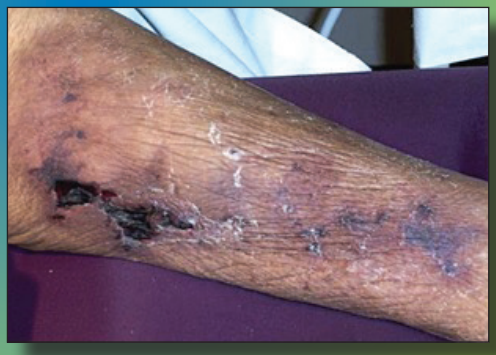
Continuing Medical Education

The Effects of Renal Disease on Wound Healing

Here's what you need to know about this relationship.

BY KYLE SCHOLNICK, DPM



Goals and Objectives

After completing this CME, the reader will:

1) Understand the effects of renal disease and dialysis on foot ulcers.

2) Learn how to diagnose uremic neuropathy.

3) Appreciate the challenges both patients and podiatrists have in treating diabetic patients with renal disease.

4) Understand the dermatologic manifestations of renal disease.

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*Following this article, an answer sheet and full set of instructions are provided (pg. 140).—**Editor***

Although diabetes is a well-known cause of foot ulcerations—dialysis, end-stage renal disease (ESRD) and chronic kidney disease (CKD) have proven to be independent risk factors in the development and course of diabetic foot ulcerations. Previous authors have reported foot ulcers to be in 5-10% of people with diabetes, 10% of people with diabetes and mild CKD, and 15-40% of people with diabetes and ESRD.[1] Hill, et al. found that ESRD was associated with a fourfold higher risk of diabetic foot complications, defined as infection, ulcer, gangrene, or amputation.[1]

Lower extremity amputations

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among individuals with co-existing diabetes and ESRD are 10 times greater than in the general diabetes population.[2] Post-operative mortality after a lower extremity amputation is 9% in patients with moderate CKD, 15% in patients with severe CKD, and 16% in dialysis patients, compared to 6% in patients with normal or mildly reduced renal function.[3] A similar study found that the one-year mortality rate after amputation was 49% in patients on hemodialysis, 23% in patients with CKD not on hemodialysis, and 14% in patients without renal disease.[4]

Diabetic nephropathy is the leading cause of ESRD and has been shown to be the primary etiology in 45% of cases.[1] Other causes of renal dysfunction include decreased renal perfusion via hypovolemia, hypotension, decreased ejection fraction, dehydration, vomiting, diarrhea, diuretic use, bleeding, infection, urinary tract obstruction, and nephrotoxic drugs that lower the glomerular filtration rate (GFR).These include NSAIDs, ACE inhibitors, vancomycin, aminoglycoside antibiotics, and contrast dye.

End-stage renal disease (ESRD) and chronic kidney disease (CKD) have proven to be independent risk factors in the development and course of diabetic foot ulcerations.

Poor Wound-Healing

Although there have been limited human studies on the effects of wound-healing in uremic patients, animal models have clearly shown that the addition of urea or uremic serum inhibits fibroblast growth and delays wound-healing.[5] Rats with renal failure have been shown to form less granulation tissue than those with normal kidney function.[6] One study on humans did show a significant correlation between ESRD and the failure of transmetatarsal amputations to heal.[7]

Abnormal levels of zinc have been reported in patients with uremia.[9] Zinc has been well documented to be imperative in wound-healing by serving as a co-factor in a zinc-dependent enzyme system that augments auto-debridement and keratinocyte migration. Zinc also confers protection against reactive oxygen species and bacterial toxins that impede wound-healing.

Iron repletion commonly used in ESRD patients to optimize erythropoiesis may inadvertently impair wound-healing in these individuals. Iron overload not only will compromise the immune system, but also causes the inhibited synthesis and release of vascular endothelial growth factor (VEGF), which helps maintain angiogenesis. Recent evidence suggests that iron depletion with deferoxamine improves tissue oxygenation and facilitates wound-healing by abrogating iron-mediated impairment of VEGF up-regulation.[10]

Iron repletion commonly used in ESRD patients to optimize erythropoiesis may inadvertently impair wound-healing in these individuals.

Patients with CKD commonly suffer from anemia from chronic disease. This is primarily due to reduced erythropoietin production by the kidney in addition to a decreased lifespan of red blood cells. The hematocrit in these patients will begin to stabilize in the 20-25% range. Anemia is associated with poor tissue oxygenation and impaired wound-healing. Lastly, CKD patients are frequently volume-overloaded, leading to extensive edema in the lower extremities, which acts as another barrier to wound-healing.

Peripheral Arterial Disease

Peripheral arterial disease (PAD) is very common in patients with kidney disease, especially those on dialysis. Not only is vascular insufficiency three times more prevalent in individuals with CKD than in those without, but the severity of PAD worsens with increased severity of CKD.[11] Therefore, CKD can be used as a predictor of future PAD events. Patients with CKD are highly predisposed to accelerated atherosclerotic plaque formation because of the presence of the traditional risk factors for peripheral vascular disease, but also other CKD-specific risk factors like chronic inflammation, malnutrition, fluid retention, alterations in the renin-angiotensin system, hyperhomocysteinemia, abnormal mineral metabolism, dyslipidemia, lipoprotein imbalances and oxidative stress.[12]

The overall prevalence of PAD among adult hemodialysis and peritoneal dialysis patients has been reported to be 25% and 19%, respectively.[13] It has also been shown that 24% of adults over 40 years old with a creatinine clearance of less than 60 mL/min. had an ankle brachial index (ABI) of less than 0.9.[14] However, vascular calcification seen in the ESRD population may influence the accuracy of results. In addition, the co-existence

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of ESRD and diabetes further complicates the interpretation of ABIs, as vascular calcification has been reported to occur in more than one-third of these patients. More accurate methods for assessing PAD in these types of patients are palpable peripheral pulses, Doppler waveforms, and toe pressures, as these measurements are less affected by calcification.

Vascular calcification occurs in CKD because as renal function decreases, phosphate clearance is reduced and hyperphosphatemia occurs. Calcium and phosphorus are deposited within the vascular bed, leading to vascular calcification. ESRD is also associated with elevated levels of parathyroid hormone, which has been linked to vascular calcification.[3] Calcium deposition is associated with adverse vascular outcomes due to stiffening of the arteries and has proven to be a major cause of PAD.

In addition to vascular calcification, chronic inflammation demonstrated by elevated C-reactive protein (CRP) significantly increases the risk of atherosclerosis. One study showed that CRP levels were found to be significantly higher in patients who developed symptomatic PAD compared to controls.[15] CRP levels are elevated in approximately one-third of hemodialysis patients.[16] Elevated CRP levels also occur in patients on peritoneal dialysis.

Hemodialysis itself has been shown to cause a drop in microvascular blood flow, diminish pedal skin perfusion, worsen underlying PAD, compromise pedal tissue, impair wound healing, and reduce pedal transcutaneous oxygen tension during and for several hours after dialysis.[17] It is thought that huge fluid shifts and the resultant hemodynamic changes during dialysis are responsible for the dialysis-mediated tissue hypoperfusion. Although hyperbaric oxygen therapy has improved wound healing in diabetics, less of a response has been seen in patients with renal failure. Only 58% of patients with renal failure improved after hyperbaric oxygen treatment, compared with 76% of patients without renal failure.[18]

Uremic Neuropathy

Uremic neuropathy is a well-known complication of ESRD, occurring in 50-60% of long-term hemodialysis patients due to the accumulation of dialyzable neurotoxins.[19] Other factors that contribute to uremic neuropathy include decreased thiamine deficiency, reduced plasma concentrations of biotin and zinc, increased plasma concentrations of phenols, myo-inositol, and hyperparathyroidism.[20] The co-existence of CKD with diabetes means that features of diabetic neuropathy will overlap with uremic polyneuropathy in CKD and ESRD patients.

Uremic neuropathy is a well-known complication of ESRD, occurring in 50-60% of long-term hemodialysis patients due to the accumulation of dialyzable neurotoxins.

Uremic polyneuropathy is typically a symmetric, distal, sensory-motor process. Injury is directly related to axon length and evolves in a stocking and glove pattern with longer axons being affected first, resulting in symptoms that are most severe in the lower extremities. Uremic myopathy leads to atrophy of the small intrinsic muscles of the feet, causing claw toes, myoclonus, and eventual paralysis. Complete recovery is nearly impossible once these late-stage motor issues occur. Uremic neuropathy also has been shown to cause a loss of the plantar forefoot fat pad beneath the metatarsal heads, leading to increased pressure and ulceration.[21]

Autonomic neuropathy is seen in 45-60% of uremic patients.[21] This results in shunting of blood away from peripheral cutaneous capillary beds, leading to microvascular insufficiency and atrophy of sebaceous and sweat glands. The resulting reduction in skin turgor, fissuring and dehydration, will reduce elasticity of the skin, impede healing, and increase the risk of damage from minor trauma. In addition, autonomic neuropathy is associated with postural hypotension and associated dizziness, leading to instability and increased susceptibility to trauma and foot ulceration. Adequate chronic dialysis may improve autonomic neuropathy and myopathy, but the impact on polyneuropathy is less well established.

Electrophysiologic studies are the most sensitive way to detect uremic neuropathy, and can also be used to monitor the course of disease once renal replacement therapy is initiated.

Electrophysiologic studies are

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the most sensitive way to detect uremic neuropathy, and can also be used to monitor the course of disease once renal replacement therapy is initiated. Motor nerve conduction velocity, often measured in the peroneal nerve, is the most common parameter used to assess motor function. Slowing of the nerve conduction velocity typically parallels the decline in creatinine clearance. Approximately 50% of patients have abnormal motor nerve conduction velocity when creatinine clearance falls to 10 mL/min.[22] Sensory nerve conduction velocity of the sural nerve is even more sensitive in detecting early dysfunction, but this is rarely needed or used.

Infected foot ulcers in those with renal disease are also more likely to harbor resistant microorganisms.[23]

Immunosuppression

Uremia in severe kidney disease alters the inflammatory response to wound-healing and compromises many aspects of the immune system, making these patients more susceptible to infection. Infected foot ulcers in those with renal disease are also more likely to harbor resistant microorganisms.[23] Uremia causes hyporeactive monocytes, depressed bactericidal action of neutrophils, compromised complement activation, diminished T and B lymphocyte function, a reduction in natural killer cell activity, and impaired function of polymorphonuclear cells, the main cells that fight bacterial infections.[24] Elevated levels of iron and calcium, anemia from chronic renal disease and dialysis have all been shown to further exacerbate disorders in polymorphonuclear cell function.[25]

Malnutrition

Malnutrition has been reported to be present in 40-70% of patients with ESRD.[26] Measurement of several circulating proteins may be used to assess nutritional status in ESRD, but there are potential limitations due to changes in protein distribution or metabolism in renal failure. The criteria used for the diagnosis of protein-energy wasting are serum albumin less than 3.8g/L, serum pre-albumin less than 30mg/dL, and serum cholesterol less than 100mg/dL.[27]

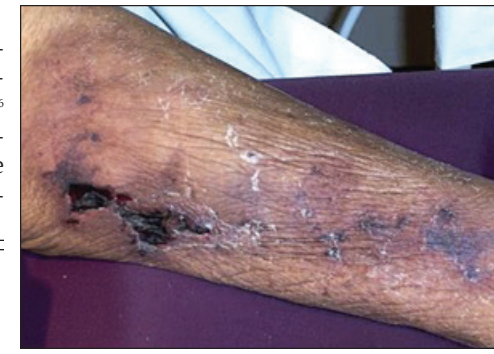

Figure 1: Calciphylaxis causing necrotic lesions

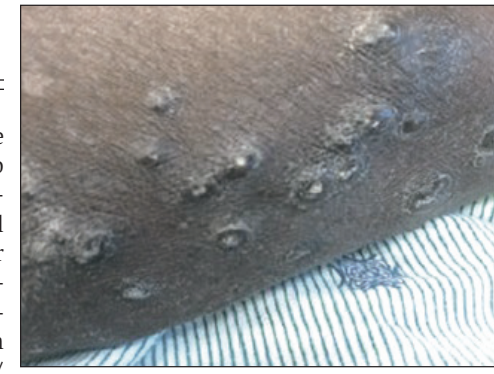

Figure 2: Perforating dermatosis

Hypoalbuminemia is a late manifestation of malnutrition due to the long half-life of albumin. Low serum albumin levels have been associated with poor wound healing and increased foot complications.[8] However, changes in extracellular volume may cause errors in assessing plasma albumin concentration. In addition, some patients on dialysis may have decreased albumin synthesis, despite adequate nutrition or an underlying inflammatory process that is responsible for the decline in albumin production. Pre-albumin, unlike albumin, has a short half-life and changes rapidly in response to alterations in nutritional status. Decreased pre-albumin levels are correlated independently with increased mortality and hospitalization due to infection.[28]

Dermatologic Disorders in Renal Disease

There are certain skin disorders that occur specifically in patients with renal disease that increase the risk of developing foot ulcers. Calciphylaxis is a condition that is characterized by small-vessel calcification and occurs in ESRD pa-

The pathogenesis of the disease is unclear, but the most accepted theories are abnormal bone and mineral metabolism, increased use of calcium-containing oral phosphate binders, vitamin D, and hyperparathyroidism.

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tients. This calcification leads to painful skin lesions, necrosis, gangrene and non-healing skin ulcers (Figure 1). Calciphylaxis has been documented to occur in 4% of hemodialysis patients.[29]

The pathogenesis of the disease is unclear, but the most accepted theories are abnormal bone and mineral metabolism, increased use of calcium-containing oral phosphate binders, vitamin D, and hyperparathyroidism.

Nephrogenic systemic fibrosis is a disorder primarily affecting the lower extremities of ESRD patients, and is characterized by induration and thickening of skin from exposure to gadolinium-based contrast dye. The thickened skin leads to breaks in the epidermis along with pruritus, predisposing patients to ulceration and superimposed infections. Avoidance of gadolinium and its derivatives in patients with advanced renal failure is imperative.

Uremic pruritus and perforating dermatosis are other common skin disorders in CKD. Perforating dermatosis, also known as acquired reactive perforating collagenosis, is a skin condition associated with CKD, dialysis, and diabetes. The lesions that form are pruritic, keratotic, dome-shaped nodules with central umbilication (Figure 2).

The causes of these lesions are a foreign body reaction to altered dermal collagen or deposition of substances in the skin that aren't removed by dialysis. Itching in uremic pruritus and perforating dermatosis leads to breaks in the skin, ulcerations, and portals for infection. Treatment for perforating dermatosis involves topical or systemic steroids, retinoids, antihistamines, phototherapy, and allopurinol, which has been shown to cause significant improvement.

Charcot in Renal Disease

ESRD is found in 30% of patients with Charcot neuroarthropathy.[30] The high prevalence may reflect the parallel development of the microvascular complications of nephropathy and peripheral neuropathy, or altered mineral metabolism and bone structure in renal disease may provide a metabolic background that is more permissive for the development of a Charcot breakdown. Hyperphosphatemia from reduced filtered phosphate load is related to the development of secondary hyperparathyroidism, which subsequently leads to the development of renal osteodystrophy.

ESRD is found in 30% of patients with Charcot neuroarthropathy.

Other renal bone diseases seen in CKD are osteitis fibrosa cystica, adynamic bone disease, and osteomalacia. These bone diseases are related to dysfunctions in bone turnover and put the renal patient at increased risk for bone fractures and Charcot disease. Bone biopsy is the gold standard for diagnosing the various types of bone disease in patients with CKD.

Poor Self-Care

Another important risk factor in ESRD patients is negligence of their own personal foot care. Dialysis patients are overwhelmed with the stringent requirements of dialysis three days per week, and they tend to overlook other aspects of their care, particularly foot care. One study found that dialysis-treated patients were less likely to inspect their feet regularly and to attend podiatry clinics. They were also more likely to engage in foot-damaging behaviors like barefoot walking.[31] Poor vision, inadequate flexibility, and reduced dexterity impair a patient's ability to inspect and perform self-care on the feet. In addition, lying on a dialysis couch for several hours three times a week could contribute to the development of pressure ulcerations on insensate heels and toes that impinge on the edge of the bed. Up to 30% of all hemodialysis patients are estimated to suffer from depression.[32] Depression is another factor that will affect compliance and influence a patient's ability to keep clinic visits to a podiatrist. Studies have shown an association between depression and poor compliance in ESRD patients on dialysis.[33]

Because of the increased morbidity and mortality of diabetic patients with renal disease, many studies have shown clear benefits of having a foot care program as part of a dialysis center. One study showed that the incidence of patients requiring amputations declined from 50% to 33% after a chiropodist became available and offered assessments and foot education.[34]

Many studies have shown clear benefits of having a foot care program as part of a dialysis center.

In the same study, the incidence of amputations declined 10% after the implementation of onsite foot care in the dialysis center.

There is clearly a wide range of disorders that develop as a consequence of renal function loss, and CKD has emerged as an independent risk factor for diabetic

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foot disease. Current guidelines on foot care should recognize advanced CKD, ESRD, and dialysis as a separate risk factor for foot disease in order to alert professionals and highlight the opportunity for prevention. To reduce the risk of foot ulcerations and lower extremity amputations, regular foot screening, intensive education in dialysis centers, and treatment should be extended to include patients with ESRD, regardless of the presence of diabetes. **PM**

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Dr. Scholnick is a podiatric foot and ankle surgeon practicing in the podiatric supergroup, Foot and Ankle Specialists of the Mid-Atlantic. His offices are located in Kensington and Columbia, MD.

SEE ANSWER SHEET ON PAGE 141.

1) What percent of hemodialysis patients suffer from depression?
- A) 10%
- B) 20%
- C) 30%
- D) 40%

2) What bone disease is seen in patients with renal disease?
- A) Osteitis fibrosa cystica
- B) Osteomalacia
- C) Charcot
- D) All the above

3) What percentage of Charcot patients have ESRD?
- A) 10%
- B) 20%
- C) 30%
- D) 40%

4) Which of the following is NOT a treatment for perforating dermatosis?
- A) Phototherapy
- B) Steroids
- C) Allopurinol
- D) Colchicine

5) How does uremia cause immune suppression?
- A) Diminishes T and B lymphocyte function
- B) Reduction of natural killer cell activity
- C) Impairs function of polymorphonuclear cells
- D) All of the above

6) What levels of serum pre-albumin are diagnostic of malnutrition?
- A) Less than 10mg/dL
- B) Less than 20 mg/dL
- C) Less than 30 mg/dL
- D) Less than 40 mg/dL

7) What is the LEAST accurate way of assessing PAD in dialysis patients?
- A) ABI
- B) Doppler waveforms
- C) Toe pressures
- D) Palpate peripheral pulses

8) What is the main cause of vascular calcification in CKD?
- A) Hypophosphatemia
- B) Hyperphosphatemia
- C) Hypoparathyroidism
- D) Hyperglycemia

9) Which of the following are causes of renal dysfunction?
- A) Urinary tract obstruction
- B) Diarrhea
- C) ACE inhibitors
- D) All of the above

10) Which nerve is MOST COMMON to test on electrophysiologic studies to determine uremic neuropathy?
- A) Sural nerve
- B) Peroneal nerve
- C) Common plantar digital nerve
- D) Sciatic nerve

11) What is the most sensitive way to detect uremic neuropathy?
- A) Motor nerve conduction
- B) Biopsy
- C) Measuring creatinine clearance levels
- D) Monofilament/vibratory testing

12) Abnormal levels of what are seen in patients with uremia that cause poor wound healing?
- A) Magnesium
- B) Phosphate
- C) Vitamin E
- D) Zinc

13) Which dermatologic disorder is caused by exposure to gadolinium-based contrast dye?
- A) Calciphylaxis
- B) Nephrogenic systemic fibrosis
- C) Uremic pruritus
- D) Perforating dermatosis

14) Uremic neuropathy is found in what percentage of ESRD patients?
- A) < 10%
- B) < 30%
- C) 50-60%
- D) 80-90%

15) At what level does hematocrit typically stabilize in CKD patients?
- A) 10-15%
- B) 15-20%
- C) 20-25%
- D) 25-30%

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16) Which of the following causes uremic neuropathy?

A) Accumulation of dialyzable neurotoxins
B) Decreased plasma concentration of myo-inositol
C) Hypoparathyroidism
D) All of the above

17) What percentage of patients with renal failure improve blood flow via hyperbaric oxygen?

A) 24%
B) 39%
C) 47%
D) 58%

18) Elevated levels of what causes decreased vascular endothelial growth factor in ESRD patients?

A) Iron
B) Zinc
C) Calcium
D) Phosphate

19) Approximately 50% of patients have abnormal motor nerve conduction velocity when creatinine clearance falls to what level?

A) 20 mL/min
B) 15 mL/min
C) 10 mL/min (correct)
D) 5 mL/min

20) In addition to vascular calcification, what else increases the risk of atherosclerosis?

A) Elevated CRP
B) Hypohomocysteinemia
C) Elevated Magnesium
D) Hyperparathyroidism

SEE ANSWER SHEET ON PAGE 141.

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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).

Facsimile Grading

To receive your CME certificate, complete all information and fax 24 hours a day to 1-631-563-1907. Your CME certificate will be dated and mailed within 48 hours. This service is available for $2.50 per exam if you are currently enrolled in the annual 10-exam CME program (and this exam falls within your enrollment period), and can be charged to your Visa, MasterCard, or American Express.

If you are *not* enrolled in the annual 10-exam CME program, the fee is $26 per exam.

Phone-In Grading

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

In the event you require additional CME information, please contact PMS, Inc., at **1-631-563-1604**.

ENROLLMENT FORM & ANSWER SHEET

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

Name _____ Soc. Sec. #_____
Please Print: FIRST MI LAST

Address_____

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.)

_____ I am not enrolled. Enclosed is my credit card information. Please charge my credit card $26.00 for each exam submitted. (plus $2.50 for each exam if submitting by fax or phone).

_____ I am not enrolled and I wish to enroll for 10 courses at $210.00 (thus saving me $50 over the cost of 10 individual exam fees). I understand there will be an additional fee of $2.50 for any exam I wish to submit via fax or phone.

Over, please

ENROLLMENT FORM & ANSWER SHEET *(continued)*

EXAM #2/16
The Effects of Renal Disease on Wound Healing (Scholnick)

Circle:

1.	A	B	C	D	11.	A	B	C	D
2.	A	B	C	D	12.	A	B	C	D
3.	A	B	C	D	13.	A	B	C	D
4.	A	B	C	D	14.	A	B	C	D
5.	A	B	C	D	15.	A	B	C	D
6.	A	B	C	D	16.	A	B	C	D
7.	A	B	C	D	17.	A	B	C	D
8.	A	B	C	D	18.	A	B	C	D
9.	A	B	C	D	19.	A	B	C	D
10.	A	B	C	D	20.	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 :

_____

_____

_____

_____

_____