stopping IV insulin infusion
- Basal and prandial insulin doses must be tailored to each patient's need;
  - stress level, oral intake, intravenous or enteral alimentation, weight, insulin sensitivity, medications (eg, steroids), and other factors
- Hospitalized patients often require higher doses of insulin because of the stress of their illness
- In addition to basal and nutritional insulin requirements, patients often require supplemental or correction doses of insulin to treat unexpected hyperglycaemia
- For supplemental insulin coverage, the rapid-acting analogues are preferred

Treatment of hypoglycaemia (blood glucose < 70 mg/dL) while the patient is on continuous insulin infusion

- Stop insulin drip AND Give dextrose 50% IV, Awake: 25 mL, Not awake: 50 mL
- Recheck BG every 20 min and repeat 25mL of D50% IV if < 60 mg/dL
- Restart insulin drip once BG is > 110 mg/dL X 2 checks.
- Restart drip with lower algorithm

Calculation of the daily insulin dose

Extrapolate from the average IV insulin dose required over the previous 6 - 8 hrs.
Give ½ as an intermediate-acting or long-acting insulin for basal coverage and ½ as a short-acting or rapid-acting insulin in divided doses before meal

E.g. average dose of IV insulin = 1.0 units/hr over the past 8 hours, TDD = 24 units, Basal = 12, Prandial 4 units three times.

Patients with acute myocardial infarction

The DIGAMI study (Diabetes Insulin Glucose in Acute Myocardial Infarction) demonstrated benefits of aggressive glycaemic control in patients with acute MI. Those with blood glucose >200 mg/dl were treated with intensive insulin treatment (IV insulin for >24 hours followed by multiple daily injections for >3 months). Significant reduction in mortality at periods even up to 3.4 years was demonstrated. The difference was even more impressive in patients considered at low risk and who had never received insulin before. The DIGAMI study underscores the importance of early and aggressive glucose control regardless of a prior history of diabetes.

Non Critically Ill Patients

- For insulin treated patients blood sugar targets pre-meals <140 mg/dL and random blood sugar <180 mg/dL, provided these targets can be safely achieved.
  - o More stringent target for those with previous tight glycemic control and
  - o less stringent target for those with severe co-morbidities.
- For those with good oral intake
  - o Use BBC
  - o Basal insulin
  - o Bolus insulin
  - o Correction doses
- For patients who are not taking anything by mouth or poor oral intake:
  - o Basal insulin along with correction doses of insulin

General insulin dosage recommendations

- **Type 1 DM**
  - o If a patient is newly diagnosed, the usual daily insulin requirement is 0.5 to 0.7 units/kg/day
- **Type 2 DM**
  - o If the patient has not been using insulin previously, the usual total daily insulin requirement is 0.4 to 1.0 units/kg/day.
  - o E.g. 70 Kg patient: The total daily dose will be 0.4 x 70 units. 50% as basal and 50% as bolus. 14 Units of Glargine/Detemir/ NPH plus 5 units of Soluble/ Rapid acting insulin analog three times a day.
  - o Monitor pre meal blood glucose if they are above 140 mg/dl add an appropriate correction dose to the planned premeal dose
- **Use of "sliding scale" insulin alone is discouraged**

  Evidence does not support this technique, as it results in unacceptably high rates of
  - o Hyperglycemia
  - o Hypoglycemia
  - o Iatrogenic diabetic ketoacidosis in hospitalized patients

Hyperglycemia in the Hospital Requires Close Follow-Up After Discharge

Previously diagnosed diabetes and/or an elevated A1C, or both

- o Preadmission diabetes care plan requires revision

Without previous diabetes diagnosis

- o Differentiation between hospital-related hyperglycemia and unrecognized diabetes requires follow-up testing (FBG or 75 gram, HbA_1C or 2 hour OGTT) once metabolically stable

Management of Patients with Diabetes During Surgery

Surgical stress can stimulate hyperglycemia and ketosis. Hypoglycemia can occur due to Sulphonylurea treatment or excessive insulin in fasting patients. Safe target of blood glucose level during the peri operative period is 7.8-10 mmol/l (140-180 mg/dl).

Preoperative management

- Assess for complications:
  - o Cardiac, renal fitness
- Admit as early as possible prior to surgery
- Closely monitor blood glucose levels
  - o 2 hourly for Type 1, ketone testing 8 hourly
  - o 4 hourly for Type 2
- Place first on morning operating list if possible
- Aim for a blood glucose of 140-180 mg/dl
- Watch nutrition
  - o 5% dextrose if fasting

OHA treated patients

- Long acting sulphonylureas should be re placed by shorter acting agents some days before surgery.
  - o Glibenclamide or Glimepiride should be stopped at least 5 days before surgery, substituting a shorter-acting one such as tolbutamide or gliclazide if necessary.
- Well controlled patients under going minor surgery require only close monitoring during the perioperative period.
- Poorly controlled patients, or those who are under going major surgery, should be managed as for insulin treated patients.

Insulin treated patients

- Continuous administration of insulin and glucose is required during surgery.
- These can be given either through separate infusion lines or mixed together with potassium to prevent Hypokalaemia.

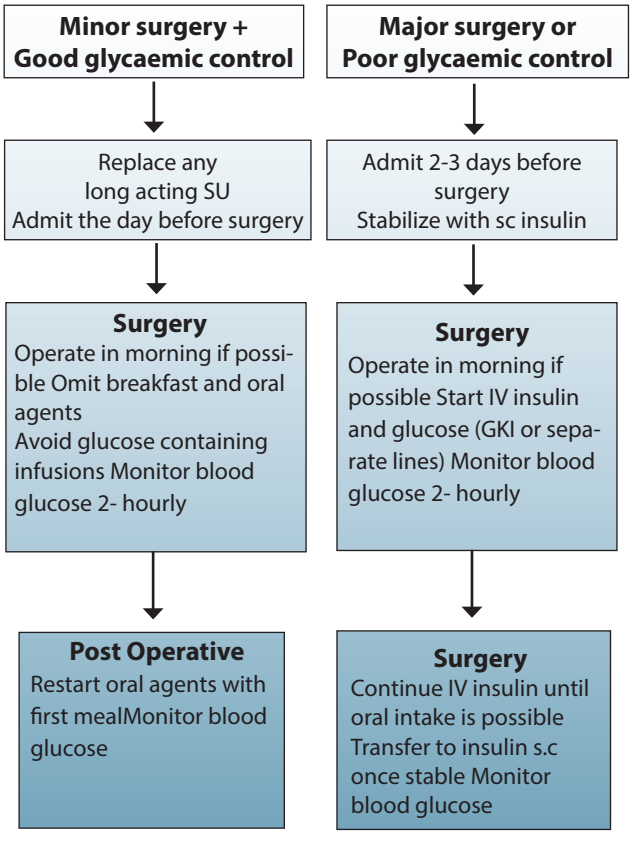
•'Separate – line' method of continuous IV glucose and insulin infusion.

- o Glucose is delivered by a drip at a constant rate of 100 ml 10% dextrose (10 g glucose) hourly.
- o The syringe driver pump administers 50 U soluble insulin in 50 ml 0.9% saline (IU /ml); the delivery rate is varied according to hourly bedside glucose monitoring, usually at 2-4U/hr.

•'GKI' infusion.

- o Add 10 mmol KCl and 15 U soluble insulin to 500 ml of 10% glucose and infuse at a rate of 100 ml/hr. (Infuse 5 hourly.)
- o Mix the bag well and label it clearly with the dosages.
- o Adjust cocktail from hourly blood glucose.
- o If glucose > 11 mmol/l (200mg/dl) change bag: 20 U insulin.
- o If glucose < 7.8 mmol/l (140 mg/dl) change bag: 10 U insulin.
- o Continue GKI until patients eat, then revert to usual treatment.
- o If GKI is prolonged (>24 hr) check electrolytes daily for possible sodium or potassium abnormalities.

Figure 9. Protocol for managing surgery in diabetic patients.



Diabetic Nephropathy

Diabetes is the most common cause of end-stage renal disease. Onset and progression of diabetic nephropathy can be ameliorated by early interventions.

Natural History of Diabetic Nephropathy

Earliest clinical evidence of nephropathy is the appearance of albuminuria.

Type 1 Diabetes: In 80% of subjects with albuminuria, the urinary albumin excretion will increase at the rate of 10-20% per year. With out intervention the GFR falls at a rate of 2-20 ml/min/year and progresses to End stage renal disease. Hypertension develops as GFR falls.

Type 2 Diabetes: Many patients have albuminuria at the time of diagnosis. With out intervention, albuminuria progresses and the GFR declines over time. Albuminuria is a marker of greatly increased cardiovascular disease risk. Therefore finding albuminuria is an indication for screening for possible cardio vascular disease and aggressive intervention to reduce risk factors.

Screening for Nephropathy

Test for albuminuria annually in

- All Type 2 patients starting from diagnosis
- Type 1 patients with duration > 5 yrs or from puberty

Method

- Albumin to creatinine ratio (ACR) in a spot urine sample
- Timed collection
- 24 hour collection along with creatinine clearance
- If ACR cannot be measured, treat as if the patient has albuminuria.

Table 9. Diagnosis of albuminuria in diabetes

Category	Spot collection (µg/mg creatinine)	Timed collection (µg/min)	24hr collection (mg/24 hrs)
NORMAL	< 30	< 20	< 30
ALBUMINURIA	>30	>20	>30

* Traditionally ACR > 300 µg/mg creatinine or >300 mg/24 hours has been called macro albuminuria, however this terminology is not in use as albuminuria occurs in a continuum.

TREATMENT OF DIABETIC NEPHROPATHY

Type 1: Commence ACEI

Type 2 : Commence ACEI / ARB

- Tight control of blood glucose values to near normoglycemia.
  - o Avoid or decrease metformin if serum cre atinine is high (> 1.5 mg/dl)
- Aim for SBP < 140
  - o Initially use ACEI /ARB
  - o Add other agents: thiazides, calcium channel blockers, beta blockers, alpha blockers, to get BP under control.
- Advice to stop smoking
- Good glycemic and BP control can prevent nephropathy or its progression
- If treated well, most patients could be expected to improve or at least slow the decline in renal function

Routine Investigations

- UFR - look for proteinuria, deposits
- Serum creatinine, and calculate estimated GFR
- Serum electrolytes
- Hb
- HbA1C every 3-6 months

Figure 11. Protocol for management

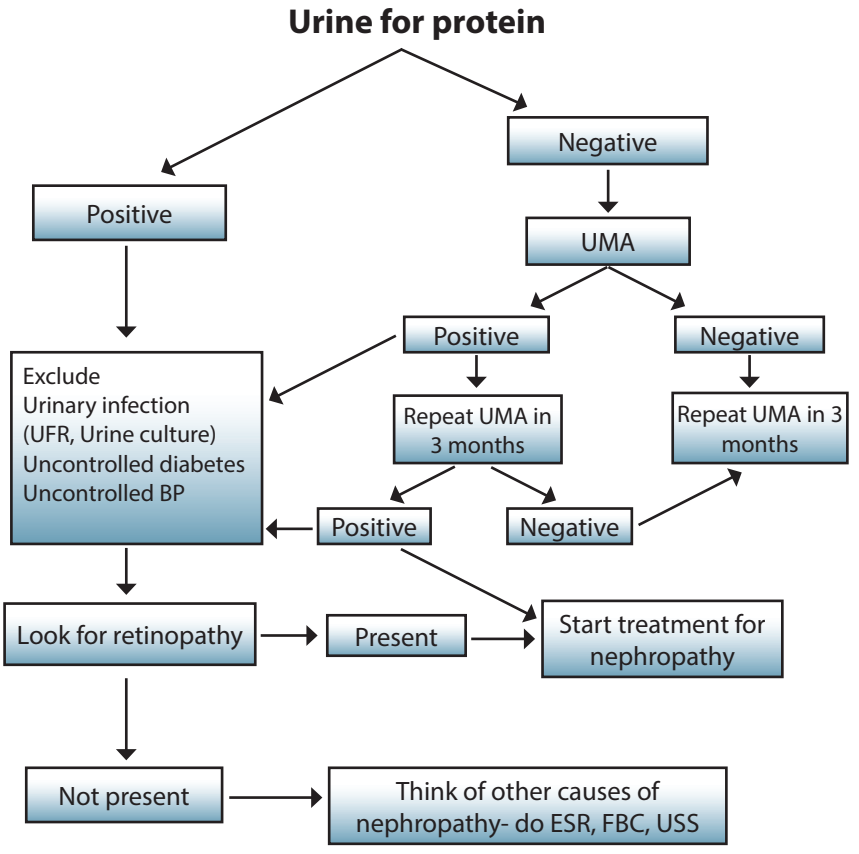


Table 10. Stages of CKD

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney Failure	<15

GFR is calculated with estimated GFR using MDRD (Modification of Diet and Renal Disease) formula as follows
GFR (ml/min/1.73m^2)= 175 x (Creatinine µmoll$^-$/88.4) $^{-1.154}$ x (Age) $^{-0.2}$ x (0.742 if female)

Table 11. Management of CKD in Diabetes

GFR (ml/min/1.73m^2)	Management
All Patients	Yearly eGFR, albuminuria
45 - 60	eGFR, albuminuria every 6 months check K^+, Hb, Calcium, phosphorous, PTH annually Ensure Vitamin D adequacy and supplement if required Refer to Nephrologist if non diabetic renal disease is suspected: active sedimentor red cells on UFR, rapid fall in eGFR, rapid progression of proteinuria or massive proteinuria
30 - 44	eGFR every 3 months check K^+, bicarbonate, Hb, Calcium, phosphorous, serum albumin, PTH every 3-6 months
<30	Refer to a nephrologist

Diabetic Retinopathy

Diabetic retinopathy is the most common cause of new onset of blindness in the adults. It is a microangiopathy affecting the retinal vasculature which can result in visual impairment progressing to blindness.

Pathogenesis of DR

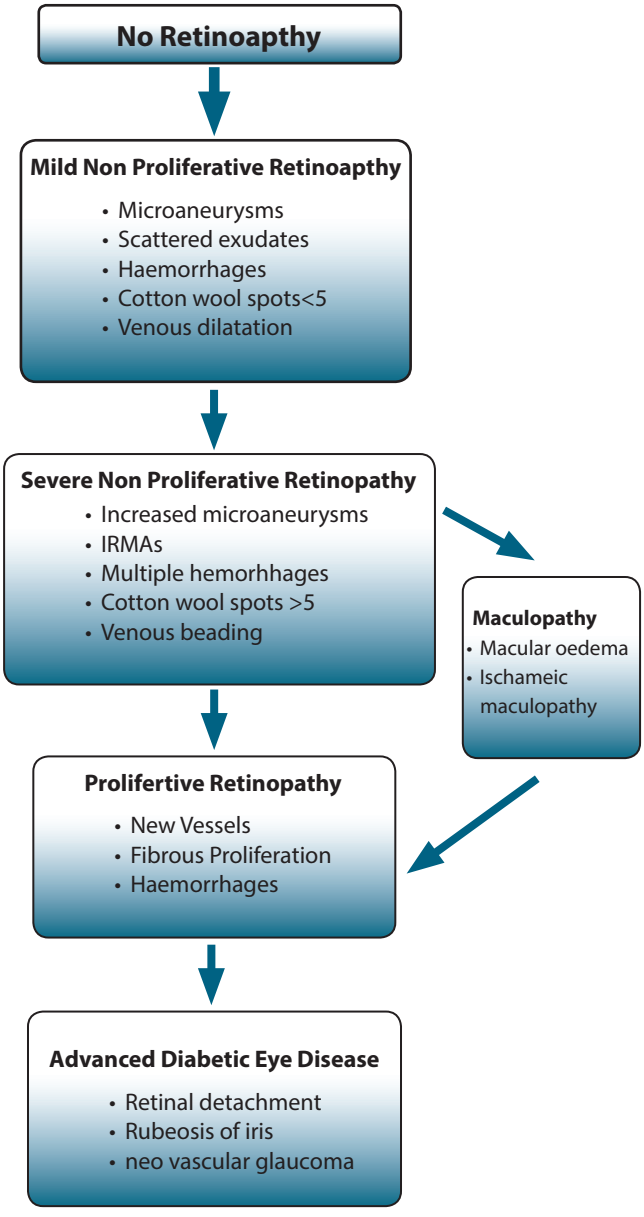
- Capillary Basement Membrane thickening
  - o Despite the multiple layers of basement membrane, micro aneurysms are permeable to water and large molecules, allowing the accumulation of water and lipid in the retina.
- Loss of pericytes
  - o The absence of pericytes weakens the capillaries and permits micro aneurysms, to develop. Later, endothelial cells proliferate and lay down layers of basement membrane material. Fibrin may accumulate within the microaneurysm along with erythrocytes, and the lumen of the microaneurysm may actually be occluded.

Proliferative vessels usually arise from veins and often begin as a collection of fine, naked vessels. When they arise on or within 1 disc diameter of the optic disc, they are referred to as neovascularization of the disc (NVD). When they arise further than 1 disc diameter away, they are called neovascularization elsewhere (NVE).

Risk factors for developing DR

- Duration of diabetes
- Type 1
  - o 27% in 5-10 years
  - o Up to 90% in over 10 years
  - o After 20 years can rise to 95%
- Type 2
  - o Difficult to determine because of uncertainty of onset.
  - o In some, the diagnosis of diabetes is made only after an ophthalmologist discovers the retinopathy.
  - o 11 to 13 years after the onset 23%.
  - o After 16 or more years, it was 60%.
- Hypertension
- Renal disease
- Increased blood lipids
- Pregnancy

Figure 12 Classification of diabetic retinopathy



Treatment
Diabetic macular oedema

- Exudative-
  - o Focal laser treatment
  - o Triamcinalone injection
  - o Intravitreal Fluocinolone
  - o VEGF antibody
- Ischemic - no treatment

Figure 13. Indications for referral to ophthalmologist

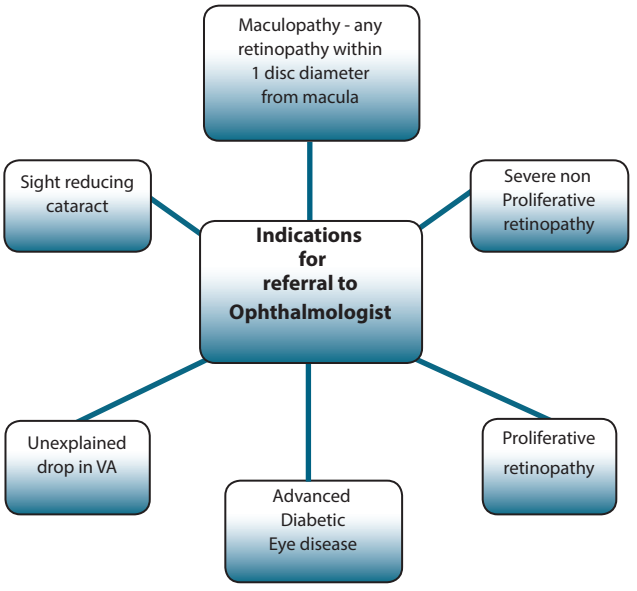
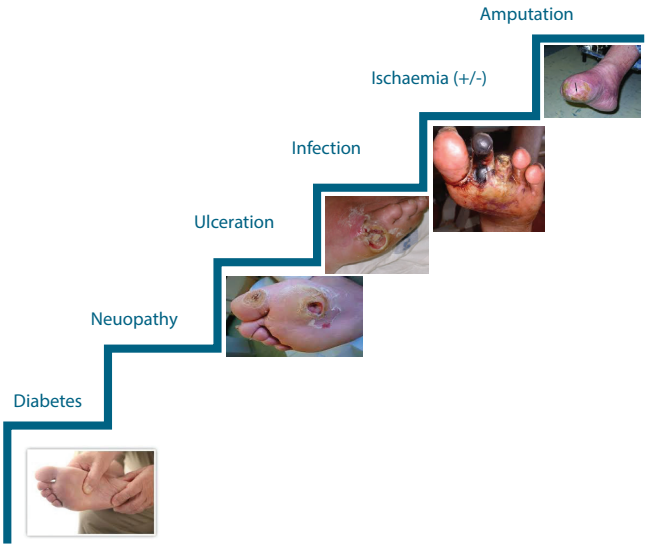


Figure 14. Stairway to amputation



Non-proliferative diabetic retinopathy

- Mild to moderate – control risk factors
- Moderate to severe – Pan retinal photocoagulation

Proliferative diabetic retinopathy

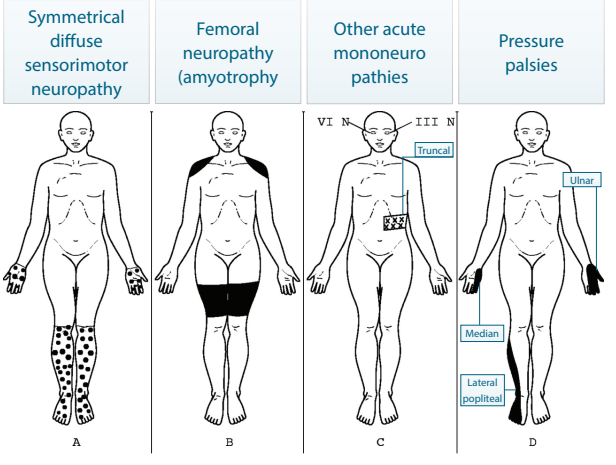
- NVD / NVE – Panretinal photocoagulation
- Vitreous haemorrhage – Vitreoretinal Surgery
- Traction Retinal Detachment – Vitreoretinal Surgery

Diabetic Neuropathy and Diabetic Foot

Diabetic neuropathy results in morbidity and amputations. It could be symptomatic or asymptomatic. Eraly recognition and intervention can prevent complications such as development of ulcer leading to amputation.

Figure 14 depicts the stairway to amputation where sensory loss plays a major role in ulcer causation and non-healing.

Figure 15. Classification of diabetic neuropathy



Classification of Diabetic Neuropathy

- Hyperglycemic neuropathy (rapidly reversible)
- Symmetrical Polyneuropathy
  - o Chronic sensory Polyneuropathy
  - o Acute painful diabetic polyneuropathy
  - o Autonomic neuropathy

- Focal Neuropathies & Multifocal Neuropathies
  - o Focal-limb neuropathy
  - o Cranial neuropathy
  - o Proximal-motor neuropathy (amyotrophy)
  - o Truncal radiculoneuropathy

Peripheral Neuropathy

Peripheral neuropathy affects 40-60% of diabetic patients. Incidence increases to

- 20% within 10 years of disease
- 50% after 20 years of disease

Symptoms of peripheral neuropathy are:

- o Numbness
- o Hyperasthesia
  - ◊ Burning
  - ◊ Tingling
- o Weakness
- o Autonomic changes- alterations in blood flow and sweating

Reasons for Foot Ulcers

- o Ulcer risk is high due to partial or complete foot insensitivity - unperceived injury due to Loss of Protective Sensation(LOPS)
- o Dry and cracked skin due to autonomic neuropathy.
- o Motor neuropathy causes imbalance in the muscles resulting in structural changes in the foot.

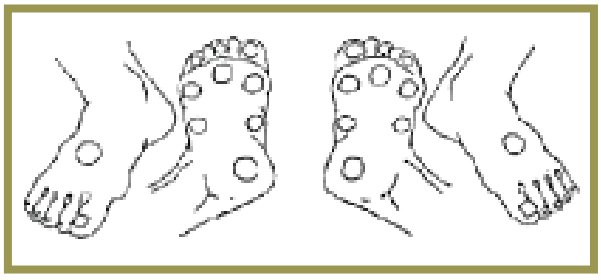
Neurological Assessment

- o 10-g monofilament + 1 of the following 4
  - ◊ Vibration using 128-Hz tuning fork
  - ◊ Pinprick sensation
  - ◊ Ankle reflexes
  - ◊ Vibration Perception Threshold

Monofilament Testing For Neuropathy

5.07 Curative Foot sense Monofilament applied to the planter surface of the foot to the point of buckling (10 Gms of pressure). Failure of patient to sense this pressure indicates Loss of Protective Sensation (LOPS)

Figure 16. Locations to test for neuropathy with monofilament



Prevention of foot ulcers and Amputations

- Recognize, treat, and protect deformities
  - o Prominent metatarsal heads
  - o Flat foot (loss of arches)
  - o Charcot's foot
  - o Calluses
- Use of appropriate foot wear, education, and callus removal are mandatory
- Encourage patients to take care of their feet
- Examine feet and footwear at every visit.
- Offer annual comprehensive foot examination for all patients with diabetes.
- More frequent examination will be required for those who have problems.
- The foot examination should include:
  - o Inspection (footwear, dry skin, callus, fissures, amputations, ulcers, deformities)
  - o Assessment of vascularity
    - ◊ Palpation of dorsalis pedis and posterior tibial pulses are most reliable
    - ◊ History of claudication may be absent due to neuropathy or patient not walking
    - ◊ Ankle-Brachial-Pressure Index (ABPI) <0.9. This may be elevated despite poor flow.
  - o Testing for loss of protective sensation (LOPS).
- Risk stratify based on findings (see Table 12)
  - o Risk factors that are used for risk stratification include:
    - ◊ Previous ulcer or amputation

    Sensory neuropathy

    Peripheral vascular disease

    Deformity or callus

o Risk stratification enables patients to be managed in a cost effective manner, with more frequent follow up and more aggressive management for patients with increased risk.

◊ Sensory neuropathy
◊ Peripheral vascular disease
◊ Deformity or callus

o Risk stratification enables patients to be managed in a cost effective manner, with more frequent follow up and more aggressive management for patients with increased risk.

Table 12. Risk Classification of diabetic foot

Risk Category	Definition	Recommended Action	Review
Low Risk Foot	No risk factors No previous ulceration	Foot care education Optimize metabolic control	Annually
High Risk Foot	One Risk Factor No previous ulcer	Special footwear Offer intervention Optimize control	Every 3-6 months
Super High Risk Foot	Previous Ulceration/ Amputation or Two of the Risk Factors	Special footwear Offer intervention Optimize control	Every 2-3 months
Foot Emergencies	Ulcer, injury, infection	Assess depth and VIP (Vascular, infection, pressure) Manage as appropriate	Every 1-2 months

Drug Treatment of Painful Peripheral Neuropathy

Burning pain

- Tricyclic antidepressants
- Capsaicin

Lancinating pain

- Carbamazepine
- Gabapentin
- Phenytoin
- Lidocaine, mexiletine

There is no proven role for any vitamins or lipoic acid in the management of diabetic neuropathy.

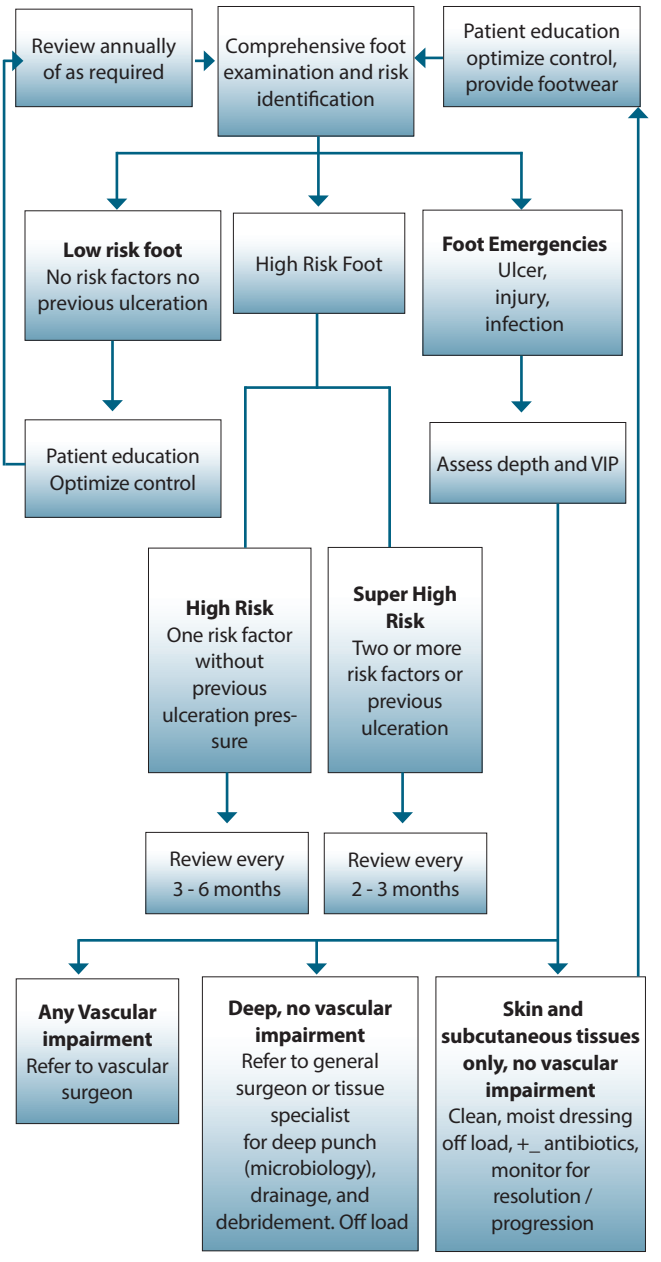
Other specific tests e.g. gastric emptying studies could be done

Treatment of DAN

Gastro paresis

- Prokinetic drugs
  - o Metoclopramide
  - o Domperidone
  - o Erythromycin
- NG drainage
- Intrajejunal feeding

Figure 17. Flowchart for Diabetic Foot Management



Manifestations of Diabetic Autonomic Neuropathy (DAN)

Figure 18. Symptoms and signs of DAN

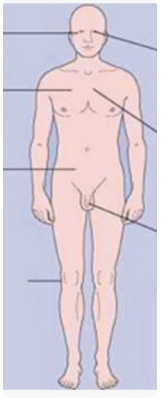


Table 13. Investigation of DAN

	Normal	Abnormal
Heart-rate variation during deep breathing Maximum-minimum (bpm)	>15	<10
Heart rate increase on standing15s after standing (bpm) 30:15 ratio	>15 >1.04	<12 <1.00
Heart rate change during Valsalva Maximum: minimum ratio	>1.21	<1.20
Postural fall in systolic BP 2 min after standing (mmHg)	<10	>30

Diarrhoea

- Codeine phosphate
- Loperamide
- Antibiotics for bacterial overgrowth
  - Oxytetracycline
  - Erythromycin
- Clonidine

Erectile Dysfunction

- Sildenafil or Tadalfil
- Intracavernosal or intraurethral Prostaglandin

Postural Hypotension

- Fludrocortisone

Hypertension and Diabetes

The UK Prospective Diabetes Study and the ALLHAT studies demonstrated significant benefits from intensive BP reduction in diabetic patients. In these large studies inexpensive Thiazide diuretics, ACE inhibitors, Beta blockers and Calcium Channel blockers were shown to be effective in lowering mean blood pressure in hypertensive patients with type 2 diabetes and in reducing the risk of:

- Any diabetes related endpoint
- Diabetes related deaths
- Micro vascular endpoints

Targets of blood pressure in diabetes

- SBP < 140
- And DBP <90
- The Cardiovascular risk doubles at increment of 20/10 beginning at a BP of 115/75. Therefore in those in whom a lower BP can be achieved easily could aim for a lower BP.

Management

Life style modifications

o Lose weight, if overweight (Target BMI 23)
o Limit alcohol intake
o Increase physical activity
o Reduce salt intake
o Stop smoking
o Limit intake of foods rich in fats and cholesterol

Factors affecting choice of antihypertensive drug

o The cardiovascular risk profile of the patient
o Coexisting disorders
o Target organ damage
o Interactions with other drugs used for concomitant conditions
o Tolerability of the drug
o Cost of the drug

Table 14. Antihypertensives and their usual doses

Class of drug	Example	Usual maintnance dose
Diuretics	Hydrochlorothiazide	12.5-25 mg daily
β-blockers	Atenolol	50-100 mg daily
Calcium channel blockers	Amlodipine Nifidipine SR	5-10 mg daily 20-40 mg b.d
ACE- inhibitors	Captopril Enalapril Ramipril Lisinopril	6.25 -50 mg b.d /t.d.s 5-20 mg daily/b.d 2.5-10 mg daily 5-20 mg daily
α-blockers	Prazocin Doxazosin	0.5- 6 mg t.d.s 1-8 mg daily
Angiotensin-II receptor blockers	Losartan Telmesartan Irbesartan	50-100 mg daily 40-80 mg daily 150-300 mg daily

Diuretics

- Act by decreasing blood volume and cardiac output
- Decrease peripheral resistance during chronic therapy
- Drugs of choice in elderly hypertensives

Drawbacks

Hypokalaemia, Hyponatraemia, Slightly elevates lipids, Hyperuricaemia (hence contraindicated in gout). Not safe in renal and hepatic insufficiency

Beta blockers

- Block β1 receptors on the heart
- Block β2 receptors on kidney and inhibit release of renin
- Decrease rate and force of contraction and thus reduce cardiac output
- Drugs of choice in patients with co-existent coronary heart disease

Drawbacks

Adverse effects: lethargy, impotence, bradycardia. Not safe in patients with co-existing asthma. Have an adverse effect on lipids. May induce hypoglycemic unawareness.

Calcium channel blockers

- Block entry of calcium through calcium channels
- Cause vasodilatation and reduce peripheral resistance
- Drugs of choice in elderly hypertensives and those with co-existing asthma
- Neutral effect on glucose and lipid levels

Drawbacks

Adverse effects: Flushing, headache, Pedal edema

ACE inhibitors

- Inhibit ACE and formation of angiotensin II and block its effects
- Drugs of choice in co-existent nephropathy and heart failure

Drawbacks

Adverse effect: dry cough, hypotension, angioedema, hyperkalaemia

Angiotensin II receptor blockers

- Block the angiotensin II receptor and inhibit effects of angiotensin II
- Drugs of choice in patients with co-existing nephropathy especially in those who cannot tolerate ACE inhibitor
- Many clinical trial results demonstrate that Fewer cases of new onset diabetes occur if an ACE or an ARB is included in therapy
- Diabetic patients, especially those with proteinuria, have a better outcome if an ACE or an ARB rather than a CCB is included in therapy

Drawbacks

Adverse effect: dry cough, hypotension, angioedema, hyperkalaemia

Alpha blockers

- Block α-1 receptors and cause vasodilatation
- Reduce peripheral resistance and venous return
- May be the preferred drug in prostatic hyperplasia
- Exert beneficial effects on lipids and insulin sensitivity

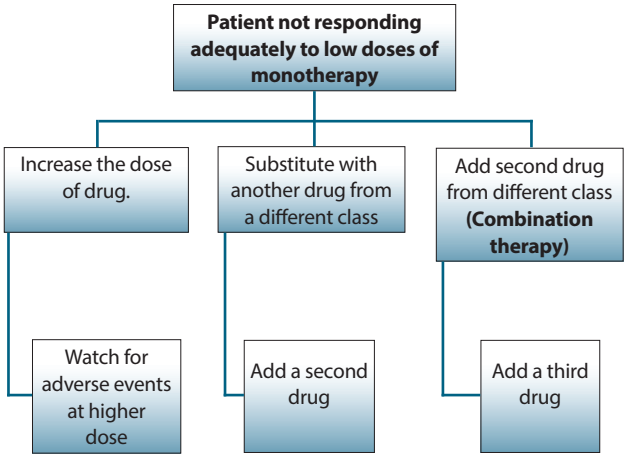
Drawbacks

Adverse effects: Postural hypotension

Combination therapy for hypertension

- With any single drug, not more than 25–50% of hypertensives achieve adequate blood pressure control
- Consider initiating therapy with 2 agents if BP 20/10 above target

Figure 19. Options for control of



Diabetes and Lipids

Types of Dyslipidaemia in diabetes

- Hypertriglyceridaemia
- Hypercholesterolaemia
- Post prandial hyperlipidaemia
- Low HDL
- Preponderance of small dense LDL
- Elevated Lipo protein(a) Lp(a)

High LDL - Cholesterol is strongly associated with atherosclerosis and CHD events and 10% increase in LDL level results in a 20 % increase in CHD risk. The small and dense LDL cholesterol is known to be highly atherogenic and is increased in patients with diabetes. At any level of cholesterol small dense LDL increase is a risk factor for CHD.

Hypertriglyceridaemia is also independently associated with increased risk of CHD events regardless of the cholesterol levels. Normal TG level is < 150 mg/dl. Very high TG (>1000 mg/dl/ 11.3 mmol/l) increases risk of pancreatitis. For each 1 mmol (88 mg / dl) increase in plasma TG, coronary disease risk for men increases by 32% and for women coronary disease risk increases by 76 %.

HDL cholesterol has a protective effect for risk of atherosclerosis and CHD. Low level (<40 mg/dl in men and < 50 mg/dl in women increases the CHD risk. HDL cholesterol tends to be low when TG is high. Combination of high TG and low HDL are a powerful risk factor for cardiac event or CHD death. HDL is lowered by smoking, obesity and physical inactivity.

Serum Lp (a) is an independent risk factor for CAD in diabetic patients. People with Lp (a) levels in the top third of baseline measurement are at about 70% increased risk of CHD compared with those in the bottom third.

Dyslipidaemia in South Asians

Diabetes enhances atherogenecity of the lipids. In a diabetic patient, controlling the lipids is even more important than controlling the glucose. South Asians have high incidence of atherogenic lipid profile (ALP) which comprises of high triglycerides, high small dense LDL, low HDL, high Apo B-100 and low Apo A. This ALP is associated with 3-4 fold increase in the risk of CAD

This atherogenic lipid profile is present in

- o Insulin resistant individuals
- o Diabetics

Lipid management for prevention of CVD

- All adults with an additional cardiovascular risk factor should be started on moderate or high intensity statin therapy.
- All patients > 40 years even without risk factors should be started on moderate intensity statin therapy
- There is no need to use specific targets and adjust when an appropriate statin regime is used
- Follow up lipid profile may be helpful in monitoring compliance and is not necessary once the patient is stable on therapy.

Table 15. Intensity of Statin Therapy

Moderate intensity	High intensity
Atorvastatin 10 -20mg	Atorvastatin 40 – 80 mg
Rosuvastatin 5- 10 mg	Rosuvastatin 20 – 40 mg
Simvastatin 20 – 40mg	
Pravastatin 40 – 80 mg	

Table 15. Intensity of Statin Therapy

	LDL	HDL	TG
Rosuvastatin10 mg	-52	+14	-10
Atorvastatin10 mg	-39	+6	-19
Simvastatin 20 mg	-38	+8	-12
Pravastatin 20 mg	-32	+2	-11
Fluvastatin 20 mg	-22	+3	-12

Special Situations:

- o In those >75 years: initiation of treatment should be individualized depending on benefits, side effects and drug interactions
- o Statin is contraindicated in pregnancy.
- o Combination therapy can be considered in:
  - ◊ High risk patients who have less than anticipated response to statins
  - ◊ Patients unable to tolerate less than recommended intensity of a statin
- o For patients with elevated triglyceride levels (150 mg/dL) and/or low HDL cholesterol (40 mg/dLfor men, 50 mg/dL for women) - Intensify lifestyle therapy and optimize glycemic control.

- For patients with fasting triglyceride levels >500 mg/dL (5.7 mmol/L), evaluate for secondary causes and consider medical therapy to reduce risk of pancreatitis.
- Lipid Management in Secondary prevention of CVD : High-intensity statin therapy

Antiplatelet Agents

Antiplatelet agents in Primary prevention

Consider aspirin therapy (75mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year CV risk > 10%). Initiation of Aspirin therapy should be individualized taking into account the age and bleeding risk for the patient, as the potential adverse effects from bleeding may likely offset the potential benefits.

Antiplatelet agents in Secondary prevention

- For patients with CVD and documented aspirin allergy or intolerance, clopidogrel (75 mg/day) should be used.
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome.

Figure 20. Indications for antiplatelet therapy

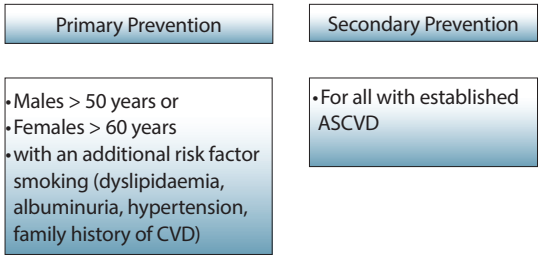
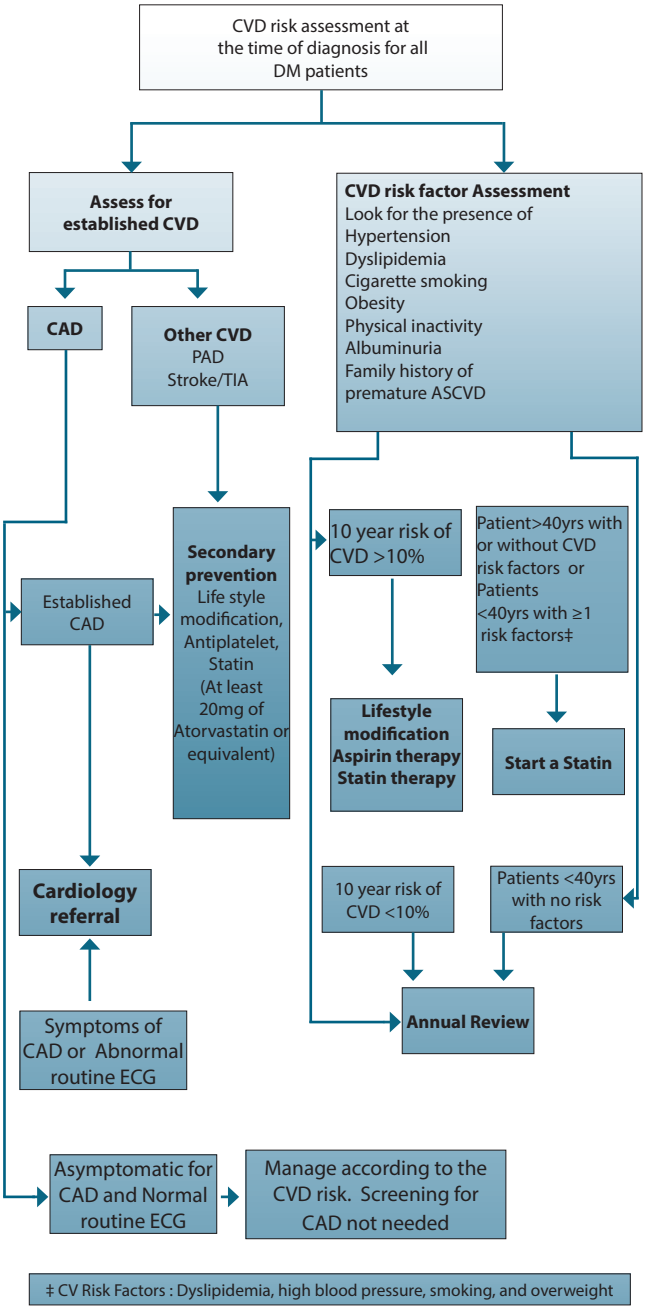


Figure 21. CV Risk factor assessment and management



Diabetes in Pregnancy

Prevalence of diabetes during pregnancy has been increasing. The majority is Gestational Diabetes Mellitus.The remainder is Type1 and Type 2.

Gestational Diabetes Mellitus(GDM)

Defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Definition applies whether treatment is insulin or diet only; and condition persists after pregnancy or not.

Significance of GDM

- Usually diagnosed between 24th and 28th week of pregnancy
- Insulin resistance typically ends after delivery but increased risk for type 2 diabetes later in life
- 2 in 3 chance of GDM occuring in future pregnancies

Metabolic physiology in Pregnancy

- Characterised by fasting hypoglycemia due to insulin- independent glucose uptake by placenta
- Post prandial hyperglycemia
- Carbohydrate intolerance due to diabetogenic placental hormones.
- Insulin resistance increases exponentially during 2nd trimester and levels off towards the end of 3rd trimester.

Effect of hyperglycemia on foetus

- Diabetic embryopathy: ancechephaly, micro-encephaly and congenital heart disease
- Spontaneous abortion
- Increased placental transfer of glucose causes
  - o Fetal hyperglycaemia
  - o Fetal hyperinsulinaemia
- Macrosomia-birth injury
- Neonatal Hypoglycemia
- Jaundice
- Hypocalcemia
- Polycythemia-higher risk for breathing problems and rapid heart rate
- HOCM
- Polihydramnios
- Sudden foetal death

Maternal Risks

- Pre-eclampsia
  - o Hypertension
  - o Proteinuria
  - o Edema
  - o Risk of placenta detaching from uterus
- Increased chance of cesarean delivery
  - o Harmful if infant is carried >40 weeks
  - o Large baby = increased risk of injury

Risk Factors for developing GDM

- Ethnic group a high prevalence of GDM
- Obesity (BMI>24)
- Diabetes in immediate family
- Previous unexplained still birth
- Age over 25yrs
- Previous baby > 3.5kg
- Random blood glucose > 7mmol/l (126mg/dl)
- Smoking
- Polyhydramnios

Who Should Be Tested?

- All Sri Lankan pregnant women should be screened because of the high prevalence
- BMI >24 before pregnancy
- Diabetes in first degree relative
- Previous unexplained still birth
- Previous baby > 3.5kg
- Glycosuria >1 time before 20 wks >2 time after 20 wks.
- Polyhydramnios
- 40 years who have not had a baby for 5 years
- RBS > 126 mg/dl at booking or at 24 -28 weeks

Screening Technique

- Assess risk at first visit (Booking): moderate to high risk should be retested with OGTT (Cost – effective)
- If negative; retest at 24-28 weeks
- There is disagreement on Cut offs and How to diagnose. ADA recommendations and Sri Lankan recommendations are given below

One step strategy

75g OGTT

- Laboratory based in seated posture
- Normal diet (150 g carbohydrate/day) for at least 3 days prior
- Overnight fast of 8 hours and not more than 14 hours

Table 17. One step strategy ADA recommended cut offs

	Plasma glucose cut offs
Fasting	≥5.1 mmol/l (92 mg/dl)
1h	≥10.0 mmol/l (180mg/dl)
2h	≥8.5 mmol/l (153mg/dl)

Two- step strategy

Step 1.

Initial screening– PG 1hour after 50 mg oral glucose(non fasting) If PG ≥140 mg/dl (7.8 mmol/l) or **130 mg/dl(7.2) in high risk populations ; proceed to Step2.** Perform 100g OGTT in fasting state

Table 18. Cut offs for 100g OGTT

	Carpentre/Coustan	National Diabetes Data Group
Fasting	95 mg/dL (5.3mmol/L)	105mg/dL L (5.8mmol/L)
1h	180 mg/dL L (10.0mmol/L)	190 mg/dL L (10.6mmol/L)
2h	155 mg/dL L (8.6mmol/L)	165 mg/dL L (9.2mmol/L)
3h	140 mg/dL L (7.8mmol/L)	145 mg/dL L (8.0mmol/L)

Sri Lankan recommendation
Initial screening at ANC booking:
Do a 2 hour postprandial PG
(after a standard Sri Lankan meal). If this >120 mg/dl proceed to 75g OGTT in first trimester to detect previously undiagnosed T2DM

Glycemic Targets in Pregnancy

Table 19. Maternal capillary glucose targets for mothers with GDM

Pre prandial	≤95 mg/dL	≤5.3 mmol/L
One hour post prandial	≤140 mg/dL	≤7.8 mmol/L
Two hour post prandial	≤120 mg/dL	≤6.7 mmol/L

For women with pre-existing Type 1 or Type 2 Diabetes optimal glucose targets are given in Table 20. As the hypoglycaemia risk is higher these should be achieved without causing excessive hypoglycaemia.

Table 20. Optimal maternal glucose targets in mothers with pre-existing DM.

Premeal, bed time and over night	60-99 mg/dL (3.3-5.4 mmol/L)
Peak post prandial glucose	100-129mg/dL (5.4- 7.1 mmol/L)
HbA1C	<6.0%

Monitoring

- Self monitoring of blood glucose at home is ideal. Monitoring pre and post meal blood glucose is recommended.
- If these targets cannot be achieved with out significant hypoglycemia slightly higher targets can be considered.
- If SMBG not possible intermittent monitoring of serial blood sugar profile in the hospital should be done.
- Due to increased red cell turn over, HbA1C levels fall during pregnancy.
- HbA1C should be used as a secondary measure during pregnancy, next to SMBG and repeated monthly

Management of GDM

- Treatment starts with medical nutrition therapy, exercise and glucose monitoring, aiming for targets.
- About 70-80% of women can control GDM with lifestyle modification alone.
- Insulin is the recommended treatment for GDM
- Randomised controlled trials show efficacy and short-term safety of Glyburide and Metformin Both agents cross the placenta and long-term safety data are not available.

Management of Pre-Gestational DM in Pregnancy

- Insulin is the preferred agent for management (because of the lack of long term safety data for other agents)
- Frequent titration of insulin dose is required to match changing requirements.
- In 1st trimester, required daily insulin dose often decreases.
- Rapidly increasing insulin resistance in 2nd trimester requires weekly or biweekly increase in insulin dose.
- Of the total daily insulin requirement, a small proportion is given as basal insulin and greater proportion as prandial insulin.
- Women with Type 1 DM have increased risk of hypoglycaemia during 1st trimester. Frequent hypoglycaemia can result in intra uterine growth retardation
- Retinopathy can worsen in the setting of sudden tightening of glycaemic control.
- Insulin resistance drops with the delivery of placenta, and much less insulin is required in post partum period

Anti Hypertensive Drugs in Pregnancy

- In pregnancy complicated by diabetes and chronic hypertension, controlling blood pressure within target range is important as it contributes to long-term maternal health.
- Lower blood pressure may be associated with impaired foetal growth
- During pregnancy ACEI and ARB blockers are contra indicated as foetal damage can occur.

- Effective and safe antihypertensives during pregnancy.
    - Methyldopa
    - Labetalol
    - Diltiazem
    - Clonidine
    - prazocin

Table 21. Target BP in pregnancy

Systolic BP	110-129 mmHg
Diastolic BP	65-79 mmHg

Postpartum Care

- Educate weight and diet management skills during breast feeding period to prevent development of Type 2 DM
- Women with GDM should be screened for undiagnosed or persistence of Type 2 DM
    - Screening Frequency: Initial screening at 6-12 weeks postpartum using non-pregnancy criteria
    - Every 1-3 years thereafter.
- Both intense lifestyle modification and metformin delay or prevent developing diabetes in women with history of GDM and impaired glucose tolerance.
- Contraception options should be reviewed at regular intervals.

Long Term Considerations

- Increased risk of Type 2 DM after pregnancy-obesity and factors that lead to insulin resistance enhance risk
- Offspring of women with GDM at increased risk of
    - Obesity
    - Glucose intolerance
    - Diabetes in late adolescence & young adult hood

Emergencies In Diabetes Hypoglycemia

Hypoglycemia is common in individuals with type1 and insulin treated type 2 diabetes, At-risk individuals must be asked about symptomatic and asymptomatic hypoglycemia at each visit Neural tissue is dependent on the continuous supply of glucose. Interruption of glucose delivery for more than a few minutes leads to central nervous system dysfunction, impaired cognition and eventually coma.

- Initial response (at plasma glucose 3.6-3.8 mmol/l) to hypoglycaemia is release of counter-regulatory hormones (Glucagon, Epinephrine)
- Autonomic symptoms develop at a glucose level of around 3.2 mmol/l.
- Cognitive function starts to decline at around 3mmol/l.
- Activation of sympathetic-adrenal system occurs in those who retain awareness of hypoglycaemia before significant cerebral dysfunction occurs and alert them to take appropriate corrective measures.
- Inability to recognise impending hypoglycaemia (hypoglycaemic unawareness) occurs as the sympatho-adrenal activation occurs at a lower glucose level than that for cognitive dysfunction, which leads to serious episodes of hypoglycaemia.
- Factors leading to impaired physiological defence to hypoglycaemia are
    - Increased duration of diabetes
    - Very tight glycemic control
    - β-blockers
    - Extremes of age
    - Sleep
    - Alcohol

Definition:

A clinical state with low plasma glucose concentration (Usually <2.7 mmol/l or 50 mg/dl), usually associated with signs and symptoms.

Table 22. Symptoms and signs of hypoglycemia

Autonomic hyperactivity	Neuroglycopenia
Giddiness	Blurred vision
Weakness	Diplopia
Pallor	Lethargy
Tremulousness	Headache
Nervousness	Inability to concentrate
Anxiety	Loss of memory
Irritability	Confusion
Hunger	Inappropriate affect
Palpitation	Bizarre behaviour
diaphoresis	Motor dysfunction
	Sensory dysfunction
	Paralysis
	Seizure
	Coma

Individuals vary on their threshold value for symptoms and potential harm. Even within the individuals the level could vary after recent hypoglycemia. An alert for hypoglycemia threshold is 70 mg/dl (3.8 mmol/L)

Factors Causing or Predisposing Hypoglycaemia

Excessive insulin levels

- Excessive dosage- error by patient/doctor, poor matching to life style and needs, deliberate over dosage
- Increased insulin bioavailability-exercise, changing to human insulin, renal failure, and Partial β-cell recovery in honeymoon period in type 1 patients.

Increased insulin sensitivity

- Counter regulatory hormone deficiency- Addison's, Hypopituitarism, weight loss, physical training, postpartum
- Inadequate carbohydrate intake- missed/ small/ delayed meals, eating disorders/ vomiting, gastro paresis, breast feeding.

Other factors

- Exercise- Acute-accelerated absorption, Delayed- glycogen depletion
- Alcohol- inhibits hepatic glucose production
- Drugs-sulphonylureas (especially long acting ones), drug interaction : salicilate, sulphonamide
- Hypoglycemia unawareness and hypoglycemia associated sympathoadrenal failure (HASF)
  In some individuals the first sign of hypoglycemia is confusion. This occurs due to sympathoadrenal failure which is usually due to a recent major hypoglycemia. Avoidance of hypoglycemia for a period improves the sympathoadrenal response to hypoglycemia.
- Hypoglycemia is more likely in elderly and those with multiple comorbidities. A major hypoglycemia is associated with higher mortality risk in individuals. This high risk for mortality is not caused by hypoglycemia, but hypoglycemia is an indicator of either major organ malfunction and higher mortality risk.

Treatment of Hypoglycemia in Diabetes

Emergency Management:

- Establish diagnosis of hypoglycemia using a capillary sample
- Glucose (15-20g) is the preferred treatment for the conscious individual with hypoglycemia; although any form of carbohydrate that contains glucose can be used. After 15 minutes if capillary glucose shows continued hypoglycemia the treatment should be repeated, once the capillary glucose returns to normal, a meal or snack should be taken to prevent recurrence of hypoglycemia.
- Added fat in the diet may retard or even may prolong acute hypoglycemia.
- If oral administration not possible; IM Glucagon 0.5-1mg- can be administered by relative/ paramedic/ nursing staff.
- If there is no recovery with in 10 min, IV glucose must be given.
- After recovery oral carbohydrate should be taken.

Or

- 50% Dextrose 20-30 ml into a large vein, with a saline flush to reduce risk of thrombophlebitis.
- Failure to recover with in 60 min indicates possible brain damage. IV infusion of 10% dextrose should be started to maintain blood glucose around 10-11 mmol/l.
- Dexamethasone should be considered.
- Some patients may fully recover after 48 hours of coma.
- Insulin treated patients who are stable for > 1 hour after treatment can be discharged.
- Patients on long acting sulphonylurea or insulin need glucose monitoring for 24 hours.
- Insulin treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be advised to increase their glycemic target at least for several weeks in order to partially reverse hypoglycemia awareness and reduce risk of further episodes.
- In diabetic patients with type 2 diabetes, hypoglycemia is associated with greater risk for dementia.

Strategies to Prevent Hypoglycemia

- Education
  - Identifying causative factors e.g. delayed meal, too much of insulin, illness
  - Education on hypoglycemia and correction strategies
  - Understanding on how the drugs work
  - Learning to use insulin physiologically

- Dietary Changes
  - Consistent diet plans
  - Snacks (in between meals and late night snack)
  - Using prandial insulins coupled with meals
- Exercise Management
  - Pre exercise carbohydrate
  - Carrying snacks when going for a strenuous activity
- Medication Adjustement
  - Insulin: dose, type of insulin, and frequency.
  - Sulfonyureas: Adjustment of dose, and type of Sulfonylurea
  - Option of non-hypoglycemia causing agents
- Glucose Monitoring
- Target Adjustments
  - Individualized targets to prevent hypoglycemia

Diabetic Ketoacidosis

Diabetic Ketoacidosis (DKA) is a prominent cause of morbidity and mortality in Type 1 DM. DKA can occur in Type 2 DM during severe intercurrent illness.

Cardinal biochemical features of Diabetic Ketoacidosis are

- Hyperketonaemia (urine Ketone ++ or plasma ketone +)
- Metabolic acidosis (bicarbonate<15 mmol/L)
- Hyperglycaemia (plasma glucose >250 mg/dl)

Pathogenesis

- Absolute/ relative deficiency of insulin
- Raised catabolic counter regulatory hormones (glucagon, catecholamines, cortisol, growth hormone)
- Hepatic overproduction of glucose and Ketones
- Free fatty acids are shunted into ketone body formation due to lack of insulin; the rate of formation exceeds the capacity for their peripheral utilization and renal excretion.
- This results in:
  - Metabolic acidosis
  - Ketogenesis
  - Fluid and electrolyte depletion: Approximate losses due to major osmotic diuresis are
    - Water 5Litres
    - Na^+ 500 mmol, Cl^- 350 mmol
    - K^+ 300-1000 mmol
    - $Ca2^+$ 50-100 mmol
- With progressive dehydration, acidosis, hyper-osmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose

Clinical Features

- Polyuria, nocturia, thirst
- Weight loss
- Weakness
- Blurred vision
- Acidotic respiration (air hunger)
- Acetone smell in breath (nail varnish remover)
- Abdominal pain, leg cramps
- Nausea, vomiting
- Confusion, drowsiness, Coma

  - Early manifestations are mild and include vomit ing, polyuria, and dehydration
  - More severe cases include Kussmaul respirations, odor of acetone on the breath
  - Abdominal pain or rigidity may be present and mimic acute appendicitis or pancreatitis
  - Cerebral obtundation and coma ultimately ensue
  - Classic presentation of diabetes in children is a history of polyuria, polydipsia, polyphagia, and weight loss, usually for up to one month

Precipitating factors

- Infections
- New Type 1 DM
- Treatment errors (too little or no insulin)
- Other stressful conditions (Stroke, Myocardial Infarction, Trauma, drugs)

DKA must be differentiated from acidosis and coma due to other causes such as hypoglycemia, uremia, gastroenteritis with metabolic acidosis, lactic acidosis, salicylate intoxication, encephalitis.

Clinical Assessment

- History
  - Precipitating cause?
  - Current treatment problems, Medication
- Examination
  - Dehydration
  - Hypotension
  - Ketosis (acetone breath)
  - Precipitating cause(e.g. pneumonia, urinary infection)
  - Diabetic complications (cardiovascular disease)
  - Hypothermia

- Gastric stasis

- Bedside investigations
  - Blood glucose
  - Urinary & plasma Ketones
- Laboratory investigations
  - Glucose, Na, K, Cl, HCO3, urea, Creatinine
  - Osmolality, Ketone bodies
  - Anion gap, lactate
  - Arterial blood gas
  - ECG
  - FBC
  - CXR
  - Cultures

Pitfalls

- Smell of acetone may not be apparent
- Fever may be absent
- Neutrophil count- may be non specifically raised
- K+ may be temporarily raised despite severe total body loss (acidosis causes K +efflux from cells)
- Na+ May be falsely lowered by high lipid and glucose
- Creatinine may be falsely elevated (assay interference by ketones)
- Transaminases and Creatinine Kinase may be non specifically raised

Treatment of Diabetic Ketoacidosis
Goals of Treatment

- Correction of fluid loss with intravenous fluids
- Initiation of insulin therapy to correct catabolism, acidosis and hyperglycemia.
- Correction of hyperglycemia with insulin
- Correction of electrolyte disturbances, particularly potassium loss
- Treatment of concurrent infection, if present

Intravenous Fluids and Electrolytes

- Volumes: 1L/hour x 3, thereafter adjusted according to need Usually 4-6 L in first 24 hours

- Fluids:
  - Isotonic saline
  - Hypotonic saline if Na>150 mmol/L
  - 5% Dextrose 1L 4-6 hourly when blood glucose has fallen to 10 mmol/L or 180 mg/dl (This enables more insulin to be used to slowly correct the acidosis)

- Sodium bicarbonate if pH <7.0
- Potassium:
  - No K in first Litre
  - Thereafter <3.5: 40 mmol, 3.5-5.5: 20 mmol
  - Serum K+ is often elevated, though total body K+ is depleted.
  - K+ is started early as resolution of acidosis and the administration of insulin will cause a decrease in serum K+.
- Sodium:
  - "Pseudohyponatremia" is often present
  - Expect that the Na level will rise during treatment
  - Corrected Na = Measured Na + {(glucose - 100) x 0.016}.
  - If Na does not rise, true hyponatraemia may be present (possibly increasing cerebral edema risk) and should be treated.

Bicarbonate is almost never administered

- Bicarbonate administration leads to increased cerebral acidosis.
- Indications for bicarbonate administration include severe acidosis leading to cardio respiratory compromise.

Insulin

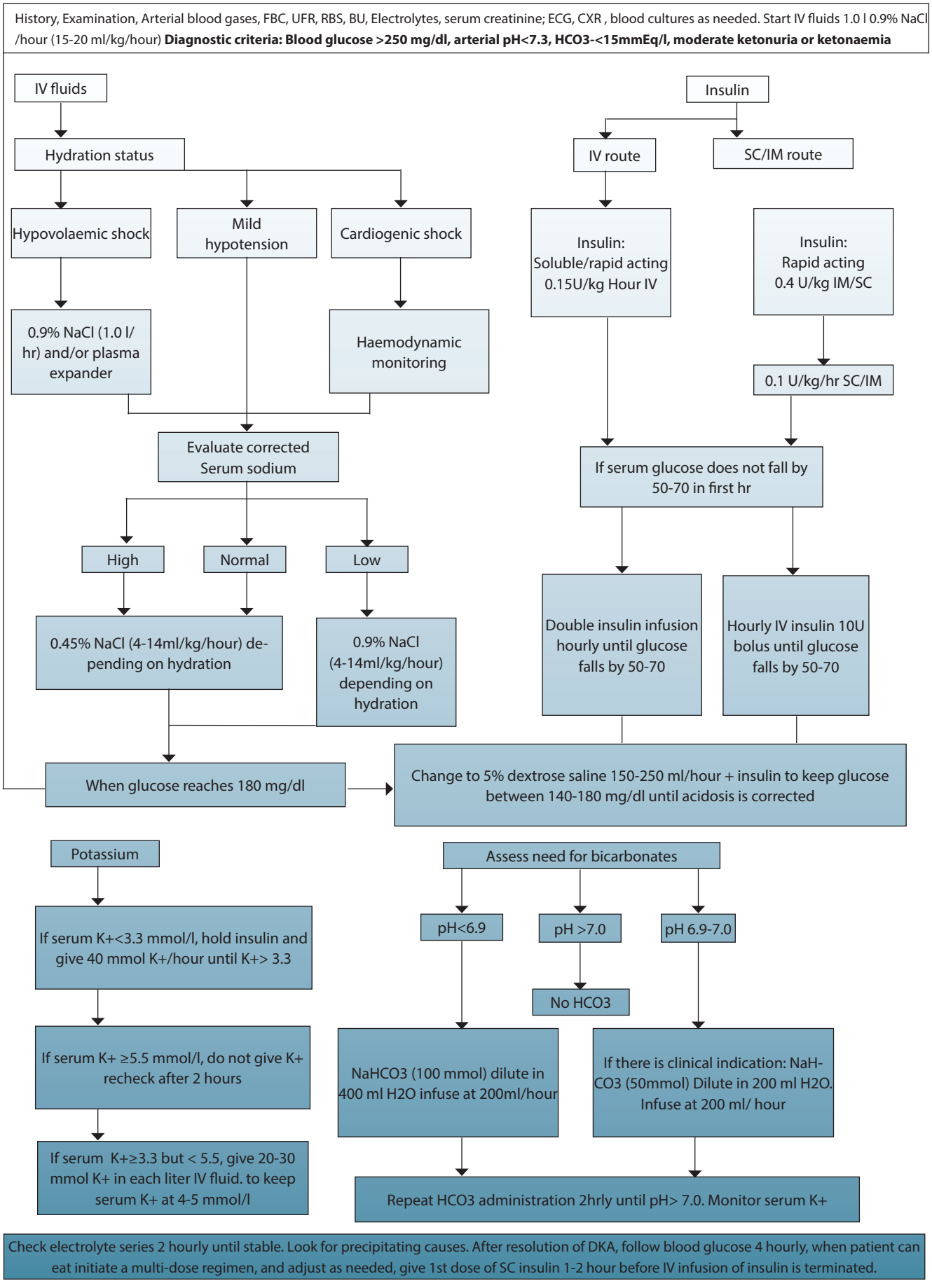
- Continuous IV infusion:
  - There is no need to give a major correcting bolus. Slow low dose is the best for correction of acidosis.
  - 5-10 U/Hour until blood glucose <10 mmol/L (0.1 U/kg/hour)
  - Thereafter 1-4 U/Hour to maintain glucose 5-10 mmol/L until ketoacidosis is corrected

or

- Intramuscular or s.c. injections:
  - 20 U IM or 20 U rapid acting insulin Sc
  - Then 5-10 U/Hour until blood glucose has fallen to 10- 15 mmol/L
  - In severe acidosis peripheral circulation may be shout down and insulin may not be absorbed from the periphery

- Continuous infusion of low-dose insulin IV (~ 0.1 U/kg/hr) is effective, simple, and physiologically sound
- Goal is to slowly decrease serum glucose (< 100 mg/dl/hr)
- Insulin is used to treat acidosis, not hyperglycemia
- Insulin should never be stopped if ongoing acidosis persistsusion.

Figure 22. Protocol for management of patients with DKA



- Frequent laboratory and blood gas analyses are obtained to ensure ongoing resolution of metabolic acidosis.
- When the acidosis is corrected, the continuous insulin infusion may be discontinued and subcutaneous insulin initiated.
- With the regimen, DKA is usually fully corrected in 36 to 48 hours.

Other Measures

- Meticulous clinical and biochemical records
- Search for and treat precipitating causes (e.g. infection, myocardial infarction)
- Hypotension usually responds to adequate fluid replacement
- Nasogastric tube if conscious level is impaired
- Urinary catheter if conscious level is impaired or no urine passed in 4 hours of starting therapy
- Continuous ECG monitoring

Complications of diabetic Ketoacidosis

- Cerebral oedema
- Adult respiratory distress syndrome
- Thromboembolism
- Rhabdomyolysis
- Cardiac arrhythmia

Non-Alcoholic Fatty Liver Disease In Diabetes

Non-Alcoholic Fatty Liver Disease (NAFLD)

- A syndrome with liver pathology that resembles alcoholic hepatitis, in non-alcoholics.
- It is part of a spectrum from steatosis (Non Alcoholic Fatty Liver), Non Alcoholic Steato Hepatitis to cirrhosis.
- Can lead to end stage liver disease (in 20%) and all the complications of cirrhosis including hepatocellular carcinoma.
- Co-exist with and may worsen other liver diseases.
- Patients with NAFLD have increased overall mortality compared to aged matched individuals.
- It is very common and rising in prevalence in Asia-pacific region due to change in traditional lifestyles.

Definitions

Table 23. Definitions in NAFLD

Nonalcoholic fatty liver disease(NAFLD)	Encompases the entire spectrum of liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis
Nonalhocolic fatty liver (NAFL)	Presence of hepatic steatosis with no evidence of hepatocellular injury in theform of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal.
Nonalcoholic steatohepatitis	Presence of hepatic steatosis and inflammation with hepatocyte injury(ballooning) with or without fibrosis. This can progress to cirrhosis, and liver failure, and rarely liver cancer
NASH cirrhosis	Presence of cirrhosis withcurrent or previous histological evidence of steatosis orsteatohepatitis
Cryptogenic cirrhosis	Presence of cirrhosis with no obviousetiology. Patients with cryptogenic cirrhosis have many metabolic risk factors such as obesity and metabolic syndrome.

Risk factors of NAFLD

- Almost invariable association with Insulin resistance (>98%). So it is considered as hepatic manifestation of metabolic syndrome.
- >70% of patients with NAFLD have family history of Type 2 DM and/or IGT or Type 2 DM.
- Excessive Body Mass Index (BMI) and visceral obesity are well-recognized risk factors for NAFLD.
- High serum Triglyceride and low HDL levels are common in individuals with NAFLD.
- Increasing age, male gender and certain ethnic origins have higher risk of NAFLD (non- Hispanic blacks < non- Hispanic whites < Hispanics).

Table 21. Target BP in pregnancy

Conditions with established associations

- Obesity
- Type 2 diabetes
- Dyslipidaemia
- Metabolic syndrome

Conditions with emerging associations

- Polycycstic ovary syndrome
- Hypothyroidism
- Obstructive sleep apnoea
- Hypopituitarism
- Hypogonadism
- Pancreato duodenal resection

Table 25. Common causes of secondary hepatic cirrhosis

macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C
- Wilson' disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinaemia
- Medications (eg.,amiodaron, methotrexate,tamoxifen, corticosteroids)

microvesicular steatosis

- Reye's syndrome
- Medications (valproate, anti retroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (eg.,LCAT deficiency, cholesterol ester storage disease, Wolman disease)

When to Suspect NAFLD?

- Unexplained elevation of liver enzymes (ALT ,AST ,GGT & ALP)
- Unexplained Hepatomegaly
- Imaging changes of the liver
- Type 2 DM
- F/H of Type 2 DM, hyperlipidaemia & fatty liver
- Weight gain, expanding waistline

Diagnosis of NAFLD

Diagnosis of NAFLD requires

1. There is hepatic steatosis by imaging or histology
2. There is no significant alcohol consumption. (<21drinks on average per week in men and <14drinks in women. 1 alcoholic drink= 10 g of alcohol per one drink unit.)
3. There are no coexisting causes for chronic liver disease.

Evaluation

- When evaluating a patient with suspected NAFLD it is essential to exclude competing aetiologies for steatosis and coexisting common chronic liver disease, Eg., Haemochromatosis, autoimmune liver disease, chronic viral hepatitis and Wilson's disease.
- Persistently elevated serum feritin and increased iron saturation and homozygote or heteroaygote C28Y HFE mutations may warrant a liver biopsy.
- High titres of serum auto antibodies and other features of autoimmune liver disease (very high ALT/AST, high globulin levels) should prompt a more complete work-up for autoimmune liver disease.
- Biochemistry and imaging (US, CT, MRI)do not reliably assess statohepatitis and fibrosis.
- Serum CK18 (cytokeratin) is a promising maker for identifying steatohepatitis,

NAFLD Fibrosis Score

NAFLD fibrosis score is a clinically useful tool for identifying patients with higher chances of having bridging fibrosis and / or cirrhosis. Calculated using published formula. (http//nafldscore.com)

- BMI
- Hypreglycemia
- Platelet count
- Serum albumin
- AST: ALT >1

ELF (enhanced liver fibrosis) panel

Plasma levels of matrix turnover proteins: hyaluronic acid, TIMP-1 and PIIINP

Transient Elastography

Measures liver stiffness non- invasively. Successfully identifies advanced fibrosis in patients with hepatitis B, and C. Failure rate is higher in obese.

Liver Biopsy

- Liver biopsy is the most reliable test to diagnose steatohepatitis and fibrosis.
- It is considered in patients with increased risk to have steatohepatitis and advanced fibrosis
- Liver biopsy is limited by cost, sampling error, and procedure related morbidity and mortality.
- Presence of metabolic syndrome is a strong predictor for presence of steatohepatitis in patients with NAFLD. Its presence can be used to target patients for liver biopsy.
- Liver biopsy should be considered in patients with suspected NAFLD in whom other aetiologies for hepatic steatosis and chronic liver disease cannot be excluded without biopsy.

Approaches to Management

- Management of NAFLD consist of treating liver disease as well as associated metabolic comorbidities.
- Educate on beneficial changes to correct insulin resistance. (physical activity, Diet) - proven benefit.
- Optimize blood glucose control
- Treat lipid disorders
- Weight reduction

Diet

- Hypocaloric diet
- Aim is slow, gradual weight loss. Rapid wt loss is associated with fibrosis.Loss of 3-5%of body weight improves steatosis. Greater weight loss , up to 10% may be needed to improve necrosis.
- Reduce central obesity.

Exercise

- Exercise alone in adults with NAFLD may reduce hepatic steatosis, but its effect on other aspects of histology remains unknown.

Other Measures

- Avoid alcohol
- Avoid unnecessary medications including herbal products
- Statins can be used to treat dyslipidaemia. Need careful monitoring of AST/ALT if Statins or Fibrates are used.

Drug Treatment

Insulin sensitizers:

- Thiazolidinediones: Pioglitazone may improve both ALT and histology and can be used to treat patients with biopsy proven NASH, but leads to weigh gain. Long-term safety and efficacy is not known.
- Metformin has no significant effect on liver histology (ina single multi center RCT) and is not recommended as a specific treatment for NASH.

Anti – Oxidants:

- Vitamin E 800 IU/day improves liver histology and is considered as a first line drug in non diabetic patients with NASH.
- Its usefulness in diabetes, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis is not established.

Others

- Ursodeoxycholic acid is not recommended for treatment of NAFLD or NASHas it does not improve liver histology.
- Omega -3fatty acids may be used to treat hypretriglyceridaemia, and its usefulness in NAFLD is not proven..
- Hepatic steatosis associated with total parenetral nutrition can be prevented with supplemental of choline.
- Gastric bypass may be considered in those with BMI> 35 and leads to improvement in hepatic steatosis.
- Liver transplantation is indicated in appropriate candidates with advanced cirrhosis caused by NASH.

Difficult to Control Diabetes

Brittle diabetes
is a term used to describe metabolic instability sufficient to disrupt the patient's life, whatever the cause is. Some diabetic patients have marked fluctuations in blood glucose with hyper and hypoglycemia. This usually occurs in Type 1 DM but also in long standing T2DM. Their high variations in blood sugar cannot be easily explained. It is important to review the patient physically, bio chemically and psychologically to determine the cause of 'brittleness'. Metabolic instability could be predominantly severe hyperglycaemia or hypoglycaemia or mixture of both. The best approach to brittle diabetes is to look for causes that may lead to wide swings in plasma glucose concentrations.

Insulin Resistance

Requirement of insulin dose of more than 2.0 U/Kg / day indicate a significant underlying problem in a non obese adult patient. This could be due to apparent or genuine insulin resistance.

Puberty is an insulin resistant state mainly because of increased Growth Hormone secretion at this time. In children with type 1 diabetes puberty is often marked by a rise in glycemia and increased insulin requirement.

Obesity
Insulin sensitivity is impaired in obesity and physical inactivity. Excessive insulin dosage per se can lead to worsening obesity, and insulin resistance with poor metabolic control.

Infection that is serious enough to cause fever often induces acute hyperglycaemia and an increase in insulin requirement. Chronic infections like tuberculosis, occult infection in the diabetic foot or abscesses associated with colon and kidney can some times result in insulin resistance leading to brittle diabetes.

Endocrine disorders causing excessive secretion of counter regulatory hormones (acromegaly, Cushing's syndrome, Thyrotoxicosis, and Pheochromocytoma) may not be clinically obvious in a diabetic patient with worsening hyperglycaemia.

Drugs such as glucocorticoids and β-agonist can cause insulin resistance

Apparent Insulin Resistance
Apparent insulin resistance is commonly due to the patient deliberately taking less insulin or not taking insulin altogether, to prevent obesity or to escape difficult situations at home or work.

Eating disorders like Anorexia nervosa or Bulimia and related problems like self induced vomiting, laxative and diuretic abuse may be present.

Narcotic drug addiction can lead to brittle diabetes by causing metabolic instability especially during the stressful period of drug withdrawal, when hyperglycaemia and ketoacidosis are common.

Problems with insulin absorption, distribution or clearance are rare and proven in exceptionally rare instances. Lipohypertrophy, induced by repeated injections in the same site can impair subcutaneous absorption of insulin, but the effect is small.

Insulin antibodies could develop for impure insulin, which can bind insulin and form immune complexes and reduce the circulating levels. With the wide spread use of purified and particularly human insulin this problem is now disappearing. Insulin receptor and post receptor defects have been attributed to severe insulin resistance in a few patients.

Somogyi phenomenon is a dramatic increase in early morning glycaemia which may be related to a rise in counter regulatory hormones during the night. This is initiated by excessive dose of insulin for the caloric intake or activity pattern there by causing nocturnal hypoglycaemia. The physiological response to hypoglycaemia is the secretion of counter regulatory hormones which in turn induce hyperglycaemia. Falling levels of circulating insulin also causes rising blood sugars in the morning.(Dawn phenomenon) Changing the insulin dosage or regimen should readily correct metabolic instability.

Table 26. Causes of severe hyperglycaemia in spite of insulin treatment

Table 26. Causes of severe hyperglycaemia

Errors in injecting insulin

- Inappropriate dosage or timing
- Air drawn up in the syringe
- Poor injection technique
- Wrong insulin dos

Defects in insulin pharmacokinetics (All are very are)

- Binding insulin antibodies
- Excessive insulin clearence
- Genetic defects in or beyond insulin receptor

Defects in insulin action

- Insulin receptor defects-rare
- Post receptor defects- Obesity,
- Type 2 diabetes
- Drugs – Glucocorticoids, Beta- agonists, narcotics
- Counter regulatory hormone disturbance- Puberty (increased GH secretion)
- -Dawn phenomenon (Somogyi effect)
- Endocrine hypersecretion syndromes- Cushing's, Acromegaly,Hyperthyroidism, Pheochromocytoma Infections –TB, abscesses, wound infection

Recurrent Hypoglycaemia

15 – 20% of patients with brittle diabetes present with recurrent hypoglycaemia.

Causes of Recurrent Hypoglycemia

- 'Hypoglycemia associated sympathoadrenal failure (HASF)': In individuals with very strict glycaemic control, decreased symptom perception of hypoglycaemia occurs because of reduced counter regulatory hormone response.

o Most common cause is recent antecedent hypoglycaemia.

o Diabetic autonomic neuropathy could cause or contribute to hypoglycaemic unawareness through complex mechanisms.

o Factors leading to impaired physiological defence to hypoglycaemia:

  - Increased duration of diabetes (autonomic failure)
  - Very tight glycemic control
  - β-blockers
  - Extremes of age
  - Sleep
  - Alcohol

- Gastro paresis is a cause of brittle diabetes which is often overlooked. Insulin therapy is designed to match the absorption of food to the absorption of insulin. Any mismatch between these two factors will lead to wide swings in blood glucose between hyperglycaemia and hypoglycaemia. Treatment of gastro paresis often results in improvement in blood sugar control.
- Vomiting of any cause, malabsorption, notably coeliac disease which can be associated with type 1 diabetes can cause severe hypoglycaemia.
- Hypoglycaemia can be profound following pancreatectomy or chronic pancreatitis as loss of α cells impair the counter regulatory glucagon response.
- Advanced renal failure reduces clearance of insulin through kidneys and hypoglycaemia can occur if insulin dosage is not reduced.
- Endocrine gland failure (Hypopituitarism, hypoadrenalism, hypothyroidism) resulting in hormone deficiency also can cause hypoglycaemia.
- Like hyperglycaemia, hypoglycaemia can be deliberately induced by surreptitious intake of insulin, avoidance of food, or excessive and inappropriate exercise. There could be underlying psychiatric or psychological problems.

Table 27. Causes of recurrent hypoglycemia

Impaired awareness of warning symptoms- beta blocker treatment
Over treatment with insulin
Adrenal Insufficiency
Hypopituitarism
Chronic vomiting
Diabetic gastro paresis
Malabsorption
Loss of glucagon secretion (pancreatectomy, chronic pancreatitis)
Alcohol abuse

Mixed Glycaemic Instability

25% of all patients with brittle diabetes manifest mixed metabolic instability. Most patients have no apparent cause though hypoadrenalism, chronic pancreatitis, pancreatectomy or recurrent infections like sinusitis, tonsillitis can cause a mixed metabolic instability. Most often mixed instability is due to inappropriate insulin regimen or life style. Idiopathic brittle diabetes refers to cases in which glycemic instability has no obvious cause.

Management

- First step in evaluation of patients with brittle diabetes is checking the patient's diabetic education, treatment regimen, injection techniques and activity pattern. Frequent monitoring of blood glucose especially in the early hours of the day will help establish possible dawn phenomenon or Somogyi phenomenon.
- Rise in insulin level and corresponding fall in blood sugar level can be determined following a test dose of insulin under controlled conditions. All patients with apparently unexplained insulin resistance have normal insulin and glucose profiles after injection of insulin under controlled conditions indicating non-compliance is responsible.
- Continuous glucose monitoring can be useful in this group of patients, particularly in those with nocturnal hypoglycemia.
- Investigations to exclude infections (WBC, ESR, CRP, UFR, &culture), Narcotic drug addiction (Urinary screen for narcotic drugs), and endocrine disorders could be under taken whenever appropriate. Insulin antibodies and insulin receptor antibodies can be determined in special centers.
- Where there is predominant hypoglycaemia, an 8.00 am serum cortisol should be measured in patients who manifest signs or symptoms of adrenal insufficiency. Pituitary function tests, gastric emptying studies and tests for malabsorption are indicated when appropriate.
- Should no cause for genuine insulin resistance is evident, and then the possibility of factitious insulin resistance should be explored. A formal psychiatric and psychological assessment of the patient and the family may guide to the diagnosis
- Management of brittle diabetes can be frustrating and demoralizing to the diabetes team and the family. Mortality is high in these patients due to ketoacidosis, hypoglycaemia and severe complications like renal failure. Team approach involving diabetes specialist nurse, the physician, social worker, psychologist and the psychiatrist is probably the most likely to succeed.
- Intensive insulin regimens with multiple daily injections or various Insulin Infusion methods have been tested and proven effective in a few cases.
- For the brittle diabetes that is not controlled by the new strategies of insulin treatment, with poor quality of life and increased rate of diabetic complications, pancreatic transplant is considered.
- By good organization and delivery of medical care diabetes that is difficult to control can be detected early and effective treatment may avoid further complications in these patients.

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