Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Drugs used in osteoporosis

Color index:
Important
Note
Extra

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Editing File

Mind map

Treatment of osteoporosis

Reset back the balance of remodeling

Anti-Resorptive Agents:

1-Bisphosphonates
Most commonly used

2-RANKL inhibitors

3-Strontium

4-Androgen analogues

5-Estrogen Analogues

6-SERMS (Raloxifene)

7-Calcitonin

Bone Anabolic Agents:

Parathyroid hormone ,Teriparatide (PTH analogue)

Strontium (dual effect)

Replace what is missing (Ca , Vit D , Na, fluoride)

Used to enhance the strength by the formation of fluorapatite. It is considered only when trabecular bone is reduced in presence of normal cortical bones.

Dr ishfaq said the next few slides are only for better understanding

For better understanding

osteoporosis

- **Osteo:** is Latin for “bone”.
- **Porosis:** means “porous or full of holes”.
- **“Osteoporosis”** means bones that are full of holes”.
- Osteoporosis can develop without symptoms (the silent disease).

TYPES OF BONE

Cortical

is **hard**, compact, dense bone.
(example: mid-section of larger, long- bones of arms and legs).

Trabecular

spongy, porous and flexible bone
(example: end of the wrist, hip and the spine).

Healthy bone

- Bone is living tissue, which is constantly being broken down and rebuilt, a process called remodeling.
- Bone is renewed like skin, hair and nails.

BONE “REMODELING”

It includes:
1) Resorption-removes old, dead or damaged bone.
2) Formation-replaces old bone with new bone which done by osteoblast cells.

BONE “REMODELING”	
OSTEOCLASTS- PHASE 1	Cells called osteoclasts (think “C” for cutting of bone) seek out old bone or damaged bone tissue and destroy it, leaving small spaces (resorption)
OSTEOBLASTS – PHASE 2	Cells called osteoblasts (think “B” for builder) use minerals like calcium, phosphorus, and vitamin D to fill in the spaces with new bone (formation)

For better understanding

Steps to building healthy bones

- Calcium & vitamin D
- Limit Caffeine & Alcohol
- Exercise
- Don't Smoke

You build bone until about age 30

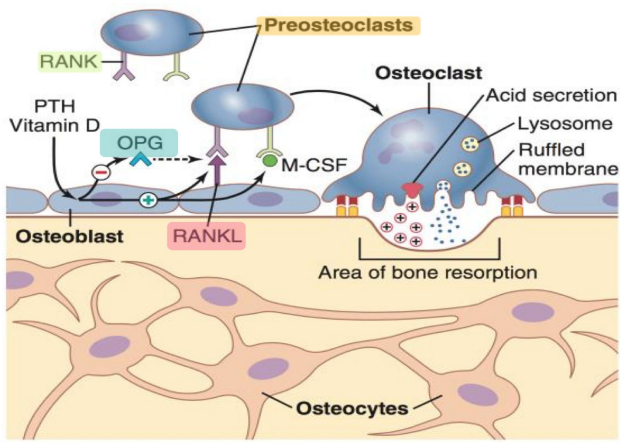
Bone component

- ❏ **Inorganic components** 65% of mass + consists of crystalline calcium phosphate salts (hydroxyapatite, HAp).
- ❏ **Organic components** 35% of mass + consists of osteoblasts, osteoclasts and osteocytes.

Bone forming cells	Bone resorptive cells
• Osteogenic cells mesenchymal in origin are found on all bone surfaces. • Osteoblasts forms osteoid framework & help in its mineralization.	Osteoclasts Reside in pits (resorption bays) that form by eaten bone surface. Secretes lysosomal enzymes (collagenase & metalloproteinase) + hydrochloric a. dissolve bone matrix.

BONE REMODELING

- It occurs under the control of systemic hormones, body mineral contents & local autocrine-paracrine secretions (Cytokines, Growth Factors, PGs).
- It is meant to maintain calcium homeostasis & to renew bone in repair of microdamage & microcracks.



RANK will make osteoclast mature and OPG will bind with RANK receptors and inhibit RANK effect

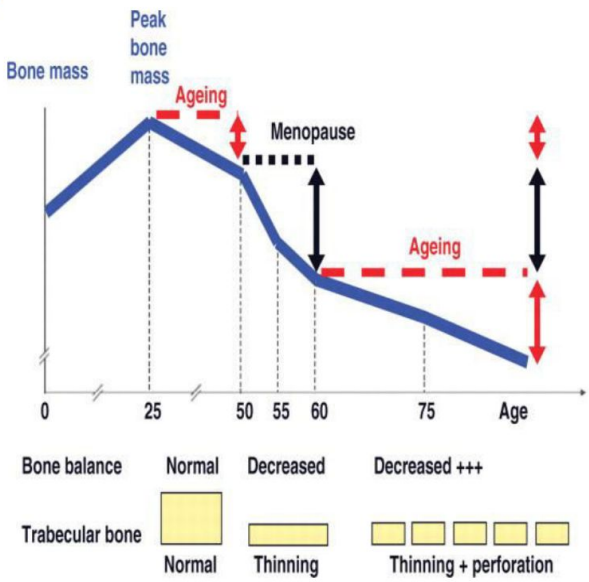
Osteoporosis

- ★ A complex of endocrinological disorders of bone and mineral metabolism (bone resorption > formation)
- ★ It'll lead to low bone mass + disruption of bone architecture + reduced bone strength and increased risk of fractures.

For better understanding

osteoporosis risk factors

Potentially modifiable	Non-modifiable
➢ Current cigarette smoker. ➢ Diet low on calcium or Vit.D. ➢ Sedentary lifestyle. ➢ Glucocorticoids anticonvulsants ➢ (lacking the - physical activity and movements) ➢ Body weight. ➢ Environmental risks (especially in elderly). ➢ Poor eyesight.	• Personal history of fracture. • 1st degree relative has a history of fractures. • Race (Caucasian or Asian). • Elder people • Poor health • Dementia. • Hormonal disorders. • Neoplastic disorders - • Metabolic abnormalities



- **BONE LOSS & AGING:** The first 5-15 years after menopause a woman can lose approximately 25 - 30 % of trabecular bone & approximately 10 – 15 % of cortical bone
- Aging → decline in bone density. Menopause → great decline in bone density
- Bone loss often occurs without symptoms or warning signs

Inadequate gonadal hormone production is a major cause of osteoporosis in men & women. Estrogen replacement therapy at menopause is a well-established means of prevention.

Anti-Resorptive Agents

Bisphosphonates

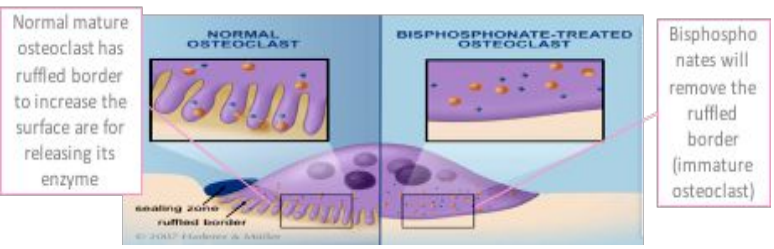
Non-Nitrogenous

- Etidronate
- Clodronate
- Tiludronate

Nitrogenous

Very common

- Alendronate (orally)
- Ibandronate (IV)
- Risedronate (orally)
- Zoledronate (IV) Very potent



Bisphosphonates (Most commonly used)

Mechanism Of Action

- Are compounds that have two phosphonate (PO_3) groups.
- Are structurally similar to pyrophosphate (component of bone matrix)

1. They preferentially "stick" to calcium→ concentrate in **bones**, bound to hydroxyapatite, decreasing its solubility and making it more resistant to osteoclastic activity 'prevent osteoclasts from working'.(predominant mechanism)
2. They prevent bone resorption by inhibiting osteoclast function.

- Their relative potencies for osteoclast inhibition is the most with 3rd generation "Zoledronate"

3. BLOCK STEPS IN CHOLESTEROL SYNTHETIC PATHWAY IN OSTEOCLAST that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity→ Stop function→ apoptosis (increased death of osteoclast)

Bisphosphonates

P.K

- Poorly abs (< 10%), food impair absorption more so must be given on an empty stomach. infused IV.
- $t_{1/2}$: 1 hr.
- Half of absorbed drug accumulates in bones,remainder →excreted unchanged in urine. (dose is adjusted in patients with renal impairment)
- In bone it is retained for months, depending on bone turnover.

M.O.A

- **How do they inhibit osteoclasts?** It is taken up by osteoclast then blocks steps in cholesterol synthetic pathway within osteoclast then and end up by osteoclast apoptosis.

Uses important

Osteoporosis, 2ndary to menopause, glucocorticoids	**Pagets Disease** (They have hypercalcemia & we need the ca+2 to be deposited in bones).	**Malignancy**- associated hypercalcemia

Dosing

- Once weekly, or on two consecutive days each month
- Should be taken in **upright position (to avoid esophagitis).**
- Separate 4 hrs before giving Ca, Mg, Al containing drugs
- **Note** : calcium and vit.D supplementation given during bisphosphonate therapy don't ingest it along with bisphosphonate, give a gap as mentioned above,why? Because bisphosphonate will inhibit the absorption of Ca and vitamin D

ADR Very important

- **GIT irritation;** nausea, vomiting, gastritis , ulceration,esophagitis,to avoid: give large amount of water to avoid risk of the tablet getting stuck in the esophagus
- **Gastro-esophageal reflux + ulcerations**,to avoid: give on empty stomach while sitting in upright for 30 min
- Flu like manifestations (fever,chills)upon IV infusion (in high dose)
- **Osteo-necrosis** of the jaw [mandible > jaw] more upon long use with IV infusion preparation usually after dental surgical procedures.
- If a dental implant or extraction is already planned, delay **bisphosphonate therapy** for a few months until healing of the jaw is complete
- **Atrial fibrillation** > women with alendronate zoledronate

Saq bisphosphonate GIT ADRs

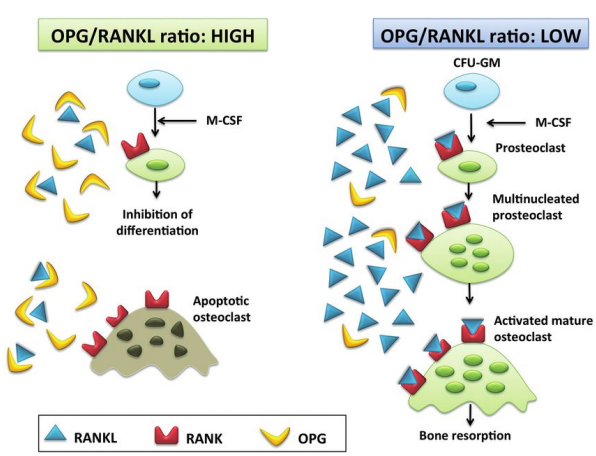
C.I

- Decreased renal function because it's excreted in the kidney
- Peptic ulcer / esophageal reflux

RANKL Inhibitors (Denosumab)
"still under investigation"

M.O.A	➢ It is a fully human MOA (a human monoclonal antibody) that mimics the activity of osteoprotegerin(OPG). ➢ It binds to RANKL, expressed by osteoblasts→ Block RANKL from interacting with RANK expressed on pre osteoclasts→ decrease Osteoclastogenesis(no mature osteoclasts). ➢ It binds also to mature osteoclast →increase its apoptosis, So net effect:decrease **bone resorption** ➢ RANKL binds to its receptor RANK on the surface of precursor and mature osteoclasts, and stimulates these cells to mature and resorb bone. OPG, which competes with RANK for binding to RANKL, is the physiological inhibitor of RANKL. Denosumab binds with high affinity to RANKL, mimicking the effect of OPG.
Uses	➢ It is **extremely expensive** and reserved for patients who can not tolerate or respond to bisphosphonate
P.K	➢ Administered **Subcutaneously every 6 month** Better than bisphosphonate
ADR	➢ Infections:urinary & respiratory (Due to the immunological nature of the drug). ➢ Eczema & skin rash (Due to the immunological nature of the drug). ➢ Pancreatitis
C.I	➢ In patients with **hypocalcemia**,bc Denosumab decreases serum calcium concentration. Antagonise calcium (Correct Ca & Vit D levels before starting denosumab),why we give Ca? will basically denosumab inhibit osteoclasts which regulate Ca level in the blood, so if osteoclast inhibited the Ca level in the blood will be low

**↑ RANK = ↑ maturation & activation of osteoclast = ↑ resorption.
OPG = physiological antagonist that bind to RANKL and inhibit it from binding to its receptor. *team 436



Anti-Resorptive Agents + Bone Anabolic Agents

Strontium "Strontium Ranelate"

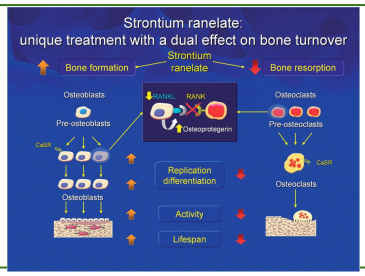
M.O.A

- Sr2+, is a divalent cation, resembling Ca2+ in atomic & ionic properties. It is orally active as distrontium.
- 1st drug to possess **"dual or double action"** i.e has both anabolic & anti- resorptive effects resulting in a rebalance of bone turnover in favor of bone formation.
- **Effects on osteoblasts:**
  - Since it is like Ca, it acts as agonist on **Ca Sensing Receptor [CaSR]** ; which is a GP coupled receptor that enhances differentiation of preosteoblast to osteoblast → increase bone formation
  - It stimulate the expression of OPG → increase RANKL binding → -ve of osteo-clustogenesis → decrease bone resorption.
- **Effects on osteoclasts:**Acts as agonist on Ca Sensing Receptor [CaSP] →suppress differentiation of preosteoclast to osteoclast → increase osteoclast apoptosis → decrease bone resorption

(Click here to see a very helpful illustration) *436 team

P.K

- Orally with a modest bioavailability 25%
- Binds partially to plasma proteins and strongly to bones
- $T^{1}/_{2}$ 60hrs
- Excreted mainly by the kidney



Uses

- **Osteoporosis**, secondary to **menopause**, **glucocorticoids**, ...
- **Malignancy-** associated hypercalcaemia

C.I

- In severe renal disease.
- In hypersensitivity to it
- **In increased risk of venous thromboembolism** (in immobile patients)
- **In phenylketonuria** (is an inborn error of metabolism that results in ↓metabolism of the amino acid phenylalanine)
- and drugs containing phenylalanine

Interaction

- Food specially containing **milk**+ its products • **Antacids**
- Oral **tetracycline** & **quinolones** chelate it

because it binds with them and it decrease their absorption

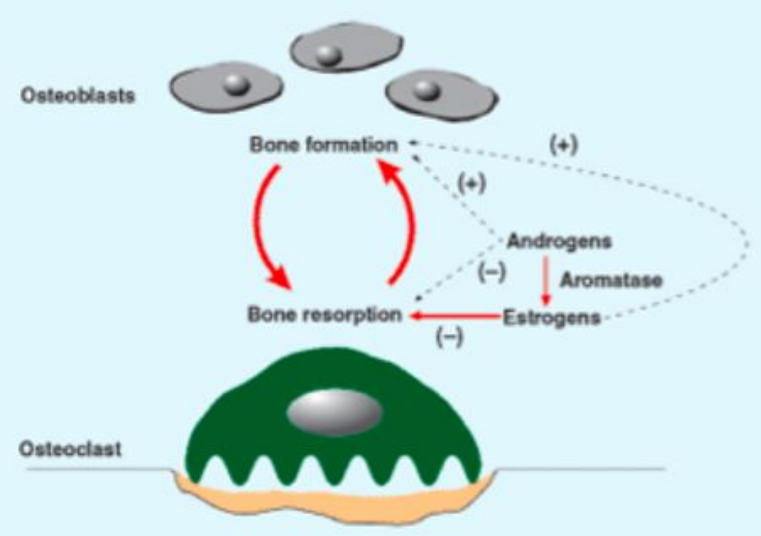
Precautions: 2hrs spacing, to avoid interaction

ADR
Self limiting

- **GIT irritation**; nausea, vomiting, headache, eczema. All resolve in 1st 3 months. (Reversible)

Anti-Resorptive Agents

	Estrogen "Estrogen is neuroprotective"	Androgen
	➢ **Estrogen in females & Androgen in males are essential for normal bone remodeling.**	
Idications	When to use Estrogen? ➢ If **hysterectomy** (the surgical removal of the uterus): **use Estrogen only**. ➢ If uterus is present: Estrogen +Progestins (progestins given to lower risk of cancer) ➢ As Hormonal replacement therapy (HRT): Menopausal symptoms ➢ SERMs (Selective Estrogen Receptor Modulator, e.g. Raloxifene): Menopause/Elderly.	➢ Androgen: For elderly men only.
M.O.A	➢ **Increase osteoclast apoptosis** ➢ **Inhibit osteoblast apoptosis** ➢ Decrease Number & depth of resorption cavities ➢ Increase release of growth factors from osteoblasts ➢ Decrease release of inflammatory cytokines causing resorption.	
ADR	➢ As a Hormone replacement therapy: - Risk of breast cancer. - Vaginal bleeding. - Venous thromboembolism.	



Anti-Resorptive Agents

SERMs (selective estrogen Receptor modulator) e.g. Raloxifene

The only drug that have both anti-resorptive agent & bone anabolic effect

General info

- Raloxifene is the **1st selective estrogen Receptor modulator** (SERM) for prevention and treatment of osteoporosis.
- Modulator: can be either agonist or antagonist..

M.O.A

- Antiestrogens that exhibits partial agonistic action; acting as an agonist in bone & an antagonist in some female sex organs

Effect on organ	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol (Estrogen analogues)	++	++	++	++	++	++
Raloxifene	-	-	-	-	+	+

The point from this table is to know that: Estradiol has ADRs on most of organs unlike Raloxifene (just little effect on CVS and bone)

Advantages

- Increase **bone density** (2%) & decrease fracture risk (30%).
- No stimulation of breast or endometrial tissue.
- No need for progestin in women with uterus. Progesterone is protective factor against cancer
- Decrease LDL.
- Good for women with risk of uterine and breast cancer. Don't use Estradiol
- Lower risk of thromboembolism compared to estrogen

Disadvantages

- May increase hot flushes.
- No effect on HDL.
  no protection for CVS

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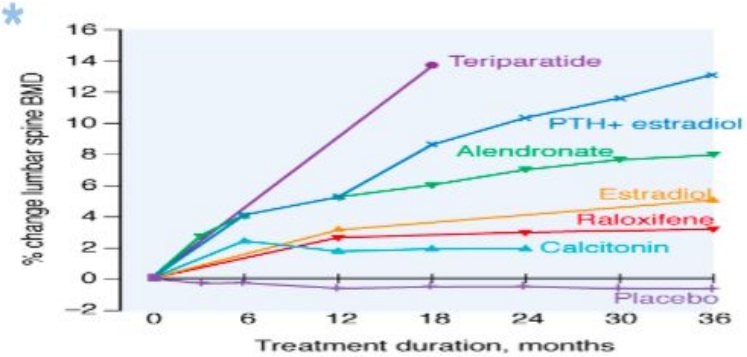

Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition*: www.accessmedicine.com

No that important

Relative efficacy of different therapeutic interventions on bone mineral density of the lumbar spine

Summary

	Bisphosphonate	Denosumab
MAO	➢ blocks steps in cholesterol synthetic pathway within osteoclast then and end up by osteoclast apoptosis.	➢ Block RANKL from interacting with RANK expressed on pre osteoclasts→ decrease Osteoclastogenesis ➢ It binds also to mature osteoclast →increase its apoptosis, decrease bone resorption
indications	Osteoporosis secondary to -Menopause. -Glucocorticoids. 2. Pagets disease. 3. Malignancy-associated hypercalcemia.	-
ADRs	➢ GIT irritation ➢ Gastro-esophageal reflux ➢ Flu like ➢ Osteonecrosis of the jaw ➢ Atrial fibrillation	➢ Infections: urinary & respiratory ➢ Eczema & skin rash ➢ Pancreatitis
C.I	➢ Decreased renal function ➢ Peptic ulcer / esophageal reflux	➢ In patients with hypocalcemia

Summary

	Strontium	Estrogen & Androgen	SERMs Raloxifene
M.O.A	Has both anabolic and anti-resorptive effects **-Effects on osteoblasts:** enhances differentiation of preoteoblast to osteoblast → increase bone formation **-Effects on osteoclasts:** suppress differentiation of preosteoclast to osteoclast → increase osteoclast apoptosis → decrease bone resorption	-Increase osteoclast apoptosis -Inhibit osteoblast apoptosis -Decrease Number & depth of resorption cavities -Increase release of growth factors from osteoblasts -Decrease release of inflammatory cytokines causing resorption.	Antiestrogens that exhibits partial agonistic action; acting as an agonist in bone & an antagonist in some female sex organs
P.K	Partially bound to plasma proteins and strongly to bone. Excreted by kidney.	_____	_____
Uses/indications	-Osteoporosis, secondary to menopause, glucocorticoids, ... -Malignancy- associated hypercalcaemia	-If hysterectomy: Estrogen -If uterus is present: Estrogen +Progestins -As Hormonal replacement therapy (HRT): Menopausal symptoms SERMs e.g. Raloxifene: Menopause/Elderly. -**Androgen: For elderly men only.**	**Advantages:** -Increase bone density (2%) & decrease fracture risk (30%). -No stimulation of breast or endometrial tissue. -No need for progestin in women with uterus. -Decrease LDL. -Good for women with risk of uterine and breast cancer. -Lower risk of thromboembolism compared to estrogen
C.I	-In severe renal disease. -In hypersensitivity -In increased risk of venous thromboembolism -In phenylketonuria	_____	**Disadvantages:** -May increase hot flushes. -No effect on HDL.
ADRs	GIT irritation; nausea, vomiting, headache, eczema. All resolve in 1st 3 months.(reversible)	As a HRT (estrogen): -Risk of breast cancer. -Vaginal bleeding. -Venous thromboembolism.	“Little side effects on bones and CVS

Questions

1- Bisphosphonate increase osteoclast apoptosis by blocking:

A- Free fatty acid pathway B- Triacylglycerol pathway
C- Cholesterol pathway D- Protein pathway

2-53 yo male patient with renal failure have been diagnosed recently with osteoporosis, which drug would the physician prescribe:

A- Bisphosphonate B- Denosumab
C- Strontium D- Estrogen

3- A female patient known to have peptic ulcer, which drugs should be avoided to treat her osteoporosis:

A- Bisphosphonate B- Denosumab
C- Strontium D- Estrogen

4- A 25 yo patient came to the ER complaining of burning pain during urination, microbiology lab found bacteria in urine indicating urinary tract infection. In history, patient said he is on medication for osteoporosis, which drugs could cause this manifestation:

A- Bisphosphonate B- Denosumab
C- Strontium D- Estrogen

5- Which of the following is an adverse effect of Bisphosphonate:

A- Respiratory infection B- Pancreatitis
C- Venous thromboembolism D- Osteonecrosis of the jaw

6- Which of the following is contraindicated in severe renal disease?

A- Bisphosphonate B- Denosumab
C- Strontium D- Estrogen

7-Which of the following has both Anabolic and Anti-resorptive effect?

A- Bisphosphonate B- Denosumab
C- Strontium D- Estrogen

8- In case of hysterectomy, which of the following drugs should be used?

A- Androgens B- Androgens + Estrogens
C- Estrogens + Progestins D- Estrogen Only

9- Which of the following is not a SERM Advantage?

A- Decrease bone density B- Decrease LDL.
C- decrease fracture risk D- Lower risk of thromboembolism

10- Which of the following ADRs is from HRT (estrogen)?

A- Risk of breast cancer. B- vomiting
C- eczema D- Pancreatitis

1-C
2-B
3-A
4-B
5-D
6-C
7-C
8-D
9-A
10-A

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Thanks for those who worked on the lectures :

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Notes by

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References:

- ✓ Doctors' slides and notes
- ✓ 436 pharma team

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