Review on Hypertension: Common Hazards of Steroids

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ABSTRACT: The most serious side effect of corticosteroid use is hypertension, which must be taken into consideration when choosing a patient's course of treatment because it increases the risk of cardiovascular disease and other complications. Numerous illnesses are treated with corticosteroid medications, also referred to as steroids or anti-inflammatory drugs. They are not the same as anabolic steroids, which some individuals frequently use illegally to add muscle mass. Systemic corticosteroids have significant risks despite being crucial in the management of many inflammatory and immunologic diseases. The more serious side effects of systemic corticosteroid therapy include osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, Cushing's syndrome, psychological disorders, and immunosuppression, especially when given in high doses for extended periods of time. This comprehensive paper covers these adverse events and provides useful guidelines for their prevention and management, based on both the most recent research and the authors' clinical experience.

KEYWORDS: Hypertension, Steroid, Hazard effects, Aldosterone, Prednisone, Dexamethasone.

INTRODUCTION:-

Hypertension is a common medical condition that affects many people (high blood pressure). High blood pressure may have come up frequently in conversation with our friends and family. It might appear to be a common medical issue that is safe.

Hypertension has a significant impact on cardiovascular disease. Adults with hypertension make up almost one-third of those who are currently undiagnosed, and of those who are, about half do not take antihypertensive medications. The World Health Organization (WHO) has estimated that high blood pressure kills at least 9 million people annually, either directly or indirectly [1]. As a prevalent preventable cause of cardiovascular disease and mortality, hypertension has a significant negative impact on older people's independence and quality of life. The quality of life and independence of older people can be greatly affected by hypertension, a common preventable cause of cardiovascular morbidity and death [2]. The fact that you might not experience any symptoms until your hypertension is severe is one of its most dangerous aspects. Most people with hypertension don't exhibit any symptoms. As a result, hypertension is referred to as the "silent killer."

The sum of systemic vascular resistance and cardiac output is used to calculate blood pressure. A rise in either cardiac output or systemic vascular resistance, or even both, may be observed in people with arterial hypertension as a result. Cardiovascular output is frequently increased in younger patients, but in the elderly, vasculature stiffness and rising systemic vascular resistance play a major role. [3]

Blood pressure is the amount of pressure that your body's blood exerts against the walls of your arteries and other significant blood vessels.

Blood pressure is determined by two means:

- **Systolic blood pressure:** It is the amount of pressure in your arteries when the heartbeats.
- **Diastolic blood pressure:** It is the amount of pressure in your arteries between heartbeats.

Blood pressure readings are expressed as two numbers and are expressed in millimetres of mercury (mm Hg). The first number denotes systolic pressure, while the second number denotes diastolic pressure.

The first number denotes systolic pressure, while the second number denotes diastolic pressure. When your blood pressure readings are higher than usual, you have hypertension. A blood pressure reading of 140/80 mm Hg or higher is generally regarded as hypertension.

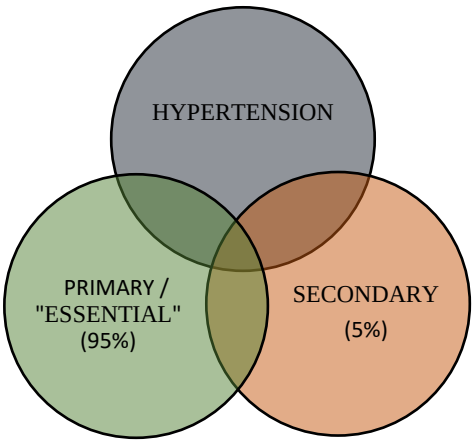


Fig. 1 The relative frequency of primary and secondary hypertension

1.1 Types of Hypertension:

Primary hypertension (Major):- The most common type of hypertension is primary hypertension, also referred to as essential hypertension. The cause of this hypertension is not known with certainty. The hypertension is not being caused by any obvious underlying illness, disorder, or condition. Instead, lifestyle, diet, and genetics all contribute to hypertension.

Secondary hypertension (Minor):- A less frequent variation of the disease, secondary hypertension, develops as a result of a particular condition. Hypertension can be a side effect of conditions like sleep apnea, tumors, and kidney failure.

Common symptoms of hypertension:

For this reason, it is essential that blood pressure is measured regularly some of the commonly prevailing hypertension symptoms are:

- Nose bleed
- Severe headaches
- Lack of clarity in vision
- Chest pain
- Increased heart rates
- Shortness of breath
- Pounding in your neck, chest, ears
- Profuse sweating

Table No. 1:-Classification of blood pressure for adults

Blood Pressure Classification	Systolic blood pressure mmHg	Diastolic blood pressure mmHg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage1 Hypertension	140–159	or 90–99
Stage2 Hypertension	≥160	or ≥100

1.2 Differential diagnosis:-

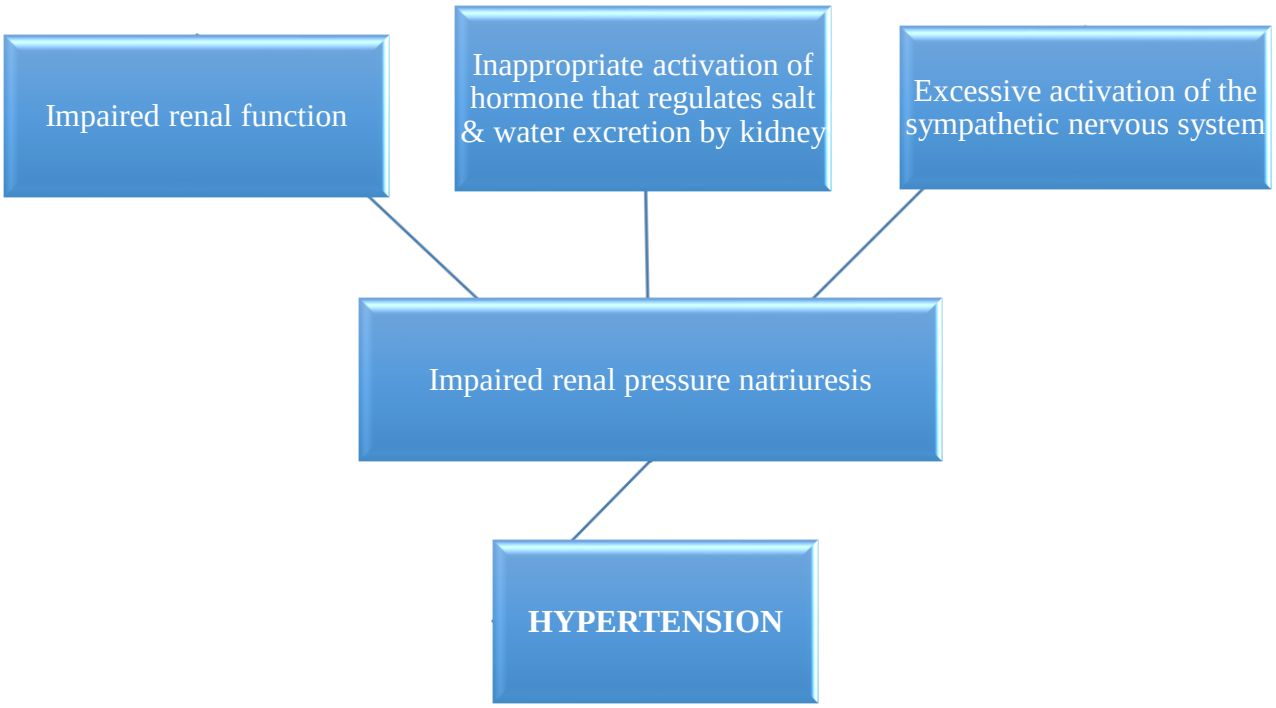
Following are the conditions where hypertension has an identifiable cause, unlike primary hypertension.

Table No. 2 Causes of hypertension

Cause	Features
Cushing syndrome & other glucocorticoids excess states	Truncal obesity, glucose intolerance & purple striae
Pheochromocytoma	Labile hypertension, paroxysms of hypertension accompanied by headache, palpitations, pallor, & perspiration
Primary aldosteronism & other mineral corticoids excess states	Unprovoked hypokalaemia
Reno vascular hypertension	Onset of hypertension before 30years, or after 55 years of age Abdominal bruit Accelerated hypertension Resistant hypertension Flash pulmonary enema Renal failure of uncertain etiology Acute renal failure precipitated by therapy with an angiotensin-converting enzyme inhibiter (ACEI) or angiotensin receptor blocker (ARB)
Sleep apnoea	Obesity, snoring, day time somnolence, resistance hypertension
Thyroid	Goitre, features of dysthyroidism
Parathyroid disease	Hypocalcaemia

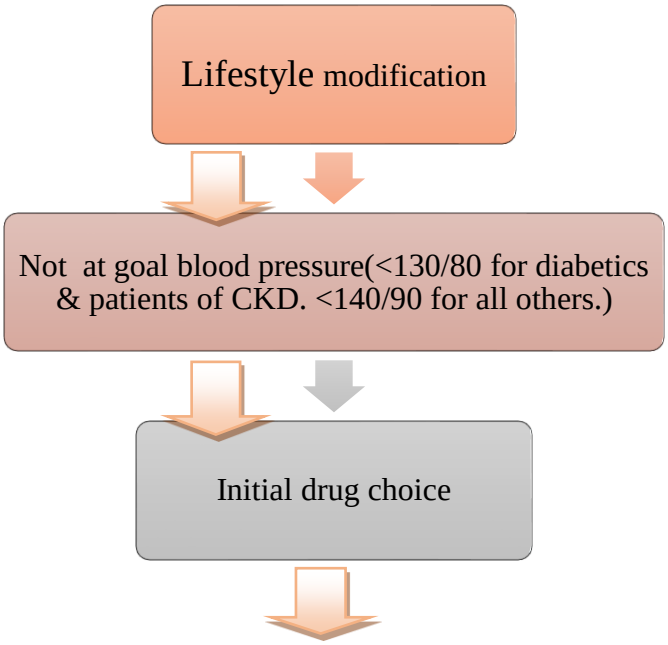
1.3 PATHOPHYSIOLOGY OF HYPERTENSION:

Fig No. 2 Pathophysiology of hypertension



Pathophysiological changes that lead to hypertension and techniques for physiological blood pressure control (BP). The renal-body fluid feedback system, which includes pressure natriuretic—a high-BP-induced increase in salt and water excretion by the kidney that causes a decrease in BP—achieves long-term BP management. Impaired renal function, altered activation of the hormones that regulate salt and water excretion by the kidney (like those in the renin-angiotensin-aldosterone system), or excessive sympathetic nervous system activation can all lead to impaired pressure natriuretic (see accompanying Hurst's Central Illustration). Successful therapy necessitates resetting pressure natriuretic towards normal BP because increased BP in hypertensive patients is sustained by a change in pressure natriuretic so that a sodium balance is maintained at higher BP [8].

1.4 Treatment algorithm:-



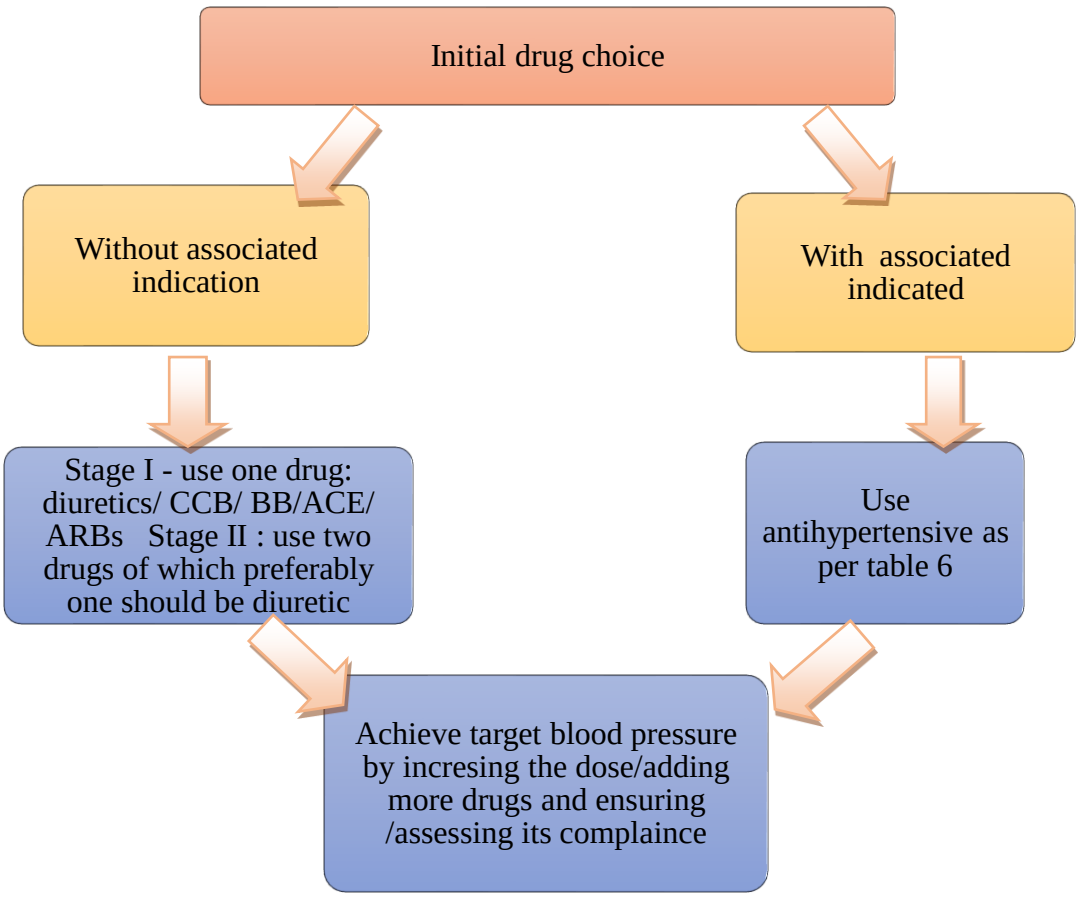


Fig No.3 Treatment algorithm of hypertension

1.5 Steroids:

Synthetic drugs known as corticosteroids closely resemble the hormone cortisol, which is naturally produced by your adrenal glands. The term "steroids" is frequently used to describe corticosteroids. The testosterone-related steroid chemicals that some athlete's abuse are not the same as corticosteroids [4].

Since their discovery about 80 years ago, steroids have been used extensively in the treatment of many disease states. The potent anti-inflammatory and immune-modulating properties of steroids are responsible for many of their therapeutic effects [5].

Steroids work as:

Steroids work by minimising the issue and lowering immune system activity. The process by which the immune system of the body defends itself against infection and foreign agents like bacteria and viruses is known as inflammation. The immune system, the body's defence mechanism, however, malfunctions in some disorders. This might induce inflammation to attack the body's tissues, causing harm. Inflammation symptoms include:

- Redness
- Warmth
- Swelling
- Pain.
- Upset stomach
- Weight gain in the belly, face and back of the neck.
- Problems with mood swings, memory, behaviour, and other psychological effects, such as confusion or delirium

The production of inflammatory molecules is suppressed by steroids. This reduces the likelihood of tissue damage. Steroids also inhibit immune system function by changing how white blood cells work [4].

Treatment with glucocorticoids, whether local or systemic, has the potential to cause ocular hypertension by altering the morphology and biochemistry of the trabecular meshwork, which lowers the effectiveness of aqueous outflow. By binding to and activating glucocorticoid and mineralocorticoid receptors, glucocorticoids have an impact on the body. The two 11beta-hydroxysteroid dehydrogenase isoezymes play a crucial role in controlling glucocorticoid activity at the preceptor level. In order to understand how glucocorticoid activity at the preceptor level is affected by the location of glucocorticoid target receptors and isoezymes of 11beta-hydroxysteroid dehydrogenase (11beta-HSD) in human and rat ocular tissues, this study examined those factors [6].

Classification of steroid

Natural- Mineralocorticoid & Glucocorticoid
Aldosterone hydrocortisone

Synthetic- 1.Short acting: hydrocortisone (8-12hrs.) Cortisone
2. Intermediate acting: prednisolone, (12-36hrs.) Triamcinolone

3. Long acting (36-72hrs) dexamethasone, betamethasone
4. Inhalation: fluticasone, budesonide, beclamethasone
5. Topical: clobetasol, mometasone desonide
6. Mineralocorticoid: fludrocortisone.

1.6 Pathophysiology of Hypertension caused by Glucocorticoids:

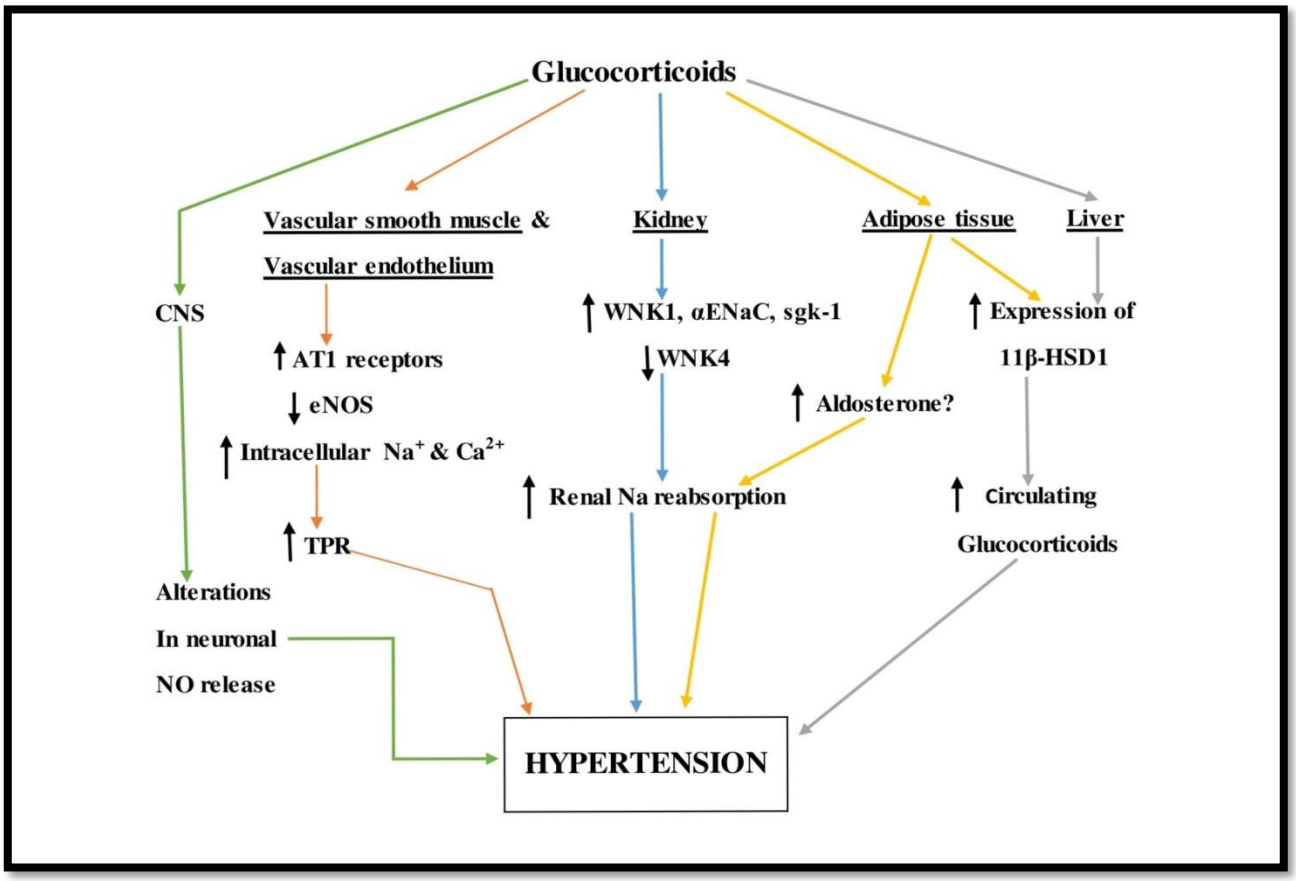


Fig No.4 Pathophysiology of Hypertension caused by Glucocorticoids

(i) Action CNS
(ii) Action on Vascular smooth muscle & vascular endothelium
(iii) Action on kidney
(iv) Action on adipose tissue
(v) Action on liver

i. Glucocorticoids on the CNS cause hypertension by altering neuronal no release through an increase in glucocorticoids receptor (nuclear receptor).
ii. It affects vascular smooth muscle and endothelium via the AT1 receptor (angiotensin 1 receptor), which inhibits the enzyme eNOs (nitric oxide synthesis), which raises intracellular Na2+ and Ca2+ and increases total peripheral resistance, resulting in hypertension.
iii. Action on Kidney
WNK1 is activated, and WNK4 is inhibited.
Epithelial sodium channels and SGK1 are activated by lysine (k) protein kinases, and WNK1 is activated by lysine (k) protein kinases, which regulates the two Na+ channels.

i. Epithelial sodium channel (eNaC)
ii. SGK1 (serum and glucocorticoid regulated kinases 1) which contributes to Na+ reabsorption of K+ elimination
iii. Inhibition of WNK4 result in imbalance between NaCl reabsorption K+ secretions. It leads to increase in Na+ reabsorption which hypertension
iv. Acts on adipose tissue :- in adipose tissue glucocorticoids result in
(a) Acts on liver:- in liver glucocorticoids results in increase expression of 11β HSD1 (11β-Hydroxysteroid dehydrogenase type 1):- resulting circulating glucocorticoids
(b) It leads to hypertension.
v. Acts on liver:- in liver glucocorticoids results in increase expression of 11β HSD1 (11β-Hydroxysteroid dehydrogenase type 1):- resulting circulating glucocorticoids

1.7 Aldosterone-

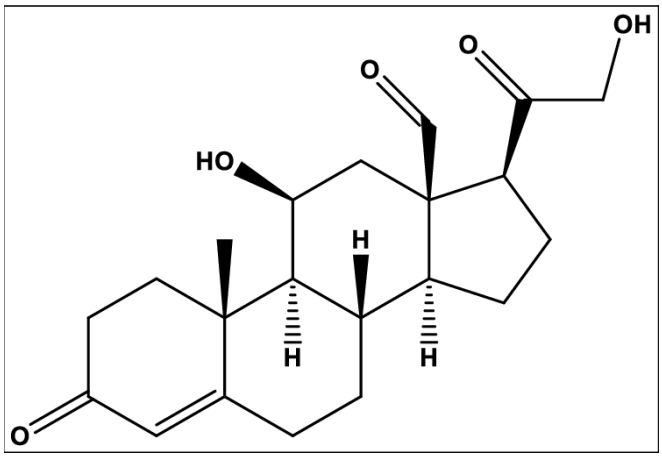


Fig. No. 5 Structure of Aldosterone

A steroid hormone called aldosterone controls blood pressure control, water retention, and salt absorption [10]. Primary aldosteronism, which is characterised by elevated aldosterone levels and decreased renin activity, is frequently responsible for secondary hypertension. [11] In high-risk populations like those with congestive heart failure, acute myocardial infarction, and coronary artery disease, aldosterone has been linked to long-term adverse health outcomes like cardiovascular events and death [12,13]. Although amply supported in animal models, the relationship between aldosterone and atherosclerosis is still debatable in humans. Furthermore, much less is known about the long-term health effects of elevated aldosterone concentrations in the general population [14,15] because aldosterone levels are frequently only assessed when an excess (i.e., primary aldosterone's) is suspected.

Aldosterone Levels and Renin Activity:

A competition-based radioimmunoassay (DiaSorin) and a radioimmunoassay (DiaSorin) were used to measure the levels of aldosterone and PRA, respectively. Angiotensin I production in nanograms per millilitre of sample per hour was used to define PRA (ng/mLh=g/[Lh]). Aldosterone was divided by PRA to get the ARR. Additionally, we divided people into two groups based on their PRA levels: intermediate to unsuppressed renin phenotype (PRA >0.5 g/(Lh)) and suppressed renin phenotype (PRA 0.5 g/(Lh)) (Lh). 18 We mixed intermediate and unsuppressed phenotypes in our primary study to maintain statistical power [16].

Aldosterone and Blood Pressure:

Your body's water content increases as a result of aldosterone causing the kidneys to retain salt. Your body retains more water the more aldosterone your adrenals produce. More water in the body increases blood volume because the circulatory system is a closed system. Increased blood volume is the cause of higher blood pressure [15].

Your body typically does this on its own to maintain blood pressure. It encourages your adrenals to produce more aldosterone when it notices a drop in blood pressure, which raises blood pressure. Problems develop when this natural mechanism malfunctions, as it does in AFS [15].

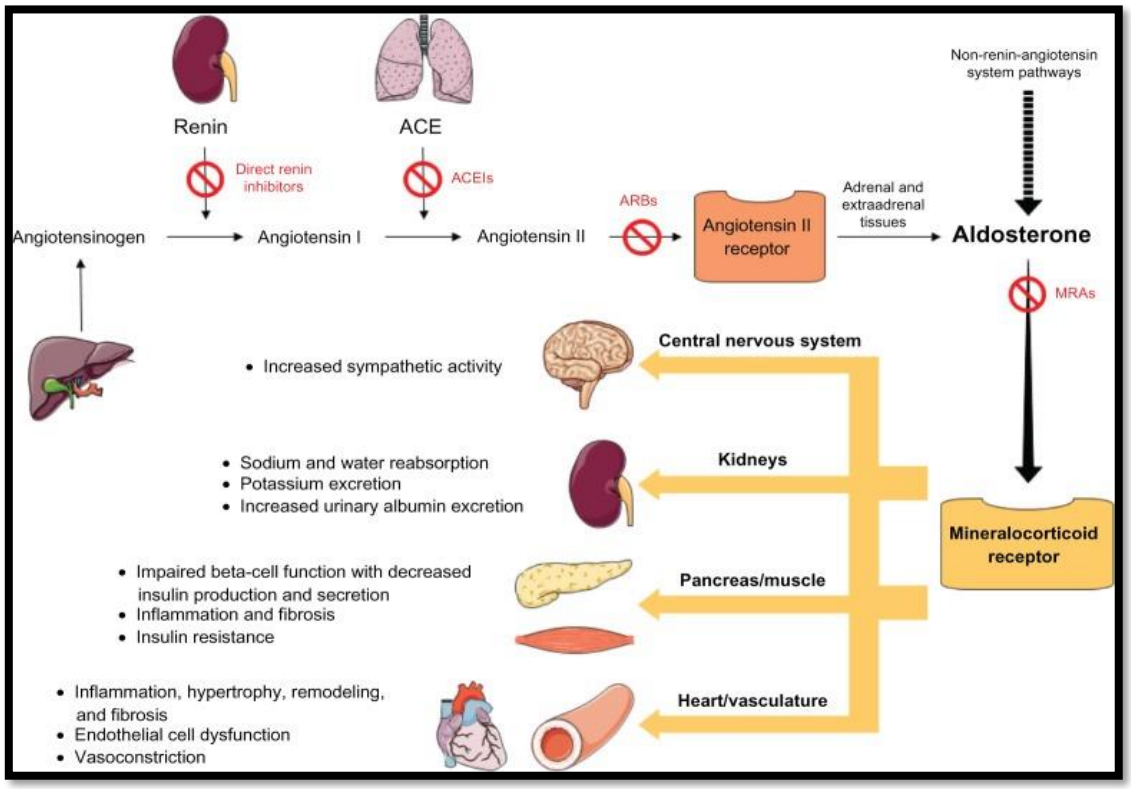


Figure No. 6 MOA of Aldosterone

1.8 Mechanism Of action Aldosterone

Aldosterone was previously thought to play a significant role in controlling the balance of sodium, potassium, and water. But a fresh perspective on aldosterone and how it affects human health and disease is quickly taking shape the vascular.

MRAs, also referred to as aldosterone antagonists, have been shown to be helpful for patients with a variety of clinical conditions, such as PA, primary and resistant hypertension, HF, and CKD. Summarises the pharmacological properties of spironolactone, eplerenone, and canrenone, the three main MRA drugs. Progesterone-like in structure, Spiro lactone is a non-selective, competitive MRA that is transformed into active metabolites in the liver [8]. Previously, it was believed that aldosterone was crucial in regulating the equilibrium of sodium, potassium, and water. However, a novel viewpoint on aldosterone and its impact on human health and disease is quickly emerging. MRAs, or aldosterone antagonists, have been demonstrated to be beneficial for patients with a range of clinical conditions, including PA, primary and resistant hypertension, HF, and CKD. Summarises the pharmacological characteristics of the three main MRA medications, spironolactone, eplerenone, and canrenone. Spiro lactone, a non-selective, competitive MRA with a progesterone-like structure, is converted into active metabolites in the liver [8].

Function of aldosterone:

The major purpose of aldosterone is to assist control blood pressure. Aldosterone helps to this critical function in several ways:

The retention of water by your body in your blood, which increases blood volume, is made possible by aldosterone's effect on sodium rise.

Aldosterone instructs your kidneys and intestines to increase the amount of salt or potassium they produce in your urine or deliver into your bloodstream (pee)

All of these steps are necessary for returning blood pressure levels to a safe range once they have dropped.

The pH (acid-base balance) and electrolyte levels of your blood are indirectly maintained by aldosterone.

Symptoms of high aldosterone:

The following are signs and symptoms of primary aldosteronism (high aldosterone levels):

- Blood pressure is high (hypertension)
- Headache
- Muscle weakness, particularly if potassium levels are extremely low
- Excessive thirst and urine
- If you are having these symptoms, you should consult with your doctor[16]

Symptoms of low aldosterone:

Low aldosterone levels (hypoaldosteronism) can produce the following symptoms in general:

- Blood pressure is too low (hypotension)
- Muscle fatigue
- Nausea
- Palpitations in the heart
- Heartbeat irregularity (arrhythmia)
- Additional symptoms may occur depending on the aetiology of hypoaldosteronism.

Addison's disease, for example, can produce changes in your skin, such as darkening on scars and in skin folds, as well as low blood sugar levels, due to low cortisol levels (hypoglycemia). It is critical to consult your healthcare physician if you are having any of these symptoms [16].

1.9 Prednisone:

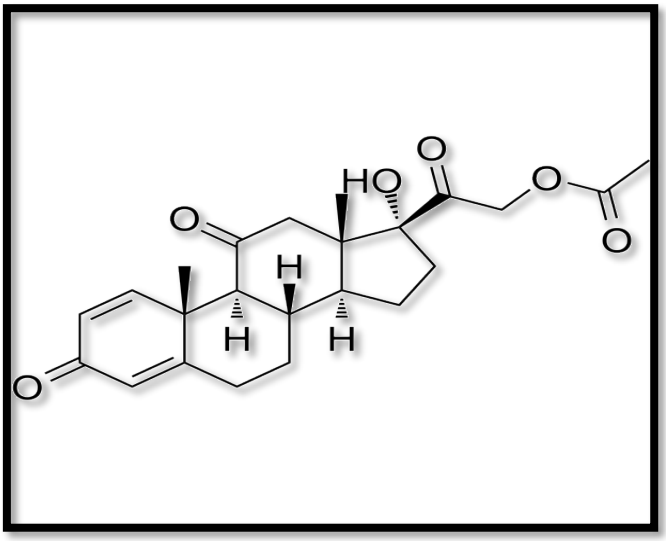


Figure No.7 Structure of Prednisone

Prednisone is a synthetic glucocorticoid steroid that reduces inflammation. It is physiologically inactive and is converted to prednisolone in the liver. Prednisone is a delayed-release corticosteroid that has been approved by the FDA to treat a wide range of conditions, including acute exacerbations of multiple sclerosis, immunosuppressive/endocrine, rheumatic, collagen, dermatologic, allergic states, and ophthalmic, respiratory, hematologic, and neoplastic diseases. One class of corticosteroid is

prednisone (cortisone-like medicine or steroid). It boosts the immune system and lessens allergic reactions like swelling, redness, and itching. This activity will also highlight the mechanism of action, adverse event profile, and other critical elements for members of the interprofessional team who administer prednisone to patients, such as dosing, pharmacodynamics, pharmacokinetics, monitoring, and pertinent interactions.

Mechanism of Action:

Prednisone inhibits polymorph nuclear leukocyte movement and reverses increased capillary permeability to reduce inflammation. Additionally, it weakens the immune system by reducing its volume and activity. Antineoplastic effects in developing lymphocytes may be accompanied by impaired glucose transport, phosphorylation, or cell death activation. It might suppress prostaglandins, which block the brain's emetic centre's innervation, to have antiemetic effects [17].

Prednisone is a pro-drug of prednisolone that mediates the effects of glucocorticoids. A glucocorticoid with anti-inflammatory and immunomodulatory properties is prednisone.

Following cell surface receptor attachment and entry, prednisone enters the nucleus, binds to, and activates specific nuclear receptors, leading to altered gene expression and suppression of pro-inflammatory cytokine production. This medication inhibits cell differentiation, lowers the number of circulating lymphocytes, and induces apoptosis in tumour cell types that are sensitive to it.

The actions of glucocorticoids are mediated by nuclear processes that alter DNA replication.

The most frequent side effects of prednisone include hyperglycaemia, insomnia, increased hunger, hypertension, osteoporosis, oedema, adrenal suppression, cataracts, and sluggish wound healing [17].

Adverse effects:

People who receive glucocorticoids in high dosages or for an extended period of time are more likely to experience negative effects. A high dose of prednisone is 40 mg daily or more. Possible side effects include skin brittleness, weight gain, an elevated risk of infections, and fractures. The effects of hypertension, hyperglycaemia, and dyslipidaemia on the cardiovascular and metabolic systems are all substantial [18].

Adrenal insufficiency is another adverse reaction that is frequently identified when a patient is hypotensive and unresponsive to fluids, vasopressors, or cardiogenic medications following stressful operations or while suffering from sepsis. If there is a suspicion of adrenal insufficiency, treatment should start right away with 100 mg of hydrocortisone administered every eight hours.

Weaning patients off of high doses of glucocorticoids after more than five days is advised.

1.10 Dexamethasone:

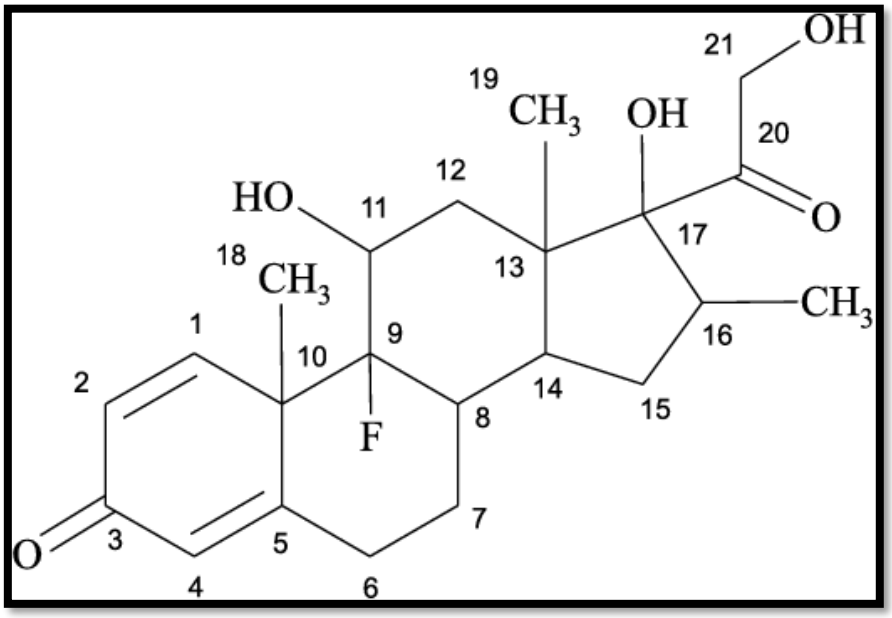


Figure No. 8 Structure of dexamethasone

Contrary to naturally occurring cortisol and corticosterone, dexamethasone is the most potent synthetic glucocorticoid with essentially pure glucocorticoid action. Numerous inflammatory and autoimmune diseases can benefit from dexamethasone's potent anti-inflammatory and immunosuppressive properties. Dexamethasone is additionally used to treat multiple myeloma, reduce the vasogenic edema brought on by brain tumours, and treat adrenal insufficiency. Dexamethasone increases blood pressure in men despite its capacity to bind to mineralocorticoid receptors; this is demonstrated by the absence of urinary salt retention and an increase in body weight [23].

Unrelated to sodium loading or retention, dexamethasone raises blood pressure. Okuno et al. confirmed that oral 1% NaCl sodium loading had no effect on the hypertensive effects of dexamethasone (30–60g/day, 2.5mg/L drinking fluids) in rats [21].

1.11 Mechanism of Action Dexamethasone:

Hypertension is a well-known side effect of glucocorticoids, both naturally occurring and manufactured. Dexamethasone is a powerful synthetic glucocorticoid with several therapeutic uses. Dexamethasone-induced hypertension (DEXHT) models have been used to study the mechanisms of glucocorticoid-induced hypertension because it has purely glucocorticoid activity with

negligible mineralocorticoid effects. This review looks at the properties and processes of DEX-HT in both human and experimental animal models. The roles of hemodynamics, volume, the renin-angiotensin-aldosterone system, the sympathetic nervous system, vasodilators including nitric oxide, vasoconstrictors, and reactive oxygen species in the pathogenesis of DEX-HT are discussed, as well as the differences between hypertension caused by naturally occurring steroids.

Common side effects

The more common side effects that can occur with dexamethasone include:

- Nausea
- Vomiting
- Swelling
- Anxiety
- High blood glucose
- High blood pressure
- Headache

Serious side effects and their symptoms can include the following:

Serious side effects:

- Unusual tiredness
- Unusual dizziness
- Unusual digestive upset
- Blood in your stool, or black stools
- Blood in your urine
- Unusual bleeding or bruising
- Unusual swelling throughout your body, or bloating in your abdomen (stomach area)
- Changes in mood or thoughts, or mood disorders such as depression.

NEED OF WORK:

Prednisone is one of many corticosteroid medications that can result in sodium retention and dose-related fluid retention. The most fluid retention is brought on by corticosteroids with potent mineralocorticoid effects, such as hydrocortisone and fludrocortisone. Dexamethasone, triamcinolone, and betamethasone are a few examples of corticosteroids that lack significant mineralocorticoid activity but still have the potential to cause minor fluid retention. Patients with pre-existing hypertension may experience worsening blood pressure control when corticosteroid-induced fluid retention is started because it can be severe enough to lead to hypertension. The overstimulation of the mineralocorticoid receptor, which causes sodium retention in the kidneys, is the main mechanism of corticosteroid-induced hypertension. This causes the volume to expand, which in turn raises blood pressure. Therefore, in order to reduce the emergence of this adverse effect, the smallest effective dose and shortest course of steroid therapy must be found.

FUTURE SCOPE:

- Practitioners need to be aware that these medications could worsen existing conditions or create new ones. It is crucial to understand the clinical effects of prescribing these medications.
- Systemic corticosteroids are frequently used to treat a variety of inflammatory and auto-immune diseases. Despite these medications' benefits, long-term use (especially at high doses) is associated with potentially serious side effects, including hypertension, which can affect not only the GI tract but also the musculoskeletal, endocrine, cardiovascular, central nervous, and gastrointestinal systems. By closely monitoring the patient and implementing preventive measures, such as using lower strength medications and the smallest effective dose required to treat the underlying problem, many of these side effects can be minimized.
- Patients ought to be aware of the potential side effects (AEs), such as hypertension, associated with the use of systemic corticosteroids, as well as methods for altering one's lifestyle that may help reduce the likelihood of these events. Advising patients to get help from a doctor if they feel.

CONCLUSION:

Many different diseases are treated with corticosteroid medications (anti-inflammatory). Steroids frequently and problematically cause clinically relevant side effects, regardless of dosage or route of administration. The most serious side effect of corticosteroid use is hypertension, which must be taken into consideration when choosing a patient's course of treatment because it increases the risk of cardiovascular disease and other complications.

The clinical use of corticosteroids should be the main focus of evidence-based prescribing.

There are a number of serious side effects, some of which are life-threatening, that make corticosteroid withdrawal difficult. As a result, choosing to administer corticosteroid therapy always necessitates careful evaluation of the relative risks and benefits for each patient.

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