Why Diabetic Foot Wounds Become Chronic

Discovering why is the key to healing these ulcers.

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Objectives

After completion of this article, one should be able to:

1) Analyze the barriers to wound healing in the diabetic patient.

2) Describe the role that vascular disease plays in delaying wound healing in the diabetic patient.

3) Summarize the importance of adequate control of bioburden and proper wound bed preparation.

4) Discuss the critical role of proper offloading of diabetic foot ulceration.

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*Following this article, an answer sheet and full set of instructions are provided (pg. 130).—**Editor***

Almost 26 million people, or about 8% of the population in the United States have diabetes. Current statistics suggest that approximately 25% of diabetic patients will develop a foot ulceration during their lifetime, and about 15% of these ulcerations will ultimately lead to some form of lower extremity amputation.[1,2] Diabetic foot ulcers have been estimated to cost between $7,439 and $20,622 per episode. Despite medical and biotechnology advances, diabetic foot ulcerations remain a costly and challenging clinical problem, far too often leading to prolonged treatment regimens and debilitating complications for patients. When compared to some of the leading cancers, including breast, colon, and leukemia, neuropathic diabetic foot ulcerations have been shown to have an increased five-year mortality rate and are more costly to treat.[3,4]

Metabolic changes within the body contribute to the wound being "stuck" in the inflammatory phase of healing.

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In recent years, there has been an explosion of new wound care products on the market to facilitate wound closure, including amniotic membrane allografts, bioengineered tissue products, and negative pressure wound therapy, advancing the practice of wound care. Coupled with the basic principles of diabetic foot ulcer treatment including bioburden management, sufficient arterial inflow, adequate pressure reduction and proper wound bed preparation, this ensures a proper arsenal to successfully treat chronic DFUs.

Cellular and Proteomic Abnormalities of the Diabetic Wound

The normal wound healing cascade consists of four predictable stages including hemostasis, inflammation, proliferation, and remodeling. The cellular and physiological actions during these stages occur in a complex, but predictable, fashion. Initially, once there is a break in the skin barrier, platelets aggregate to form a clot.

These platelets then de-granulate, releasing an abundance of growth factors into the wound that are responsible for recruiting macrophages and neutrophils to the injured tissue. The macrophages and neutrophils then secrete inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and matrix metalloproteinases (MMPs) that enzymatically degrade the injured tissue matrix and remove bacterial debris.

As the damaged cellular matrix is removed and the bacterial contents are cleared, the quantity of inflammatory cells reduce, and the wound then progresses on to the proliferative and remodeling stages of healing.[5] The proliferative phase of healing is an anabolic process that relies on adequate nutrition, hydration, vitamins, and minerals to support tissue healing.[6] During the proliferative phase, fibroblasts are producing collagen, vascular endothelial cells are producing new vessels, the wound begins contracting through the activity of myofibroblasts, and keratinocytes begin migrating to re-epithelialize the wound. Finally, the remodeling phase of healing involves the removal of unorganized type III collagen to a more native, robust type I collagen.

Myofibroblast cells are responsible for contraction of the wound during the healing cascade.

This normal process of healing is interrupted in diabetic patients, as this patient population often presents with chronic, non-healing wounds. Shaheen et al. demonstrated in 2003 that the percentage change in foot ulcer area at four weeks is a predictor of healing at 12 weeks.[7] Tracking the progression of wound healing can be utilized to determine the probability of healing potential for patients and assess if there are impending roadblocks to eventual healing. Proper understanding of diabetic foot ulcer pathophysiology lays the foundation for prompt recognition and appropriate management.

People with diabetes are more susceptible to complications associated with their wounds due to their chronic hyperglycemic state. These metabolic changes within the body contribute to the wound being "stuck" in the inflammatory phase of healing.[8,9] Hyperglycemia can also contribute to the relative immunocompromised status of the patient. Hyperglycemic conditions create a deficiency in the patient's cellular immunity, reducing the phagocytic activity of neutrophils, and bacteri-

It has been estimated that about 60% of chronic wounds have a biofilm present, versus 6% of acute wounds.

cidal activity of the immune system.[10] If the host's immune system becomes compromised, the bacteria will contribute to the release of pro-inflammatory cytokines including IL-1, IL-6, and TNF-alpha.

Prolonged presence of bacteria in a wound environment also increases the quantity of MMPs and decreases the level of endogenous tissue inhibitor of matrix metalloproteinases (TIMPs). This imbalance between MMPs and TIMPs causes degradation of growth factors, destruction of extracellular matrix tissue, and a reduction in cell proliferation and migration.[5] Furthermore, the hyperglycemic state decreases keratinocyte migration, thereby delaying re-epithelialization of the wound bed.[11]

Trengove and colleagues[12] discovered that chronic wounds have an inflammatory protease level 100 times greater than do acutely healing wounds. Prolonged elevated levels of proteases within a wound bed not only degrade damaged extracellular matrix tissue and bacterial debris, but also destroy host native tissue. Elevated counts of proteases and inflammatory cytokines within a chronic wound bed dramatically reduce and inactivate growth factors, which are proteins necessary to coordinate the wound healing cascade.[12]

With an increase in MMP activity and decreased cellular responsiveness to growth factors, chronic wounds lack healing potential. Therefore, the wound will remain chronically inflamed and lack the ability to recruit the cells needed to progress the wound to the proliferative and remodeling stages of healing. Moreover, chronic wound

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exudate diminishes the activity and proliferation of dermal fibroblasts,[13] a critical cell in the dermal tissue responsible for recruiting growth factors and producing collagen.

In addition to cellular and proteomic effects of the chronic hyperglycemic state, the diabetic foot wound milieu is also affected by other internal and external factors and stresses such as adequacy of micro-vascularity, balance of wound bioburden, and plantar pressure induced by ground reactive forces during ambulation. Therefore, proper ongoing assessment of arterial inflow, bioburden management, and pressure reductions are the pillars of diabetic foot ulcer management.

Hyperglycemia and Vascular Disease

Intact arterial vascular supply is critical for normal healing to provide proper oxygenation to the wound. Adequate oxygen tension helps increase fibroblast proliferation to produce collagen, stimulate angiogenesis, induce keratinocyte migration resulting in re-epithelialization of the wound surface, and help prevent wound infection through the production of reactive oxygen species (ROS).[14,15] With the development of an acute wound, there is an initial period of hypoxia that stimulates the release of growth factors and inflammatory cytokines within the wound. Patients with adequate arterial inflow will restore a normal physiologic oxygen tension within the wound, promoting fibroblast production of collagen, angiogenesis, and eventual wound contraction.[14]

Local tissue hypoxia helps set the stage for chronic inflammation within the wound bed. Diabetic persons with peripheral arterial disease will maintain a hypoxic wound environment, inducing prolonged inflammation and a chronic wound.[14] Without restoration of in-line arterial flow to the foot, diabetic patients will have inadequate arterial perfusion and decreased potential of healing.

Persons with diabetes are especially vulnerable to developing arterial insufficiency of both the small and large vessels. It has been suggested that an HgA1C level of greater than 7.0 mg/dL increases an individual's risk for developing peripheral arterial disease (PAD). Every 1% increase in HgA1C level is associated with a 26% increased risk for developing PAD.[16] Hyperglycemia also results in elevated C-reactive protein (CRP) levels. Elevated CRP helps promote apoptosis of endothelial cells, resulting in decreased skin perfusion.[17]

Hyperglycemia can further contribute to vascular disease by impeding the production of nitric oxide, a natural endothelial vasodilator. This decreased production of nitric oxide causes an increase in vascular vasoconstriction, thickening of the arterial tunica intima layer, and increase in platelet aggregation, thereby reducing local tissue oxygenation.[18,19]

Moreover, advanced glycemic end products (AGEs) are hypothesized to play a significant role in the pathophysiology of diabetic complications, including ischemia. The Maillard reaction is a complex process in which chronic hyperglycemia results in the formation of advanced glycosylation end-products (AGEs).[11,20]

AGEs are thought to bind to and create a thickening of the basement membrane of blood vessels, causing a local decrease in tissue perfusion. The surface of collagen molecules also can be altered through the activity of AGEs, leading to decreased tissue repair and prolonged inflammation within the wound bed.[21,22]

In addition to good glycemic control, the diabetic patient must therefore be evaluated for clinical clues of lower extremity arterial disease throughout the treatment process. If the physical examination reveals non-palpable pedal pulses, or if a non-healing wound is present, current literature and consensus statements suggest proceeding with the evaluation of non-invasive arterial studies. According to the American College of Cardiology and the American Heart Association, adults over 65 years of age, adults over 50 years of age with a history of diabetes or smoking, and those with a non-healing wound should all be screened with ankle-brachial index (ABI testing).[23]

However, ABI testing can be misleading in persons with diabetes due to the high prevalence of calcification of the tunica media of the arterial wall. Approximately 80% of diabetic patients have been documented to have falsely elevated ABIs, versus only 20% in persons without diabetes.[24] Therefore, absolute toe pressures or toe-brachial index readings may be a better predictor of wound healing potential in the diabetic population.[25] If a diagnosis of PAD has been suspected via non-invasive arterial studies, follow-up evaluation with a computed tomography angiogram or prompt referral to a vascular specialist has been recommended.

During the normal gait cycle, two periods of peak plantar pressure are generated: first on the heel during heel strike, and second on the forefoot during propulsion.

Bioburden

An intact skin barrier is the body's most robust protector from bacterial invasion. The normal flora present on the skin as well as the acidic pH help prevent microbial invasion and infection. Following a discontinuity in the skin surface, the body becomes vulnerable to infection. An estimated 61% of diabetic foot ulcers become infected[26] and the longer the wound remains open, the greater the risk of complications. Bacteria release endo-and exotoxins within the wound, causing an increased inflammatory response as well as enzymatic degradation of the

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extracellular matrix tissue, thereby disrupting the healing potential. Microbes present within the wound environment may not only lead to devastating infections, but also compete for the nutrients and oxygen, essentially depriving the wound of vital resources.[27]

Following a break in the skin, endogenous normal skin flora and exogenous bacteria from the environment begin invading the wound;[28] therefore, all open wounds are considered contaminated. A contaminated wound is a wound that has planktonic, non-replicating bacteria on the wound surface.[29] Despite the presence of bacteria in contaminated wounds, treatment with topical or systemic antibiotics is not generally recommended.

Colonized wounds are defined by bacteria that adhere to the wound bed and begin to replicate, but do not mount an immune response and do not interfere with healing.[27] These wounds also do not need to be treated with the utilization of topical antimicrobial or systemic antibiotics. Over-utilization of antibiotic therapy removes the skin's normal flora, allowing more virulent pathogenic bacteria to proliferate and compromise tissue repair.

The remodeling phase of healing involves the removal of unorganized type III collagen to a more native, robust type I collagen.

Critically colonized wounds have an increased quantity of replicating bacteria that does have a direct negative impact on tissue healing and are clinically identified by necrotic debris, friable granulation tissue, increased exudate, and malodor.[28] As the bacteria continue to multiply within the wound bed, they begin to irreversibly adhere and create an organized biofilm. It has been estimated that about 60% of chronic wounds have a biofilm present, versus 6% of acute wounds.[30]

Biofilm present on a wound surface becomes resistant to antibiotics and phagocytosis by neutrophils,[31] partially due to the fact that they embed in a polysaccharide matrix, which is refractory to topical and systemic antibiotic penetration, thus creating a high probability for delayed wound healing. Even with disruption of the polysaccharide matrix through debridement, biofilms can begin to reorganize within 24 hours and become fully re-organized within three days following debridement.[32] Thus appropriate wound bed preparation is critical for adequate bioburden management. If not managed appropriately, biofilms will contribute to the inflammatory status of chronic wounds and intermittent tissue infections due to the release of bacteria to peri-wound tissue.

Adequate wound bed preparation through the removal of nonviable tissue is considered to be a cornerstone of wound healing. Necrotic tissue present in a wound bed can serve as a medium for bacterial growth, help delay re-epithelialization and prolong the inflammatory phase of healing.[33] Proper wound bed preparation can help transform a chronic wound environment to an acute wound by reducing the levels of proteases and cytokines.[34] Debridement of the wound bed occurs naturally during the inflammatory phase of healing, where recruited neutrophils and macrophages clear cellular and bacterial debris from the wound bed. This autolytic process of endogenous protease and enzyme degradation and removal of damaged tissue allows the wound to progress on to the proliferative and remodeling stages of wound healing. Despite this process occurring naturally, additional surgical debridement of the wound bed has been shown to accelerate the rate of diabetic foot ulcer healing.[35] Most commonly, chronic wounds will require serial weekly debridement to remove all non-viable tissue and promote ingrowth of healthy granulation tissue.

The hyperglycemic state decreases keratinocyte migration, thereby delaying re-epithelialization of the wound bed.[11]

Clinical infection, as defined by the Infectious Disease Society of America (IDSA) in the 2012 Clinical Practice Guideline, is diagnosed by the presence of two of the following findings: warmth, erythema, pain, induration, or the presence of purulent drainage.[36] Due to the high prevalence of soft tissue and bone infections in the diabetic foot, routine evaluation of the diabetic foot ulcer for signs of infection is critical. Keeping this in mind, diabetic patients with an immunocompromised status may be unable to mount a traditional immune response due to impaired cellular and humoral immunity and limited polymorphonuclear leukocyte function.[37]

Clinical situations exist that increase the probability of developing an infection such as concomitant peripheral vascular disease, wounds present for greater than thirty days, history of recurrent foot ulcerations, loss of protective sensation, and renal disease.[36] Prompt recognition of the clinical signs of infection and appreciation of an individual's infectious risk factors are necessary to help avoid serious complications, including loss of limb or life.

Neuropathy and Plantar Pressure

The pathogenesis of the diabetic foot ulceration combines factors, including increased plantar pressure and repetitive stress on the insensate foot.[38] Diabetic patients are at an increased risk of developing neu-

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ropathy due to nitric oxide blocking, the Maillard reaction, and shifting of the polyol metabolic pathway.[39] Sudomotor dysfunction is considered a component of autonomic neuropathy, which presents as a deregulation of sweat glands by the sympathetic nervous system. For the diabetic patient, this can contribute to anhidrosis, leading to dry and xerotic skin.

Diabetic patients also present with thicker and more rigid tissue due to increased non-enzymatic cross-linking of collagen,[40] resulting in skin that is less resilient and more prone to breakdown. Complicating this issue, sensory neuropathy causes a loss of protective sensation to the diabetic foot, thus the patient does not feel the skin breakdown.

Finally, motor neuropathy presents as contracture of tendons and thickening of joint capsules due to glycosylation of these tissues. This creates an intrinsic foot structure with decreased ankle joint range of motion, digital contractures, and increase of peak plantar pressure with weight-bearing forces. This triad of motor, sensory, and autonomic neuropathy increases the risk of tissue breakdown in the diabetic patient.

During the normal gait cycle, two periods of peak plantar pressure are generated: first on the heel during heel strike, and second on the forefoot during propulsion. Therefore, the heel and the forefoot are the anatomic sites most at risk for ulceration,[38] and are the most critical sites to offload to facilitate wound closure. Vertical stress due to ground-reactive forces during ambulation is the direct force placed upon the foot that compresses and damages normal healthy tissue. Shear is the other force imposed on the foot that is a side-to-side stressor.[38] The combination of shear and vertical pressures contribute to the chronicity of a diabetic foot ulcer, as it has a decreased potential to withstand the daily repetitive stress and disrupt the healing cascade.

Paramount to wound healing is the pressure redistribution on the plantar foot to effectively off-load the wound. A clinician can address the vascularity, bioburden, nutritional status, and glycemic control of the patient, but if the foot is not effectively offloaded, the ulceration will often become chronically inflamed and not heal.

Chronic wounds have an inflammatory protease level 100 times greater than do acutely healing wounds.

Piaggesi and co-workers[41] demonstrated the histopathological benefits of the offloaded wound. Patients in this study were randomized into two different groups. Group A had surgical excisional debridement without offloading of the diabetic foot wound, and group B received sharp debridement to healthy bleeding tissue followed by application of a total contact cast. The wound beds from group A had increased inflammatory cells, degraded extracellular matrix, and diminished granulating tissue. Group B, with adequate plantar pressure mitigation, had decreased inflammation, decreased necrotic debris, and increased granulating tissue on the wound bed.[41] This study demonstrated that ineffective offloading contributes to diabetic wounds being "stuck" in the inflammatory phase of healing.

Pressure reduction via the use of half-shoes, removable cast walkers, and total contact casts have been suggested in the treatment algorithm for diabetic foot ulcers. Half-shoes function to limit the propulsive phase of gait, but are less effective than both removable cast walkers and total contact casts at reducing peak plantar pressure.[42] Removable cast walkers function to lock the ankle in position and decrease the propulsive phase of gait. The primary concern with the removable cast walker is patient compliance and the ease of removing the device. Total contact casting forces compliance due to the inability to remove the cast, and this has been considered the gold standard in pressure reduction. Total contact casting has demonstrated forefoot plantar pressure reductions of up to 92%[42] and many also reduce inflammation and edema in the involved leg, facilitating the normal physiologic healing process. An effective offloading plan is therefore considered a cornerstone in the diabetic foot ulcer treatment plan.

Every 1% increase in HgA1C level is associated with a 26% increased risk for developing PAD.

Conclusion

The socioeconomic and biomedical burdens posed by diabetic foot ulcers and their complications are worsened by the steep rise in the incidence of diabetes. Numerous intrinsic and extrinsic factors such as hyperglycemia and wound bioburden result in a diabetic foot ulcer becoming chronic, and the chronic diabetic foot wound is often a precursor to impending infection and limb amputation. Comprehensive assessment and efficient treatment of diabetic foot ulceration are therefore critically important to achieve a favorable outcome. An understanding of the normal healing cascade may help provide a foundation for which the treating physician can provide wound care. However, knowledge of how hyperglycemia and other intrinsic and extrinsic factors can physiologically affect these otherwise nor-

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mal processes and causes distortions in the wound-healing cascade will help enable proper diagnosis and treatment. The pillars of diabetic foot ulcer treatment including adequate arterial circulation, bioburden management, wound bed preparation, and pressure mitigation through proper offloading; all need to be appreciated to reasonably expect a positive result. **PM**

AGEs are hypothesized to play a significant role in the pathophysiology of diabetic complications, including ischemia.

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CME EXAMINATION

SEE ANSWER SHEET ON PAGE 131.

1) What phase of healing do diabetic patients often get "stuck" in, preventing a progression towards successful wound closure?

A) Inflammation
B) Proliferation
C) Hemostasis
D) Remodeling

2) Which type of cells are responsible for contraction of the wound during the healing cascade?

A) Keratinocyte
B) Fibroblast
C) Myofibroblast
D) Elastin

3) According to the American Heart Association, which group of patients should be screened with ankle-brachial index testing?

A) All adults > 50 years of age
B) All persons with diabetes > 40 years of age
C) All adults > 40 years of age with a history of smoking
D) All persons with diabetes > 50 years of age

4) An estimated _____ percent of chronic wounds have a biofilm present.

A) 25%
B) 40%
C) 60%
D) 80%

5) Which type of neuropathy contributes to the development of a diabetic foot ulceration?

A) Autonomic
B) Sensory
C) Motor
D) All of the above

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6) During the normal gait cycle, when does the foot encounter peak plantar pressure?

A) Heel strike and midstance
B) Midstance and toe-off
C) Midstance and propulsion
D) Heel strike and propulsion

7) According to the Infectious Disease Society of America (IDSA), how many following findings should be present to diagnose the presence of infection: warmth, erythema, pain, induration?

A) 1
B) 2
C) 3
D) 4

8) Which of the following clinical situations increase the risk of infection?

A) Peripheral vascular disease
B) Chronic wounds present > 30 days duration
C) History of recurrent foot ulcerations
D) All of the above

9) Which of the following clinical findings are suggestive of a critically colonized wound?

A) Necrotic debris
B) Friable granulation tissue
C) Malodor
D) All of the above

10) An estimated _____ percent of diabetic foot ulcerations become infected.

A) 15%
B) 30%
C) 45%
D) 60%

SEE ANSWER SHEET ON PAGE 131.

PM's CME Program

Welcome to the innovative Continuing Education Program brought to you by *Podiatry Management Magazine*. Our journal has been approved as a sponsor of Continuing Medical Education by the Council on Podiatric Medical Education.

Now it's even easier and more convenient to enroll in PM's CE program!

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(1) Each participant achieving a passing grade of 70% or higher on any examination will receive an official computer form stating the number of CE credits earned. This form should be safeguarded and may be used as documentation of credits earned.

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(3) All answers should be recorded on the answer form below. For each question, decide which choice is the best answer, and circle the letter representing your choice.

(4) Complete all other information on the front and back of this page.

(5) Choose one out of the 3 options for testgrading: mail-in, fax, or phone. To select the type of service that best suits your needs, please read the following section, "Test Grading Options".

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There is **no charge** for the mail-in service if you have already enrolled in the annual exam CME program, and we receive this exam during your current enrollment period. If you are not enrolled, please send $26.00 per exam, or $210 to cover all 10 exams (thus saving $50 over the cost of 10 individual exam fees).

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You may also complete your exam by using the toll-free service. Call 1-800-232-4422 from 10 a.m. to 5 p.m. EST, Monday through Friday. Your CME certificate will be dated the same day you call and mailed within 48 hours. There is a $2.50 charge for this service if you are currently enrolled in the annual 10-exam CME program (and this exam falls within your enrollment period), and this fee can be charged to your Visa, Mastercard, American Express, or Discover. If you are not currently enrolled, the fee is $26 per exam. When you call, please have ready:

1. Program number (Month and Year)
2. The answers to the test
3. Your social security number
4. Credit card information

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ENROLLMENT FORM & ANSWER SHEET

Please print clearly...Certificate will be issued from information below.

Name _____ Soc. Sec. #_____
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City_____ State_____ Zip_____

Charge to: _____Visa _____ MasterCard _____ American Express

Card #_____Exp. Date_____

Note: Credit card is the only method of payment. Checks are no longer accepted.

Signature_____ Soc. Sec.#_____ Daytime Phone_____

State License(s)_____ Is this a new address? Yes_____ No_____

Check one: _____ I am currently enrolled. (If faxing or phoning in your answer form please note that $2.50 will be charged to your credit card.)

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Over, please

ENROLLMENT FORM & ANSWER SHEET *(continued)*

EXAM #9/16
Why Diabetic Foot Wounds Become Chronic (Jaffe and Wu)

Circle:

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

Medical Education Lesson Evaluation

Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]

1) This CME lesson was helpful to my practice ____

2) The educational objectives were accomplished ____

3) I will apply the knowledge I learned from this lesson ____

4) I will makes changes in my practice behavior based on this lesson ____

5) This lesson presented quality information with adequate current references ____

6) What overall grade would you assign this lesson?

A B C D

How long did it take you to complete this lesson?

_____hour _____minutes

What topics would you like to see in future CME lessons ? Please list :

_____

_____

_____

_____

_____

_____

_____