

FACTORS THAT IMPAIR TISSUE REPAIR (IMPORTANT):

Reparative process is affected by multiple factors that impact its speed, intensity, degree and perfection, an individual may suffer from only one or multiple factors:

If these factors are in, you won't have an effective reparative process, either it will be delayed or it will be improper

1. Infections:

- the enemy of surgeons and patients who undergo a surgery.
- if the wound gets infected (**super-added infection**) ⑦ all the reparative process will be interrupted ⑦ the proper healing process will be delayed.
- it prolongs inflammation and potentially increases the local tissue injury.
- **In hospitals where there is good quality insurance, each surgeon will have a specific parameter for postoperative wound infections. For example, good surgeons protect their wounds and prepare the patient well then the incidence of postoperative wound infection is very low. The more the postoperative wound infections, the worse the technique, so all of us as physicians must try and do our best to protect the wound as much as possible and prevent postoperative infections.**

Antibiotics are used as an infection-avoidance in cases of

*severe acute injury or *high-risk surgery or

*intraabdominal surgery; where the risk of infection or postoperation infection is high.

- In case of surgeries, patients are covered eight hours before surgery by antibiotics to prevent infections.

<p>2.Diabetes mellitus: most important example on comorbidities الأمراض المصاحبة</p>	<ul style="list-style-type: none"> - Diabetes have short- and long-term complications, that negatively impact the reparative process.(diabetic vasculopathy,the narrowing of the small to intermediate blood vessels at multiple organs) <p>Patients suffering from diabetes/glycosylation of the blood stream ((specially those who have a longstanding history of diabetes or uncontrolled blood sugar)):</p> <ul style="list-style-type: none"> *need extra time for healing, *higher risk on developing wound infections (you have to take care when dealing with a wound in patients who have chronic DM) *need more support, *experience delay in their reparative process,it will take longer time (impropereness) *experience negative impact on GFs&mediator's activation. <p>_ The more you control diabetes,the more you provide proper healing</p>
<p>3. Nutritional status:</p>	<ul style="list-style-type: none"> - Proper nutrition is important for proper healing. - Patients who are well-nourished will have proper reparative process.Otherwise,a delay in the reparative process occurs. - Patients who are malnourished,who are not eating well(they don't have metabolic balance) cannot have proper repair.

	<p>That's why these days those factors should not be a big issue unless the patient has specific diseases that prevents him/her from proper nutrition such as malabsorption syndrome, chronic disease, elderly patients who live alone, those are thin, weak and emaciated patients. If surgeons have the option to delay the surgery, they will admit the patient to the hospital giving them better nutrition, and building up their metabolic status and then apply surgery for them</p> <p>Patients who are debilitated (منهك), lost a lot of weight, suffering malnutrition, need additional parenteral nutrition (PN/مغذي/مصل) before doing any surgery/medical intervention for them; to raise up their immunity and to build up their protein balance.</p>
4. Steroids: strong antiinflammatory drug	<ul style="list-style-type: none"> - Number of people uptaking steroids is increasing (bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, and cancer patients) Some cancer patients need to have additional steroid treatment - A very critical drug, causes delay in the reparative processes (instead of 1-2 weeks).
	<ul style="list-style-type: none"> - Steroids are inhibitors in the main stem (phospholipase A2) of the arachidonic acid metabolism. (so both arms we mentioned before are hard-hit, ultimately delaying the reparative process, because inflammation process is inhibited)
	<ul style="list-style-type: none"> - In case of surgeries you should prevent the patient from taking steroids; since in addition to slow healing process steroids cause low immunity, so the chance of

	<p>infections is higher. For example when carrying out an abdominal surgery to a young healthy patient who doesn't take steroids usually sutures are removed on the day 10 or 12 post surgery, while those who are taking steroids like cortisone their wound healing will take a little bit longer time (maybe one or two weeks more)</p>
	<ul style="list-style-type: none"> - If Patients taking steroids had a severe tissue damage, you must properly think about the treatment.
<p>5. Mechanical factors:</p>	<p>Such as increased local pressure or torsion, Causing improper healing process.</p> <p>Ex: a smoker patient suffering from obesity, chronic obstructive lung disease or bronchitis, continuous coughing, needed a major surgery in their abdomen, ⑦ you must take care of their abdominal wound; because the surgery causes increase in intra-abdominal pressure that will impact the strength of the sutures which may result in: improper healing and sometimes: Wound Dehiscence.</p> <p>Wound Dehiscence: when a surgical incision reopens either internally or externally.</p> <p>So these patients may have extra padding and special belts tightly tied to the abdomen to prevent wound rupture and preserve suture stability when coughing.</p>
<p>6. Poor Perfusion: important</p>	<ul style="list-style-type: none"> - Poor perfusion occurs due to any of these: severe ischemia, atherosclerosis, hypertension, hyperlipidemia. - Patient with diabetes, hypertension and ischemic heart disease will have an element of peripheral vascular disease, the perfusion and blood supply to his lower limbs isn't normal, because of stenosis in his arteries

	<ul style="list-style-type: none"> - Patients suffering from poor perfusion, and undergo surgery⑦ *need more time for healing (like in cases of peripheral vascular disease) *need more attention concerning their current status(perfusion status) and nutrients
	<ul style="list-style-type: none"> - Antibiotics help in improving the healing process even if it takes longer time.
	Any organ needs proper blood supply for proper repair
7. Foreign bodies:	<ul style="list-style-type: none"> - Such as fragments of steel, glass, needle, medical equipment(rods or plates,may be inserted in bone fractures), or even bone, all lead to postoperative infection and impede and delay healing process. -
	<ul style="list-style-type: none"> - After every single surgery you must remove all of such foreign bodies.YOUR BODY DOESN'T LIKE FOREIGN SUBSTANCES
	<ul style="list-style-type: none"> - Sometimes removing a foreign body from the tissue causes more damage than keeping it inside, so you can either keep it inside for a while and remove it later, or keeping it forever (if it is too small and removing it will cause more damage, and the body is able to repair with its existence).
8. Type and extent of tissue injury:	<ul style="list-style-type: none"> - A facial wound or an incision in the face of a 15-yrs-old child will quickly heal (a couple of days), i.e. Sometimes you remove the suture in the 5th/6th day.
	<ul style="list-style-type: none"> - On the other hand, if a 75-yrs-old smoker with severe atherosclerosis, peripheral vascular disease, had to do a varicose vein surgery or bypass surgery, then the wound will take longer time; because the type of the injury is more extent and the location of injury is different.

	<ul style="list-style-type: none"> - The more extensive is the tissue injury, the more time to be repaired and the less perfect the repair is Small, quick and simple injury—the reparative process is fast and it is good as the pre-injury status In contrast, extensive tissue injury in cases of fractures or accidents so the repair takes longer time and it will be imperfect
9. Site of injury:	<ul style="list-style-type: none"> - Ex: abdominal wounds heal slower than facial/in the head/in the tongue wounds.
	<ul style="list-style-type: none"> - All injuries and wounds depend on the site of injury and the extent of the injury (for example facial surgeries will result in a fast healing and sutures removal because organs are very vascular and the blood supply is excellent, while in leg surgeries sutures are kept for two weeks until you remove them)

✚ Notice that multiple factors may occur in one patient altogether

ABNORMAL HEALING

Not all repair processes are completely perfect, **problems** in healing processes can occur and if so, they will lead to abnormal healing, such problems are:

- 1) Deficient scar formation
- 2) Excessive repair
- 3) Contractures

1st: DEFICIENT HEALING/SCAR FORMATION

Causes include poor perfusion, severe ischemia in the lower limbs

- sometimes the formed scar is deficient and weak, and this deficiency leads to serious complications such as; wound dehiscence.

Wound dehiscence: when the wound is opened because of increased intra-abdominal pressure.

★ Those sutures are okay.

★ The wound here has been opened because the sutures could not stand the increased mechanical intra-abdominal pressure. Severe intra abdominal pressure which isn't controlled

★ in cases of wound dehiscence.



- We have to provide antiseptic environment and protect the wound from infection.
- **Treatment/prevention:** At the moment of opening the wound you cannot go back and close it, **you have to let it heal by granulation tissue** from the bottom to the surface, and this takes long time (weeks and months).
- When dealing with wounds of patients suffering from obesity, cough and COPV, we must be ready and put stronger sutures, keep adding gauze and dressing and keeping it for longer time to prevent this (dehiscence) from happening.
- It could occur in another place other than the abdomen.

- Examples are mainly ulcers; every type of ulcers has a different pathophysiology and different underlying mechanism:

A. Venous leg ulcers

- ✓ They are superficial and dusky,
- ✓ Classic Venous ulcer,
- ✓ Occur due to excessive venous insufficiency and stagnation of the venous system in the lower limb,
- ✓ The common area of these ulcers is: The medial area of the lower leg,
- ✓ They are grey to blue.

Ulcers that Are due to of extreme back pressure in the venous system in the lower limbs due to abnormalities of the valves in the veins(they move the blood in one direction toward the heart)

B. Arterial ulcers

- ✓ Deep,
- ✓ Occur due to severe ischemia in the blood supply of certain branches of an artery.

Cases:patients with varicose veins, longstanding DM,people who stand during work hours like teachers

Ulcers that happen because of severe arterial perfusion insufficiency,like in patients with peripheral vascular disease,patients with severe diabetes, severe atherosclerosis from smoking, hypercholesterolemia, ischemic heart



Ulcers that are usually combined between arterial and venous ulcers(020) in patients with uncontrolled diabetes especially in the lower leg,they are difficult to heal,they get infected

C. Diabetic ulcers

- ✓ Deep arterial ulcer,
- ✓ Occur in **diabetic patients**; due to **peripheral neuropathy** (diabetes affects all the organs including the neural sensory neurons). So, they will develop what we call "**Diabetic foot**", which represents gangrenes and ulcers in the diabetic-patient foot. Nowadays, there are a lot of clinics taking care of the diabetic foot of these patients.



Decubitus ulcers:Ulcers that occur to patients who are in the hospital especially ICU,like patients with neurological diseases or stroke

D. Pressure sores/Bed ulcers

- ✓ The picture shows a back of a patient who **stayed in the bed for a long time**,
- ✓ Occur in patients with **quadriplegia or severe CNS illness**,
- ✓ due to the pressure on their back which leads to ischemia to that area, followed by **deep ulcers**,
- ✓ Nowadays, such ulcer type is considered as a significance of malpractice and bad nursing care,
- ✓ The protocol followed for such patients is: mobilizing them every 15-30 mins. Now, new and specific beds are manufactured for such patients, with multiple bubbles that electrically move up and down, trying to distribute the pressure on the patients back, **so the best treatment is by prevention, through those beds or good nursing.**



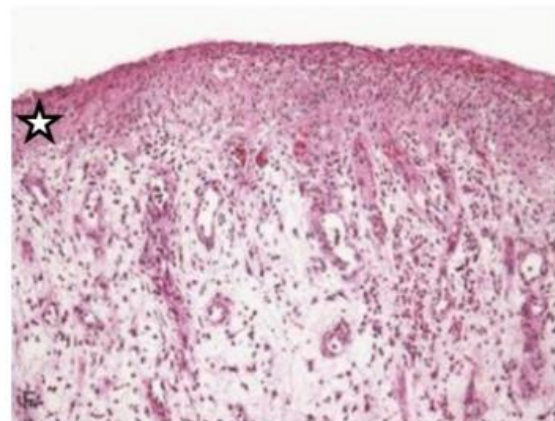
There will be pressure against bony prominences especially behind the buttock muscles,and this will cause pressure on the blood supply

A cross section of any of these ulcers will look like this:

E: Discontinuity, big deep ulcer in the squamous mucosal epithelium surface of the skin.

★**F: The floor of the ulcer:** angiogenetic granulation tissue, occurs as a response to this ulcerative morphology of the inflammatory response.

Sometimes it fails to reepithialize and close the gap because it's big enough



All these deficient healing conditions are better to be prevented than dealing with them after they occur

2nd: EXCESSIVE SCARRING

Instead of having a small, simple and thin scar tissue, this will have a little bit more scars

• Hypertrophic scar:

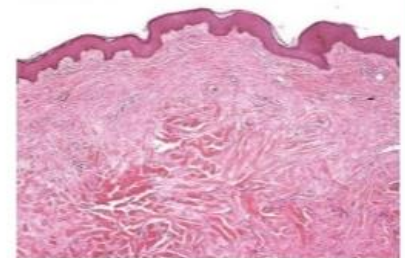
- ✓ Subcutaneous,
- ✓ Treatment: **-excision** (استئصال); trying to clean up the scar tissue by certain surgical types. Or **-utilizing some local anti-inflammatory medications** like steroid cream; to decrease the amount of scar tissue.
- ✓ In cases of surgery: the patient will have instead of a small, insipient, inapparent scar, there will be more scar formation (hypertrophic scar) due to some reasons.



• Keloid:

- ✓ Subcutaneous,
- ✓ A specific type of hypertrophic scar,
- ✓ Occurs more in **dark pigmented people**; that any small surgery can induce big excessive scar tissue like keloid.
- ✓ Sometimes it is really difficult to treat,
- ✓ It runs through families, **We see these scars more in African-American people**
- ✓ The picture shows: a lot of fresh, large scars of simple cutaneous tumors → healing by exuberant keloid material.
- ✓ basically, if you take a section from this and examine it under the microscope, you see **abundant dense bundles of collagen type I**, abnormally located causing squamous cell elevation. The more you manipulate them surgically, the more scars you will have.
- ✓ sometimes it is hard to differentiate between keloid and hypertrophic ulcers under the microscope, so you depend on the family history and the pigment of the patient whether it is dark or light.

Treatment is with surgery or steroid creams



Both Hypertrophic scar and Keloid, are cosmetically not nice, and can also affect the function if it involves in a joint or in an area which is sensitive for movement.

• Exuberant granulation tissue (proud flesh):

- ✓ Rare.

• Aggressive fibromatosis (desmoid tumor):

- ✓ Subcutaneous/ deep.

They are benign but they can be lethal by causing local destruction of end organs rather than metastasis

• Contractures

They can occur everywhere, common locations include the palm of the hand, some are congenital like in the penis pyeronie's disease

So either the scar will be deficient, and this is bad because it will result in a poor reparation process, that any additional weaker or simple trauma can disrupt the scar which is supposed to protect the underlying structures. On the other side there will be excessive reparative process and scar formation that sometimes can interfere with your daily functions

They contain additional amount of scar formation, additional amount of fibroblasts, additional amount of collagen type 1

FIBROSIS OF ORGANS

The changes which we have talked about concerning fibrosis **in tissues**, can occur **in vital organs**. Info:

- ❖ A very serious condition,
- ❖ Sometimes it causes increase in morbidity or mortality probability,
- ❖ Due to: **excessive deposition of collagen and ECM proteins**.
i.e.: after continuous infections or continuous immunologic injury, whether this injury is in the liver/kidney/pancreas/spleen, this leads to:
inflammation→repair, inflammation→repair, inflammation→repair
this results in: more formation of scar tissue. After 5/10/15/20 years, excessive fibrosis in that particular organ will impact the **vital functions** of that organ.
- ❖ **TGF-β** is the most important mediator in fibrosis, **Loss of function by fibrosis**
- ❖ Scar tissue formation and fibrosis in vital organs causes diseases, mainly:

1) Liver Cirrhosis

- ❖ Severe fibrosis, almost end stage,
- ❖ Almost 95% of livers tissue is replaced by fibrosis, causing liver failure,
- ❖ The patient must be treated, if not, they will die,
- ❖ Treatment: either transplantation or stopping the process of fibrosis,
- ❖ Liver failure with no transplantation increases mortality probability,
- ❖ In the west region, the most common cause of liver cirrhosis is alcoholism,
- ❖ In our region, the most common cause is chronic hepatitis C.

2) Idiopathic lung fibrosis

- ❖ Interstitial lung fibrosis,
- ❖ These patients represent lung fibrosis with unknown reason (etiology), that's why it is called 'idiopathic'
- ❖ The whole lung will be replaced by fibrosis scar tissue,
- ❖ The patient cannot breathe or utilize their lungs,
- ❖ some undergo lung transplantation, if not, the mortality probability is high.

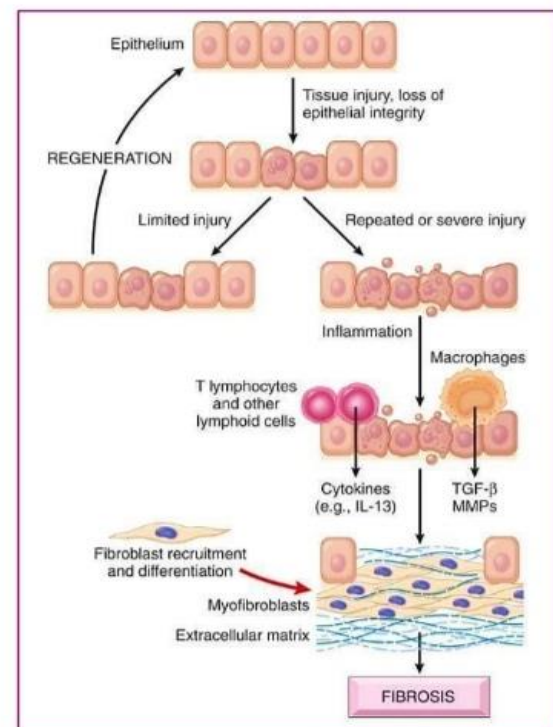
3) ESKD (end stage kidney disease), the last stage of long-term (chronic) kidney disease.

- ❖ If a patient is diagnosed with chronic renal disease, and is already suffering from hypertension (hypertensive nephropathy, a kidney disease caused by damage from hypertension) or diabetes (diabetic nephropathy, a serious kidney-related complication of type 1 diabetes and type 2 diabetes), such patient needs continuous follow up by their clinicians to get sure that the impact of the underlying disease (hypertension/diabetes) gets decreased by close follow up, so that ESKD gets delayed or treated very early.

- ❖ A lot of diseases that affect the kidney end up in causing severe and marked parenchymal renal fibrosis,
- ❖ under the microscope at late stages we can describe the biopsy by: “end stage kidney disease”,
- ❖ diagnosis with ESKD requires collaboration between **pathologists** (looking at the renal biopsy, seeing severe fibrosis in the kidney) and **clinicians** (following up the patient to identify if the patient had history with untreated diabetes or hypertension or glomerulonephritis... (since those diseases increase the probability of ESKD)).

A cartoon explaining excessive scar fibrosis, which leads to loss of function in some of these vital organs:

- If the injury is very small and the extent is limited → regeneration will occur quickly, and the tissue goes back to its original normal state.
- But in cases of severe tissue injury **or** repeated attacks of severe injury such as; repeated attacks of hepatitis C in the liver, this is the result →
 - *inflammation and recruitment of inflammatory cells,
 - *repair by scar formation induced by **TGF-β**,
 - *forming more fibrous tissue, instead of regeneration,
 - * the same cycle keeps repeating again and again and again, within couple of years, depending on the intensity of the injury, this will lead to severe fibrosis in that organ, if:
 - liver→ liver cirrhosis
 - kidney→ ESKD
 - lung→ Idiopathic interstitial lung fibrosis.



Summary

Cutaneous Wound Healing and Pathologic Aspects of Repair

- The main phases of cutaneous wound healing are inflammation, formation of granulation tissue, and ECM remodeling.
- Cutaneous wounds can heal by primary union (first intention) or secondary union (secondary intention); secondary healing involves more extensive scarring and wound contraction.
- Wound healing can be altered by many conditions, particularly infection and diabetes; the type, volume, and location of the injury are important factors that influence the healing process.
- Excessive production of ECM can cause keloids in the skin.
- Persistent stimulation of collagen synthesis in chronic inflammatory diseases leads to tissue fibrosis, often with extensive loss of the tissue and functional impairment.

If you
made it
till here

Then you
are a
super hero
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