Introduction Endocrines : Pathophysiology

Endocrine system consisting highly Integrated and widely distributed group of organs that orchestrate a state of Metabolic equalibrium among various organs of the body.

Endocrine hormone is called by the blood from its

site of release

↓

To its target cells that are distant from their site of synthesis

In response to it target tissue secretes factors that down regulate the activity of gland which produces stimulating hormone

" Process known as feed back Mechanism "

Several processes can disturb the normal activity of Endocrine system - like

- Impaired synthesis
- Release of Hormones
- Interaction b/w Hormones & their target tissues
- Abnormal responses of target organs.

Diseases can be generally classified as.

1. Diseases of underproduction / overproduction of hormones. and resulting biochemical and clinical consequences.
2. Diseases associated with the development of Mass lesions, such lesions might be Nonfunctional or might be associated with overproduction or underproduction of hormones.

Hormones consist of 3 broad classes

1. Peptides
2. Steroids
3. amino acid

} derivatives.

Among 3 peptides hormones represent largest class

They are :—

1. Growth hormone
2. Adrenocorticotropic hormone
3. Insulin

Steroid hormones are derived from cholesterol

They include :

1. Cortisol
2. Aldosterone
3. Androgens.

Amine group : Derived from Thyrosine amino - acid

Includes 1. Thyroid hormones → T_3, T_4

2. Catecholamines → Epinephrine
   Nor "
   Dopamine.

Physiology of Endocrine system

Trophic / Releasing } hormones from Hypothalamus

↓ Act on Pituitary

Ant Pitu | Post Pitu

Releasing → Trophic ↓ on glands ↓ Target cells

Releasing — Trophic hormones

1. Thyrotrophin
2. Gonadotrophin
3. ACTH

} act on Anterior pituitary

↓ Stimulate to Release Trophics ↓ prolactin, Growth hormone

Thyroid Stimulating Hormone

Thyroid

T3 ↓ T4

FSH, LH

Gonads

Ovaries ↓ Testis

Estrogens, Progesterone, ↓ Testosterone

Adrenal

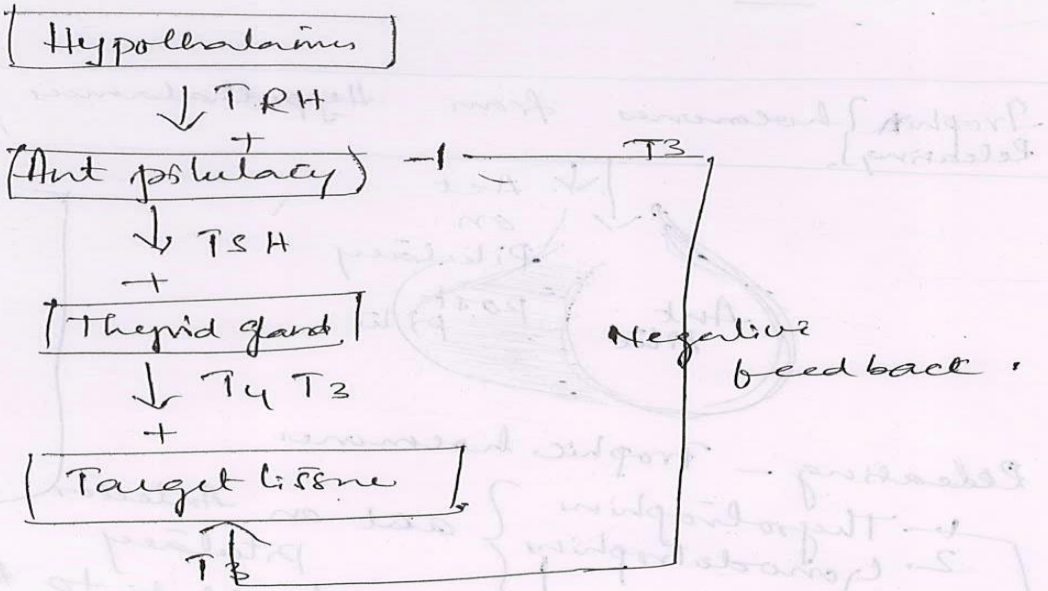
Aldosterone ↓ androgens

Post pituitary

oxytocin

ADH

Regulation of Thyroid Hormones



Hypothalamo pituitary axis → primary point of Regulation occurs at step of TSH Release from ant pituitary by TRH

— T4 Thyroxine → from Thyroid gland delivered to body tissues via blood streams

— When Thyroid levels are low. Hypothalamus produces Thyrotrophin Hormone TRH.

— when free T3 acts on ant pituitary to reduce release of TSH Secretion

Thyroid disorders

Because of over or under function of Thyroid gland as thyroid hormone maintain body Metabolism

Disorders of Thyroid

1. Hyperthyroidism
2. Hypothyroidism
3. Goiter
4. Thyroid cancer.
5. Thyroid Nodules.

Hypothyroidism: It occurs due to "deficiency of thyroid Hormone"

"As it is responsible for body's Metabolism" its absence is associated with Slow Metabolism

Hyperthyroidism classified: 1. primary → Excessive production of thyroxin by gland"
2. Secondary → Exogenous administr of thyroid hormone.

- ✱ Releasing preformed thyroxin ← Ex: 1. Thyroiditis →
- ✱ Ectopic hormone production ← 2. Struma Ovarii
- ✱ Producing TSH-like substance stimulate thyroid gland ← 3. choriocarcinoma

Signs & symptoms :

Nervousness
Irritability
Palpitation
Tachycardia
Heat intolerance
↑sed sweating
Tremors
wt loss
Frequent bowel Movements / Diarrhoea
Lower Extremity Edema
Sudden paralysis.
Menstrual disturbance.
Mental "

Etiology :

Toxic diffuse goitre " Graves disease "
Toxic adenoma
Toxic Multinodular goitre.
Painful subacute thyroiditis
Excessive pituitary TSH
Excessive ingestion of thyroxine.
Trophoblastic disease.

Pathophysiology : Hyperthyroidism / thyrotoxicosis is a stage results from ↑sed amounts of TH.

Primary is more common
Secondary is less common (caused by TSH secreting pituitary adenoma)

In serum usually T_3 ↑ses more than T_4 B coz of ↑sed secretion of T_3 as well as conversion of T_4 to T_3 in peripheral tissues.

Hypothyroidism characterised by loss of normal regulatory control of TH secretion

→ Action of TH on body is stimulatory
Result Hypermetabolism

↓

↑sed sympathetic Nervous system activity

↓

↑sed secretion of Hypothalamic & pituitary & Gonadal hormones.

← Excessive amount of Thyroid Hormone stimulate Cardiac system & ↑ses adrenergic receptors

↓ Resulting

Tachycardia
↑sed cardiac output, ↓stroke volume

↓ Leads

-ve Nitrogen balance, lipid depletion and resultant state of Nutritional deficiency

↓

Hyperparathyroidism

Hypothyroidism: Where thyroid gland stops producing sufficient concentration of T4 & T3 with ↑sed TSH levels.

When there is requirement of T3 & T4 where the conc of TH is at minimum level Pituitary gland release TSH controlled by TRH secreted by hypothalamus

Symptoms : Memory loss
Hair loss
Dry & rough skin
Constipation
↑ed Cholesterol levels
Depression.
Fatigue.

Etiology : 1. Autoimmune disease : Hashimoto's thyroiditis.
Auto immune disorder occur the immune system produces auto antibodies that attack own tissues.

2. Treatment for hyperthyroidism : Where treated with too much of radio active iodine or anti thyroid Medications to reduce / Normalize thyroid function.

3. Thyroid surgery : Large portion of gland when removed. diminish thyroid function

4. Radiation therapy : Given in cancers of Head & Neck was the part of treatment

5. Medications : Lithium → used in psychiatric disorders

Pathophysiology.

" Primary Hypothyroidism " → loss of functional thyroid tissue

↓ leads to

↓ed production of TH

" Secondary Hypothyroidism " → pituitary's failure to synthesize adequate TSH / Lack of TRH

→ Pituitary tumors compress the pituitary cells / consequences of their treatment —

→ Causes sec Hypothyroidism.

Tertiary : includes Traumatic brain injury
Subarachnoid Hemorrhage
pituitary infarction

Normal Regulation

Hypothalamus
↓
TRH (Thyrotrophin releasing Hormone)
↓
Ant pituitary
↓
Thyroid stimulating Hormone TSH
↓
Thyroid gland
↓
T_4 → T_3
Thyroxine — Triiodothyronine.

Hypothyroidism

Dysfunction (Tertiary)
↓
Decreased TRH

Pituitary dysfunction (Secondary)
↓
↓sed or Normal TRH

Destruction / Inflammation (Primary)
↓
↓sed T_4 T_3
↑sed TSH

Diagram of primary, Secondary & Tertiary Hypothyroidism

Goitre : Enlargement of thyroid gland called Goitre.

Thyroid gland consists of 2 lobes present ——— of the throat one on either side of ——— pipe connected by means of Isthmus

- Controlled by pituitary gland which prompts the thyroid to ——— T_4 & T_3 by releasing TSH.

Excessive stimulation" of thyroid by TSH can Result in a "Goitre"

Three types of Goitre
1. colloid Goitre : Endemic
2. Non toxic : Sporadic
3. Toxic Nodular / Multinodular Goitre.

Colloid : Develops due to lack iodine which is Essential for producing thyroid hormones. People who live in Iodine ~~deficient~~ areas develop this type of Goitre.

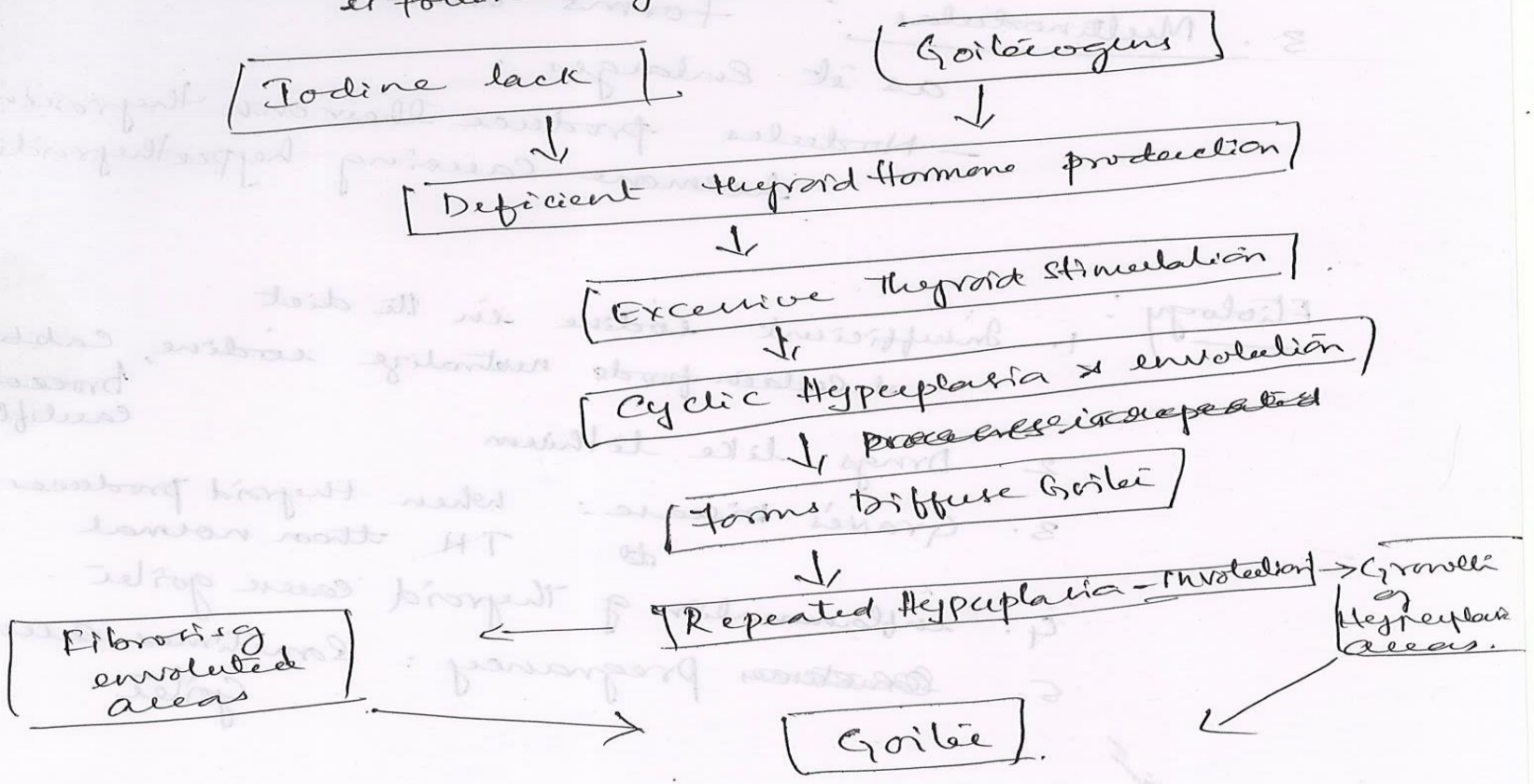
2. Nontoxic : Cause May be due to some Medication like lithium used in Psychiatric disorders.
- Here Thyroid function is healthy, doesn't affect Thyroid production.

3. Multinodular : Forms one or more nodules as it Enlarges
- Nodules produce their own thyroxine hormone causing hyperthyroidism

Etiology : 1. Insufficient iodine in the diet
" certain foods neutralize iodine, cabbage, broccoli cauliflower
2. Drugs like lithium
3. Graves disease : when thyroid produces more TH than normal
4. inflammation of thyroid cause goiter.
5. ~~Genetics~~ Pregnancy : Sometimes cause goiter.

Pathophysiology: Deficient thyroid hormone
Causes Excessive stimulation
which leads Hyperplasia of follicular
epithelium & also formation of New
follicles.

Hyperplasia stage
is followed by involution where fibrinogen occurs.



Graves Disease :

- Trend More in women.
- Cause not clearly known but genetic factors interact with Environmental factors and play a vital role in pathogenesis of autoimmune thyroid disease.

Pathophysiology : Graves Results in the form of type II Hypersensitivity

Where → Stimulation of thyroid by auto antibodies directed against thyroid receptors.

They are called thyroid stimulating immuno globulin (TSI / TSAbs / TRAbs)

TSI stimulation of TSH receptors in gland Results Goitre Hyperplasia & ↑se the Synthesis of TH Especially T3.

↑sed levels of Thyroxine affect every system in the body & Results in TSH production by pituitary is inhibited by usual Negative feed back loop.

(14)

Signs & Symptoms: TSI contribute 2 Major distinguishing clinical Manifestations of Graves disease.

1. Opthalmopathy Graves → affects More than 1/2 of the people ē Graves
2. pretibial Myxedema.

2 catagories of ocular Manifestations

1. Functional: Resulting from hyper activity of sympathetic division of ANS – Lag of upper lid and downward gaze.

2. Infiltrative: orbital contents ē Enlargement of Ocular muscles

Changes in TSH receptor auto antibodies react ē receptors on orbital fibroblasts

↓

↑se secretion of Hyaluronic acids
orbital fat accumulation
Inflammation
↓
Edema of orbital contents result in Exophthalmos (protrusion of Eyeball)

Treatment :- Antithyroid drugs
Radioactive Iodine
Surgery.

Pretibial myxedema → do not require ☆ treatment
Surgical orbital decompression
Glucocorticoids help in progressive opthalmopathy

Diabetes Mellitus : It is a ch Metabolic disease

↓ which causes

High blood glucose levels in the body

↓

Due to defects in insulin production / function

Insulin is a hormone released by pancreas when We eat food.

Insulin allows food (Glucose) into Enter into the cells

If Insulin is not being used by cells

or

If body unable to make insulin

?

What happens - - - -

Sugar builds up in the blood

Causing Hyperglycemia

↓

Is the state where high Glucose levels - More than Normal

Normal blood glucose values : 80 to 120 mg/dl

(2)

Diagnosis of DM is made by any one of ~~two~~ three } below Criteria }.

1. Random Blood glucose (RBS) > 200 mg/dl
   & Signs & symptoms
2. Fasting Glucose concentration greater than 100 mg/dl on more than one occasion.
3. Oral glucose tolerance test: Glucose concentration > 200 mg/dl 2 hrs after glucose load.

75 gm Glucose
Fasting — 95 mg/dl
After 1 hr — 180 mg/dl
2 hr — 155 mg/dl
3 hr — 140 mg/dl

Individuals & fbs less than 100 mg/dl
or
— < 140 mg/dl following OGTT } Considered as **Euglycemics**

If fbs > 100 mg/dl but < 126 mg/dl
or
OGTT values > 140 mg/dl but less than 200 mg/dl

→ considered as **Impaired glucose tolerance** " also known as **prediabetics** "

Classification: WHO recognizes 3 Main forms of DM

1. Type I → Insulin Dependent / Auto immune destruction of Insulin producing cells.
2. Type II → Non Insulin Dependent / Insulin resistance
3. Gestational DM: During pregnancy — Due to enteraction b/w fetal needs & Maternal Metabolic Control.

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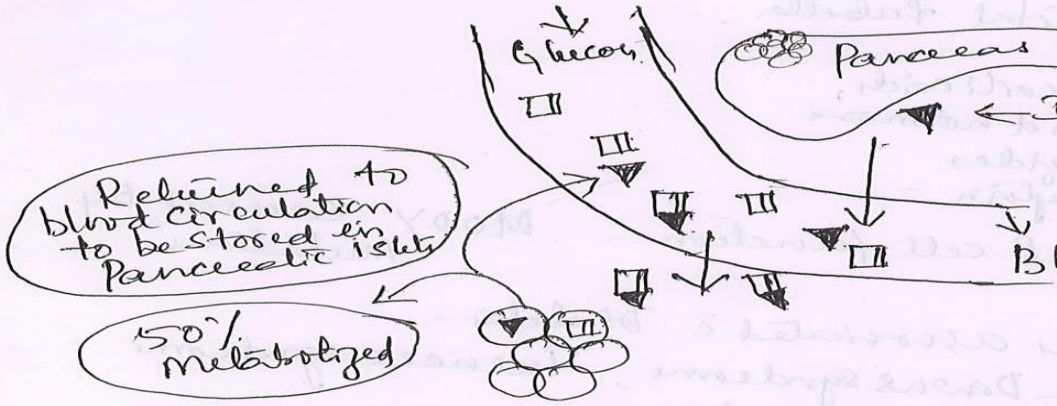
4. Genetic defects of Insulin chain
5. Pancreatic defect — Exocrine part ch. pancreatitis
   Pancreatectomy / Trauma
   Neoplasia
6. Endocrinopathies → Acromegaly, Cushings syndrome
   Pheochromocytoma
   Glucagonoma
7. Infection: Cytomegalovirus
   Coxsackie B virus
   Congenital Rubella.
8. Drugs — Glucocorticoids
   Thyroid hormone
   Thiazides
   Phenytoin
9. Genetic defect of B cell function — MODY caused by Mutations
10. Genetic syndromes associated ± Diabetes -
    Li Le Dawns syndrome, Turners syndrome
    Klinefelter syndrome

Type I : Autoimmune
Characterized by Pancreatic 'B' cell destruction and absolute deficiency of Insulin
Seen in children & younger than 20 yrs of age.
10 – 15% have type I

Type II : Its in combination of Resistance to insulin action and an inadequate secretion by B cells of Pancreas.
90 – 95% — Have type II

Mechanism of Insulin release in Normal pancreatic B cells.



← Insulin released from B cell in response due to rise in blood glucose

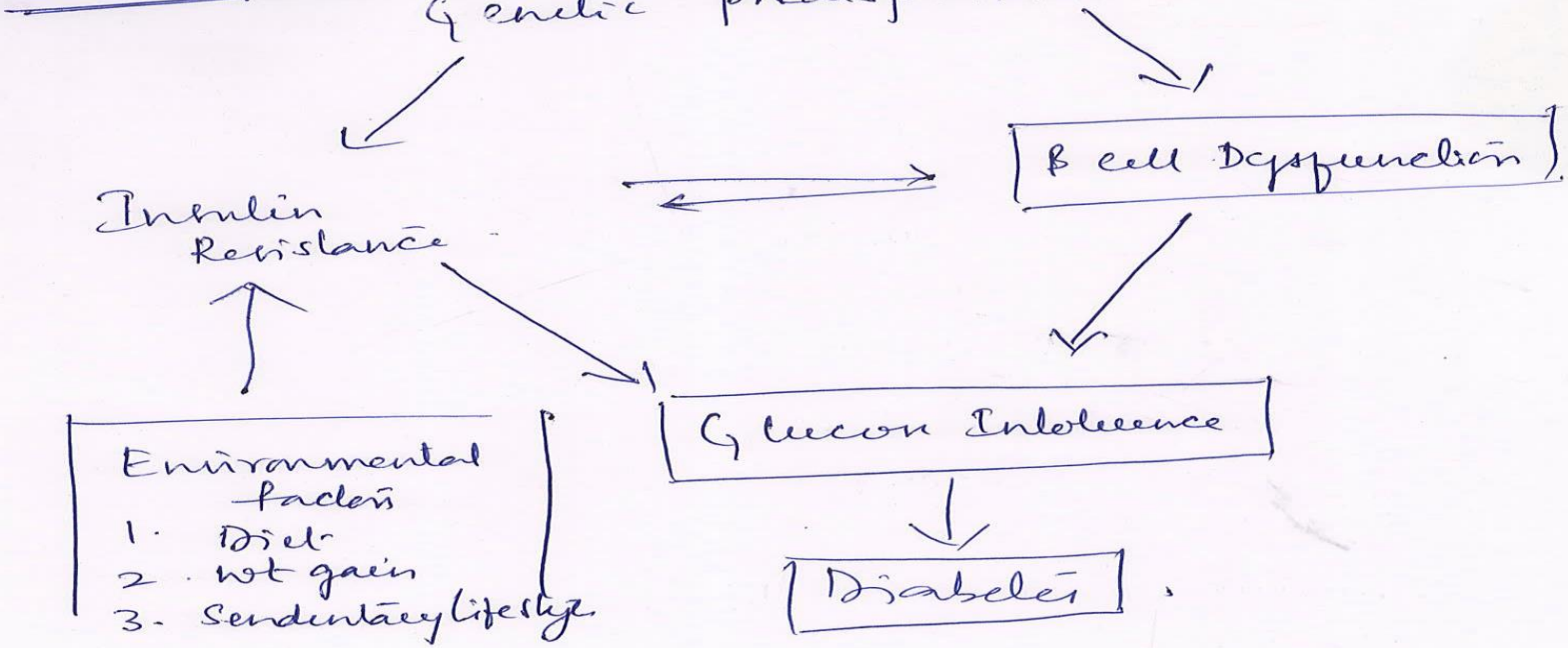
2. Insulin helps body cells (Muscles & Adipose) to absorb glucose from blood to use or to store (as glycogen in liver & muscle)

Physiology in Normal Subject

1. Normal Insulin secretion to Insulin Stimulator in the food.
2. Insulin Stimulates Glucose uptake by tissues like Muscle, adipose tissue and liver.
3. Suppression of hepatic glucose production.

Maintenance of Normal glucose homeostasis is dependent on the above three processes.

Evolving DM :-



Gestational Diabetes: Due to inadequate Insulin Secretion
Resembling type 2
occurs due to interaction b/w fetal needs & maternal Metabolic Controls

occurs 2% - 5% of all pregnancies

It is transient, Temporary
But still damage the health of fetus or mother
20 - 50% of women c GDM develops Type II later in her life.

It is treatable if Not treated → Results → Macrosomic babies
fetal Malformation
congenital heart disease.
Cardiac anamolies.
CNS
Skeletal Muscles Malformation

Epidemiology
Worldwide prevalence of DM increasing
Globally as of 2011 → Estimated 366 million people c DM.
which → America
→ Type II is 90% of cases
→ Type II is rising in Every country c 80% of People living in Low - Middle Income Countries.

Symptoms :
3. { polyuria
poly dipsia [Dipsia].
poly phagia. } Develop particularly fast in children. i.e Type I
May be absent or slow in Type II

4 - Wt loss
5 - Fatigue

When Glucose concentration in blood is High
↓
Reabsorption of Glucose in proximal renal tubule is incomplete
So part of Glucose remain in the urine
Causes Glycosuria (Glucose in urine)
This causes ↑ed osmotic pressure of urine
inhibits the reabsorption of water
resulting ↑ed production of urine (polyuria)
— Hence ↑ed fluid loss from blood causes
volume lost of blood volume which is
replaced by water held in body cells
causing dehydration → ↑ed thirst.

Pathophysiology : Clinical Onset of Type I often abrupt (1)

The autoimmune process many yrs before the disease becomes Evident ie Progressive loss of insulin reserves. over time

Clinical Manifestations of Hyperglycemia and ketoacidosis occur late in the course when More than 90% B cells destruction.

Fundamental abnormality in type I is

"failure of self tolerance in T cells"

— due to defective clonal deletion of self reactive T cells in the thymus.

and also defect of in the functions of regulatory T cells or resistance of

Then activated T cells traffic to pancreas where they cause B cell injury.

Type II DM : β cells Exhaust their capacity to adapt to long term demands of Peripheral insulin resistance.

2 pathological defects in Type II diabetes

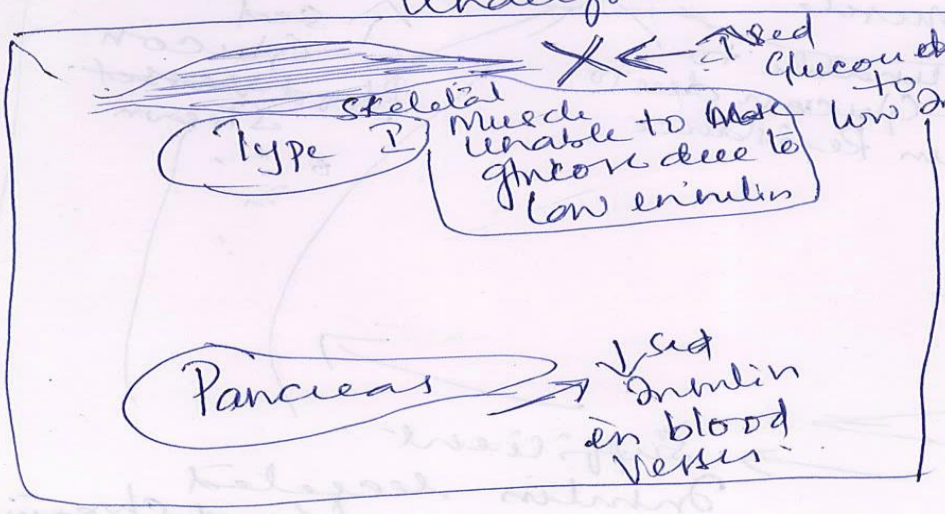
1. Impaired insulin secretion by dysfunctional β pancreatic cells
2. Impaired insulin action through Insulin resistance.

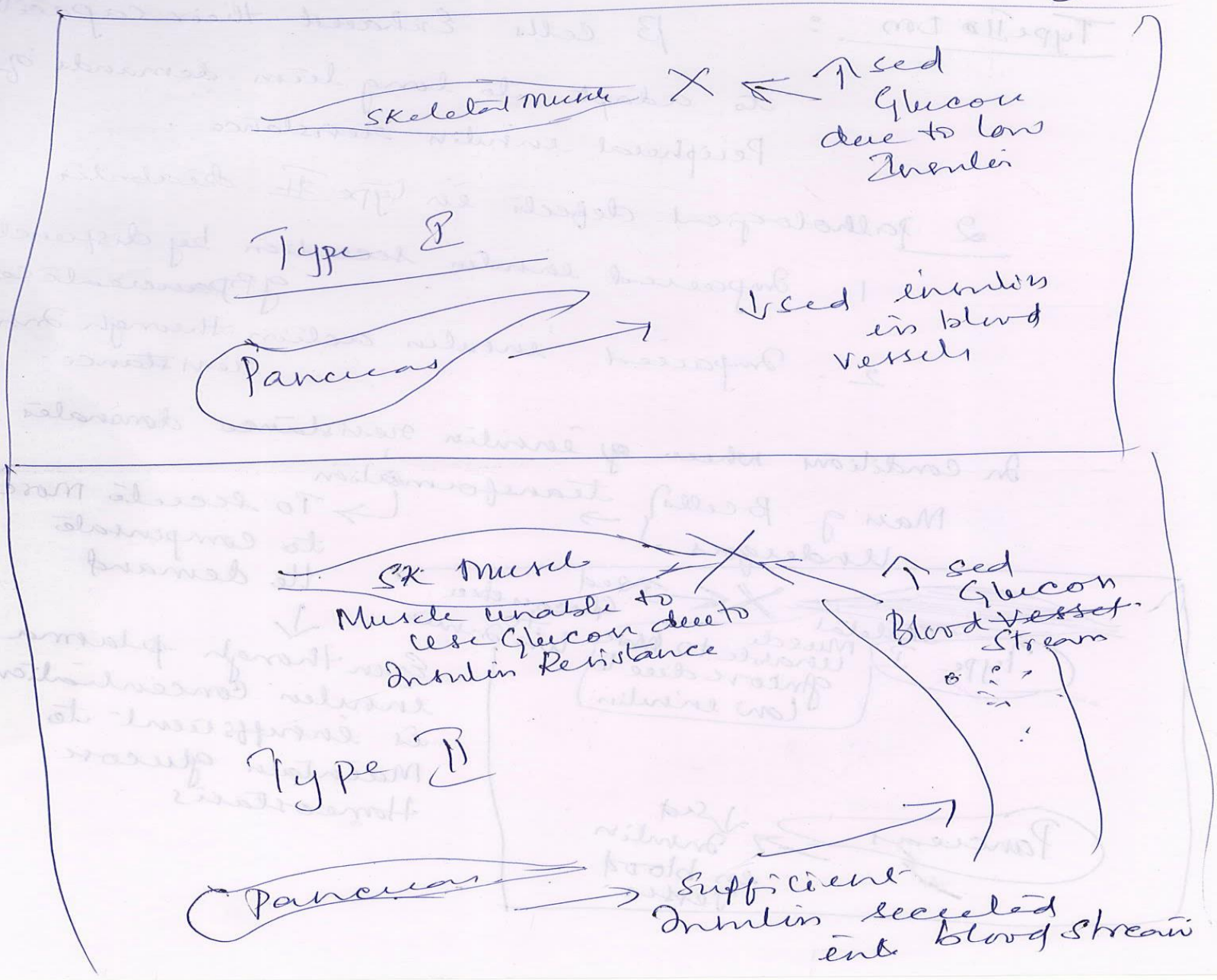
In conditions where of insulin resistance dominates

Many β cells undergoes → transformation → To secrete more to compensate the demand

↓

Even though plasma insulin concentration is insufficient to Maintain glucose Homeostasis




Skeletal Muscle
↑ sed Glucose due to low Insulin
Type I
Pancreas
↓ sed insulin in blood vessels
Sk. Muscle
Muscle unable to use Glucose due to Insulin Resistance
↑ sed Glucose Blood Stream
Type II
Pancreas
Sufficient Insulin secreted into blood stream

Treatment : Aim in treating DM is by controlling Elevated blood sugars without causing abnormally low levels

Type - I treated by Insulin
Exercise
Diabetic Diet.

Type II — Wt reduction
Diabetic diet
Exercise.
} when these measures fail to control Elevated blood sugars

Oral Medications are used.
If oral still insufficient insulin is considered.

Wt reduction & Exercise ↑se the sensitivity of Insulin & helps to control blood sugar Elevations

Medications are designed
1. To ↑se the insulin output by the pancreas
2. To ↓se the amount of glucose released from the liver.
3. ↑se the sensitivity of - cells to Insulin
4. ↓se the absorption of Carbohydrates from Intestines by slowing gastric Emptying

Metformin → oral hypoglycemic agent.
causes decrease glucose output from liver.
can be used itself or in conjunction to other agents.

Glitazones : ↑se sensitivity of cells to insulin (Muscle & fat)
Pioglitazone & Rosiglitazones are New thiazolidinediones.
Act within one hr of administration