

# PATHOLOGY

Sheet no. 9



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## QUICK REVIEW

-Repair: is the last step in inflammation, where healing occurs, mediated by many GFs like VEGF, angiopoietin, and TGF-B... it has 3 phases:

1) angiogenesis: proper angiogenesis is required to avoid abnormalities in healing, especially in diabetes and atherosclerosis cases, mediated by Angiopoietin and TGF-B, MMPs,...

2)activation, stimulation, and migration of fibroblasts mediated by TGF-B, which is found abundantly in severe fibrosis in neoplasia or cancer.

3)remodeling: conversion of early immature soft delicate scar to mature scar by cross-linking of collagen predominantly by disulfide bonds and converting collagen 3 to 1 obtaining stronger collagen, it is mediated by MMPs and TIMPs.

 Summary

### Repair by Scar Formation

- Repair occurs by deposition of connective tissue and scar formation if the injured tissue is not capable of regeneration or if the structural framework is damaged and cannot support regeneration.
- The main steps in repair by scarring are clot formation, inflammation, angiogenesis and formation of granulation tissue, migration and proliferation of fibroblasts, collagen synthesis, and connective tissue remodeling.
- Macrophages are critical for orchestrating the repair process, by eliminating offending agents and producing cytokines and growth factors that stimulate the proliferation of the cell types involved in repair.
- TGF- $\beta$  is a potent fibrogenic agent; ECM deposition depends on the balance among fibrogenic agents, matrix metalloproteinases (MMPs) that digest ECM, and the tissue inhibitors of MMPs (TIMPs).

## FACTORS THAT IMPAIR TISSUE REPAIR (IMPORTANT)

These are the factors that impact the reparative process, they are important for sake of your career and your exam:)

\*Remember: these 3 factors may overlap

: it is preferable to prevent these factors than treat them!

### 1. Infections

- is one of the most important causes of delayed healing; it prolongs inflammation and potentially increases the local tissue injury -the biggest enemy of wound healing, especially the surgical ones -the key performance measure(KPM), the more the susceptibility for the infection, the worst the surgical techniques indicator.

## 2. Diabetes mellitus

- a most important example of comorbidities الأمراض المصاحبة
- is a metabolic disease that compromises tissue repair for many reasons, and is an important systemic cause of abnormal wound healing.
- it delays healing, specifically if it is uncontrolled
- prevalence in Jordan=45% of diabetes and prediabetes.
- characterized by hyperglycemia
- diabetic patients` blood sugar becomes sweeter(glycosylation) , causing damage for most tissues
- diabetes may cause vasculopathy, enteropathy, ophthalmopathy, and nephropathy.
- diabetes should be controlled by drugs
- if a diabetic patient had an abscess, trauma, or postsurgical wounds, he would receive special care by antibiotics to prevent infections for proper wound healing

## 3. Nutritional status

- has profound effects on repair; protein malnutrition and vitamin C deficiency, for example, inhibit collagen synthesis and retard the healing
- nowadays, especially in Jordan, malnutrition is rarely found, however in some developing countries it would exist
- severe malnutrition results from improper food style, ex: hypoproteinemia, anorexia nervosa
- case: a patient suffers from vomiting and had lost 30 Kgs, and was diagnosed with a gastrointestinal stromal tumor

The procedure: is to gain some weight, +ve metabolic balance, vitamins, and protein supplements to make the surgery

#### 4. Steroids

-have well-documented anti-inflammatory effects, and their administration may result in weak scars because they inhibit TGF- $\beta$  production and diminish fibrosis. In some instances, however, the anti-inflammatory effects of glucocorticoids are desirable. For example, in corneal infections, glucocorticoids(steroids) may be prescribed (along with antibiotics) to reduce the likelihood of opacity due to collagen deposition

-inhibitor for phospholipase, though inhibiting Leukotrienes and prostaglandin synthesis

-The number of people up taking steroids is increasing(bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, and cancer patients) need longterm steroid therapy.

-Some cancer patients need to have additional steroid treatment

-A very critical drug causes a delay in the reparative processes (instead of 12 weeks)

-so if a patient taking steroid drugs, he has to stop the dose if it is possible before 6-7 weeks of the surgery, and if he cannot, he has to recognize that recovery will take longer, the chance for postoperative infection is more, and the chance for abnormal scar is more.

#### 5. Mechanical factors

-such as increased local pressure or torsion may cause wounds to pull apart (dehisce)

-For ex: if an old obese smoker with COPD undergoes surgery, then the chance for proper healing is less

It is dealt with by antitussives to prevent cough, and stronger and more sutures have to be done

\* it is preferable to prevent these causes than treat them!

#### 6. Poor perfusion

Perfusion:التروية

- decreasing in blood supply(ischemia)
- resulting either from arteriosclerosis and diabetes or from obstructed venous drainage (e.g., in varicose veins (الدوالي), also impairs healing.
- diabetes may cause vasculopathy and neuropathy, so diabetic patients may not feel pain, prolonging the healing
- de-suturing depends on the patient`s health and social status

## 7. Foreign body

- such as fragments of steel, glass, or even bone impede healing.

Sometimes you can't removing the foreign body and it will cause more damaging, so you are allowed in a certain situation to keep it in for a while and remove it later or just keep it forever, if it's a small needle inside a soft tissue of the foot, sometimes trying to remove it will cause more damage keep it, the body will itself repair and contain it by a foreign body in a reaction by scar tissue and it will stay forever, but in general the presence of a foreign body in a wound or any healing process will delay it.

## 8. Type and extent of tissue injury

-affects the subsequent repair. Complete restoration can occur only in tissues composed of cells capable of proliferating; even then, the extensive injury will probably result in incomplete tissue regeneration and at least partial loss of function. Injury to tissues composed of nondividing cells must inevitably result in scarring; such is the case with the healing of a myocardial infarct.

-a knife injured patient will be dealt with more flexibility than a crushed accident-injured person.

It is important because the facial wound or an incision in the face of child who is 15 years old will quickly heal and it takes probably a couple of days, sometimes you remove the suture in the fifth or in the sixth days

On the other hand, if you had somebody who is 75 years old, if a smoker with severe atherosclerosis, peripheral vascular disease and you have to do a very cause vein surgery or bypass surgery, the wound will take longer because the type of injury is more and the location of injury is different.

## 9. Site of injury

-The location of the injury and the character of the tissue in which the injury occurs also is important. For example, in inflammation arising in tissue spaces, (e.g., pleural, peritoneal, synovial cavities), small exudates may be resorbed and digested by the proteolytic enzymes of leukocytes, resulting in the resolution of the inflammation and restoration of normal tissue architecture. However, when the exudate is too large to be fully resorbed it undergoes organization, a process during which granulation tissue grows into the exudate, and a fibrous scar ultimately forms.

-Facial injury would recover in 5 days, the abdominal injury needs 10 days while lower limb injury takes 2 weeks as an example.

## ABNORMAL HEALING

### 1. Deficient scar formation (fewer scar forms)

These are seen in numerous clinical situations, as a result of local and systemic factors.

### 2. Excessive repair ( more scar forms)

### 3. Contractures (excessive repair)

## DEFICIENT HEALING:

It causes ulcer: the morphologic characteristic of inflammation, it is a discontinuation in mucosal (epithelial) surfaces.

### 1• Venous leg ulcers:

Mostly in the lateral aspect of the lower limb, they expose to chronic venous congestion.

### 2• Arterial ulcers:

More severe deep ulcers than venous ulcers, due to severe poor perfusion, atherosclerosis, or hypertension.

-more prevalent in diabetic patients due to decreased blood supply especially the peripheral ulcers.

### 3• Pressure sores, ulcers

#### 4• Diabetic ulcers:

- in uncontrolled diabetes.
- there are special diabetic foot clinics for special cares.
- if ischemia happens in a diabetic patient, it will cause vasoconstriction.
- peripheral diabetic neuropathy causes feelingless, so severe injuries may happen without early treatment.

#### 5• \*\*\* Wound dehiscence

Now, let's see some beautiful ugly pictures:(

## WOUND DEHISCENCE:

- de-suturing of the injury due to high local pressure and this pressure could be caused by coughing.
- it happens often in abdominal walls.
- needs secondary repair(high rate of granulation formation and infections).
- it happens due to weak sutures and worse surgical techniques.
- Again, surgeons have to take care of the wounds, if the injured person is obese, more plasters, belts, gauze is needed, and so on.



Note: the doctor said that A and B figs are venous ulcers, but in the book and 2020 sheet, B is arterial, and that makes sense.

## VENOUS ULCER



-develop most often in elderly people as a result of chronic venous hypertension (**pressure**) which may be caused by severe varicose veins or congestive heart failure. Deposits of iron pigment (hemosiderin) are common, resulting from red cell break down, and there may be accompanying chronic inflammation. These ulcers fail to heal because of poor delivery of oxygen to the site of the ulcer.

-located commonly in the medial view of the lower third leg.

-the skin is bluish

-happens due to venous blood congestion

-noticed grossly(YOU HAVE TO MEMORIZE THE PHENOTYPE) -happens in varicose veins

-mainly it's superficial



## ARTERIAL ULCER



- develop in individuals with atherosclerosis of peripheral arteries, especially associated with diabetes. The ischemia results in atrophy and then necrosis of the skin and underlying tissues. These lesions can be quite painful.
- with more extensive tissue necrosis
- noticed grossly and located in the medial area of the lower third of the leg.

## DIABETIC ULCER



- diabetic foot
- affect the lower extremities, particularly the feet. Tissue necrosis and failure to heal are the results of small vessel disease causing ischemia, neuropathy, systemic metabolic abnormalities, and secondary infections. Histologically, these lesions are characterized by epithelial ulceration and extensive granulation tissue in the underlying dermis.
- distal peripheral deep portion of the foot
- black area indicates infected gangrene

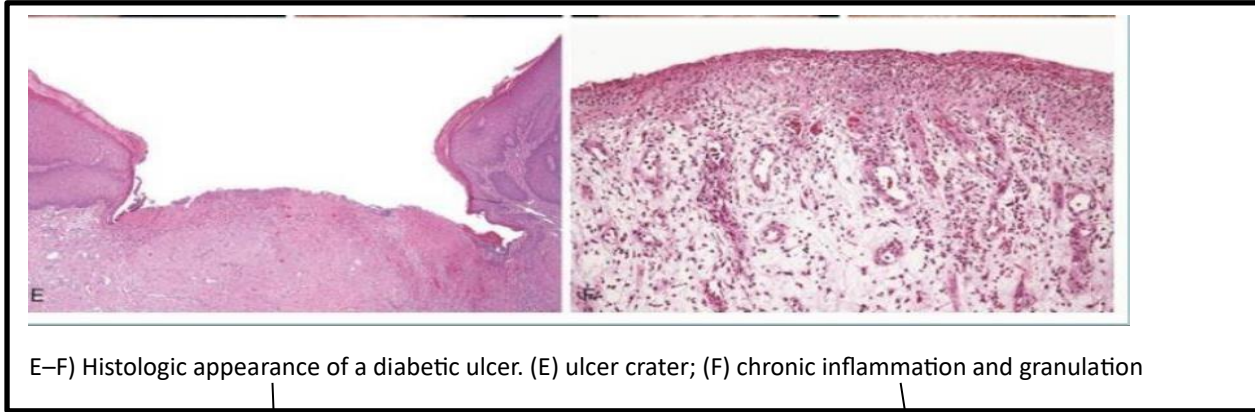
- very deep that the bone will almost appear
- diabetic patients have a higher risk to develop a distal peripheral arterial ulcer
- noticed grossly from the location and the color

## PRESSURE SORE

pus



- known as bed ulcer or pressure ulcers also
- areas of skin ulceration and necrosis of underlying tissues caused by prolonged compression of tissues against a bone, for example, in bedridden, immobile elderly individuals with numerous morbidities. The lesions are caused by mechanical pressure and local ischemia.
- it is located in the lower back in the buttock area
- it happens to stroke patients who stay in the hospital bed and need nurses to fluctuate them
- if they stay in state for a long time like 3 hrs. then pressure generates between the bone and skin with the bed, causing obstruction in vessels and decreasing blood supply
- always indicates poor care(poor nursing care)
- they have introduced new electrical beds that can actuate the patients constantly



E-F) Histologic appearance of a diabetic ulcer. (E) ulcer crater; (F) chronic inflammation and granulation

It is a discontinuation of squamous epithelium, so it is ulcer

Granulation tissue full with fibroblasts

## EXCESSIVE SCARRING:

-Healing is R5 of inflammation but when collagen 1 and cross-linking increase, it will make defects.

-the study of excessive repair is still unobvious; it is said that it is caused by defects of TIMPs and MMPs

-the causes of it relate to the genetics of the family - types:

- **Hypertrophic scar**
- **Keloid:** it is more dangerous
- **Exuberant granulation tissue (proud flesh):** rarely happens, very excessive granulation tissue to an extent that it goes out of the wound (طالع فوق الجلد)
- **Aggressive fibromatosis (desmoid tumor):** tumor with excessive fibrosis. You won't be asked about it in the exam, further details about it will be explained in the next semester.
- **Contractures:** You won't be asked about it also.

\*both deep and superficial fibromatosis interfere abnormally with the function

Proud flesh from



google

-Fig A is a hypertrophic scar, cosmetically unpleasing especially if it's in an apparent area like leg ,etc.

-Fig B is a keloid scar, it is more exaggerated than the Hypertrophic. Keloid is more common in dark skin people; African people are the most susceptible to this.

-surgery to remove keloid isn't valuable, it also reappears, so often steroid creams are taken also.

-fig C is representing a cross section under the microscope and shows too many mature scars and collagen type 1 and large number of cross-linking.



## FIBROSIS OF ORGANS:

\*the desirable outcome of acute inflammation is 99.9% complete resolution

\*in acute inflammation, more systemic manifestation happens, and less tissue damage

\*in chronic inflammation, repair happens, so more scar formation and fibrosis

\*continuous fibrosis may lead to complete damage and loss of function.

Ex:

-continuous fibrosis in the liver causes cirrhosis, which interferes with the function. Liver has a high reserve capacity, only 10% of its mass is needed for the normal

biological function, this indicates both good news and bad news, good because it's a vital organ so we need it to be capable of regeneration, but this is bad also because when a damage occurs in the liver you won't sense it until very large percentage of it gets damaged.

-continuous fibrosis in the kidney causes renal failure because of overproduction of TGF- $\beta$ , known as ESKD (endstage kidney disease).

-when a tumor happens, you might not be able to recognize tumor cells under the microscope because of the excessive production of TGF- $\beta$  which causes severe fibrosis (scar tissue), so tumor cells may not appear in that large fibrosis, so diagnosis of tumors becomes harder.

- **Scar and fibrosis: excessive deposition of collagen and ECM.**
- **Continuous infections and immunologic injuries cause organ fibrosis and loss of function**
- **TGF- $\beta$  is the most common cytokine of fibrosis**
- **Examples: liver cirrhosis (severe fibrosis of the liver, when 85-90% of the liver get damaged, manifestations start to appear), Idiopathic lung fibrosis, ESKD**

The following picture represents 2 cases of response to tissue injury. On the right there is a continuous (inflammatory response then fibrosis). Happens more often in chronic active diseases.

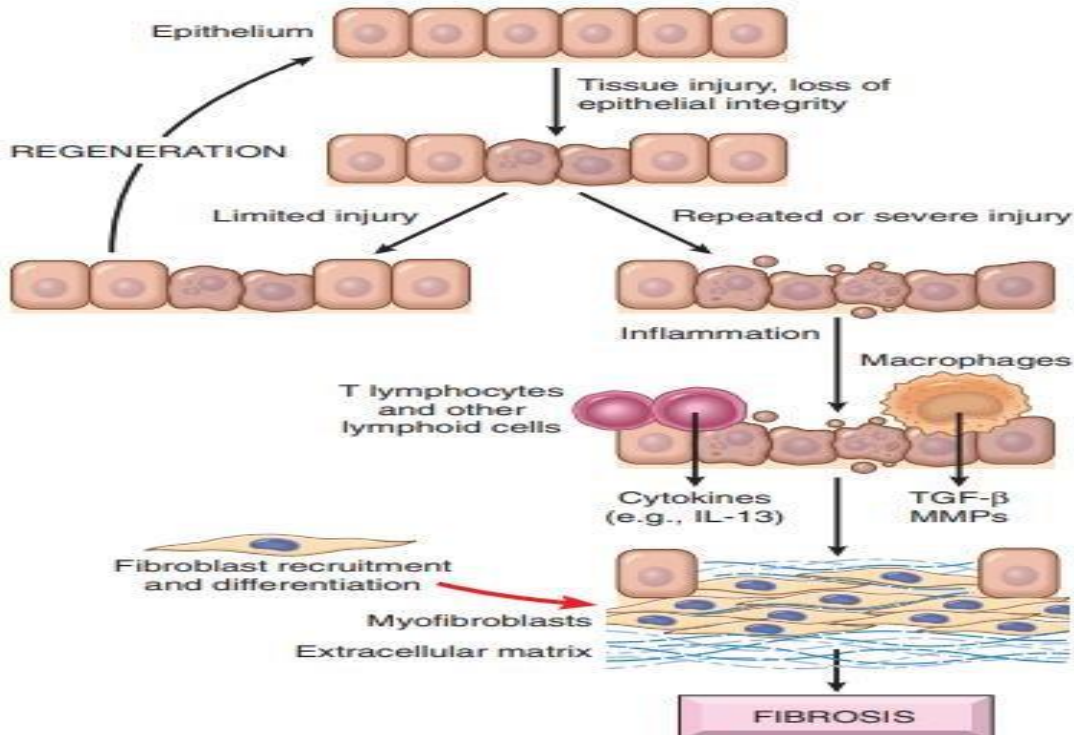


Fig. 3.29 Mechanisms of fibrosis. Persistent tissue injury leads to chronic inflammation and loss of tissue architecture. Cytokines produced by macrophages and other leukocytes stimulate the migration and proliferation of fibroblasts and myofibroblasts and the deposition of collagen and other extracellular matrix proteins. The net result is replacement of normal tissue by 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.

## PAST PAPER

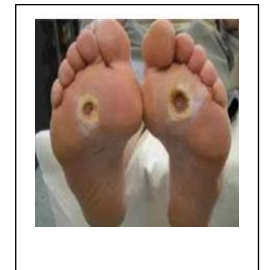
### 1. choose the correct :

- A. Abnormal excessive repair and the scar formation
- B. side effects of using see a certain type of surgical sutures
- C. occurs in patients with a pre-existing atherosclerosis
- D. lateral genic result due to bad surgical technique
- E. Wound dehiscence



### 2. choose the correct :

- A. Severe ischemia due to atherosclerosis
- B. Friction burn of skin and subcutaneous tissue
- C. radiation injury for squamous cell carcinoma of the leg
- D. traumatic serious inflammation of the skin and subcutaneous tissue
- E. varicose veins of lower limbs



### 3. Bed "pressure" sores are best described as?

- A. Diabetic foot ulceration with superadded infection
- B. Serous-type inflammation with complicating infection
- C. avoidable ulcer due to bad nursing/home care
- D. stress ulcer from severe chronic diseases
- E. mild superficial ulcers that are easy to heal

### 4. this picture is:

- A. Deep ulcer with atherosclerosis
- B. nonhealing gangrene with fungal infection
- C. Wound dehiscence
- D. Inflamed leg with dilated blood vessels



### 5. Which of the following is true about bed ulcers:

- A. Always fatal
- B. Impossible to deal with
- C. preventable
- D. Appear as an intact epithelial surface under the microscope

A A C A C