DIABETES MELLITUS

TREATMENT

Oral

1) Biguanides
2) Sulfunylureas
   meglitinides
3) Thiazolidinediones
4) DBP4⊖
5) SGLT⊖
6) α-glucosidase⊖

Injectibles

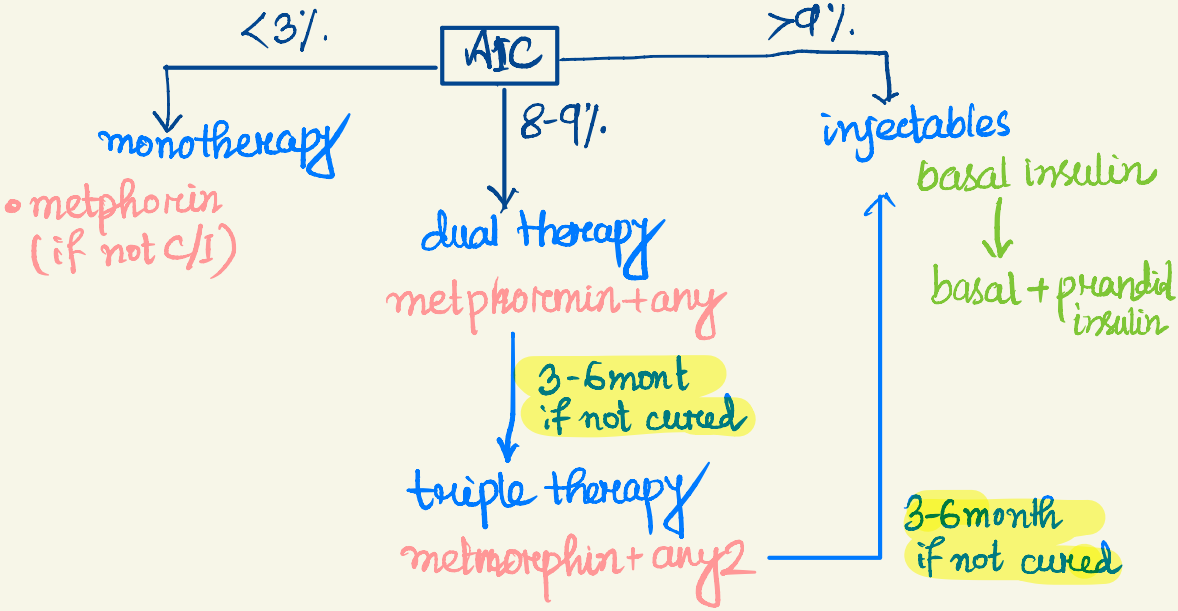
1) Insulin
   - Rapid
   - short acting
   - Intermediate
   - long acting
   - ultralong
2) GLP-1 analogue
3) Amylin analogue

- combined PPARα/γ⊕. Saroglutazin
  ↳ ↓ blood sugare & TG

Ranolazine- late Na current inhibitore
Bromocriptine. Dopamine agonist
Cholestyramine. bile acid sequestrant
colesevalam.

} also has anti-diabetic properety

Protocol



Indications for straightway administration of Insulin

- Diabetic emergency
- Pregnancy
- Pre-operative pt.
- Osmotic / catabolic symptoms of diabetes
  - ↓ polydypsia
  - ↳ wt. loss severe
- micro/macrovasculare complication
  - ↳ Renal / heart failure

↑↑ HbA_1C (~ 16%.)

Goal of treatment

↓ HbA1c ⟶ ↓ micro/macrovascular complication

- microvascular
  - retinopathy
  - nephropathy
  - neuropathy
- macrovascular
  - CVS risk (MI/angina)
  - cerebrovascular risk (stroke)
  - peripheral vascular
- non-vascular
  - glaucoma
  - cataract
  - infections
    - m/c
      - candida fungi as UTI
      - bacteria

- HbA1c ~7% is safe for most patients.

Old
comorbidity
↑ hypoglycemic risk
↑ life expectancy
→ liberal HbA1c target ~8% is fine

young
no co-morbidity
↓ hypoglycemic risk
↑ life expectancy
→ strict HbA1c target ~6% even is fine

if HbA_1C is ↓ed below 6%, is there any benifits?

many trials were done

↳ tight control of HbA_1C

DCCT
- ↓ microvascular
- ↔ macro

UKDS
- ↓ micro
- ↔ macro

Achords
- ↓ micro
- ↔ macro
- ↑ mortality

even 1y after relaxation of additional tight control microvascular benifits are sustained

↳ metabolic memory
legacy effect

LDL goal

pt. having CVS disease <70

no CVS disease <100

diabetes → change in metabolism → product^n of different type of LDL (very small LDL particle)

↓

↑risk of CVS disorder

>40 age ↑LDL diabetics, statins should be prescribed.

Screening of microvascular complication

Type I DM : 5y after diagnosis
except : Retinopathy (before 5y)

- macrovascular complication can't be screened

Type II DM : at time of diagnosis

- positive (beginning of organ damage) → treatment
- negative → further screening test annually

Technique

measurement of

nephropathy	retinopathy	neuropathy
• eGFR • serum creatinine • Urine micro-albumin	fundus examinⁿ	• temp. • pain • vibration minimum 2 sensation check at feet

Biaguanides

main drug - metformin.

interferes ↓ AMP kinase pathway

↓ hepatic gluconeogenesis

↓ peripheral Insulin resistance

Efficacy - high (can ↓ se 1-1.5% HbA_1C)

$Dose_{max}$ - 2-2.5 g/d (for Indians, 2g/d is enough)

at >2.5 g/d there is no extra benefit
more ↑ S/E as such.

S/E - GI lesions*

Vit B_{12} def. (on long term use)

Lactic acidosis (rare)

Metphoremin is nephrotoxic

C/I - Renal disorders

eGFR <30

S. creatinine >1.4

proteinuria >1

Metphoremin should be avoided in pre-op.
sepsis
MI
contrast administration

severe liver failure

Effect on

GI - S/E

hypoglycemia - alone never cause. (along ± other may cause ↓ potential)

DKD (🫘) - avoid when eGFR<30

ASCVD (♡) ↔ / potential benifit

CHF ↔

Bone ↔

Sulfonylureas

1st gen

chlorpropamide

tolbutamide

not used now

2nd gen

Glyburide/Glyburide (↑est t½) - relative cardiosafe

Glyburide

Glipizide

Glimepiride - relative renosafe

MoA - augment Insulin release by acting on ATP sensitive K^+ channel

makes β cell secrete insulin in glucose independent (whether high or low) manner

↓

extreme high risk of hypoglycemia

S/E- hypoglycemia
Obesity* (↑ Insulin release. Insulin is anabolic)

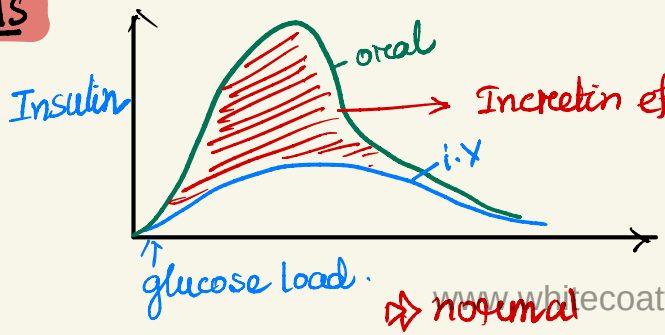
Efficacy- high (↓ HbA1C 1-1.5%)

not much safe in cardiac & renal problem.

Effect
- GI ↔
- hypoglycemia ↑↑
- DKD ↔
- ASCVD ↔
- CHF ↔
- Bone ↔

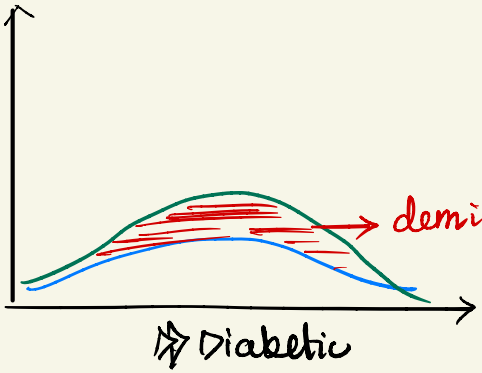
- Meglitinides are similar but short acting.
  - ↳ relatively ↓ hypoglycemic risk
  - ↳ intermediate efficacy
    - not popular drugs - expensive

INCRETINS



⇨ normal

Incretins (GLP-1, GIP) ↑se Insulin release in oral glucose load.



drug blocking DPP4 to ↑ GLP-1 → ↑ post-prandial insulin release

↓

Gliptines

Sitagliptin

GLP-1 analogue - Exenatide
Liraglutide
Albiglutide
Dulaglutide

- extremely costly ~15K/month.
- Injectable

Gliptines - ↑Insulin release

↓ GI motility ⇒ ↑satiety → useful in severe polyphagia

↓ proteinuria.

S/E - Nausea, vomiting, diarrhea, bloating, flatulence.

Arthralgia

pancreatitis

(controversial study - ↑es pancreatic cancer risk)

no clear evidence but better to avoid in H/o cancer in family ongoing cancer.

headache.

Efficacy - moderate (0.5 - 0.8%)

hypoglycemic risk: NO.

DKD, ACVD, Bone: ↔

CHF: saxagliptine, Alogliptine ↑CHF exacerbation, hospitalisation.

Linagliptine is ↑ renosafe - can be given at any stage of Renal failure

GLP-1 analogue

Preference - Dulaglutide > Liraglutide > Albiglutide

Dulaglutide: S/C once a week

Liraglutide: once a day → potent anti-obesity drug

S/E - same as gliptines

Efficacy - high (0.75-1.5%)

clinically significant weight loss.

↳ preferred in pt. BMI >35

↓

although costly, can be used in obesity

effect -

GI - S/E

DKD - beneficial

ASCVD beneficial

CHF - ↔

bone - ↔

- It is prescribable after renal transplant
- costly

SGLT-2 inhibitors

Empa
Cana
Dapa
} gliflozins

blocks SGLT-2 in kidney
↓
⊗ glucose, Na^+ reabsorption
↓
glycosuria, natriuresis
↑ed UTI risk

C/I - recurrent UTI
eGFR <30

Efficacy - Intermediate (0.5-0.8%)

hypoglycemia - nil (↔)
DKD beneficial
ASCVD beneficial
CHF beneficial (Dapagliflozin is proved to ↑ survival in CHF)

Bone - canagliflozin slightly ↑se risk of fracture

Thiazolidienediones
Glitazones

Rosiglitazone — ↑CVS disease - withdrawn
Pioglitazone

act on PPARγ

Efficacy - high
hypoglycemia ↔
GI ↔
DKD ↔
ASCVD ↔
CHF - c/I
bone harmful

- weight gain
- fluid retention
  ↓
  C/I - CHF

- bladder cancer chances ↑

α-glucosidase inhibitors

Acarbose - only approved drug

inhibit breakdown of complex carb to simple carb.

induce carbohydrate malabsorption.
↓
↓se post-prandial sugar

S/E

flatulence, bloating, abdominal cramps

C/I - eGFR < 30

Efficacy: int. (0.6%)

hypoglycemia: nil - but, if α-glucosidase⊖ taken pt. undergo hypoglycemia, he/she should be advised to take simple glucose (e.g. glucon-D powder), not snacks because glucose won't be absorbed then

DKD: ↔

ASCVD: ↔ / potential benifit

CHF ↔

bone: ↔

Amylin Analogue

Subcutaneous inj.

- ↑ satiety
- ↓ glucagon release

costly

↑↑ risk of hypoglycemia

no potential benifit in CHF, ASCVD.

not used/popular

INSULIN THERAPY

Rapid- Lispro (B^{28} lysine, B^{29} proline)
Aspart
Glulicin
Insulin analogue
B^{28} aspartic
B_3- lysine (~~Asparagine~~)
B_{29}- glu (~~lysine~~)

Short acting: Regular Insulin (Recombinant human insulin)

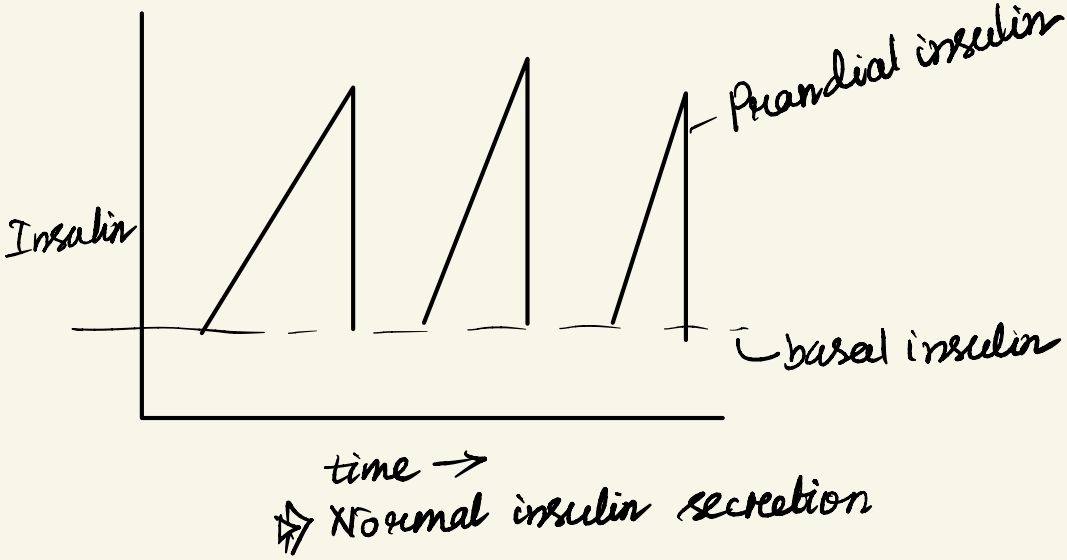
Intermediate acting: NPH
↓
not insulin analogue
- NPH = regular insulin complexed with Zn & protamine

Long acting: Glargine U_{100} / U_{300}
Determir
Degludec
↓
lasts for 34-40 hrs.
→ perfect basal insulin. 24 hrs act^{n}.

Natural INSULIN
- 21 aa } joined by
- 30 aa } -S-S-

positions
→ B_{28} Proline
B_{29} Lysin
B_{30} threonine
A_{21} aspargine.

Location of -S-S-
A_7 - B_7
A_{20} - B_{19}
A_6 - A_{11} (intrachain)



Normal insulin secretion

Insulin therapy should mimic normal insulin release.

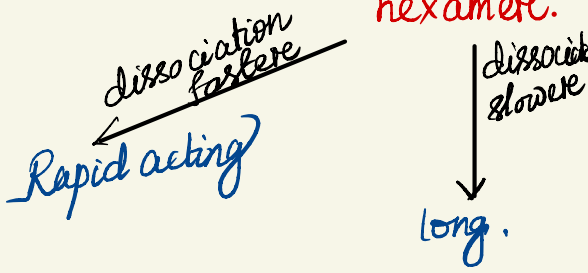
Glargine, degludec are good for basal insulin
lispro, aspart are good for prandial insulin

Glargine - A^{21}: Asn → gly
$B^{31/32}$ → Arg

Detemir - B^{30}: ~~Threonine~~ ⊗ -
B^{29}: lysine ⊕ myristic acid (F.A.) (add)

Degludec - B^{30}: ~~threonine~~ ⊗ → added a glutamic acid spacer and then hexadecanoic acid (F.A.)

Regular Insulin, on given S/C route, then forms hexamere.



on i.v. there is no hexamere formation. thus, all insulin will be same. thus, only cheapest regular insulin is used.

Regimes

1) Basal : oral + basal
2) Basal plus : basal + prandial insulin c 1 or 2 largest meal
3) Basal bolus : basal + prandial insulin c all meal.

Basal → long acting (once a day) - Glargine U_{100}
int. (twice a day - ↑risk of hypoglycemia)
↳ produce peak (NPH)
ultra long acting. Glargine U_{300}, degludec
can be taken any time during day.

Prandial → rapid > short.

↓

gold standard.

site of inj. Abdomen (↑ abs.)
post. arm
Lateral aspect of thigh.

↓

site should be rotated.

S/C insulin never cause hypokalemia.

Only Insulin that can never be mixed ē other insulin-

Glargine (acidic pH → crystalize)