A Dissertation on

"STEROID INDUCED HYPERGLYCEMIA DURING FIRST 48 HOURS OF STEROID THERAPY IN HOSPITALIZED PATIENTS"

Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032

In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE
KILPAUKMEDICAL COLLEGE
CHENNAI–600010

APRIL 2017

CERTIFICATE

This is to certify that Dr. **G. SAILENDRI**, Post-Graduate Student (July 2014 to June 2017) in the Department of General Medicine, **KILPAUK MEDICAL COLLEGE**, Chennai - 600010, has done this dissertation on "**STEROID INDUCED HYPERGLYCEMIA DURING FIRST 48 HOURS OF STEROID THERAPY IN HOSPITALIZED PATIENTS**" under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr.M.G.R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2017.

Prof.Dr.P.Paranthaman, M.D
D.T.C.D
Professor of Medicine
Department of Medicine
Kilpauk Medical College
Chennai-10

Prof.Dr.S. Ushalakshmi, M.D

Professor of Medicine
Department of Medicine
Kilpauk Medical College
Chennai-10

PROF.DR.R.NARAYANA BABU, M.D,
THE DEAN,
KILPAUK MEDICAL COLLEGE AND HOSPITAL, CHENNAI-10

DECLARATION

I, Dr. G. SAILENDRI declare that I carried out this work on "**STEROID INDUCED HYPERGLYCEMIA DURING FIRST 48 HOURS OF STEROID THERAPY IN HOSPITALIZED PATIENTS**" at Department of Medicine, Government Kilpauk Medical College Hospital during the period of April 2016 to September 2016. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, and diploma to any other University, board either in India or abroad. This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

DR.G. SAILENDRI

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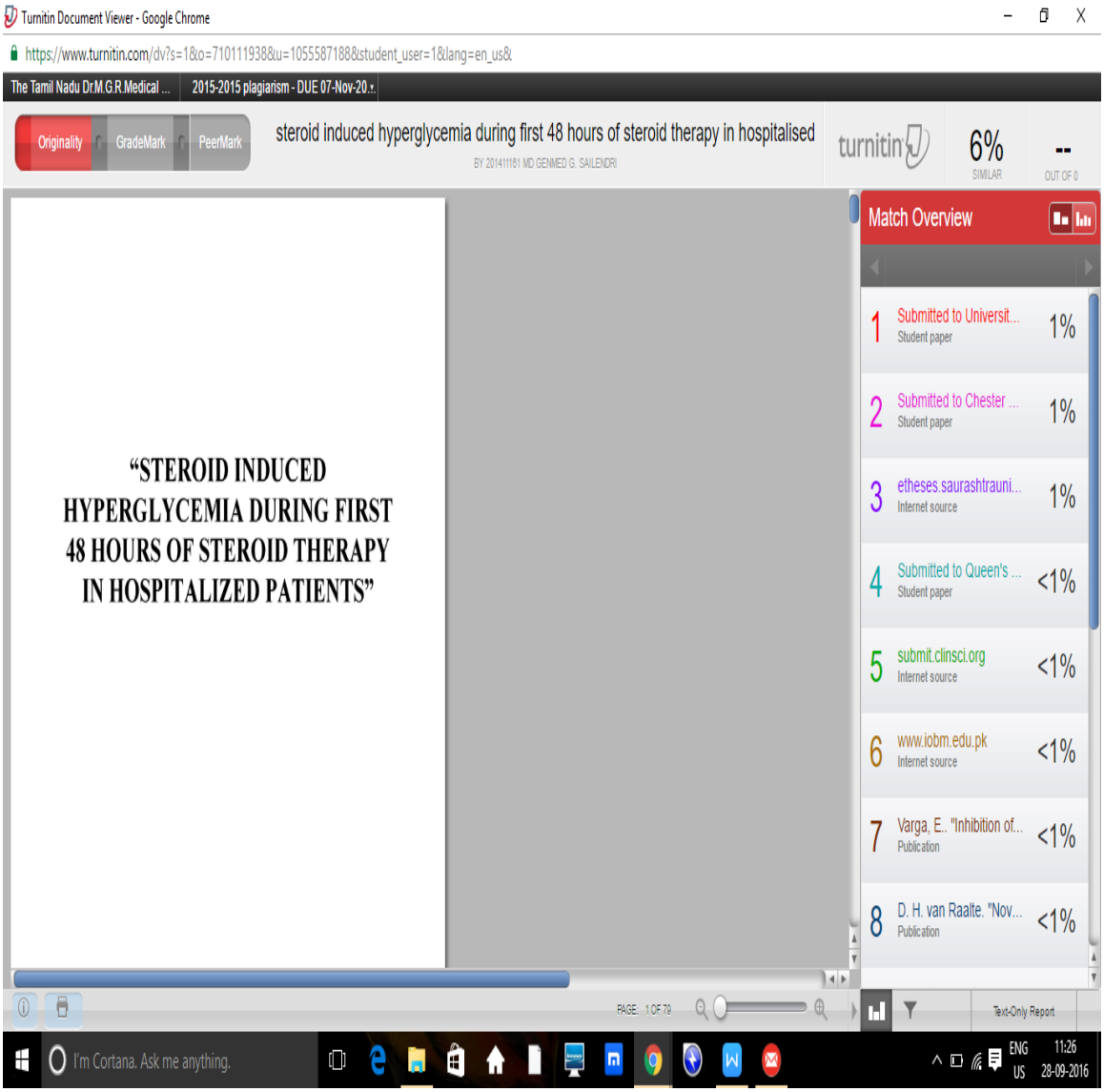
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CONTENT

INTRODUCTION

INTRODUCTION

Glucocorticoid (GC) are produced by the adrenal cortex, under the direction of hypothalamic-pituitary-adrenal axis. They are crutial for glucose, lipid and protein metabolism and therefore for energy balance.

At supraphysiological concentrations ie. > 10 mg/ day as that is their normal daily rate of secretion, GCs will exhibit their anti-inflammatory action and so used for treating a wide array of inflammatory and (AI) autoimmune conditions.

These include exacerbations of chronic obstructive pulmonary disease (COPD), a clinical manifestation of an acute-on-chronic inflammatory process in the airways, often with systemic spillover. Inspite of their enormous useful actions, usage of corticosteroid is under limitation in view of their side effect profile, which in turn is dependent on amount of drug and duration for which the drug was administered for the sake of treatment.

Side effects of steroids are mainly metabolic derangements, including the development of central adiposity, hepatic steatosis, dyslipidaemia characterised by increased plasma levels of triglyceride rich lipoproteins (TRL) and nonesterified fatty acids (NEFA), increased breakdown of skeletal muscle mass, insulin resistance, glucose intolerance and overt diabetes in susceptible individuals.

The combination of hypertension, central obesity and glucose Intolerance is called as `**Reaven's Syndrome X**' or the '**Metabolic Syndrome'**.

The most common adverse effect following steroid therapy is the development of hyper (dys) glycemia.

Hyperglycemia is an independent predictor of increased mortality in hospitalized patients with a range of comorbidities, including an exacerbation of COPD.

By opposing the actions of insulin, glucocorticoids could contribute to insulin resistance and its association with other cardiovascular risk factors.

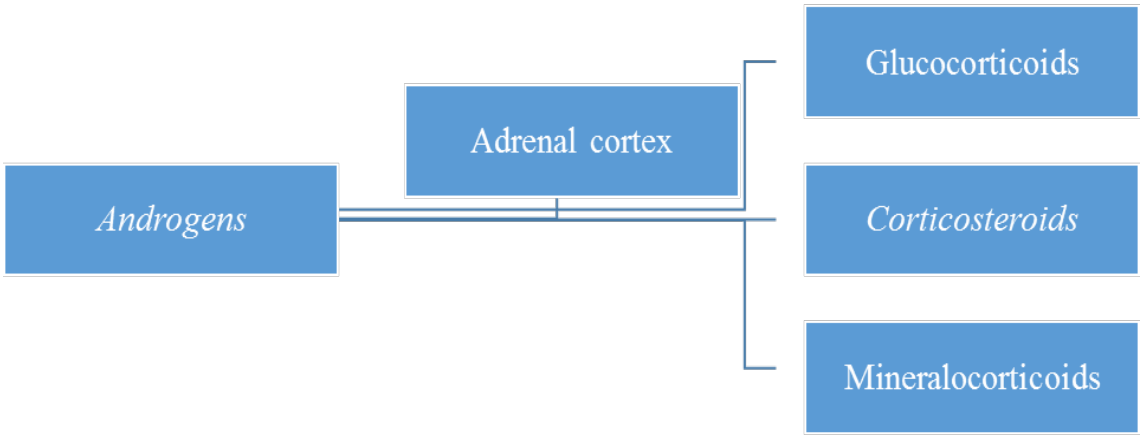
Endogenous glucocorticoid excess in Cushing's syndrome predominantly increases postprandial blood glucose concentration with fasting glucose often in the normal range. If exogenous glucocorticoids cause a similar pattern of hyperglycemia, current conventional strategies may inadequately treat postprandial hyperglycemia, and use of long-acting basal insulin may precipitate nocturnal hypoglycemia. Avoidance of hypoglycemia is important because it has been implicated as a potential cause of increased mortality in patients receiving intensive insulin therapy.

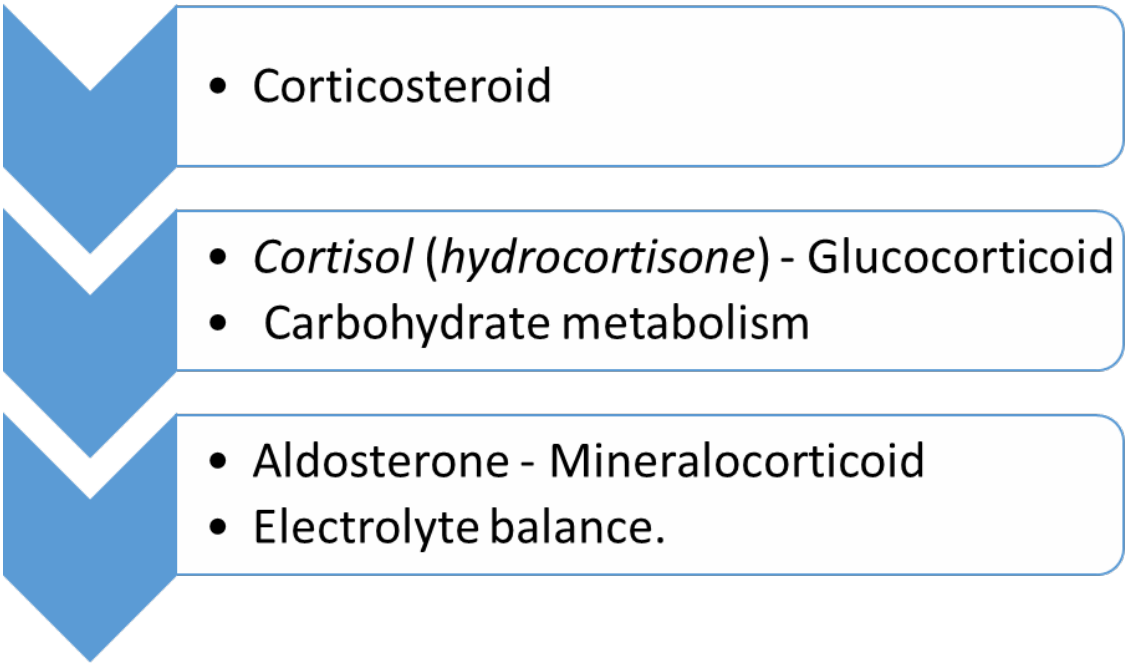
Studies showed that the glycemic rise related to steroid therapy usually begins 4 hours after the dose and usually persists for up to 16 hours.

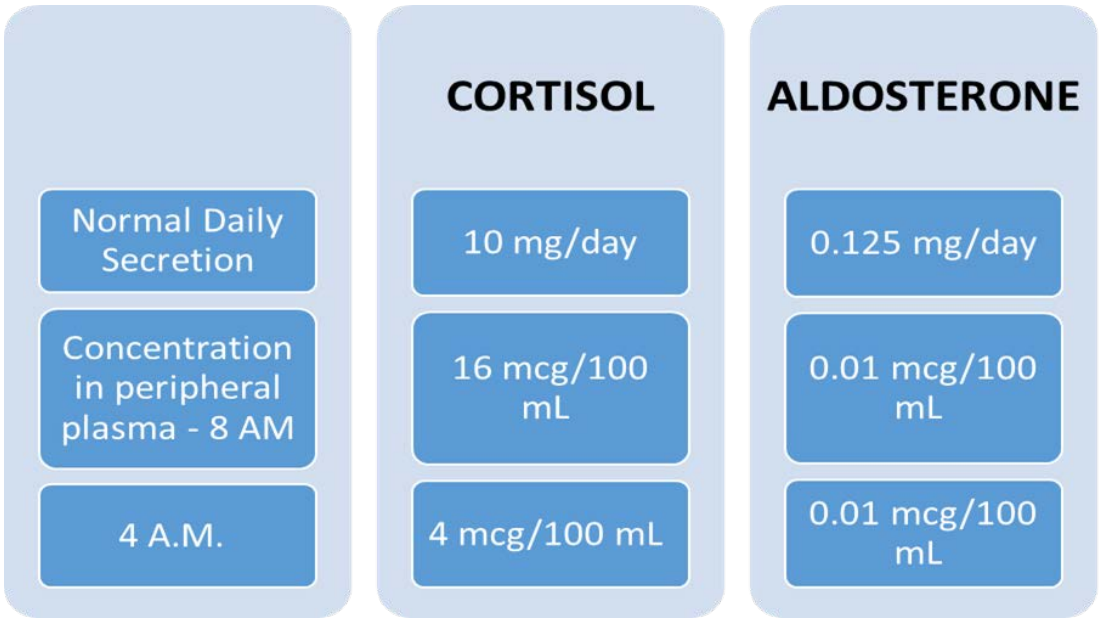
Therefore, conventional testing methods to diagnose diabetes may not be appropriate in steroid-induced diabetes. Fasting hyperglycemia may not be evident in many cases and only postprandial hyperglycemia is seen in most patients. So it is hypothesized that prednisolone causes substantial hyperglycemia, predominantly in the postprandial period. A better understanding of the glycemic effect of prednisolone will allow the development of a specific treatment strategy for prednisolone-induced hyperglycemia that targets the time of day during which hyperglycemia predominates.

REVIEW OF LITERATURE

REVIEW OF LITERATURE







REPLACEMENT THERAPY

ACUTE ADRENAL INSUFFICIENCY

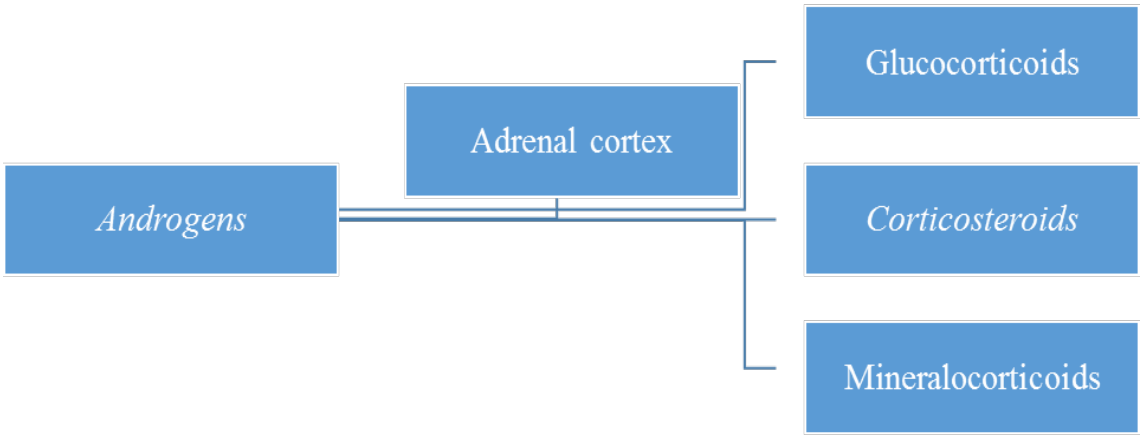
After an initial intravenous bolus of 100 mg, hydrocortisone (cortisol) should be given by continuous infusion at a rate of 50-100 mg every 8 hours. At this dose, which approximates the maximum daily rate of cortisol secretion in response to stress, hydrocortisone alone has sufficient mineralocorticoid activity to meet all requirements. As the patient stabilizes, the hydrocortisone dose may be decreased to 25 mg every 6-8 hours.

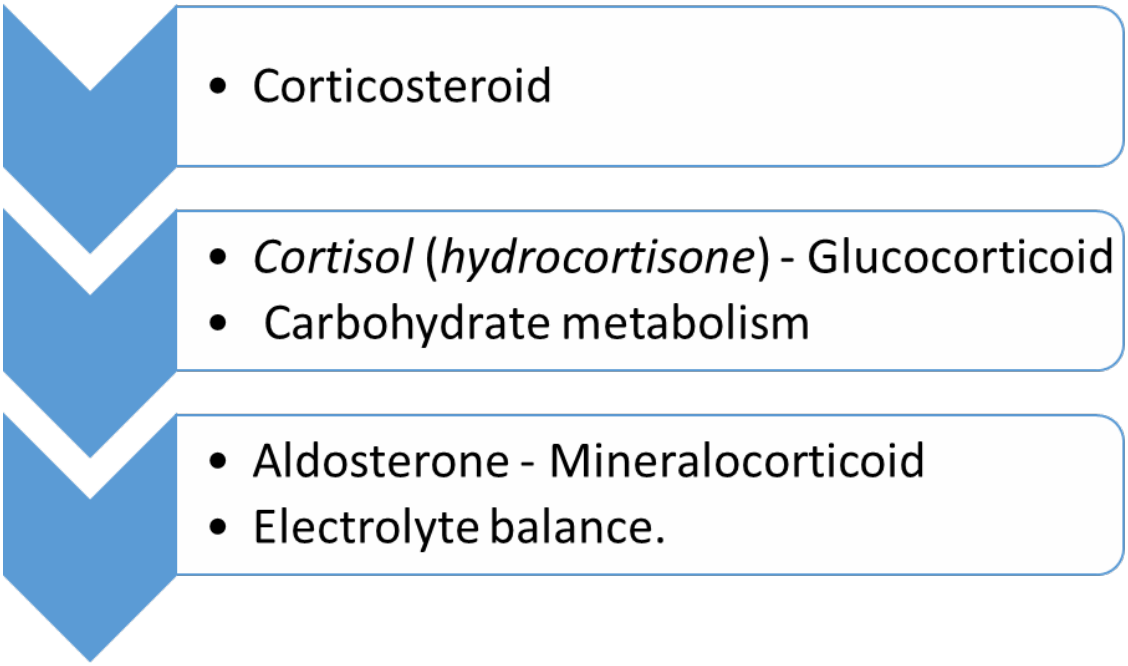
CHRONIC ADRENAL INSUFFICIENCY

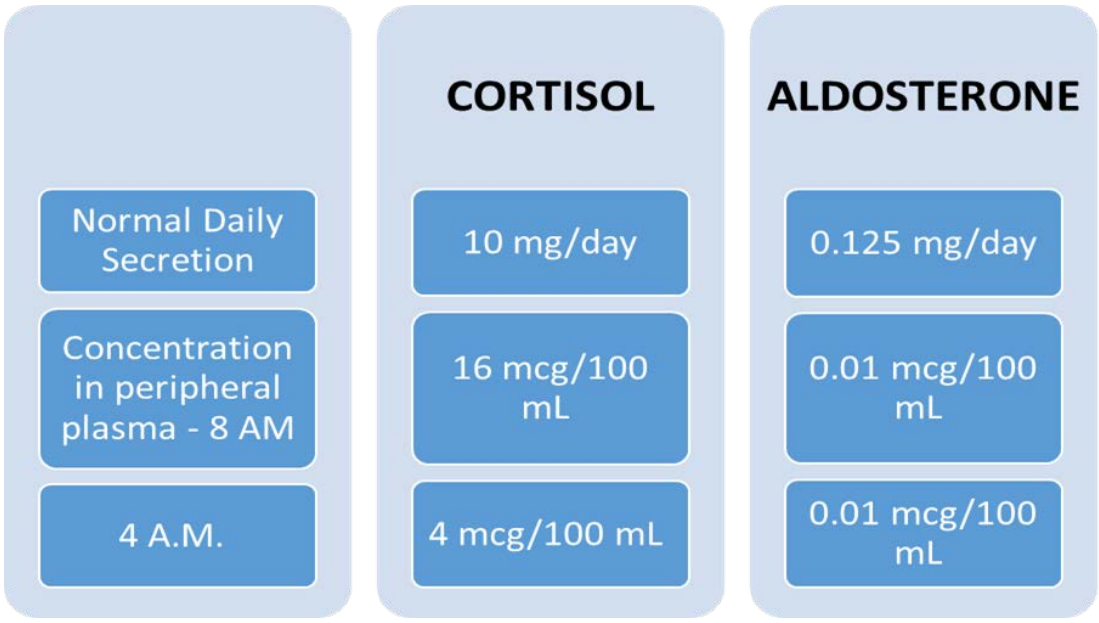
Traditional replacement regimens have used hydrocortisone in doses of 20-30 mg/day

Many authorities advocate a lower hydrocortisone dose of 15-20 mg/day divided into either two doses (e.g., 10-15 mg on awakening and 5 mg in late afternoon) or three doses (e.g., 10 mg on awakening, 5 mg at lunch, and 5 mg in late afternoon).

REVIEW OF LITERATURE







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Addison described deadly outcomes in patients with adrenal destruction in a talk to the South London Medical Society - 1849.

Brown-Séquard showed that bilateral adrenalectomy was lethal in laboratory animals

It was later shown that it is adrenal cortex, rather than the medulla, that was essential for survival in all these ablation experiments and also that the adrenal cortex regulated both carbohydrate breakdown & fluid and electrolyte balance

Reichstein and Kendall isolated and identified the adrenal steroid which had effect on carbohydrate metabolism & hence termed them as *glucocorticoids*. Thus culminating with the synthesis of *cortisone* - the first pharmacologically effective glucocorticoid

Tait and colleagues isolated and characterized the other distinct corticosteroid, *aldosterone*, that potently affected fluid and electrolyte balance and so was termed the *mineralocorticoids*

The isolation of these two distinct corticosteroids that regulated carbohydrate breakdown & fluid and electrolyte balance led to the concept that adrenal cortex comprises of two largely independent structures : an outer zone that produces mineralocorticoids and an inner zone that produces glucocorticoids and androgen precursors.

Patients with adrenal insufficiency can be brought back to normal life expectancy by just replacing them with glucocorticoids and mineralocorticoids. Thus Adrenal androgens are not essential for survival. The levels of adrenal androgens which include DHEA and its sulfated derivative - dehydroepiandrosterone usually peak in the 3rd decade of a person life and then decline progressively.

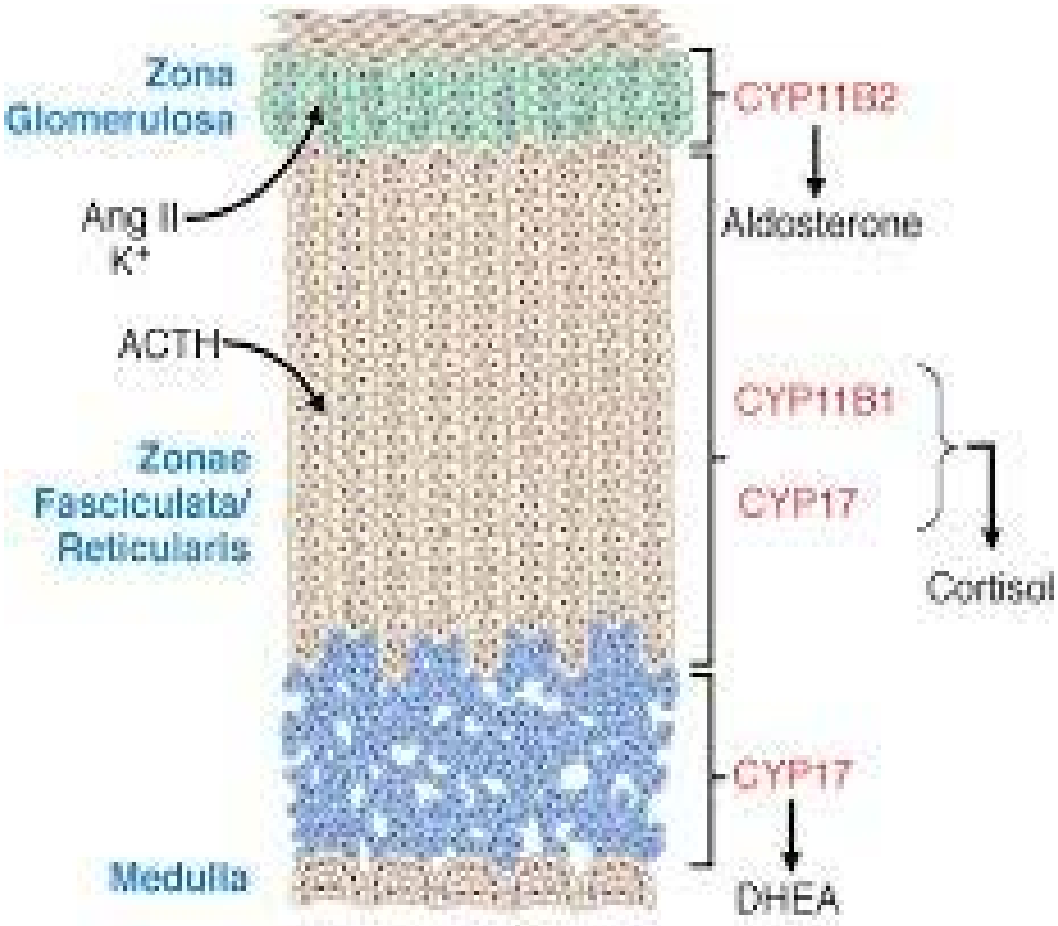
In 1912, Cushing explained patients with hypercorticism, and later he found that pituitary basophilism caused this adrenal overactivity, thus proving the link between anterior pituitary and adrenal function.
Thus ACTH was shown to be importantly needed for maintaining the structural integrity and steroid producing capacity of the inner cortical zones of adrenal gland.

Harris found the role of the hypothalamus in pituitary control. He postulated that a soluble factor produced in the hypothalamus activated ACTH release from anterior pituitary

Hench and colleagues demonstrated the dramatic effect the synthetic cortisone has in the treatment of rheumatoid arthritis

ADRENAL CORTEX

Adrenal cortex based on histology and function are separated into three areas that produce various hormones under different specific regulatory influences.



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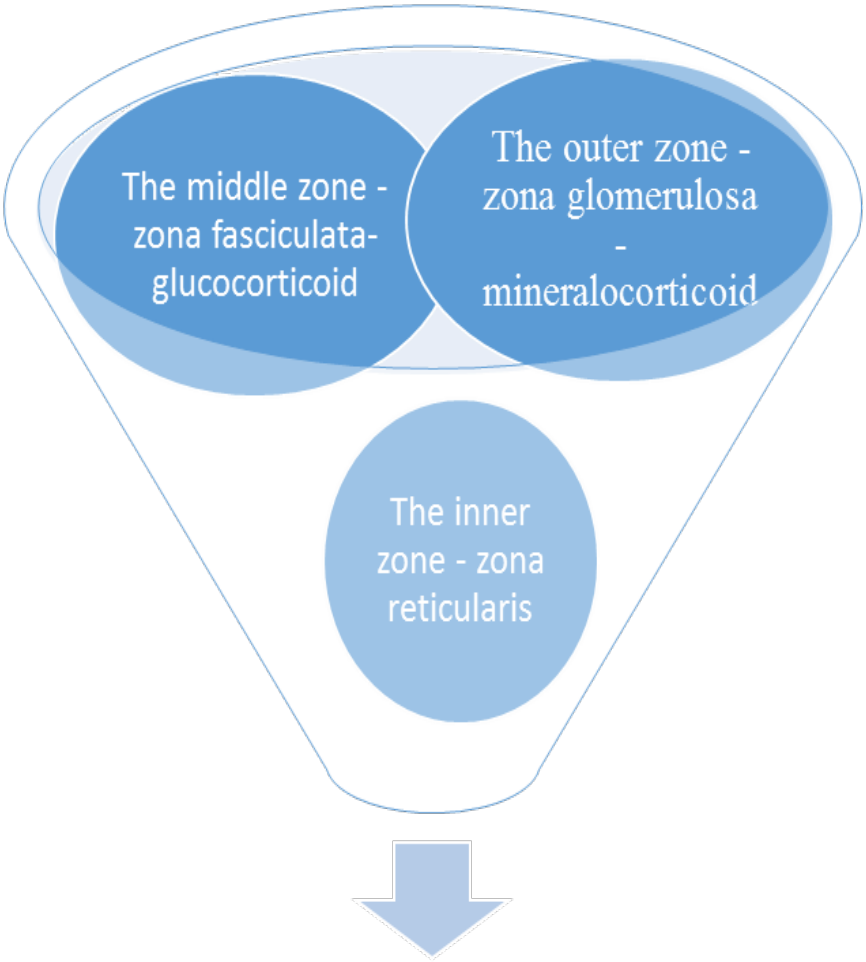


Aldosterone,

Cortisol,

DHEA and its sulfated derivative (DHEAS).

DHEAS circulates at levels 1000 times higher than DHEA. DHEAS are converted to DHEA in the periphery by DHEA sulfatase.

Cells of the zona reticularis	Cells of zona fasciculata	Cells of Zona Glomerulosa
- Express the enzyme - CYP17 that carries out an additional C17-20 lyase reaction which converts C21 corticosteroids to C19 androgen precursors	- Have very few receptors for angiotensin II - Express two enzymes - steroid 17-hydroxylase (CYP17) and 11-hydroxylase (CYP11B1), which catalyze the synthesis of glucocorticoids.	- Express aldosterone synthase (CYP11B2), an enzyme that catalyzes the terminal reactions of mineralocorticoid production - Have receptors for angiotensin II - Regulated mainly by angiotensin II and extracellular K^+.

- The outer zone of adrenal cortex does not undergo atrophy in the absence of continuous stimulation by the ACTH of anterior pituitary gland.

- In the background of persistently elevated ACTH, mineralocorticoid levels increase initially and then comes back to normal.

This phenomenon is termed as *ACTH escape*.

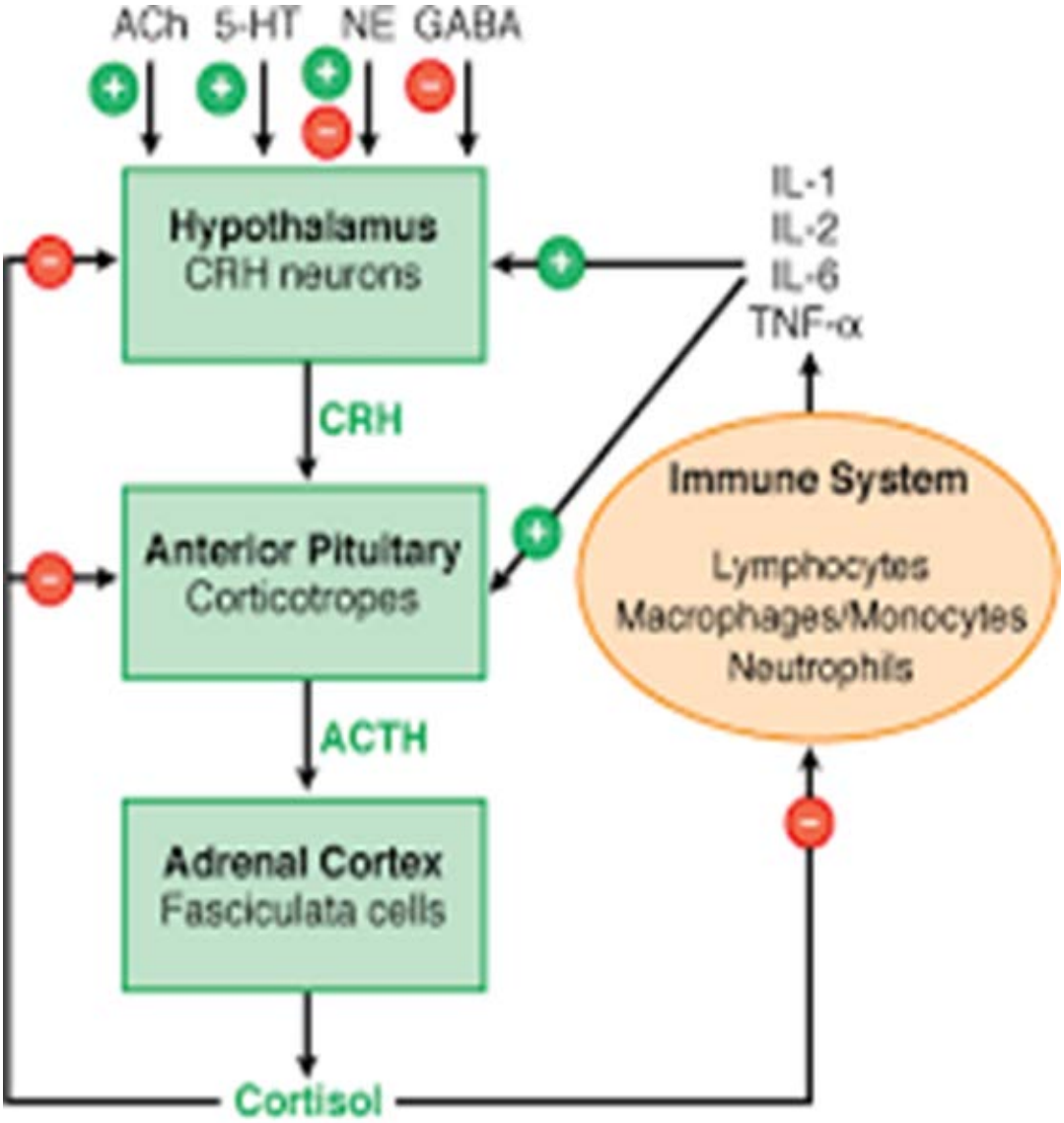
- ACTH acutely stimulates mineralocorticoid synthesis by the zona glomerulosa

The inner zones in the adrenal cortex – consisting cells of zona fasciculata & zona reticularis goes for atrophy in the absence of the anterior pituitary. So the production of glucocorticoids and adrenal androgens will get markedly impaired.

Persistently high levels of ACTH, due to either repeated administration of higher doses of ACTH (exogenously) or to excessive endogenous ACTH production will lead on to hypertrophy and hyperplasia of the inner zones - consisting cells of zona fasciculata & zona reticularis of the adrenal cortex resulting in overproduction of cortisol and adrenal androgens.

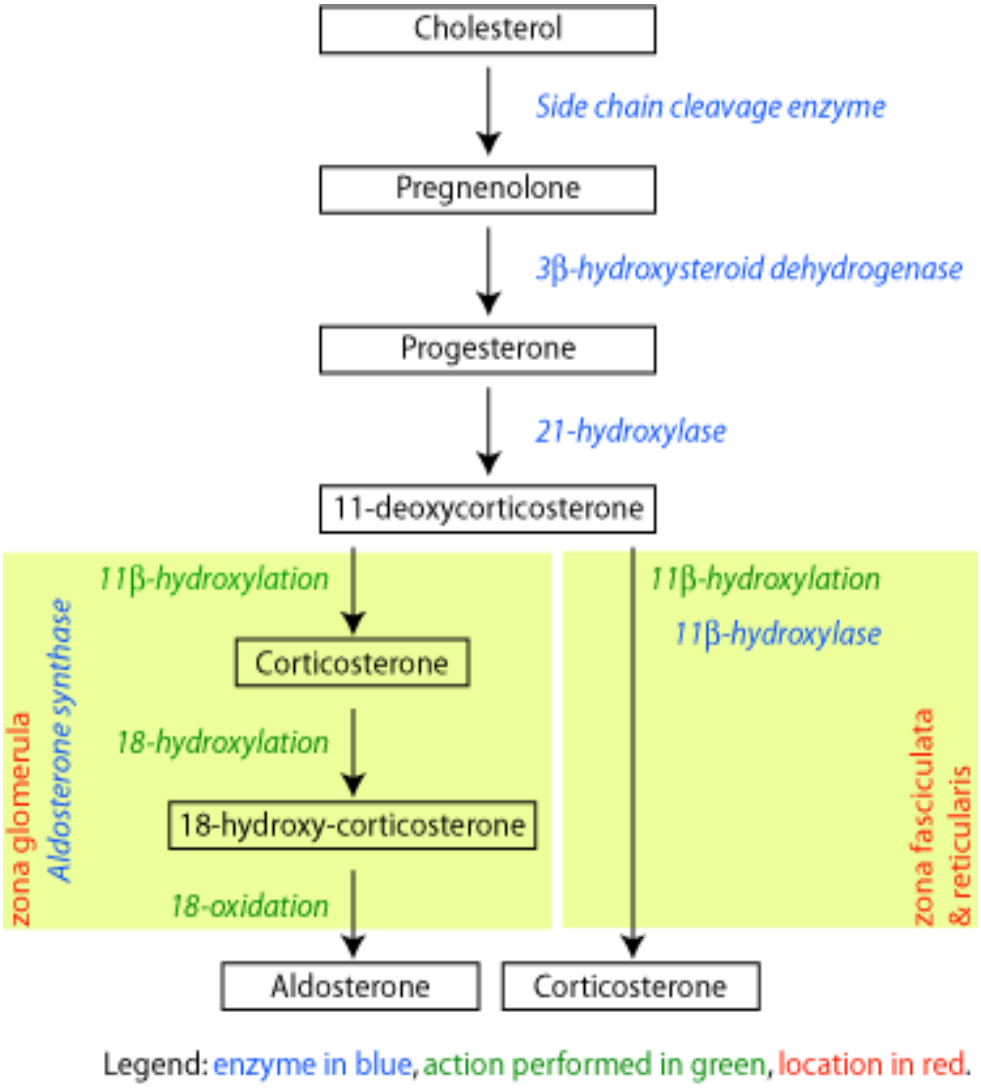
Adrenal hyperplasia is most common with congenital disorders affecting steroidogenesis. In Congenital Adrenal Hyperplasia, ACTH levels are persistently elevated as a secondary response to impaired cortisol production from adrenal cortex.

There are newer informations coming up comparing the relative roles of ACTH & other POMC-derived peptides in stimulating adrenal growth. Yet the essential role of anterior pituitary in maintaining the integrity of the zona fasciculata of adrenal cortex is indisputable.


ACh
5-HT
NE
GABA
Hypothalamus
CRH neurons
IL-1
IL-2
IL-6
TNF-α
CRH
Immune System
Lymphocytes
Macrophages/Monocytes
Neutrophils
Anterior Pituitary
Corticotropes
ACTH
Adrenal Cortex
Fasciculata cells
Cortisol

STEROID SYNTHESIS

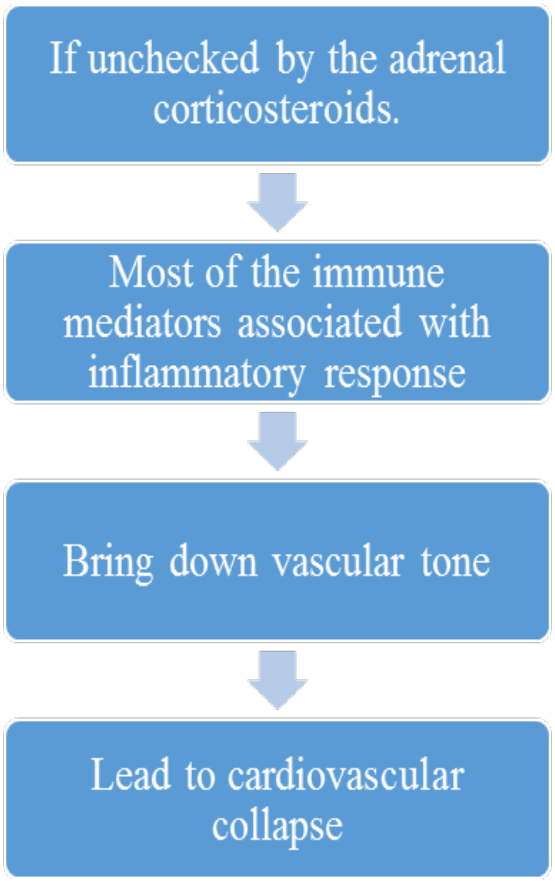
Mixed-function oxidases is the one that is commonly associated with steroid generation. They also play important roles in metabolism of xenobiotics that include drugs and environmental pollutants, and also in the synthesis of endogenous compounds like vitamin D, bile acids, fatty acids, prostaglandins, and biogenic amines apart from steroid hormone.



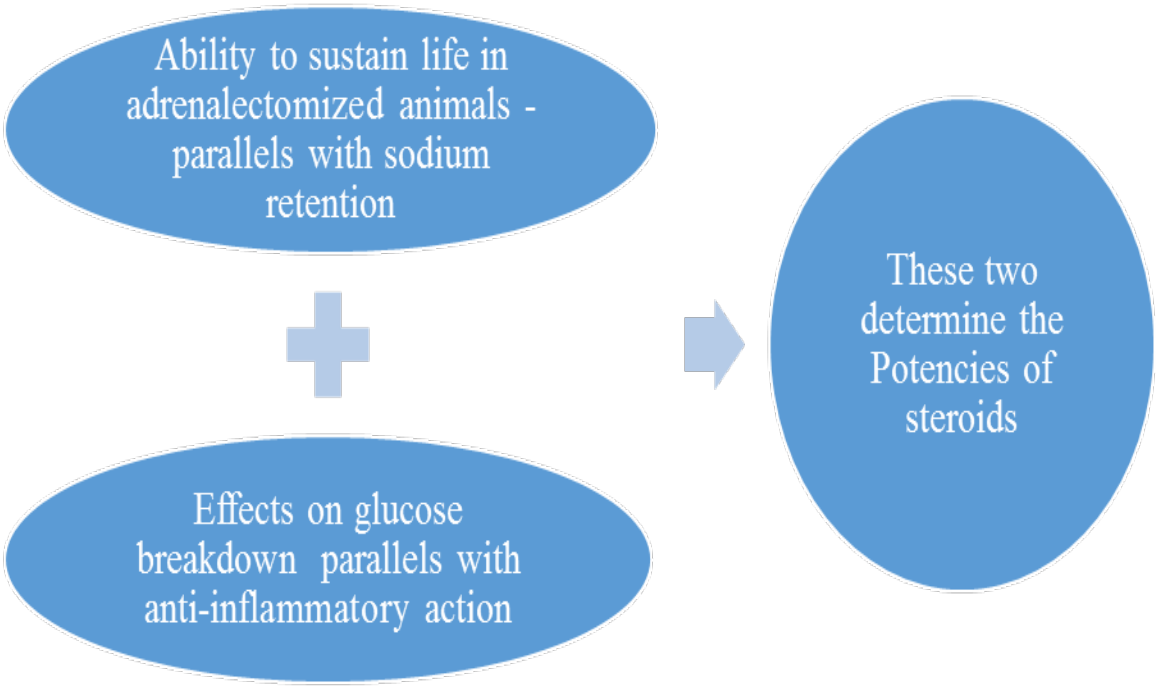
PHYSIOLOGY OF STEROID

Corticosteroids have widespread effects, that include changes in carbohydrate, protein, & lipid breakdown; maintenance of electrolyte & fluid balance; and preservation of normal functioning of the kidney, skeletal muscle, endocrine, nervous, cardiovascular & the immune system.

In addition to all the above mentioned items, corticosteroids make the organism to be endowed with the capacity to resist stressful circumstances like noxious stimuli and environmental changes.



Sometimes the action of corticosteroids are related to the presence of other hormones. For eg, in the absence of lipolytic hormones, cortisol has clearly no effect on the fastness with which lipid breakdown occurs in adipocytes. In a similar way, in the absence of corticosteroid (glucocorticoids), norepinephrine and epinephrine have only minimal effects on lipid breakdown. So administration of a small dose of glucocorticoid markedly increases the lipid degradation action of these catecholamines. These effects of corticosteroids that need concerted actions with other hormonal regulators are called *permissive*.



COMPOUND	ANTI-INFLAMMATORY POTENCY	Na^+-RETAINING POTENCY
Cortisol	1	1
Cortisone	0.8	0.8
Prednisone	4	0.8
Prednisolone	4	0.8
Dexamethasone	25	0

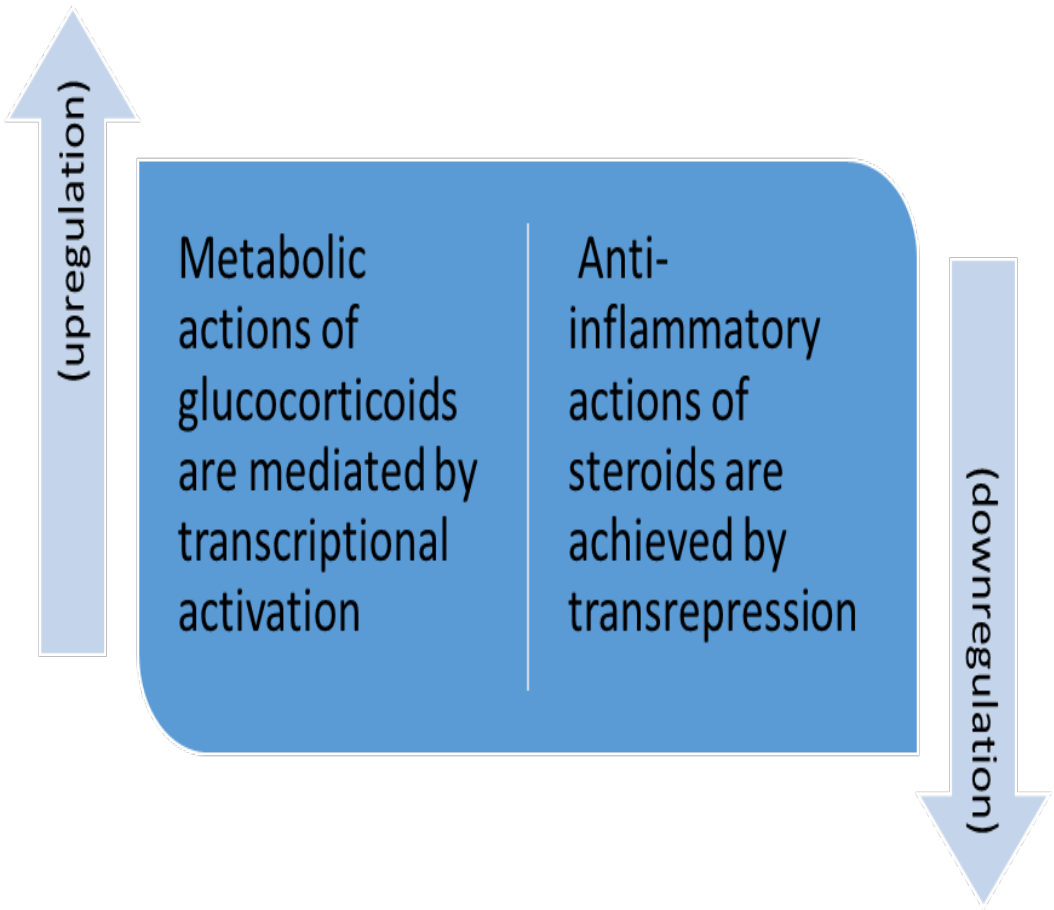
Compound	Duration of action	Equivalent dose(mg)
Cortisol	short acting (8-12 hrs)	20
Cortisone	short acting (8-12 hrs)	25
Prednisone	Intermediate (12-36 hrs)	5
Prednisolone	Intermediate (12-36 hrs)	5
Dexamethasone	Long acting (36-72 hrs)	0.75

MECHANISM OF ACTION OF CORTICOSTEROID

Corticosteroids controls the expression of corticosteroid-responsive genes in target tissue by binding to particular receptor proteins in the target tissues thereby resulting in changes in the levels of proteins produced by the different target tissues.

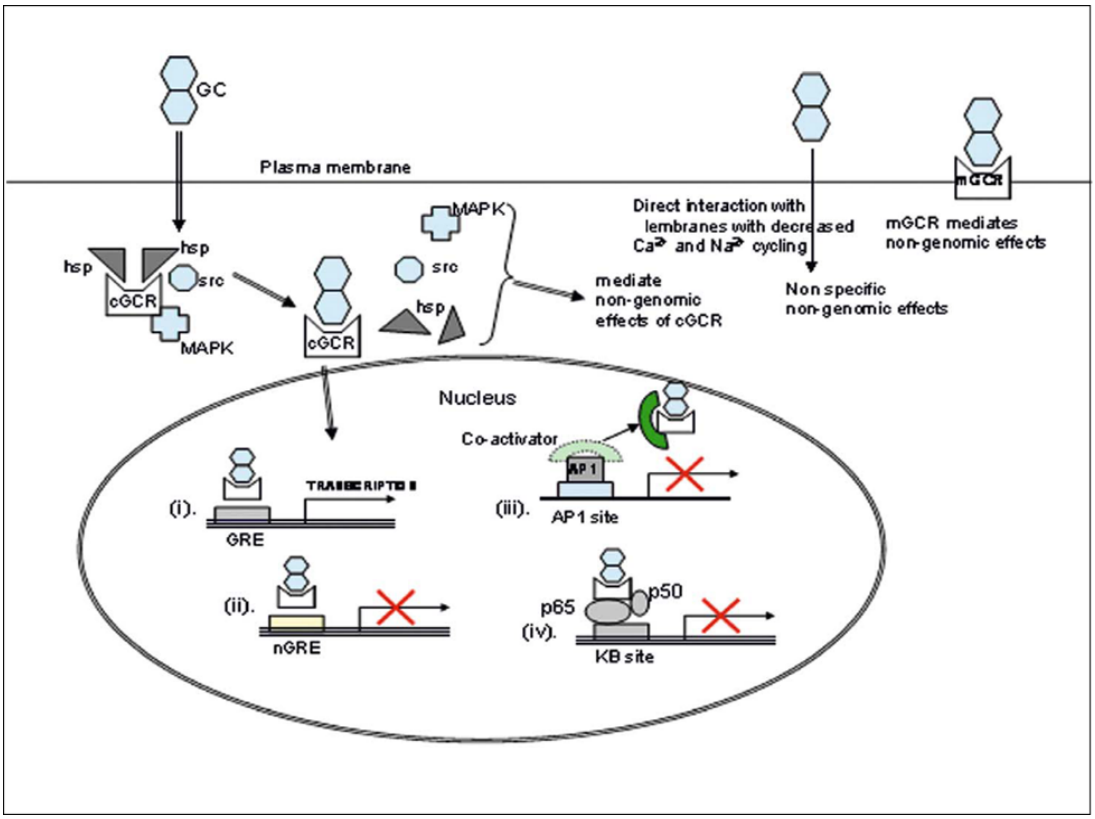
As longer time - required to modulate (transcription) gene expression and (translation) protein synthesis, actions of steroid appear late after its administration.

Though corticosteroids most of the time act by increasing gene transcription, there are proven examples in which (cortisol) glucocorticoids reduce gene transcription. Eg. Pro-opiomelanocortin gene, cyclooxygenase-2 (COX-2) gene, inducible nitric oxide synthase (NOS2) gene.



This fact suggests that selective GR ligands will have anti-inflammatory actions with very less metabolic side effects.

In addition to the above mentioned different modes of action, steroids may produce some of their immediate action by non- genomic mechanism.


GC
Plasma membrane
hsp
src
cGCR
MAPK
MAPK
src
hsp
cGCR
mediate
non-genomic
effects of cGCR
Direct interaction with
lembranes with decreased
Ca and Na cycling
Non specific
non-genomic effects
mGCR
mGCR mediates
non-genomic effects
Nucleus
Co-activator
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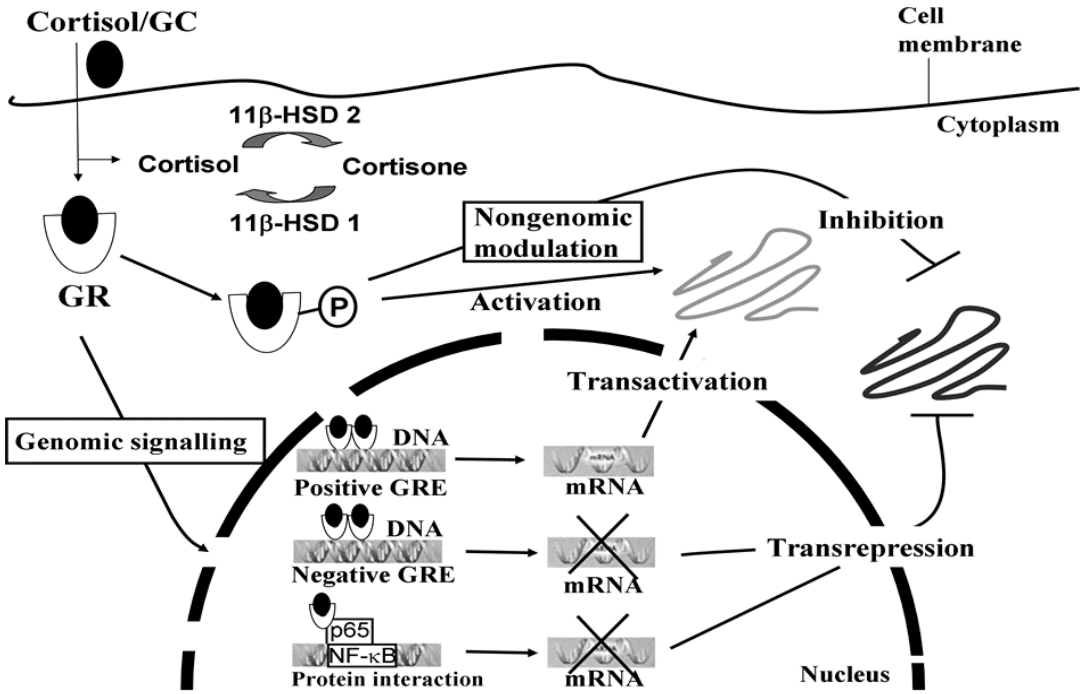
(i).
GRE
(iii).
AP1 site
(ii).
nGRE
p65
p50
(iv).
KB site


Cortisol/GC
Cell
membrane
Cytoplasm
11β-HSD 2
Cortisol
Cortisone
11β-HSD 1
GR
P
Nongenomic
modulation
Activation
Inhibition
Transactivation
Genomic signalling
DNA
Positive GRE
mRNA
DNA
Negative GRE
mRNA
Transrepression
p65
NF-κB
Protein interaction
mRNA
Nucleus

Steroid activates GR (glucocorticoid receptor) and translocates into the nucleus. The translocated GR is now complexed with proteins like (HSP) heat- shock protein 90; HSP70; and immunophilin (56,000-Da protein that bind the immunosuppressive drugs- cyclosporine and tacrolimus).

GR has 2 isoforms alpha & beta.

GR beta is a truncated dominantly negative variant which lacks around 35 amino acids at its C-terminus and so unable to bind glucocorticoids or induce gene expression.

GR beta expression is increased by tumor necrosis factor (TNF) and some other pro-inflammatory cytokines. So its increased level is thought to contribute to glucocorticoid resistance in some individuals.

In the case of partial loss of GR function, the HPA axis is reset to a higher level so as to produce compensatory increase in ACTH and cortisol secretion. This excess ACTH production increases mineralocorticoids and sex hormone production in addition to corticosteroid. Because the androgen receptor & mineralocorticoid receptor are intact, these persons present with features of mineralocorticoid excess (hypokalemic metabolic alkalosis & hypertension) with or without androgen level excess (menstrual irregularities, anovulation, infertility, acne, hirsutism, male pattern baldness). In the pediatric age group, the excess adrenal androgens will result in precocious sexual development.

Non-Receptor Mediated Mechanism for Corticosteroid Specificity

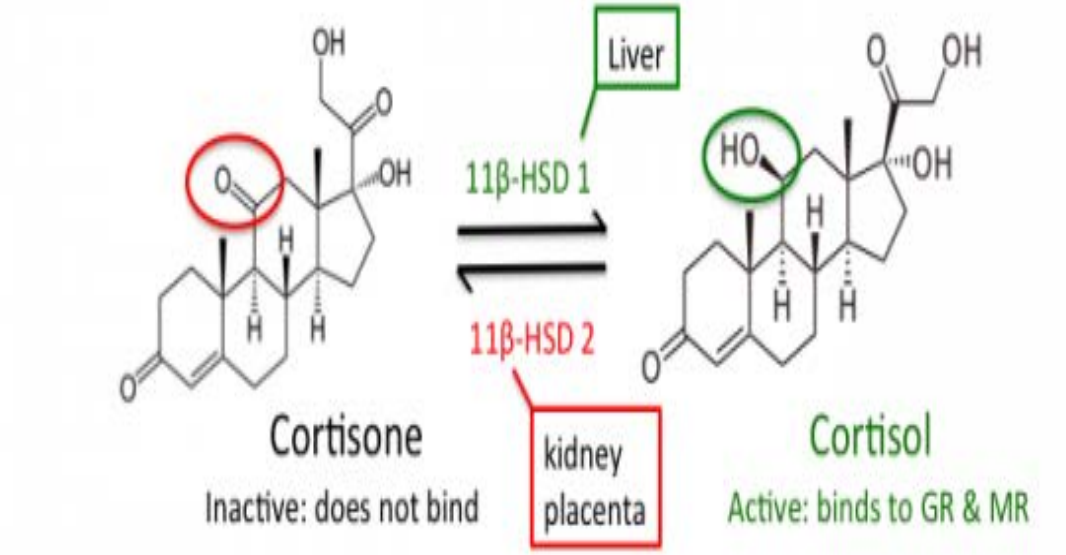
The (11betaHSD2) type 2 isozyme of 11beta-hydroxysteroid dehydrogenase plays an important role in steroid specificity especially in kidney, colon & salivary glands.

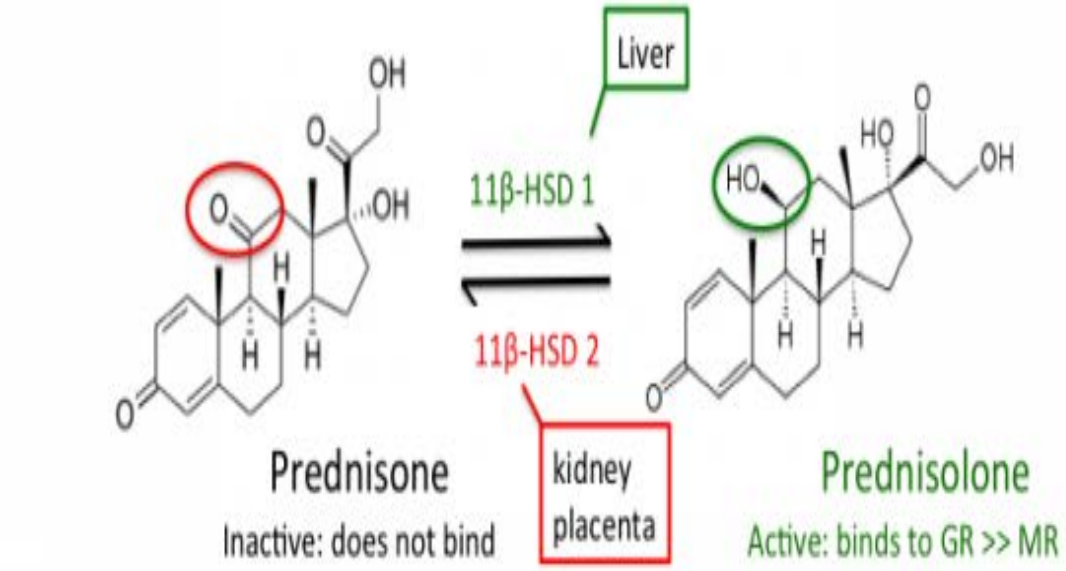
This enzyme converts glucocorticoids such as cortisol to cortisone which is receptor-inactive 11-keto derivative. As aldosterone exist in hemiacetal form which is its major form in the physiological setting - it is resistant to 11beta HSD action. Thus mineralocorticoid escapes this inactivation and maintains its sodium & water retention activity.

In the absence of 11betaHSD2, as take place in the *syndrome of apparent mineralocorticoid excess* (an inherited disease), the Mineralocorticoid Receptor is activated by cortisol, leading on to severe hypokalemia and hypertension.

A state of aldosterone excess also can be produced by inhibiting 11betaHSD with *glycyrrhizic acid* (a component of licorice) which is the cause of licorice-induced hypertension.

Modulation by 11β-hydroxysteroid dehydrogenase (HSD)





ROLE OF STEROIDS

Carbohydrate and Protein Metabolism

- Corticosteroids markedly affect protein & carbohydrate metabolism, which can be considered as protective phenomenon for glucose-dependent tissues like brain and heart from starvation.
- They stimulate the liver to synthesize glucose from and glycerol & amino acids. In the peripheral tissue, glucocorticoids bring down glucose utilization, mean while increasing the protein breakdown and the production of glutamine, and also activate lipid breakdown, all these resulting in increased levels of amino acids and glycerol for gluconeogenesis in the periphery.
- The net result is to rise blood glucose levels. Because of these effects on glucose breakdown, steroids can worsen glycemic control in individuals with overt (established) diabetes and can result in the onset of hyperglycemia in susceptible individuals.

Steroid reduces glucose uptake in thymocytes, polymorphonuclear leukocyte, adipose tissue, skin, fibroblasts. These action occur probably due to translocating the glucose transporters from the plasma membrane of these target tissue to an intracellular location. These peripheral actions of steroid are also associated with a number of other catabolic effects like negative nitrogen balance, thinning of the skin, atrophy of lymphoid tissue & decreased muscle mass.

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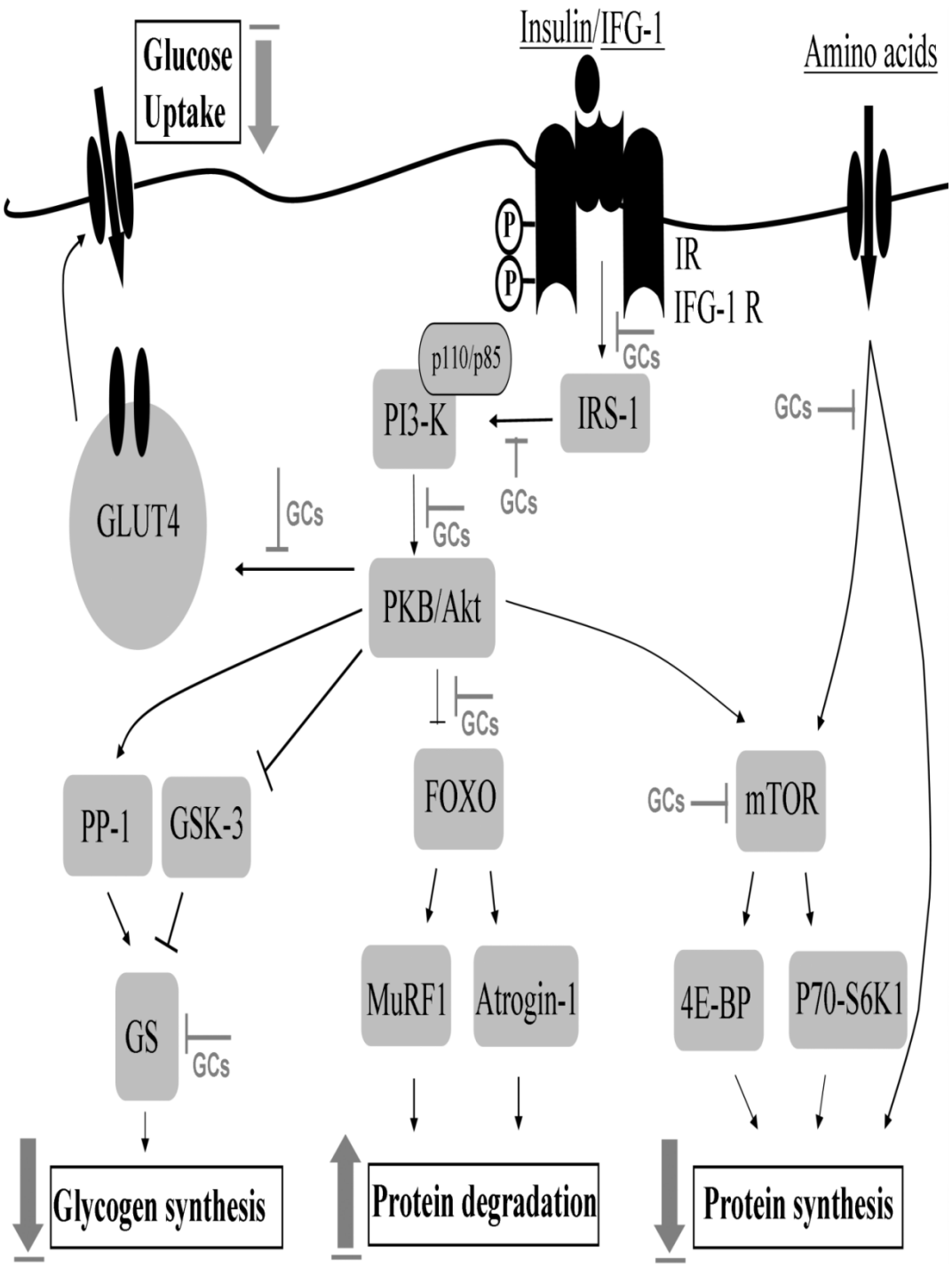
Amino acids are mobilized from a humpty number of tissues by the glucocorticoids. They reach the liver and act as substrate for the gluconeogenesis & glycogen synthesis. In the liver, steroid increases the transcription of a large number of enzymes that are needed in glucose production and amino acid breakdown (Eg. (PEPCK) phosphoenolpyruvate carboxykinase, glucose-6-phosphatase, and fructose-2,6-bisphosphatase (bifunctional enzyme).

For the regulation of PEPCK gene expression, complex interplay among insulin, glucagon, glucocorticoids and catecholamines is needed.


Glucose Uptake
Insulin/IFG-1
Amino acids
P
P
IR
IFG-1 R
GCs
p110/p85
PI3-K
IRS-1
GCs
GCs
GLUT4
GCs
GCs
PKB/Akt
GCs
FOXO
GCs
mTOR
PP-1
GSK-3
MuRF1
Atrogin-1
4E-BP
P70-S6K1
GS
GCs
Glycogen synthesis
Protein degradation
Protein synthesis

Lipid Metabolism

-Two effects are observed

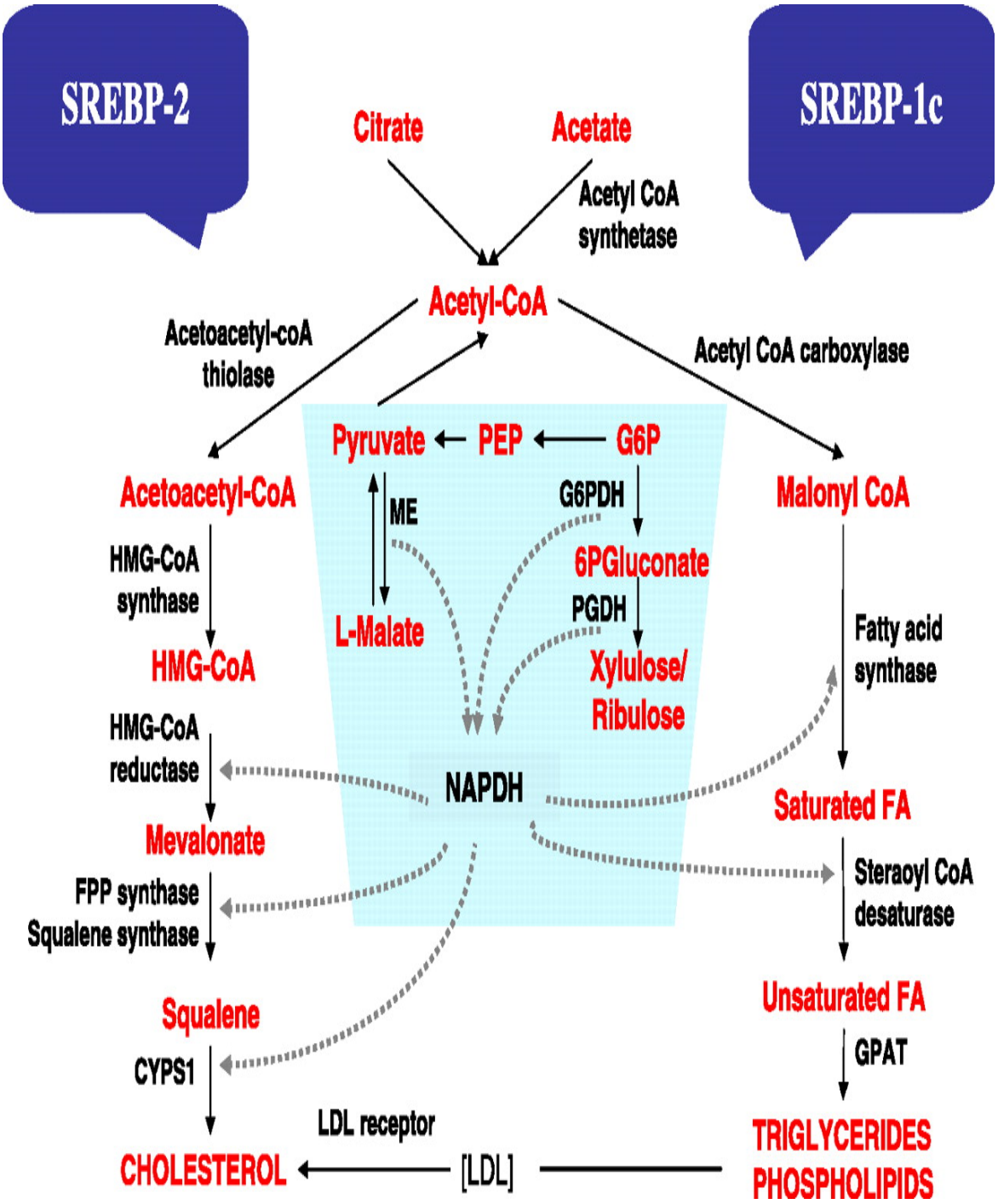
The first is the significant redistribution of body fat due to hypercorticism – endogenous or exogenous steroid - (Cushing's syndrome). So, there is increased fat in the face ("moon facies"), back of the neck ("buffalo hump"), and supraclavicular area, along with which occurs a loss of fat in the (limb) extremities

The second is the permissive increase of the lipolytic effect due to the agents like growth hormone and adrenergic receptor agonists. This results in an increase in free fatty acids in the blood after glucocorticoid administration

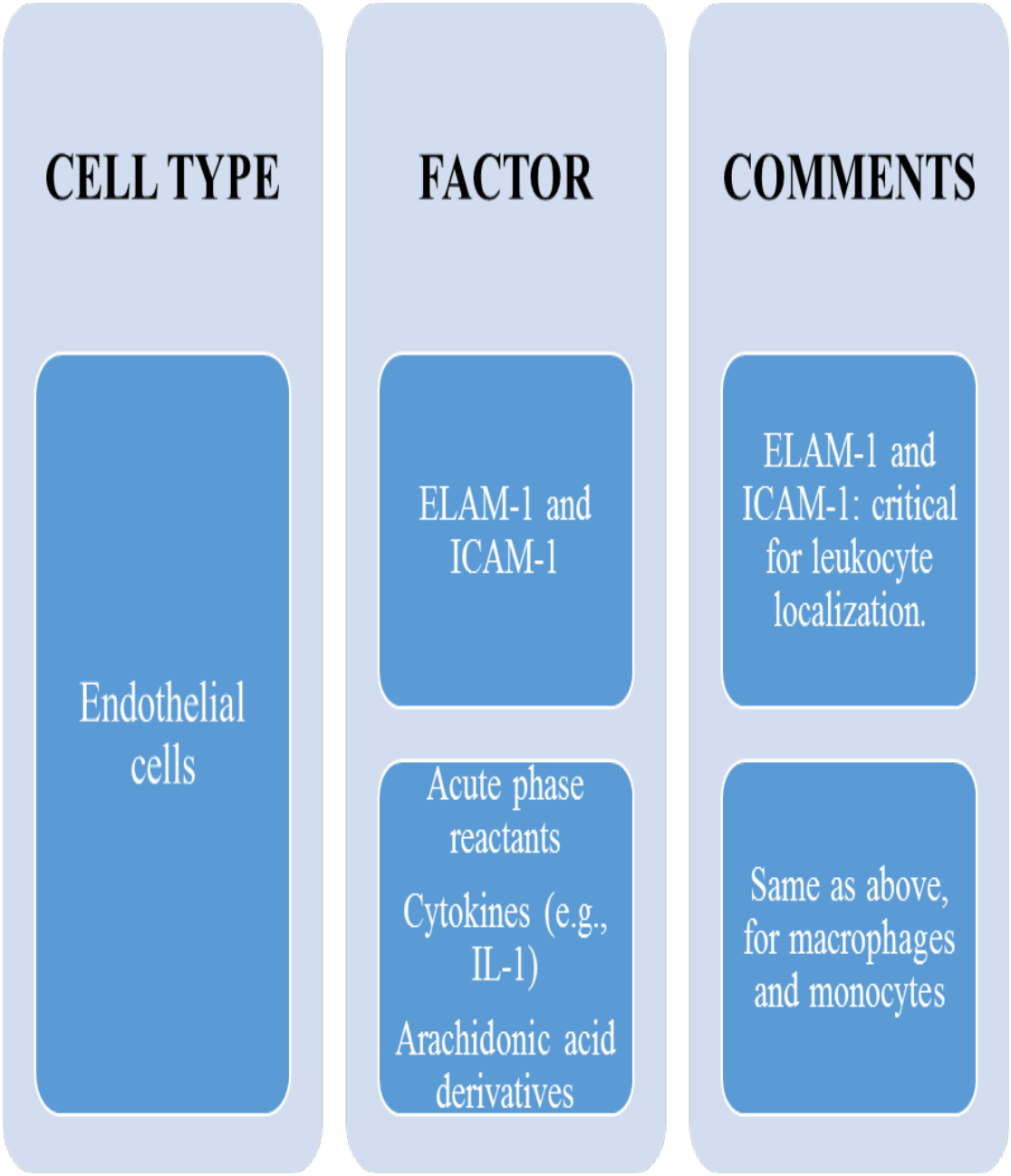
One reason for the redistribution of body fat is due to the difference in insulin & glucocorticoid sensitivity in peripheral and truncal adipocytes.

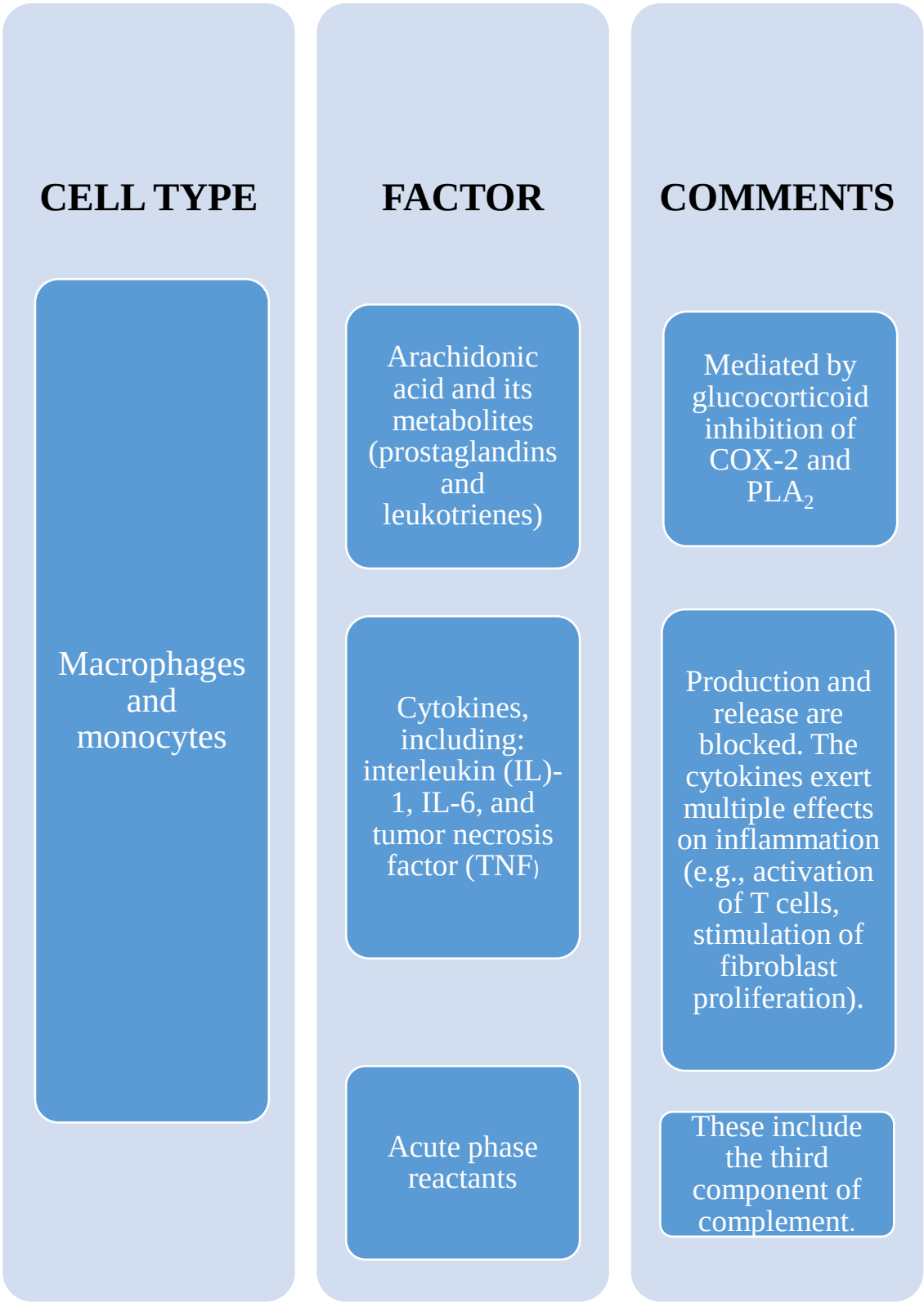
So truncal adipocytes respond mainly to increased levels of insulin which gets secreted in response to glucocorticoid-induced hyperglycemia, at the same time peripheral adipocytes are very less sensitive to insulin but respond well to the glucocorticoid-facilitated effects of other lipolytic hormones (growth hormone, catecholamines).

This differential sensitivity of steroids & other hormone may reflect differences in the expression of enzyme 11betaHSD1 which is responsible for converting cortisone (inactive form) into cortisol (active form) in target tissues.


SREBP-2
SREBP-1c
Citrate
Acetate
Acetyl CoA synthetase
Acetyl-CoA
Acetoacetyl-coA thiolase
Acetyl CoA carboxylase
Pyruvate
PEP
G6P
Acetoacetyl-CoA
ME
G6PDH
Malonyl CoA
HMG-CoA synthase
6PGluconate
PGDH
L-Malate
Fatty acid synthase
HMG-CoA
Xylulose/ Ribulose
HMG-CoA reductase
NAPDH
Saturated FA
Mevalonate
Steraoyl CoA desaturase
FPP synthase
Squalene synthase
Unsaturated FA
Squalene
GPAT
CYPS1
LDL receptor
TRIGLYCERIDES
PHOSPHOLIPIDS
CHOLESTEROL
[LDL]

Anti-Inflammatory and Immunosuppressive Effects



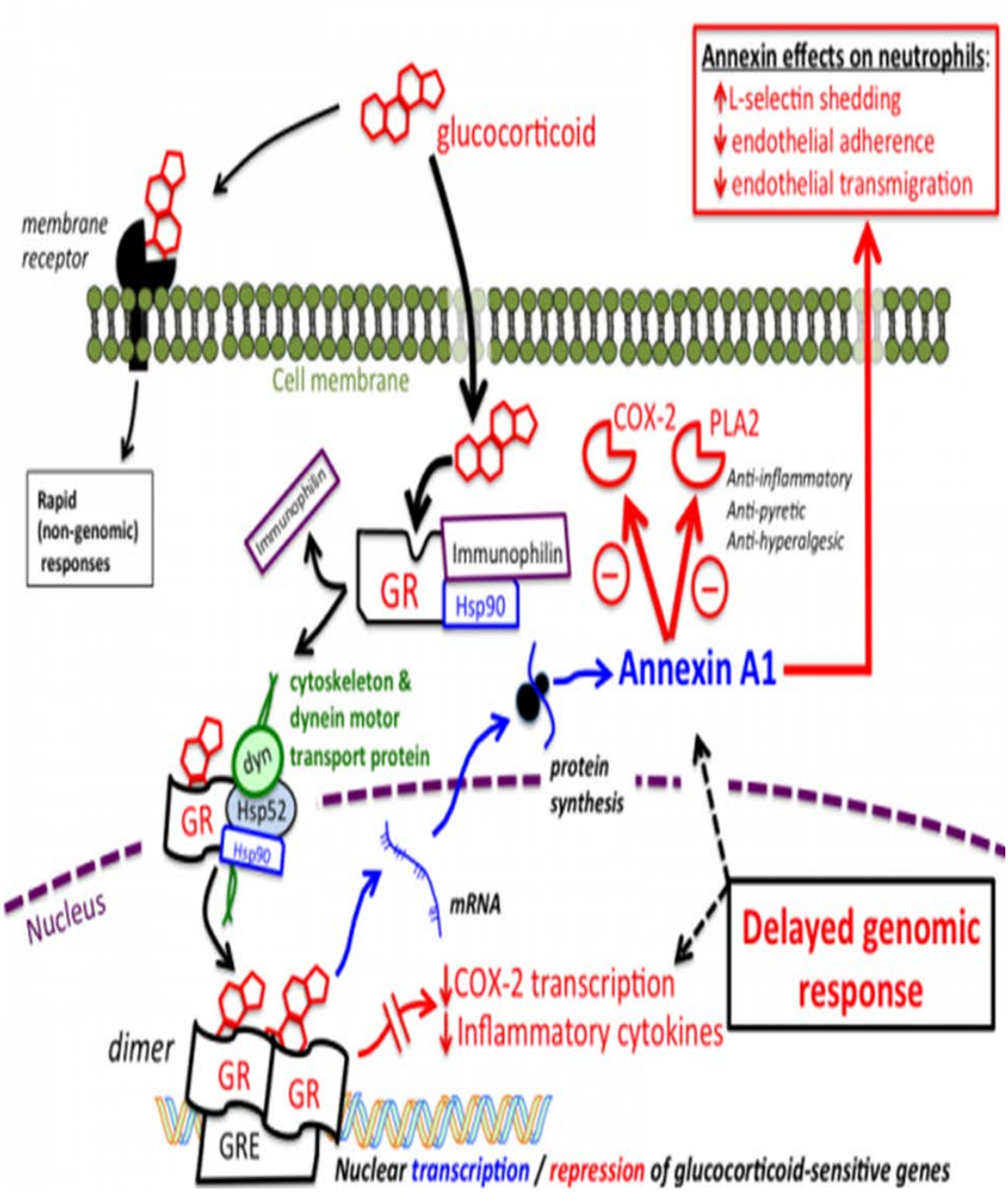

CELL TYPE
FACTOR
COMMENTS
Macrophages and monocytes
Arachidonic acid and its metabolites (prostaglandins and leukotrienes)
Mediated by glucocorticoid inhibition of COX-2 and PLA2
Cytokines, including: interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)
Production and release are blocked. The cytokines exert multiple effects on inflammation (e.g., activation of T cells, stimulation of fibroblast proliferation).
Acute phase reactants
These include the third component of complement.

CELL TYPE	FACTOR	COMMENTS
Basophils	Histamine, LTC_4	IgE-dependent release inhibited by glucocorticoids
Fibroblasts	Arachidonic acid metabolites	Same as above for macrophages and monocytes. Glucocorticoids also suppress growth factor–induced DNA synthesis and fibroblast proliferation.
Lymphocytes	Cytokines (IL-1, IL-2, IL-3, IL-6, TNF-, GM-CSF, interferon-)	Same as above for macrophages and monocytes

-Glucocorticoids can stop or inhibit inflammation in response to multiple provoking events like radiant, mechanical, chemical, infectious, and immunological stimuli.
- Though the use of steroids as anti-inflammatory agents does not rectify the underlying cause of the disease, the suppression of inflammation is of very great clinical usefulness.

In a same way, glucocorticoids are of very great value in treating diseases that occur as a result of undesirable immune reactions. These diseases range from urticaria (condition that result from undesirable humoral immunity), to those of transplantation rejection (condition mediated by undesirable cellular immune mechanisms).

Thus steroids decrease the release of vasoactive and chemoattractive factors, decreases secretion of lipolytic and proteolytic enzymes, decreases extravasation of leukocytes into the areas of injury, and thereby decreases fibrosis of that particular tissue. Steroids also reduces expression of pro-inflammatory cytokines, COX-2 and NO S2 genes.(transrepression)


Annexin effects on neutrophils:
↑L-selectin shedding
↓endothelial adherence
↓endothelial transmigration
glucocorticoid
membrane receptor
Cell membrane
Rapid (non-genomic) responses
Immunophilin
GR
Immunophilin
Hsp90
COX-2
PLA2
Anti-inflammatory
Anti-pyretic
Anti-hyperalgesic
Annexin A1
cytoskeleton & dynein motor transport protein
dyn
GR
Hsp52
Hsp90
protein synthesis
Nucleus
mRNA
Delayed genomic response
↓COX-2 transcription
↓Inflammatory cytokines
dimer
GR
GR
GRE
Nuclear transcription / repression of glucocorticoid-sensitive genes

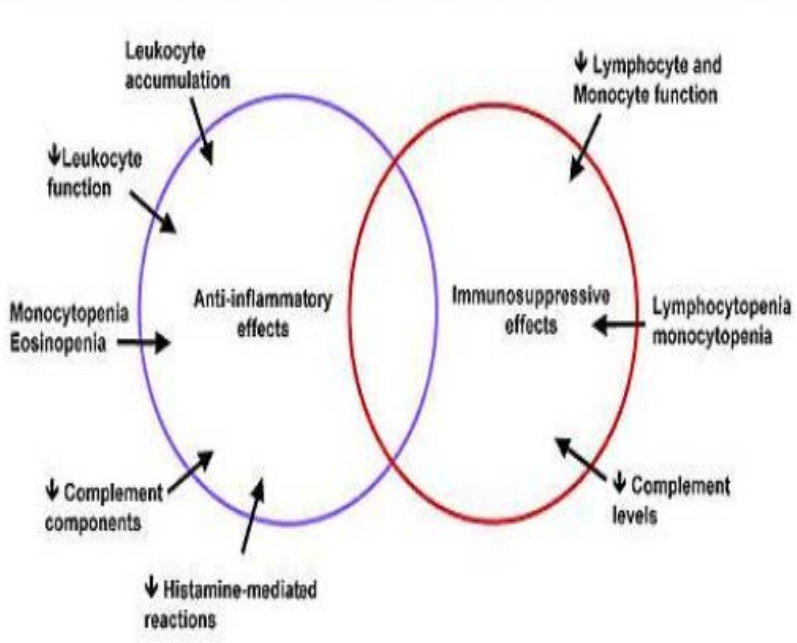


Figure 2. Anti-inflammatory and immunosuppressive effects of corticosteroids.

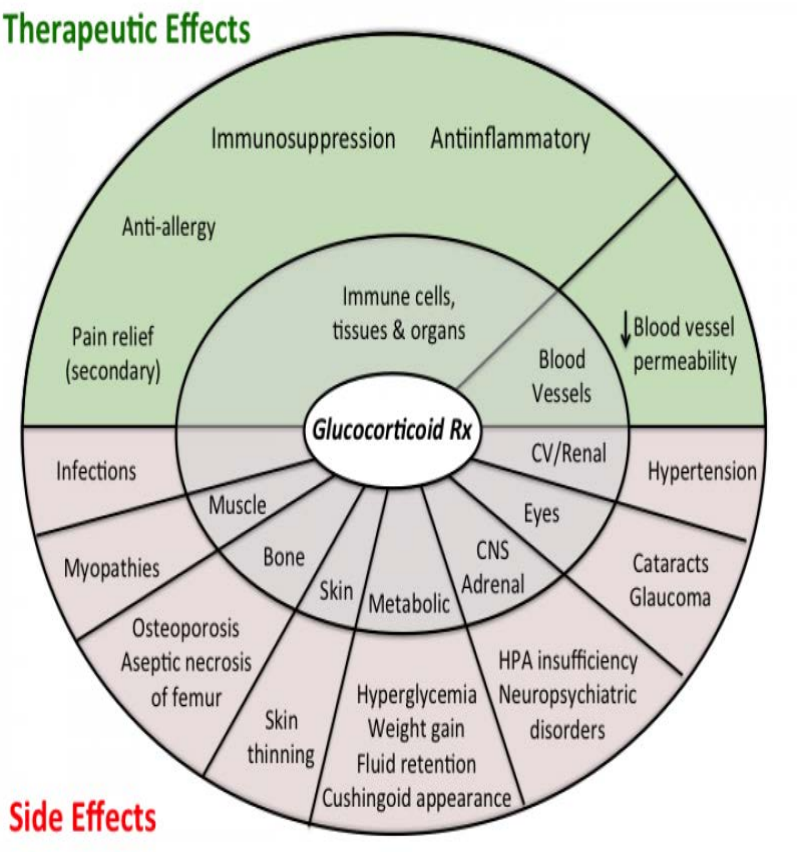


Table 3 - Side effects of glucocorticoids

Affected system	Undesirable effect
Cardiovascular	Arterial hypertension
	Congestive heart failure
Gastrointestinal	Esophagitis, gastritis, peptic ulcer
	Digestive hemorrhage
Neuropsychiatric	Psychiatric disorders in general
	Intracranial hypertension
Ophthalmic	Glaucoma
	Cataracts
Musculoskeletal	Osteoporosis
	Aseptic bone necrosis
	Myopathies
Endocrine/metabolic	Truncal obesity, supraclavicular
	and posterior cervical fat deposition
	Hirsutism, masculinization, menstrual disorders
	Growth failure in children and adolescents
	Hiperglycemia, dyslipidemia
	Negative nitrogen, potassium and calcium balance
	Sodium retention
	Hypokalemia and metabolic alkalosis
Imunne	Decrease in inflammatory response
	Higher susceptibility to infections
Cutaneous	Striae and acne, delayed wound healing
Vascular	Vasculitides
	Thromboembolism
	Arteriosclerosis

GLUCOCORTICOID & INSULIN RESISTANCE

The ‘Metabolic Syndrome’ or ‘Reaven's Syndrome X' [1] or ‘Insulin Resistance Syndrome' consists of hypertension, glucose intolerance and dyslipidaemia which is further associated with low birth weight [2,3], central obesity [4], abnormalities of thrombosis and fibrinolysis, impaired endothelium-dependent vasodilatation [5], reproductive dysfunction in women [6] and insulin resistance. All these are risk factors for cardiovascular disease.

Cortisol deficiency consists of postural hypotension, weight loss and hypoglycaemia. While cortisol excess comprises of hypertension, central obesity and glucose intolerance. Opposing the insulin action, i.e. producing a insulin resistance state is one of the main mechanism by which the above mentioned effects of cortisol excess occur.

Insulin is produced by beta part in response to increase in plasma glucose levels, specific amino acids like arginine, electrolyte- potassium and parasympathetic nervous system tone.

Insulin resistance indicate either impaired insulin- directed decrease of hepatic glucose production and or impaired insulin-dependent rise in peripheral glucose uptake. Enhanced hepatic glucose release may be most important in subjects with glucose intolerance [9] whereas impaired peripheral glucose uptake may be the major defect in subjects with normal glucose tolerance [10].

Steroid by opposing the action of insulin, increase central appetite [16].

Glucocorticoids inhibit insulin production from pancreatic beta-cells [17,19].

Central actions of Glucocorticoids may result in enhanced vagal stimulation of insulin secretion.

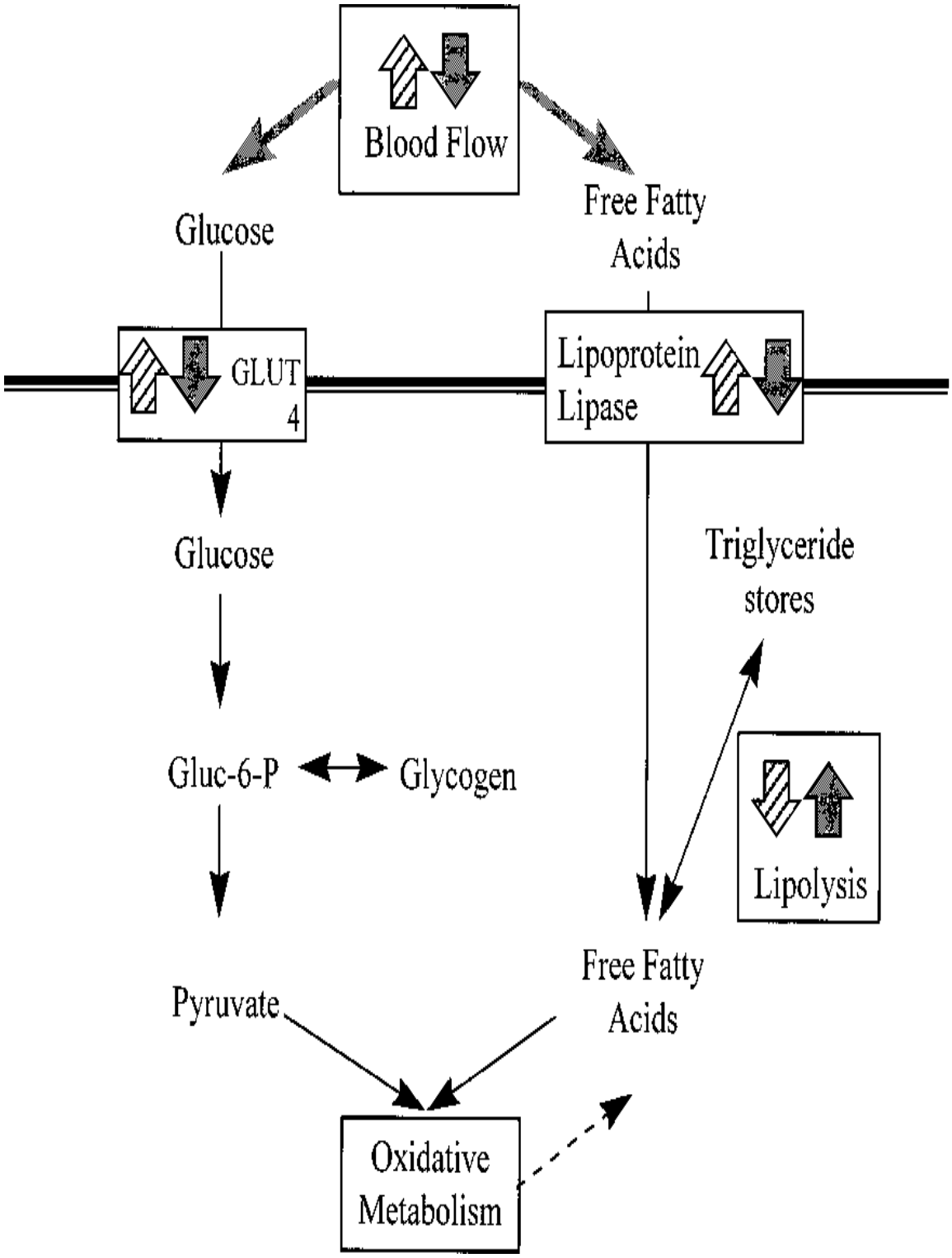
TARGET ORGAN RESPONSES TO INSULIN

Glucocorticoids can decrease insulin receptor binding affinity without decreasing insulin receptor numbers [22,23], decrease receptor number and affinity [24], have no effect on receptor affinity or number [25] or increase receptor number without affecting affinity [15].

These are the various things observed with usage of steroid.

It is now obvious to conclude that these small changes in insulin receptor number or binding affinity are not sufficient enough to explain the degree of insulin resistance seen with glucocorticoids.

TISSUE-SPECIFIC DETERMINANTS FOR INSULIN RESPONSE



In adipocytes, lipid synthesis pathways occurs predominantly.

In skeletal muscle either glycogen synthesis or oxidative metabolism (of pyruvate or free fatty acids) occurs predominantly.

GLUT 4 is expressed especially in skeletal muscle and lipoprotein lipase mainly in adipose tissue.

Actions of glucocorticoids (grey arrows) and insulin (striped arrows) are shown either as positive (arrow up) or negative (arrow down) effects in the above mentioned diagram.

The major action of glucocorticoids is to reduce insulin- mediated vasodilatation, enhance lipolysis especially by its permissive effect (ie by inducing local production of adrenaline), thus resulting in increased free fatty acid level in serum which competes with pyruvate for mitochondrial oxidative metabolism & reduce translocation of GLUT 4 to the cell surface.

So the expression of GLUT 4 is actually increased by glucocorticoids in skeletal muscle and adipose tissue in a similar way by which insulin does. However, translocation of GLUT 4 to the cell surface in response to the insulin and to other stimuli (e.g. hypoxia) is inhibited in the presence of glucocorticoids [29-33].

Thus it is made clear that oxidation of pyruvate is affected by competing substrates like non-esterified free fatty acids. Acute and not the chronic administration of free fatty acids results in insulin resistance. So

Acipimox and nicotinic acid administration lowers free fatty acid level thereby increasing insulin sensitivity [35].

Now we also know that the marked lipolysis caused by glucocorticoids is by up-regulation of phenyl-ethanolamine *N*-methyltransferase [41], which converts noradrenaline into adrenaline especially in skeletal muscle. So inhibition of this enzyme brings down glucocorticoid-induced insulin resistance [41].

It is also said that, up-regulation of peroxisome proliferator-activated gamma receptors increases lipolysis. So insulin sensitizing thiazolidinediones are exogenous ligands that can be used in case of insulin resistance as it down regulates PPAR-gamma[42].

Glucocorticoids may result in rise in circulating free fatty acids by inhibiting lipoprotein lipase [43].

Non-metabolic determinants of peripheral glucose uptake

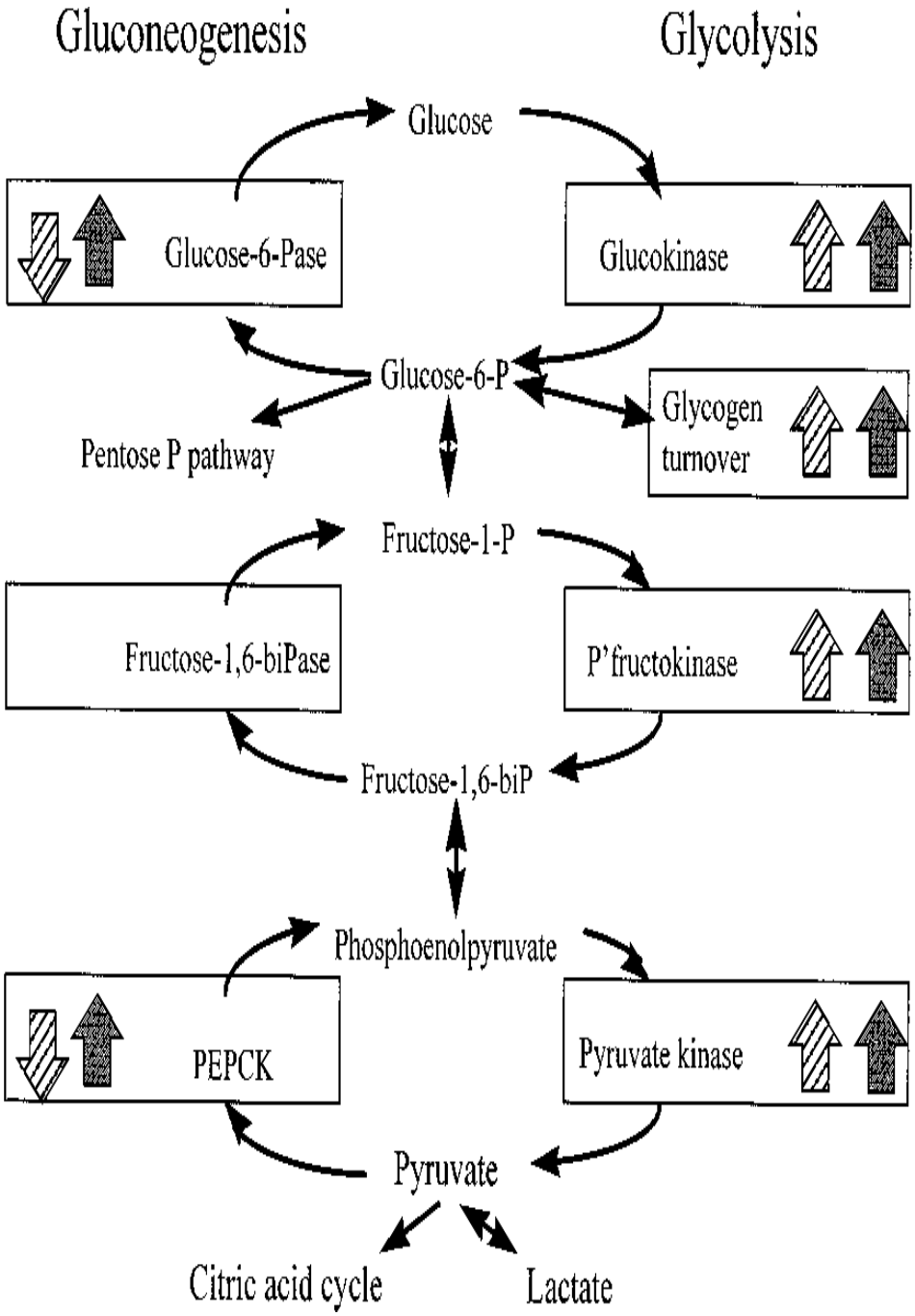
Insulin results in endothelium-dependent vasodilatation by increasing nitric oxide synthesis [44] thereby contributing to enhanced glucose uptake especially in skeletal muscle.

The impaired endothelium-dependent vasodilatation in persons with features of the metabolic syndrome results in reduced insulin action in skeletal muscle.

Glucocorticoids affects endothelium-dependent vasodilatation in humans *in vivo* [48] and thus insulin action is counterbalanced by them.

Hepatic glucose release

In some areas insulin and glucocorticoids oppose each other's actions, particularly on gluconeogenesis (PEPCK) and release of glucose from glucose 6-phosphate. In other areas, insulin and glucocorticoids do not oppose each other, especially in promoting oxidative glycolysis and increasing turnover between glucose 6-phosphate and glycogen.



AIMS AND OBJECTIVES

AIM AND OBJECTIVES

1) To study the occurrence of hyperglycemia within 48 hours in patients started on corticosteroid therapy.

2) To study the various factors associated with steroid induced hyperglycemia with special reference to the :-

   a) nature of corticosteroid used.

   b) presence of risk factors for diabetes.

Case Definition:-

Known Bronchial Asthma or Chronic Obstructive Pulmonary Disease patient aged >= 18 years, non- diabetic, on oral drugs like salbutamol and theophylline and not on any oral / inhalational steroid so far and not received any parenteral steroid in last 4 weeks admitted for acute exacerbation but not in respiratory failure (signs include cyanosis, altered mental status with spo2 < 90, heart rate < 60/ minute, systolic blood pressure < 90 mmHg) are taken as cases

Material and Method:-

Study design:- Longitudinal Descriptive study

Study period:- 6 months

Study area:- Govt. Royapettah Hospital attached to Govt. Kilpauk Medical College Chennai.

Study Population:-

Known Bronchial Asthma or Chronic Obstructive Pulmonary Disease patient aged >= 18 years, non- diabetic, on oral drugs like salbutamol and theophylline and not on any oral / inhalational steroid so far and not received any parenteral

steroid in last 4 weeks admitted for acute exacerbation but not in respiratory failure initiated on steroid therapy at Govt. Royapettah hospital attached to Govt. Kilpauk Medical College, Chennai.

Sample Size:-

Estimated prevalence of steroid induced hyperglycemia is 65%

With a precision of 10

Sample size is $\frac{1.96 \times 1.96 \times 65 \times 35}{10 \times 10} = 87$

With a 10 % margin, Sample size = 100.

Inclusion criteria:-

Known Bronchial Asthma or Chronic Obstructive Pulmonary Disease patient aged >= 18 years, non- diabetic, on oral drugs like salbutamol and theophylline and not on any oral / inhalational steroid so far and not received any parenteral steroid in last 4 weeks admitted for acute exacerbation but not in respiratory failure who are to be initiated on steroid therapy.

METHODOLOGY

Exclusion Criteria:-

- Known diabetes
- RBS 140-199 mg/dl with HbA1c >= 6.5
- Patient who received parentral steroids in last 4 weeks
- Patient on IV drip containing dextrose
- Patient in respiratory failure on mechanical ventilation / moribund state in need of iv fluid containing dextrose
- Patient on oral steroid (ex. Very severe persistent asthma patient on oral corticosteroid treatment
- Pregnant or lactating female
- Age < 18 years

Methodology:-

Known Bronchial Asthma or Chronic Obstructive Pulmonary Disease patient aged >= 18 years, non- diabetic, on oral drugs like salbutamol and theophylline and not on any oral / inhalational steroid so far and not received any parenteral steroid in last 4 weeks admitted for acute exacerbation but not in respiratory failure are taken into the study.

Patients to be initiated on steroid therapy - parenteral – hydrocortisone / dexamethasone (or) oral - prednisolone in standard doses as demanded by the clinical setting. So patients will be substratified depending on the type and dose of steroid used.

Doses of Steroids used in the study are INJECTION HYDROCORTISONE – 100 mg 8^{th} hourly, INJECTION EXAMETHASONE – 4 mg 12^{th} hourly, TABLET PREDNISOLONE 5 mg – 4 tablets 12^{th} hourly.

Capillary blood glucose (CBG) level of each patient at the time of admission (pre therapy) will be checked with the help of glucometer (ACCU – CHEK active)

2 ml of blood will be collected from each patient at the time of admission (pre therapy) and sent for HbA1c

Again CBG level of each patient at 6, 12, 48 hours after initiation of steroid therapy is checked and noted.

2 ml of blood for doing fasting lipid profile will also be sent to biochemistry lab, Govt. Royapettah hospital for processing.

Outcomes to be Studied:

Incidence of steroid induced hyperglycemia (CBG >= 200)

Is Parenteral corticosteroid having more propensity to cause hyperglycemia than oral corticosteroid ?

The time period at which hyperglycemia is more common after the administration of steroid (so that antihyperglycemic drugs can be targeted at the right time as hyperglycemia is an independent cardiovascular risk factor).

Association between risk factors like obesity, dyslipidemia, hypertension and steroid induced hyperglycemia

DEFINITION:

-BMI- (body mass index) = Weight in kg / Height in sq.m

-BMI >25 – 30 is overweight, > 30 kg/sq.m is obese

-WAIST CIRCUMFERENCE –

The bottom edge of measuring tape alligned with the top of the hip bone at the side of the waist, then measurement taken by wrapping the tape all the way around the waist.

Waist circumference < 90 cm in male, < 80 cm in female is normal

DYSLIPIDEMIA - (by IDF criteria)

-Fasting triglyceride > 150,

-HDL cholesterol < 40 in male &< 50 in female

HYPERTENSION as defined by JNC 7

DIABETES MELLITUS

as defined by American diabetes association

RBS- 200 / FBS- 126 /

HbA1C- >6.5% / 2hr PPBS- 200 mg/dl

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

The sample size in our study is 100 patients.

These patients fell into either one of the two classes which are bronchial asthma and chronic obstructive pulmonary disease.

All the patients met with our inclusion criteria.

They were administered one among the following three steroids namely Hydrocortisone, Dexamethasone & Prednisolone for their acute exacerbation.

Dose of Hydrocortisone being 100 mg iv tds.

Dose of Dexamethasone being 4 mg iv bd

Dose of Prednisolone being 5 mg 4 – 0 – 4 (oral).

We have concluded the following:

1. Number of patients allotted to each drug category

STEROID USED (dhp) * SEX Crosstabulation					
			SEX		Total
			F	M	
STEROID USED (dhp)	D	Count	9	29	38
		% within STEROID USED (dhp)	23.7%	76.3%	100.0%
	H	Count	13	25	38
		% within STEROID USED (dhp)	34.2%	65.8%	100.0%
	P	Count	11	13	24
		% within STEROID USED (dhp)	45.8%	54.2%	100.0%
Total		Count	33	67	100
		% within STEROID USED (dhp)	33.0%	67.0%	100.0%

Out of 100 patients in our study,

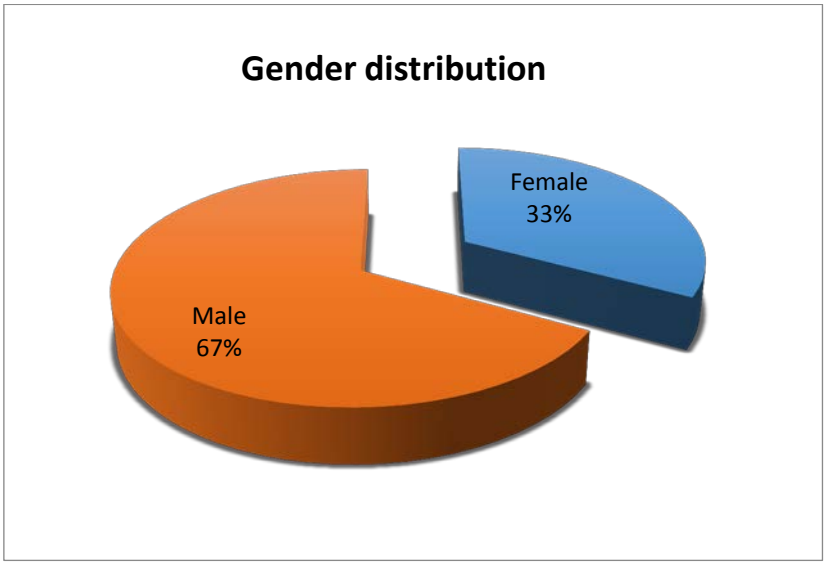
-38% were given Hydrocortisone,

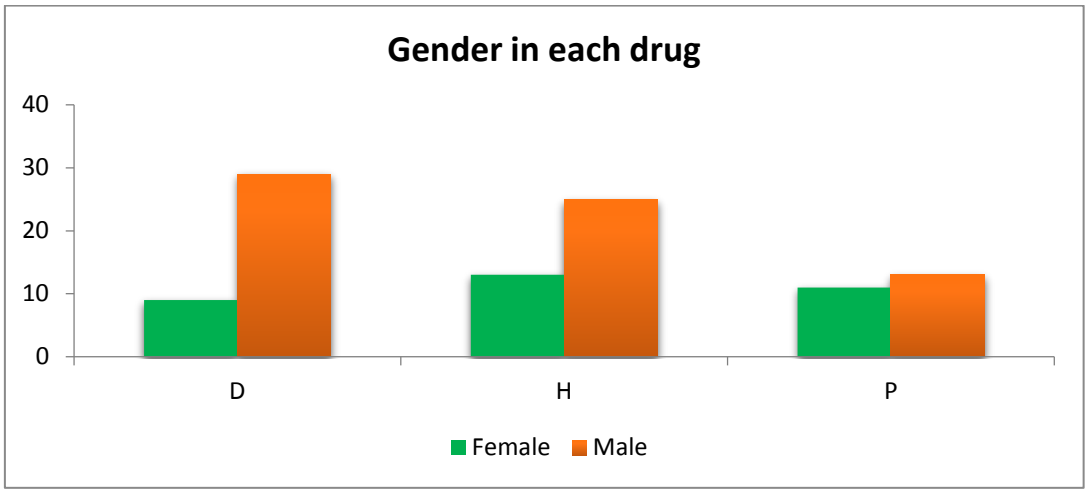
-38% were given Dexamethasone and

-24% were given Prednisolone.

2. Gender in each Drug

	Female	Male	Gender Distribution	
D	9	29	Female	33
H	13	25	Male	67
P	11	13		





3. Age Distribution

Descriptive Statistics

	N	Minimum	Maximum	Mean	St. Deviation
Age	100	35	69	52.85	7.795
Valid N (Listwise)	100				

The minimum age encountered in our study is 35 years.

The maximum age encountered is 69 years.

Among all three groups, the mean age of the patient is found to be 52 years.

AGE			
	N	Mean	Std. Deviation
D	38	52.89	7.904
H	38	52.84	7.896
P	24	52.79	7.791
Total	100	52.85	7.795

4. Drugs and their effect on CBG (capillary blood glucose)

Sub- categorical reports

a) STEROID USED = D (Dexamethasone)

	Mean	Std. Deviation	N
CBG AT ADMISSION	**105.24**	**5.410**	**38**
CBG 6 hrs	**141.11**	**22.576**	**38**
CBG 12 hrs	**162.47**	**30.642**	**38**
CBG 48 hrs	**137.95**	**22.262**	**38**

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
CBG	Sphericity Assumed	63656.651	3	21218.884	168.252	.000
	Greenhouse-Geisser	63656.651	1.061	60015.770	168.252	.000
	Huynh-Feldt	63656.651	1.066	59724.856	168.252	.0005
	Lower-bound	63656.651	1.000	63656.651	168.252	.000
Error(CBG)	Sphericity Assumed	13998.599	111	126.114		
	Greenhouse-Geisser	13998.599	39.245	356.701		
	Huynh-Feldt	13998.599	39.436	354.972		
	Lower-bound	13998.599	37.000	378.341		

(I) CBG		Mean Difference (I-J)	Std. Error	Sig.[c]	Interval for Difference[c]	
					Lower Bound	Upper Bound
1	2	-35.868*	2.940	.0005	-44.064	-27.673
	3	-57.237*	4.271	.0005	-69.144	-45.330
	4	-32.711*	2.882	.0005	-40.744	-24.677
2	1	35.868*	2.940	.000	27.673	44.064
	3	-21.368*	1.477	.0005	-25.485	-17.251
	4	3.158*	.144	.0005	2.757	3.559
3	1	57.237*	4.271	.000	45.330	69.144
	2	21.368*	1.477	.000	17.251	25.485
	4	24.526*	1.559	.0005	20.182	28.871
4	1	32.711*	2.882	.000	24.677	40.744
	2	-3.158*	.144	.000	-3.559	-2.757
	3	-24.526*	1.559	.000	-28.871	-20.182

Among 38 patients who were administered with Dexamethasone, the CBG at 6th, 12th& 48th hour were well above the normal baseline CBG. The CBG peaked at the 12th hour after the drug administration.

b) STEROID USED = H (Hydrocortisone)

	Mean	**Std. Deviation**	**N**
CBG AT ADMISSION	105.13	8.011	38
CBG 6 hrs	163.34	20.690	38
CBG 12 hrs	191.47	22.299	38
CBG 48 hrs	159.71	20.701	38

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
CBG	Sphericity Assumed	148539.70	3.00	49513.23	837.156	.000
	Greenhouse-Geisser	148539.70	1.08	137574.52	837.156	.000
	Huynh-Feldt	148539.70	1.09	136709.27	837.156	.0005
	Lower-bound	148539.70	1.00	148539.70	837.156	.000
Error(CBG)	Sphericity Assumed	6565.046	111	59.145		
	Greenhouse-Geisser	6565.046	39.949	164.336		
	Huynh-Feldt	6565.046	40.202	163.302		
	Lower-bound	6565.046	37.000	177.434		

(I) CBG		Mean Difference (I-J)	Std. Error	Sig.[c]	Interval for Difference[c]	
					Lower Bound	Upper Bound
1	2	-58.211*	2.333	.0005	-64.713	-51.708
	3	-86.342*	2.663	.0005	-93.765	-78.919
	4	-54.579*	2.322	.0005	-61.053	-48.105
2	1	58.211*	2.333	.000	51.708	64.713
	3	-28.132*	.583	.0005	-29.758	-26.506
	4	3.632*	.122	.000	3.292	3.971
3	1	86.342*	2.663	.000	78.919	93.765
	2	28.132*	.583	.000	26.506	29.758
	4	31.763*	.629	.0005	30.009	33.518
4	1	54.579*	2.322	.000	48.105	61.053
	2	-3.632*	.122	.000	-3.971	-3.292
	3	-31.763*	.629	.000	-33.518	-30.009

Among 38 patients who were administered with Hydrocortisone, the CBG at 6th, 12th& 48th hour were well above the normal baseline CBG.

The CBG peaked at the 12th hour after the drug administration.

c) STEROID USED = P (Prednisolone)

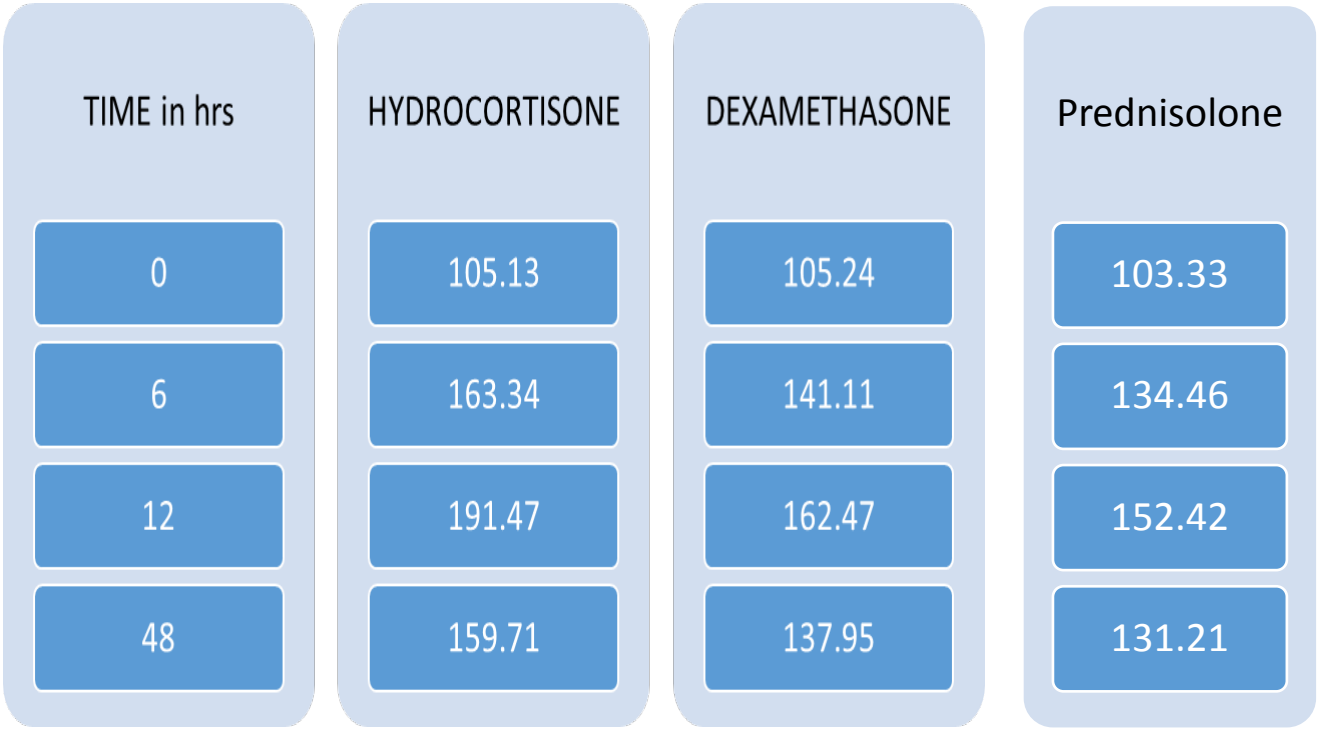
	Mean	Std. Deviation	N
CBG AT ADMISSION	103.33	5.362	24
CBG 6 hrs	134.46	21.875	24
CBG 12 hrs	152.42	31.661	24
CBG 48 hrs	131.21	21.405	24

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
CBG	Sphericity Assumed	29626.875	3	9875.625	75.165	.000
	Greenhouse-Geisser	29626.875	1.065	27806.870	75.165	.000
	Huynh-Feldt	29626.875	1.075	27570.173	75.165	.0005
	Lower-bound	29626.875	1.000	29626.875	75.165	.000
Error(CBG)	Sphericity Assumed	9065.625	69	131.386		
	Greenhouse-Geisser	9065.625	24.505	369.944		
	Huynh-Feldt	9065.625	24.716	366.795		
	Lower-bound	9065.625	23.000	394.158		

(I) CBG		Mean Difference (I-J)	Std. Error	Sig.[c]	Interval for Difference[c]	
					Lower Bound	Upper Bound
1	2	-31.125*	3.522	.0005	-41.291	-20.959
	3	-49.083*	5.569	.0005	-65.157	-33.010
	4	-27.875*	3.426	.0005	-37.765	-17.985
2	1	31.125*	3.522	.000	20.959	41.291
	3	-17.958*	2.220	.0005	-24.366	-11.550
	4	3.250*	.257	.0005	2.508	3.992
3	1	49.083*	5.569	.000	33.010	65.157
	2	17.958*	2.220	.000	11.550	24.366
	4	21.208*	2.353	.0005	14.417	27.999
4	1	27.875*	3.426	.000	17.985	37.765
	2	-3.250*	.257	.000	-3.992	-2.508
	3	-21.208*	2.353	.000	-27.999	-14.417

Among 24 patients who were administered with Prednisolone, the CBG at 6th, 12th& 48th hour were well above the normal baseline CBG.

The CBG peaked at the 12th hour after the drug administration.

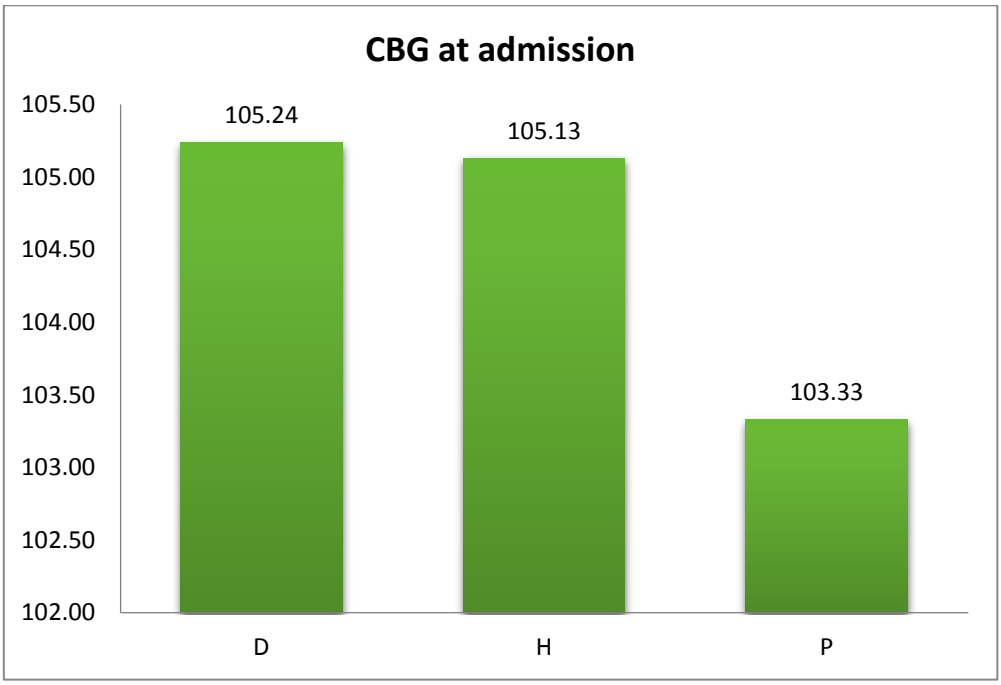


The Capillary Blood Glucose level after administration of the drug is highest (191.47) with Hydrocortisone > (162.47) with Dexamethasone > (152.42) with Prednisolone

5. Time at which CBG Peaks with respect to Drug Administration

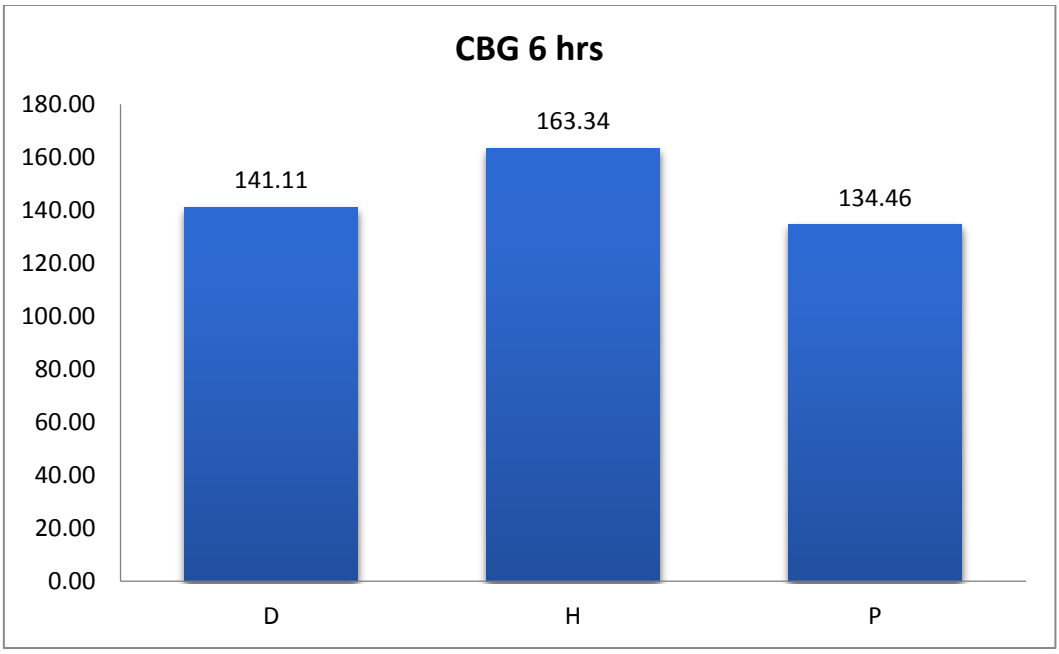
a) CBG at Baseline

	At admission
D	105.24
H	105.13
P	103.33



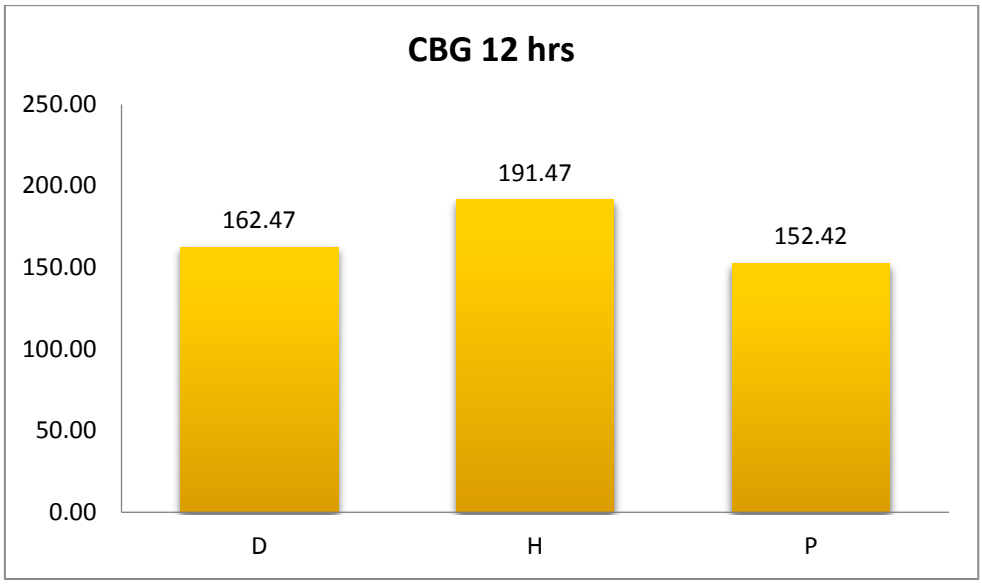
b) CBG at 6th Hour

	CBG 6 hrs
D	141.11
H	163.34
P	134.46



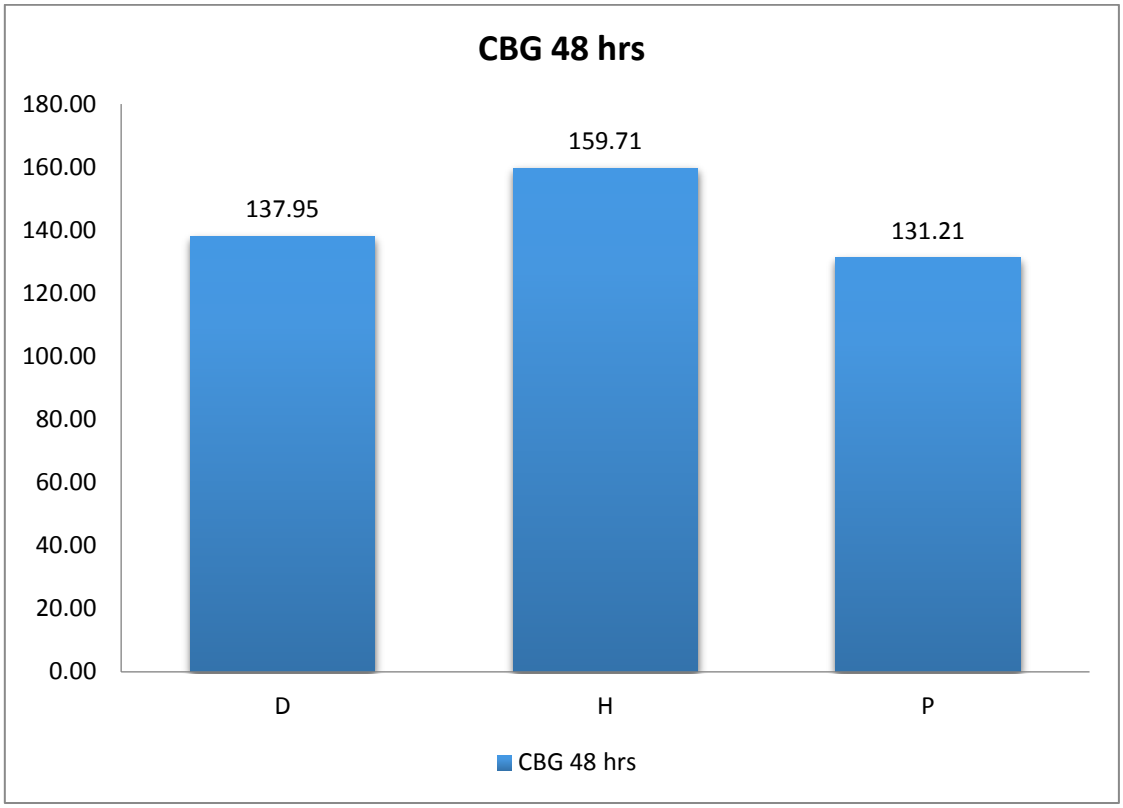
c) CBG at 12th Hour

	CBG 12 hrs
D	162.47
H	191.47
P	152.42



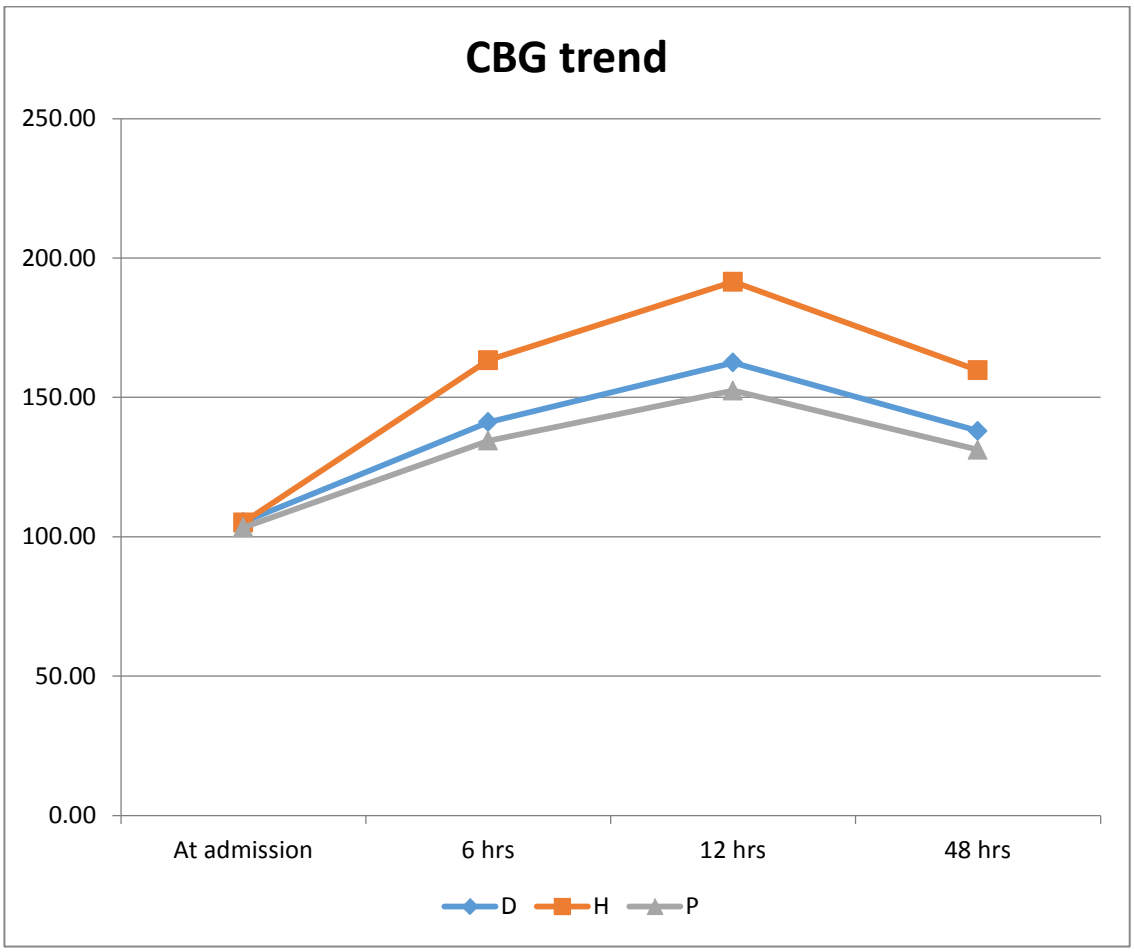
d) CBG at 48th Hour

	CBG 48 hrs
D	137.95
H	159.71
P	131.21



Dependent Variable			Mean Difference (I-J)	Std. Error	Sig.	Interval	
						Lower Bound	Upper Bound
CBG 6 hrs	D	H	-22.237*	4.980	.0005	-34.09	-10.38
		P	6.647	5.660	.471	-6.82	20.12
	H	D	22.237*	4.980	.0005	10.38	34.09
		P	28.884*	5.660	.0005	15.41	42.35
	P	D	-6.647	5.660	.471	-20.12	6.82
		H	-28.884*	5.660	.000	-42.35	-15.41
CBG 12 hrs	D	H	-29.000*	6.430	.0005	-44.30	-13.70
		P	10.057	7.308	.357	-7.34	27.45
	H	D	29.000*	6.430	.0005	13.70	44.30
		P	39.057*	7.308	.000	21.66	56.45
	P	D	-10.057	7.308	.357	-27.45	7.34
		H	-39.057*	7.308	.000	-56.45	-21.66
CBG 48 hrs	D	H	-21.763*	4.927	.0005	-33.49	-10.04
		P	6.739	5.599	.454	-6.59	20.07
	H	D	21.763*	4.927	.000	10.04	33.49
		P	28.502*	5.599	.0005	15.18	41.83
	P	D	-6.739	5.599	.454	-20.07	6.59
		H	-28.502*	5.599	.000	-41.83	-15.18

	D	H	P
At admission	105.24	105.13	103.33
6 hrs	141.11	163.34	134.46
12 hrs	162.47	191.47	152.42
48 hrs	137.95	159.71	131.21



The Capillary Blood Glucose peaks at the 12th hour after administration of any of the three drugs namely Dexamethasone, Hydrocortisone & Prednisolone.

6. Risk Factors for Steroid induced Hyperglycemia

The risk factors are:

AGE

BMI

WAIST CIRCUMFERENCE

BLOOD PRESSURE

FASTING LIPID PROFILE (serum cholesterol & triglyceride)

BASELINE HbA1C

a) Dexamethasone

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
	(Constant)	-50.700	55.999		-.905	.371
	HbA1C	-40.044	19.410	-.401	-2.063	.047
	SYS	3.296	.489	1.309	6.738	.0005

Using the backward elimination method the following regression model was arrived for predicting the CBG 12 hrs for steroid D with CBG12hrs =(HbA2c)* (-40.04)+ (SYS)*(3.296) - 50.7 and R square = 87.5 %

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-18.837	182.750		-.103	.919
	HbA1C	-27.176	27.363	-.272	-.993	.329
	SYS	3.308	.621	1.313	5.329	.000
	DIAS	1.342	1.372	.230	.979	.336
	BMI	2.162	2.629	.258	.822	.417
	WC	-.398	.425	-.108	-.936	.357
	SERUM CHO	-1.297	1.675	-.580	-.774	.445
	TGL	.128	.996	.083	.128	.899
2	(Constant)	-39.598	83.343		-.475	.638
	HbA1C	-27.690	26.634	-.277	-1.040	.307
	SYS	3.302	.609	1.311	5.423	.000
	DIAS	1.430	1.171	.245	1.221	.231
	BMI	2.136	2.579	.254	.828	.414
	WC	-.402	.417	-.109	-.965	.342
	SERUM CHO	-1.117	.904	-.500	-1.236	.226
3	(Constant)	-80.686	66.642		-1.211	.235
	HbA1C	-24.266	26.182	-.243	-.927	.361
	SYS	3.493	.560	1.387	6.235	.000
	DIAS	.817	.903	.140	.904	.373
	WC	-.229	.359	-.062	-.638	.528
	SERUM CHO	-.692	.741	-.310	-.935	.357
4	(Constant)	-84.263	65.805		-1.280	.209
	HbA1C	-24.694	25.937	-.247	-.952	.348
	SYS	3.399	.536	1.350	6.347	.000
	DIAS	.834	.895	.143	.933	.358
	SERUM CHO	-.714	.733	-.319	-.973	.337
5	(Constant)	-54.343	57.347		-.948	.350
	HbA1C	-34.595	23.620	-.346	-1.465	.152
	SYS	3.380	.534	1.342	6.327	.000
	SERUM CHO	-.201	.485	-.090	-.415	.680
6	(Constant)	-50.700	55.999		-.905	.371
	HbA1C	-40.044	19.410	-.401	-2.063	.047
	SYS	3.296	.489	1.309	6.738	.000

b) Hydrocortisone

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-233.495	169.785		-1.375	.179
	HbA1C	7.837	13.823	.121	.567	.575
	SYS	1.482	.634	.911	2.336	.026
	DIAS	2.531	1.258	.553	2.012	.053
	BMI	-2.142	2.581	-.388	-.830	.413
	WC	.639	.321	.244	1.989	.056
	SERUM CHO	.208	1.403	.139	.148	.883
	TGL	-.629	.752	-.612	-.836	.410
2	(Constant)	-212.821	95.324		-2.233	.033
	HbA1C	8.566	12.715	.132	.674	.506
	SYS	1.493	.620	.917	2.408	.022
	DIAS	2.481	1.193	.542	2.080	.046
	BMI	-1.864	1.742	-.338	-1.070	.293
	WC	.649	.308	.248	2.103	.044
	TGL	-.547	.503	-.533	-1.087	.285
3	(Constant)	-174.262	75.574		-2.306	.028
	SYS	1.488	.615	.914	2.421	.021
	DIAS	2.403	1.177	.525	2.042	.050
	BMI	-1.406	1.590	-.255	-.884	.383
	WC	.642	.306	.246	2.100	.044
	TGL	-.484	.490	-.472	-.988	.330
4	(Constant)	-168.845	75.076		-2.249	.031
	SYS	1.277	.565	.785	2.262	.030
	DIAS	2.503	1.168	.547	2.144	.040
	WC	.610	.303	.233	2.016	.052
	TGL	-.617	.465	-.601	-1.328	.193
5	(Constant)	-83.220	38.847		-2.142	.039
	SYS	.644	.305	.396	2.108	.042
	DIAS	1.559	.937	.341	1.665	.105
	WC	.578	.305	.221	1.896	.067
6	(Constant)	-26.947	19.619		-1.374	.178
	SYS	1.062	.178	.652	5.953	.000
	WC	.781	.286	.299	2.728	.010

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
	(Constant)	-26.947	19.619		-1.374	.178
	SYS	1.062	.178	.652	5.953	.0005
	WC	.781	.286	.299	2.728	.010

Using the backward elimination method the following regression model was arrived for predicting the CBG 12 hrs for steroid H with
CBG12hrs =(SYS)* (0.781)+(WC)*(1.062) - 26.947 and R square = 79.3 %

c)Prednisolone

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
	(Constant)	-353.440	45.329		-7.797	.0005
	HbA1C	71.864	11.483	.715	6.258	.0005
	WC	.939	.390	.275	2.409	.025

Using the backward elimination method the following regression model was arrived for predicting the CBG 12 hrs for steroid P with
CBG12hrs =(HbA2c)* (71.86)+(WC)*(0.939) - 353.4 and R square = 89.4 %

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-521.029	279.869		-1.862	.081
	HbA1C	59.653	41.450	.593	1.439	.169
	SYS	-.130	1.118	-.046	-.116	.909
	DIAS	1.972	2.951	.331	.668	.514
	BMI	.405	5.600	.046	.072	.943
	WC	.793	.787	.232	1.008	.329
	SERUM CHO	1.171	1.728	.549	.678	.508
	TGL	-1.029	1.541	-.700	-.667	.514
2	(Constant)	-523.072	270.170		-1.936	.070
	HbA1C	61.357	33.087	.610	1.854	.081
	SYS	-.105	1.032	-.037	-.102	.920
	DIAS	1.880	2.581	.315	.728	.476
	WC	.816	.699	.239	1.168	.259
	SERUM CHO	1.158	1.667	.542	.695	.497
	TGL	-.976	1.316	-.664	-.741	.469
3	(Constant)	-508.207	220.929		-2.300	.034
	HbA1C	59.424	26.334	.591	2.257	.037
	DIAS	1.745	2.152	.292	.811	.428
	WC	.792	.640	.232	1.238	.232
	SERUM CHO	1.102	1.532	.516	.720	.481
	TGL	-.923	1.176	-.628	-.785	.443
4	(Constant)	-419.768	181.267		-2.316	.032
	HbA1C	67.302	23.646	.669	2.846	.010
	DIAS	1.487	2.095	.249	.710	.486
	WC	1.042	.530	.305	1.965	.064
	TGL	-.309	.800	-.210	-.387	.703
5	(Constant)	-352.049	45.692		-7.705	.000
	HbA1C	61.206	17.242	.609	3.550	.002
	DIAS	.763	.915	.128	.834	.414
	WC	.909	.394	.266	2.304	.032
6	(Constant)	-353.440	45.329		-7.797	.000
	HbA1C	71.864	11.483	.715	6.258	.000
	WC	.939	.390	.275	2.409	.025

AGE AS THE RISK FACTOR

P - Value	** Highly Significant at P ≤ .01

P - Value	* Significant at 0.01 < P ≤ .05

P -Value	# No Significant at P >.05

Dexamethasone

		AGE	CBG 12 hrs
AGE	Pearson Correlation	1	.379*
	Sig. (2-tailed)		.019
	N	38	38
CBG 12 hrs	Pearson Correlation	.379*	1
	Sig. (2-tailed)	.019	
	N	38	38

Hydrocortisone

		AGE	CBG 12 hrs
AGE	Pearson Correlation	1	.338*
	Sig. (2-tailed)		.038
	N	38	38
CBG 12 hrs	Pearson Correlation	.338*	1
	Sig. (2-tailed)	.038	
	N	38	38

Prednisolone

		AGE	CBG 12 hrs
AGE	Pearson Correlation	1	.289
	Sig. (2-tailed)		.171
	N	24	24
CBG 12 hrs	Pearson Correlation	.289	1
	Sig. (2-tailed)	.171	
	N	24	24

DISCUSSION

DISCUSSION

Corticosteroid plays a significant role in our day to day practice.

The aim of this work is to understand in depth about the most common adverse effect of corticosteroid which is **hyperglycemia**.

As hyperglycemia is one among the most important factors that increases cardio-vascular risk, this study is taken up to mitigate the risk.

Through this study the following points have become evident:

1. There is rise in capillary blood glucose level after administration of steroid during all the three different times (6, 12 & 48 hours) and with respect to all the three different drugs given to the patient for their exacerbation. Thus the occurrence of hyperglycemia within 48 hours in patients started on corticosteroid therapy is proven.
2. The Capillary Blood Glucose level after administration of the drug is highest 191.47) with Hydrocortisone > (162.47) with Dexamethasone > (152.42) with Prednisolone.
3. So the risk of (dys) hyperglycemia is highest with Hydrocortisone (short acting) when compared with other two drugs (long acting).
4. Thus steroid induced hyperglycemia is more with parentral steroids than oral forms.
5. The Capillary Blood Glucose peaks at the 12^{th} hour after administration of any of the three drugs namely Dexamethasone, Hydrocortisone & Prednisolone.

Thus traditional way of testing for fasting and post-prandial blood sugar to see for dysglycemia is no longer useful in case of steroid induced hyperglycemia. Many a times it has been told in other studies that it is the post-prandial hyperglycemia that predominates than the fasting hyperglycemia in case of steroid induced hyperglycemia.

In my study there are 6 different risk factors that have been taken and analysed especially with the hyperglycemia that has occurred at 12^{th} hour of administration of any of the three corticosteroids.

In my study it is found that

1. HbA1C& Systolic BP has significant correlation for Dexamethasone.
2. Systolic BP & Waist Circumference has significant correlation for Hydrocortisone.
3. HbA1C& Waist Circumference has significant correlation for Prednisolone.

CONCLUSION

CONCLUSION

Similar to the other studies which shows that the glycemic rise related to steroid therapy usually begins 4 hours after the dose and usually persists for up to 16 hours, in my study also CBG level starts rising at 6^{th} hour, peaks at 12^{th} hour & starts to decline by 48^{th} hour after administration of steroid therapy.

Thus a better understanding of the glycemic effect of various steroid will allow the development of a specific treatment strategy for steroid-induced hyperglycemia that targets the time of day during which hyperglycemia predominates.

Current conventional strategies in treating hyperglycemia may inadequately treat postprandial hyperglycemia that occurs after steroid therapy, and use of long-acting basal insulin may precipitate nocturnal hypoglycemia.

So short acting steroid – Hydrocortisone with highest rise in CBG at all three times after its administration is to be avoided unless the clinical condition demands.

Oral Prednisolone is comparatively safer drug with less side effect (hyperglycemia) profile & ease of administration. But oral route not useful

in patients not able to tolerate oral drugs due to vomiting & especially at acute exacerbations.

It is also evident that increased waist circumference, BMI, baseline HbA1C, blood pressure are all associated significantly withsteroid induced hyperglycemia.

APPENDIX 1
BIBLIOGRAPHY

APPENDIX 1

BIBLIOGRAPHY

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APPENDIX 2
PROFORMA

APPENDIX 2

PROFORMA

Name: Age/sex:

Address: IPNO:

Diagnosis:

BMI:

Waist circumference:

Blood Pressure:

Questionnarie:

Previous history of

diabetes mellitus,

systemic hypertension,

dyslipidemia,

steroid intake,

smoking& alcoholism.

INVESTIGATIONS:

- Pre therapy Capillary blood glucose level
- Pre therapy HbA1c
- Capillary blood glucose at 6 hours of steroid administration
- Capillary blood glucose at 12 hours of steroid administration
- Capillary blood glucose at 48 hours of steroid administration
- Fasting lipid profile

TYPE & DOSE of STEROID used.

APPENDIX 3
ETHICAL COMMITTEE APPROVAL

APPENDIX 3

ETHICAL COMMITTEE APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 03/2016 Dt: 20.06.2016
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval **"STEROID INDUCED DYSGLYCEMIA DURING FIRST 48 HOURS OF STEROID THERAPY IN HOSPITALIZED PATIENTS"**- For Project Work submitted by Dr. G.Sailendri, Post Graduate in MD (General Medicine), Govt. Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

DEAN 5/8/16
Govt.Kilpauk Medical College,
Chennai – 10.
5/8/16

KEY FOR
MASTER CHART

KEY TO MASTER CHART

CBG AT 0 - Capillary blood glucose at the time of admission

CBG AT 6 - Capillary blood glucose at 6 hours after the administration of steroid

CBG AT 12 - Capillary blood glucose at 12 hours after the administration of steroid

CBG AT 48 - Capillary blood glucose at 48 hours after the administration of steroid

BP mmHg - blood pressure in mmHg

BMI - body mass index

WC - waist circumference

S. CHL - serum cholesterol

S. TGL - serum triglyceride

HbA1C - glycated hemoglobin

STEROID - steroid used in the patient

P - PREDNISOLONE

H - HYDROCORTISONE

D - DEXAMETHASONE

SEX – M - male

F - female

MASTER CHART

AGE	SEX	CBG AT 0	HbA1C	BP mmHg	BMI	WC	S.CHL	S.TGL	CBG AT 6	CBG AT 12	CBG AT 48	STEROID
38	M	100	5.7	130/80	23	91	195	124	120	134	115	P
40	M	90	5.5	120/80	19	88	180	110	143	172	140	H
36	F	90	5.5	120/80	19	78	180	110	112	132	106	D
37	M	100	5.6	126/80	22	90	186	120	119	130	115	D
35	F	90	5.5	120/80	20	79	180	110	145	174	140	H
38	M	100	5.6	124/80	21	90	184	118	153	183	150	H
40	M	110	6	140/80	27	101	200	134	150	180	146	D
36	M	100	5.5	120/80	20	89	180	110	116	135	114	D
50	M	120	6.2	150/90	28	102	210	155	189	217	185	H
55	M	100	5.6	126/80	22	92	186	120	118	130	112	P
52	F	110	5.9	140/80	28	92	200	134	149	178	145	D
58	M	108	6	142/84	28	102	201	135	151	180	148	D
55	F	100	5.5	124/80	21	80	184	118	152	181	148	H
60	M	120	6.3	152/90	29	103	212	157	188	218	185	H
65	M	115	6.3	154/92	30	105	215	160	190	220	187	H
54	M	105	6	140/84	28	102	200	134	149	180	145	D
58	F	102	5.5	122/80	21	80	182	112	119	133	115	P
45	M	105	5.6	124/80	22	91	184	114	121	132	119	D
52	M	100	5.5	120/80	20	90	180	110	117	131	114	D
46	F	100	5.5	120/80	20	80	180	110	116	123	113	P
61	F	110	6.4	150/90	30	95	212	157	172	201	168	P
66	M	108	6.4	150/90	30	105	214	159	155	184	152	D
48	M	112	6.3	152/90	30	105	216	161	185	215	182	H
51	M	94	5.5	120/80	20	90	180	110	146	175	142	H
57	M	100	5.7	126/82	22	91	186	120	120	130	117	D
60	F	100	5.5	120/80	21	81	180	110	150	178	146	H
68	M	114	5.6	152/92	30	105	215	160	192	220	190	H
62	M	108	6.3	150/90	29	104	214	159	154	185	150	D
56	F	105	6.4	150/90	29	94	213	158	180	208	175	H
42	M	100	5.5	120/80	19	88	180	110	148	177	144	H
44	F	106	6	140/84	27	85	200	134	156	185	153	H
46	M	110	6.2	154/92	30	105	215	160	178	209	175	D
52	M	120	6.4	160/96	30	105	220	165	186	215	182	D
48	F	100	5.7	124/80	21	80	184	114	122	135	120	D

57	M	102	5.6	122/80	21	90	182	112	149	179	145	H
63	M	110	6.3	150/90	30	105	213	158	177	206	174	D
57	M	100	5.6	124/80	22	91	184	114	115	123	114	P
51	F	102	5.6	122/80	21	80	182	112	116	122	113	P
42	M	106	5.9	140/90	27	100	210	155	146	176	142	P
47	M	102	5.8	130/80	25	97	195	124	152	181	149	H
49	F	100	5.5	120/80	20	80	180	110	119	128	117	D
53	M	90	5.5	120/80	20	90	180	110	141	170	136	H
56	M	98	5.5	120/80	21	90	180	110	144	173	140	H
63	F	100	5.6	120/80	21	80	180	110	113	120	112	P
55	M	110	6.3	150/90	30	105	214	159	176	205	172	D
52	F	104	5.9	130/80	24	85	195	124	122	135	120	D
54	M	100	5.6	124/80	22	91	184	114	120	133	117	D
58	M	106	5.9	132/84	24	94	196	125	156	185	152	H
56	F	100	5.6	124/80	21	80	184	114	117	121	115	P
59	M	110	6.2	148/90	28	102	211	156	182	210	179	H
41	M	120	6.4	160/90	30	105	222	167	198	227	195	H
47	M	100	5.8	130/80	25	96	195	124	140	170	136	P
45	F	100	5.6	124/80	21	80	184	114	119	125	118	P
49	M	104	5.9	130/86	26	97	195	126	157	188	154	H
52	F	100	5.6	126/80	22	82	186	118	119	129	117	D
54	M	105	6	132/90	26	97	210	155	125	135	122	D
56	M	102	5.9	130/80	25	95	195	124	151	180	147	H
53	M	108	6.1	136/90	27	98	211	156	147	177	144	P
51	F	100	5.6	124/80	21	81	184	114	118	127	115	P
59	M	108	6.1	140/90	28	102	214	159	148	178	145	P
57	M	100	5.7	126/80	22	92	186	118	119	130	116	D
56	F	104	6	130/84	25	84	195	125	156	185	152	H
61	M	106	6	132/80	26	97	196	124	154	183	150	H
62	M	102	6.2	140/80	28	102	200	134	121	131	119	D
63	F	106	6.3	140/90	28	87	213	158	146	176	142	P

69	M	110	6.4	150/90	30	105	216	161	171	200	167	P
63	M	115	6.4	160/94	30	105	224	169	185	214	182	D
65	F	110	6.4	152/90	30	90	216	161	186	215	182	H
47	M	120	6.4	160/96	30	105	225	170	180	208	176	P
52	M	105	5.9	130/86	25	96	195	125	157	186	153	H
49	F	100	5.8	128/80	23	83	188	122	119	126	115	P
50	M	110	6.1	140/90	28	103	212	157	152	182	149	D
50	F	106	6.2	140/90	27	87	211	156	151	180	147	D
54	M	110	6.3	150/90	30	105	215	160	185	213	181	H
47	F	100	5.9	130/80	24	84	195	124	146	175	142	H
49	M	104	6	130/82	25	95	196	125	122	135	120	D
46	M	100	5.9	130/80	24	94	195	124	140	169	137	P
57	M	120	6.4	160/90	32	106	220	165	195	224	190	H
53	F	110	6.3	150/90	30	90	216	161	155	185	152	D
58	M	102	6.2	140/84	28	102	201	134	149	178	145	D
62	M	110	6.3	152/90	31	106	217	162	156	185	152	D
59	F	108	6.3	150/90	30	91	215	160	182	210	178	H
64	M	102	6.2	140/90	28	102	212	157	158	187	155	H
66	M	110	6.4	156/90	30	105	218	163	179	208	175	D
56	F	110	6.4	160/90	32	92	223	168	186	214	183	H
61	M	104	6.1	144/80	27	98	202	136	150	180	147	D
51	F	100	5.6	128/80	23	83	188	122	125	138	122	H
54	M	100	5.5	122/80	22	92	182	112	120	131	118	D
43	M	100	5.8	130/80	25	96	195	124	117	124	115	P
47	M	105	6	136/90	26	97	210	155	126	135	123	D
44	F	100	5.6	126/80	22	81	186	118	122	136	120	H
48	M	110	6.2	140/90	29	104	212	157	180	207	176	H
43	F	106	6.1	140/80	28	88	200	134	148	178	145	D
49	M	110	6.4	150/90	30	105	220	165	183	211	179	H
52	M	102	5.9	130/80	24	94	195	124	142	171	138	P
56	M	108	6.1	140/90	26	96	211	156	149	180	145	D
54	F	96	5.5	120/80	20	80	180	110	115	123	113	P
59	M	104	5.8	130/80	27	101	195	124	123	135	120	D
62	M	110	6.3	150/90	31	106	221	166	173	201	169	P
57	F	100	5.8	130/80	25	85	195	124	145	176	142	H