Rheuma Facts®

A Quarterly Magazine

Serving physicians with interest in Rheumatology

13th Issue

Current News

DMARDs Triple Therapy Provides Better Cost-Effective First Line Strategy for RA, Study Finds

Results of a recent study showed that biological therapy regimens, such as Etanercept, Adalimumab, Infliximab, Golimumab, or Certolizumab, are less cost-effective compared to DMARD combination in triple therapy with Sulfasalazine, Hydroxychloroquine, and Methotrexate in the treatment of rheumatoid arthritis (RA).

Importantly, this triple therapy also was found to be as effective as biological therapies.

This finding resulted from a comprehensive cost-effectiveness analysis conducted in a study titled "Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis," published in the journal *Annals of Internal Medicine.*

According to the current guidelines from the American College of Rheumatology, biological therapies should be initiated only upon treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs).
For many patients, however, DMARDs are ineffective in the management of RA symptoms; therefore, biological medicines have become widely used, standing among the 10 top-selling drugs in the past 10 years.

This tendency has increased RA therapies' financial burden because the market value of biological drugs is much higher compared to DMARDs, which are relatively inexpensive.

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Regional and Widespread Soft Tissue Musculoskeletal Disorders

Compiled and summarized by:
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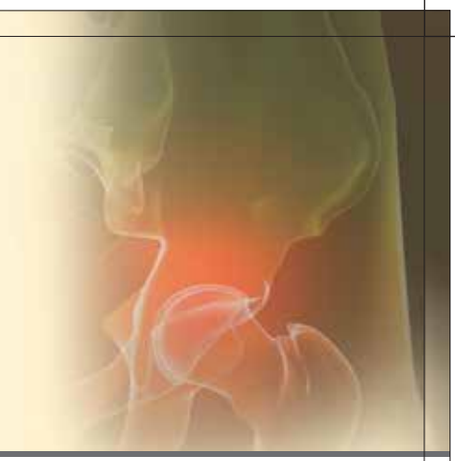

CASE 1

Wide spread Soft Tissue Pain

A 38 year-old lady presented with persistent joint pain and fatigue that have worsened over the past several months. She has had similar but milder pain for the past 4-5 years. She notes pain in her neck, shoulders, arms, back and knees. The pain interferes with her sleep most nights and she never awakens feeling rested. She has trouble making it through a full day at work because she is so tired. She has tried various over-the-counter non-steroidal anti-inflammatory therapies along with sleep aids, all without significant improvement. She denies depression but does admit to a fair amount of stress at work trying to keep up with the work load. The only past medical history is a prior diagnosis of irritable bowel syndrome. The rest of her review of systems is negative.

On joint exam, there is no synovitis or joint deformity. She has full range of motion of all extremities and passive joint movement does not reproduce her pain. On palpation though, she displays increased tenderness over multiple juxta-articular muscle groups including over her upper trapezius, posterior cervical muscles, lumbar, paraspinous, greater trochanter, medial knees and lateral epicondyles. There is discomfort with examiner resistance during strength testing, but normal strength of the upper and lower extremity muscles throughout. The rest of her examination is normal including head and neck, skin, cardiac, pulmonary, abdominal, and neurologic testing.

Laboratory evaluation is notable for CBC, CMP, ESR, thyroid studies and vitamin D levels that are normal. Hepatitis B and C testing is negative.

This patient's presentation and clinical findings are consistent with a diagnosis of fibromyalgia as the cause of her widespread chronic pain and fatigue.

In addition to fibromyalgia, what other disorders might present with chronic widespread pain and fatigue?

The differential for diffuse pain is broad. Rheumatologic causes include polymyalgia rheumatica, lupus, rheumatoid arthritis, myositis, vasculitis and scleroderma. Infectious entities that can cause chronic widespread pain include hepatitis C and HIV. Endocrinopathies such as hypothyroidism and hyperparathyroidism should be considered. Drug toxicity as a cause is best exemplified by the muscle pain complicating statin therapy. Other considerations include malignancy, neurologic disorders, sleep apnea and psychogenic pain from mood disorders.

What clinical and/or laboratory features from above are most helpful in identifying the diagnosis?

The presence of widespread tender points, along with a concurrent history of irritable bowel syndrome (IBS), is suggestive of fibromyalgia. Concurrent functional disorders such as IBS, interstitial cystitis, and TMJ syndrome may be present. In addition, there is a high prevalence of comorbid depression among patients with fibromyalgia. The syndrome can develop without a precipitating event, but has been reported following injury/trauma as well as in the setting of physical/emotional abuse (highlighting the importance of a full history during the initial encounter).

The lack of joint swelling, muscle weakness or other objective exam findings, coupled with lack of end-organ disease by lab testing, suggest a diagnosis other than a systemic inflammatory process. In general, the absence of clinical, radiographic and laboratory evidence of an inflammatory process after > 2 years of symptoms suggests a non-inflammatory etiology. The utility of laboratory testing is to rule out other etiologies. How extensive this testing should be is debatable.

Preliminary diagnostic criteria for fibromyalgia were updated in 2010 and do not include reliance upon tender points on exam.

The patient returns to review the results of her studies. Extra time is spent counseling her on the diagnosis of fibromyalgia, explaining what it is and how it can be managed. She is reassured that this is not a progressively destructive or life-threatening illness. The need for regular, daily exercise and lifestyle modification is stressed. The diagnosis and treatment of any barriers to sleep is also essential. Therapeutic options are discussed and a trial of low dose, nighttime amitriptyline is begun.

CASE 2

The patient from the case above returns for follow-up 3 months later. Sleep has improved 'somewhat' since initiation of amitriptyline, but she continues to suffer from daytime fatigue, widespread muscle pain and malaise. No focal joint issues have arisen and outside of her chronic IBS she has no other symptom complaints. She has some continued anxiety revolving around her job, but denies depression.

Her exam is similar to the prior evaluation, with diffuse muscle tenderness in response to examiner palpation, no active synovitis, and no signs of localized organ abnormality.

During discussion with the patient she expresses frustration: "I don't understand why my lab tests are normal. I have been told that amitriptyline is an anti-depressant. This isn't just 'all in my head. Can you tell me what caused this to happen?"

What is the current evidence behind the pathophysiology of fibromyalgia, and how can you use this information to provide patient-level counseling?

- Fibromyalgia stems from abnormal pain processing pathways (central amplification of pain)
- Research has identified objective evidence of decreased pain threshold on functional brain MRI as well as abnormal levels of neurotransmitters involved in pain signaling in the spinal cord and brain

  Patients with fibromyalgia have increased levels of neurotransmitters involved in ascending nociceptive pathways (substance P,glutamate), and decreased levels of neurotransmitters involved in inhibitory, descending pathways (serotonin, dopamine, norepinephrine)
- It is uncertain whether other features of fibromyalgia (mood disturbance, poor sleep, fatigue) are related to central amplification of pain
- The trigger or inciting event leading to central amplification is uncertain; the local environment at peripheral nociceptors may initially play a role, but subsequent amplification of central signaling appears to be independent of peripheral factors
- An understanding of central pain amplification is important because it is thought to have a prominent role in conditions such as IBS, interstitial cystitis, TMJ disorder, and perhaps in osteoarthritis as well

Counseling on the above is provided. It is explained that patients with fibromyalgia have dysfunctional pain processing pathways in which the 'volume is inappropriately turned up'. The patient expresses thanks for explaining her condition, but wonders if there are other treatment options other than amitriptyline.

Describe the pharmacologic and non-pharmacologic approaches to the treatment of fibromyalgia?

Non-pharmacologic therapies include patient education, exercise and cognitive behavioral therapy. Pharmacologic therapies should be tailored to individual patient symptoms such as

concurrent depression, insomnia, soft tissue pain, and/or comorbid conditions such as IBS. Pharmacologic options may include Gabapentin and Pregabalin (which may exert effect through reduction of neurotransmitters such as substance P and glutamate), Tramadol (with opioid receptor activity, but also dual serotonin / norepinephrine reuptake inhibition-SNRI), tricyclic agents (SNRI activity), Cyclobenzaprine (muscle relaxant and SNRI activity), Venlafaxine (SNRI activity) and newer agents such as Duloxetine, milnacipran and Desvenlafaxine.

CASE 3

Regional Soft Tissue Pain

A 68 year-old female is evaluated for several months of left hip pain. She has multiple medical problems including diabetes, hypertension, coronary artery disease and osteoarthritis. She has known degenerative disease of her knees and has used a cane for ambulation for several years. Five years ago she underwent lumbar surgery for degenerative disc disease. She takes 2-3 Hydrocodone-Acetaminophen tablets a day for the back and knee pain.

The hip pain is new for the past 2-3 months. She localizes the pain to the upper outer thigh overlying the greater trochanter. The pain is particularly problematic when she lies on her left side and it interferes with her sleeping. She does not note any increased pain with walking. Her knee and back symptoms are unchanged. The pain does not radiate down the leg. She denies any numbness to the area of the pain.

What is the differential for hip pain that localizes to the lateral thigh/hip region?

The first step in the evaluation of musculoskeletal pain is attempting to localize the site of pain: articular, periarticular, regional (bone or muscle), and referred sources. Developing a systemic approach to the patient presenting with acute musculoskeletal symptoms is important, and several review articles offer excellent summaries on the approach of patients with regional and diffuse musculoskeletal complaints.

The differential of hip pain should include articular abnormalities of the hip, bursa and tendon disorders, neurologic disorders, referred pain from the knee, and bone disorders. Pain from disorders of the hip articulation such as osteoarthritis and avascular necrosis generally are noted in the groin but pain may be more diffuse. Trochanteric bursitis pain is localized over the greater trochanter with tenderness elicited in that area. Meralgia paresthetica causes paresthesias and numbness over the lateral thigh. The iliotibial band syndrome, a syndrome most commonly seen in runners, causes lateral but typically distal thigh pain. Lumbar spine disease with nerve root entrapment especially involving L2 to L4 may cause pain described as in the hip and thigh, while lumbar spinal stenosis typically produces bilateral leg pain with walking. Bone abnormalities including primary bone malignancies, metastatic bone lesions, occult fractures and Paget's may present with localized hip and leg pain. Inter-abdominal abnormalities causing referred pain include abscesses, renal stones and hernias.

How does the positional nature of the pain aid in localizing the source of the pain?

Pain occurring with palpation or pressure over the greater trochanter would be most characteristic of trochanteric bursitis. Local bone abnormalities should also be considered. Unlikely in this scenario would be referred pain from an intra-abdominal or lumbar spine process.

On exam, the patient is 5'2" and weighs 180 pounds. She is stiff on arising and walks with a cane. There is no tenderness over her spine nor back. There is increased tenderness to palpation over the left greater trochanter but not on the right

side. Rotation, flexion and abduction of the left hip are normal but she notes pain in her left lateral thigh with adduction of the left hip. On knee exam there is crepitus bilaterally but no effusion. Range of motion of the knee does not reproduce the pain. Neurologic exam of the lower extremities is intact and there is no loss of sensation elicited over the lateral left thigh.

A diagnosis of trochanteric bursitis is made on the basis of the history and exam findings.

Are any additional studies warranted at this time?

No further studies are warranted giving the typical nature of the history and exam findings.

What history and exam findings would have been characteristic for degenerative hip disease, radicular pain from degenerative back disease, metastatic bone pain, referred pain from the knee and meralgia paresthetica?

Degenerative hip disease would typically cause pain with weight bearing and ambulation, and be relieved with recumbency; pain is often reproduced with active or passive range of motion testing of the hip articulation. Radicular pain from the lumbar spine should not cause localized tenderness in the hip or thigh but would instead be associated with abnormalities on neurologic testing. Metastatic bone lesions classically cause constant pain which is not positional. Meralgia paresthetica causes numbness and paresthesia over the lateral thigh.

What other potential diagnoses are in the differential? What clinical and/or exam features make these less likely?

- Long-standing diabetes can be associated with a proximal neuropathic process called diabetic amyotrophy. It causes pain, and in some cases weakness, of the proximal thigh and hip-girdle muscles. Roughly 50% of cases are unilateral. The focal nature described by the patient, localized to a specific region of the lateral thigh, would not be typical of diabetic amyotrophy. In addition, the lack of weakness and absence of severe pain are reassuring for an alternative cause.
- Subtrochanteric femur fractures can present with deep thigh pain, and should be considered in patients with long-standing bisphosphonate use with unexplained hip/thigh pain. A detailed history should be obtained regarding osteoporosis/osteopenia and use of anti-resorptive therapy. Again, the focal quality of this patient's pain is classic for trochanteric bursitis; if the patient failed to respond to typical therapy, radiographs of the hip and thigh could be considered, especially in the setting of long-term anti-resorptive therapy. The lack of increased pain with walking also makes a subtrochanteric fracture less likely.
- Improper use of assistive device (cane). A cane that is improperly fitted to a patient can result in pelvic tilting and subsequent strain on muscles and tendons in the pelvic girdle. In the standing position, the handle of the cane should rise to approximately the volar crease of the wrist.

What treatment options are available for trochanteric bursitis?

- Oral NSAIDs, ice
- Physical therapy or home exercises (with focus on stretching of the adjacent iliotibial band as well as the gluteus medius and minimus)
- Local glucocorticoid injection.The steroid injected may provide long term benefit.
- Recurrent symptoms would warrant other therapy including physical therapy and evaluation for precipitating factors (such as leg length discrepancy or hallux rigidus) or re-consideration of alternative cause (including gluteal muscle or tendon tears, or alternative conditions listed above)

Examining the Connection between Gout and Metabolic Syndrome

Compiled and summarized by:
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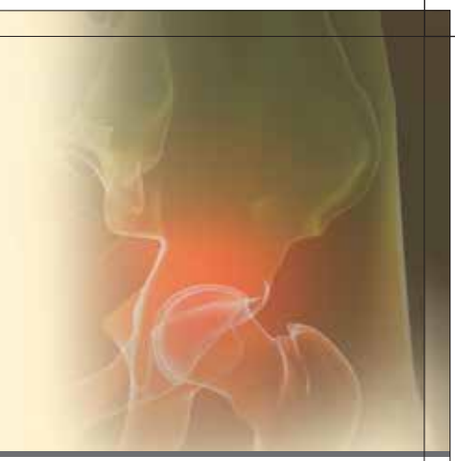


The prevalence of gout has increased substantially in recent years, and most individuals with the disease are not getting the recommended treatment. Additionally, there is increasing evidence linking hyperuricemia with the promotion of hypertension, cardiovascular disease, insulin resistance, inflammation, adipogenesis, lipogenesis, and liver disease.

In most patients, gout exists within a matrix of multiple comorbidities, many of which comprise metabolic syndrome. If we can show gout contributes to metabolic syndrome, both gout which is eminently treatable but almost universally undertreated and metabolic syndrome may be positively impacted.

Pathophysiology of Gout

Uric acid is mainly synthesized in the liver, intestines, and vascular endothelium from exogenous (mostly animal protein) and endogenous purines and is mainly found in its salt form, urate. Fructose also increases intracellular uric acid production. Its consumption has increased substantially over the last few decades, primarily due to the increased use of corn syrup as a commercial sweetener.

Serum urate levels also depend on the degree of excretion by the kidneys, and low excretion is the main factor contributing to high urate levels.

Hyperuricemia increases the risk of gout from monosodium urate crystal formation, which can occur spontaneously at a concentration of 6.8 mg/dL. Hyperuricemia may also increase the risk of urolithiasis in the form of uric acid precipitation in the renal collecting system. Uric acid solubility decrease with increasing pH.

Epidemiologic Clues

Epidemiologic studies have recently shown that there is a higher prevalence of metabolic syndrome in individuals with hyperuricemia and gout compared with controls.

The risk of metabolic syndrome was approximately 15 times higher for the highest quartile of urate compared with the lowest 2 quartiles.

Despite strong evidence of the association of hyperuricemia with the metabolic syndrome, it is still debatable whether it is a surrogate marker or a confounding risk factor, but the statistical association does not imply causality.

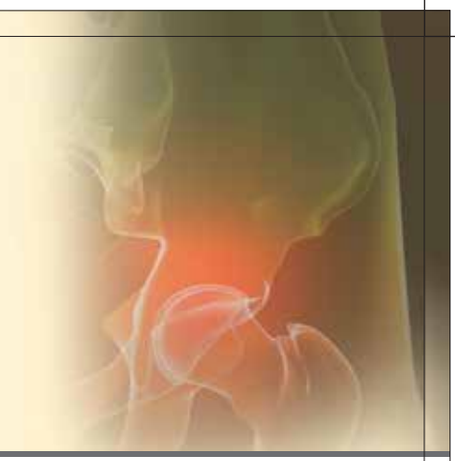
Hypertension

Elevated levels of serum urate may promote increases in blood pressure through changes produced in the vascular endothelium and kidney.

The effect was inhibited by probenecid, a urate transport blocker. In a different study, the same group showed that urate dose dependently promoted vascular smooth muscle proliferation and cell migration. Taken together, the studies suggest hyperuricemia may lead to a vascular state that is hypertrophied, with an inability of the vessels to relax.

Urate may also affect blood pressure by influencing kidney function. Hyperuricemia can cause acute renal failure through supersaturation in kidney tubules with crystal formation and obstruction. However, can elevated uric acid affect kidney function at concentrations below crystal formation? Or more importantly, can lowering high serum urate lower blood pressure?

Since hyperuricemia is commonly encountered in patients with new-onset essential hypertension, a small randomized controlled crossover trial was performed on adolescents to determine if lowering serum urate improved hypertension. Patients had newly diagnosed,



untreated, stage 1 essential hypertension with serum urate levels ≥6 mg/dL. Allopurinol or placebo 200mg was administered twice daily for 4 weeks with a 2-week washout period. Compared with placebo, allopurinol significantly reduced mean casual and ambulatory systolic and diastolic blood pressures with 20 of 30 (66.7%) in the allopurinol group achieving normalized blood pressure.

Cardiovascular Disease

It may be difficult, however, to determine whether it is the hyperuricemia or comorbidities that elevate the risk of cardiovascular events. Asymptomatic hyperuricemia is a valuable biomarker for predicting the development of incident coronary artery disease events.

Gout is an independent risk factor for developing cardiovascular disease and for higher cardiovascular mortality.

Insulin Resistance

Patients with gout are at increased risk for insulin resistance. A meta-analysis of prospective cohort studies with no evidence of heterogeneity found hyperuricemia to be an independent risk factor for incident type 2 diabetes. The authors stated that the evidence strongly supported hyperuricemia as a causal factor in the development of type 2 diabetes.

Multiple physiologic mechanisms may play a role in the association between hyperuricemia and the development of type 2 diabetes. Hyperuricemia induces endothelial dysfunction, reduces nitric oxide (important in stimulating glucose uptake), and is associated with oxidative stress.

However, can lowering serum urate improve insulin sensitivity? In a recent small study, Takir et al compared the effect of allopurinol 300 mg daily for 3 months vs observation only in patients with hyperuricemia but without diabetes. After 3 months, patients taking allopurinol showed reductions in serum urate, fasting blood glucose, fasting insulin, insulin resistance (measured by homeostatic model assessment of insulin resistance), and serum high-sensitivity C-reactive protein. The number of patients with impaired fasting glucose after 3 months compared with baseline was reduced (20% vs 75%; P <.001).

The Question of Treatment

Although limited evidence is available, an important question is whether patients with metabolic syndrome and asymptomatic hyperuricemia should be treated with ULT. Current American College of Rheumatology guidelines (2012) cite insufficient evidence for determination, while Japanese guidelines recommend treatment for serum urate levels >9 mg/dL.

Conclusion

A large percentage of individuals with gout are not receiving adequate urate lowering agent. Effectively treating gout may improve and prevent some comorbidities, though the evidence is limited. Whether patients with asymptomatic hyperuricemia should be similarly treated with urate lowering agent, and under what circumstances, remains a pressing research topic.

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Biologics Do Not Increase the Risk of Second Malignancy in Rheumatoid Arthritis Patients

Compiled and summarized by:
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Treatment with biologics does not increase the risk of a second malignancy in rheumatoid arthritis patients who have a history of cancer, according to new research findings presented this week at the 2017 ACR/ARHP Annual Meeting.

Rheumatoid arthritis (RA) is a chronic disease that causes pain, stiffness, swelling, and limitation in the motion and function of multiple joints. Though joints are the principal body parts affected by RA, inflammation can develop in other organs as well. An estimated 1.3 million Americans have RA, and the disease typically affects women twice as often as men.

Biologic disease-modifying anti-rheumatic drugs, or biologics, are used to control rheumatoid arthritis disease activity and prevent joint damage in RA patients. Despite 15 years of studying the safety of this treatment, there is still a concern that these medications, which suppress the immune system, could increase the risk of malignancy in patients with a history of cancer. A team of researchers in Denmark conducted a study of 1,678 RA patients from a national registry to determine if biologic use increased the risk of a second cancer diagnosis, in individuals who have had cancer. The study also looked at mortality rates among these patients.

"Second malignancy is an increasing challenge, as the survival after the first, primary tumor has improved substantially for most types of cancer," says Lene Dreyer, MD, Associate Professor of Rheumatology at the University of Copenhagen and a lead author of the study. "The concern for second malignancy or cancer recurrences in patients with a history of cancer diagnosis has led to some reluctance in treating this subset of arthritis patients with biologics, especially TNF-inhibitors. Consequently, some RA patients with a previous cancer are suffering from inadequate treatment of their arthritis."

RA patients who had a primary cancer diagnosis were selected from the DANBIO Registry, a national medical records database in Denmark, from 2000 to 2011. The researchers analyzed their cases to determine the hazard ratio (HR) for secondary malignancy and also deaths among this population. Of the RA patients in the study, 190 received biologics only before their primary cancer diagnosis, 220 patients received biologics only after their primary cancer diagnosis, 92 patients received biologics both before and after their primary cancer diagnosis, and 1,176 patients never received biologics.

Among the 502 patients who received a biologic at any time, the hazard ratio for developing a second malignancy was 1.11 compared to 1.00 for those who were never treated with a biologic. This was not a statistically significant increase in the risk of a second malignancy.

Researchers also looked at mortality rates among RA patients with a history of cancer but were unable to draw a clear conclusion about significant increases. When the data was adjusted for age, gender, calendar time, site of the cancer and extent of the disease, the hazard ratio for death was 1.20 among the RA patients

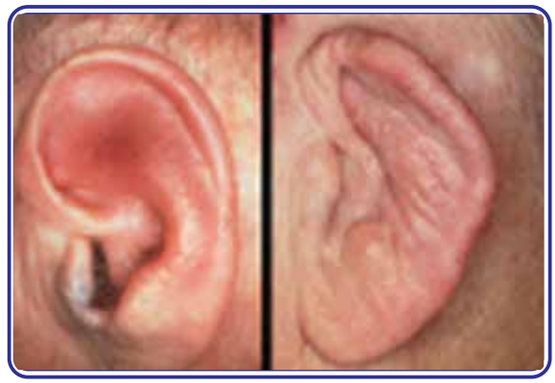
treated with a biologic only before their cancer diagnosis, compared to 1.00 for those who were never treated with a biologic. Patients who were treated with a biologic only after their cancer occurred had a hazard ratio for death of 1.36, and those who received biologics both before and after their cancer diagnosis had a hazard ratio for death of 1.22.

"It is reassuring that these results indicate no increased risk of a second malignancy in RA patients with a past cancer who used biologic therapy, and that was no major indication of an increased mortality rate among users of these medications," said Dr. Dreyer. "However, the number of patients who suffered a second malignancy was small, so our statistical analyses must be interpreted with caution. Further studies are required to confirm our findings. In the meantime, our data does provide some reassurance that biologics don't pose an immediate danger in patients with a history of cancer."

Lucky Draw Winners from Photo Quiz of 12th Issue

Question

What is the diagnosis for the given picture?



Answer

- Polychondritis

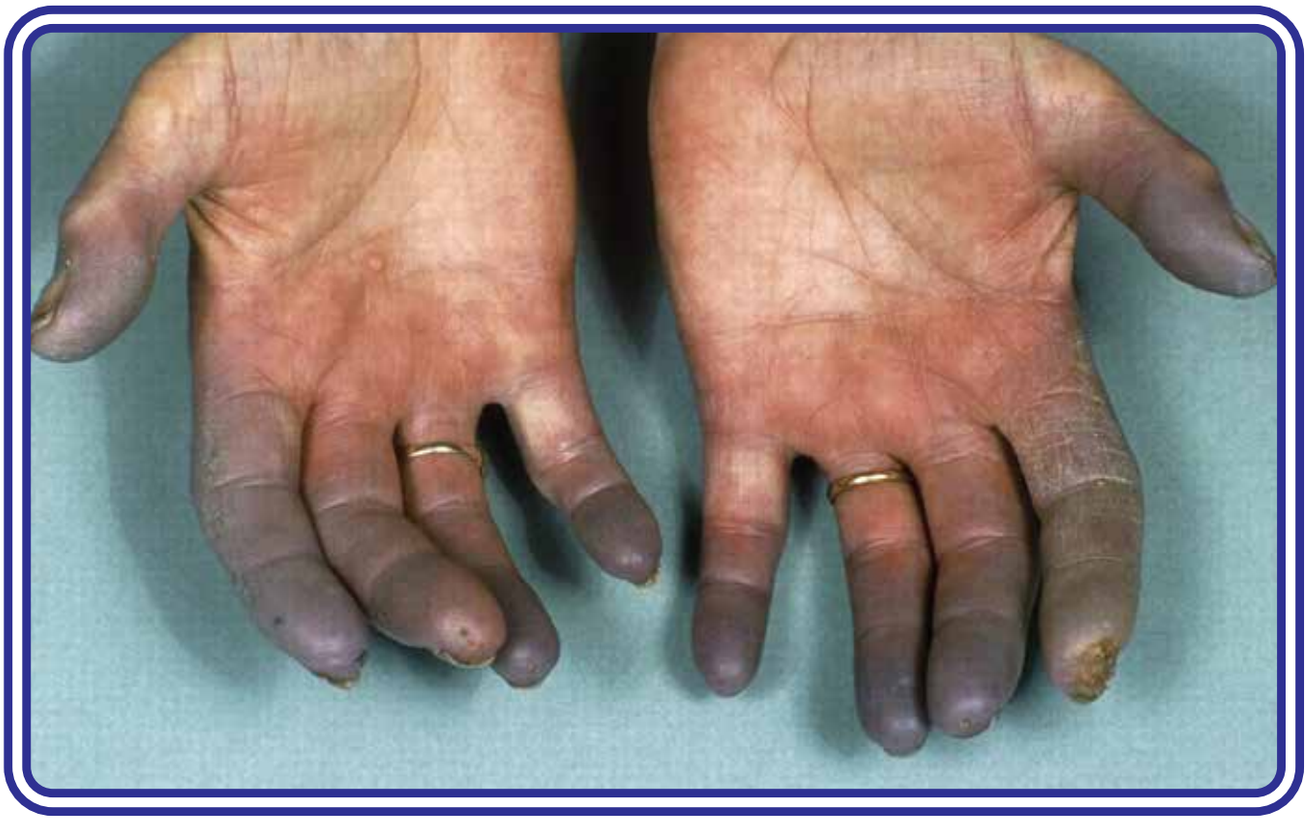
Winners of Lucky Draw

The editorial board of Rheuma Facts Magazine is pleased to announce the names of winners for the photo-quiz of the 12th issue. The lucky draw was conducted at Karachi and following are the names of the lucky draw winners randomly drawn by Dr. Ahmed Iqbal Mirza.

We congratulate the winners and once again thank all the contestants for their participation in the quiz.

1. **Dr. Basheer Ahmed**
   Abbasi Shaheed Hospital, Nazimabad, Karachi
2. **Dr. Ali Ahmed**
   Haleem Hospital, North Nazimabad, Karachi
3. **Dr. Asif Ali Deena**
   Soldier Bazar, Karachi
4. **Dr. Adeel Ahmed**
   Ibne Sina Hospital, Gulshan Town, Karachi
5. **Dr. Pervez Ahmed**
   Jinnah Post Graduate Medical Centre, Karachi
6. **Prof. Dr. Mushtaq Ahmed Sheikh**
   Chandka Medical College, Larkana
7. **Dr. Rizwan Ghafoor**
   Ibne Sina Medical Hospital, Multan
8. **Prof. Dr. Nasir Ali**
   Bahawal Victoria Hospital, Bahawalpur
9. **Prof. Dr. Azeem Akhund**
   People's University of Medical and Health Sciences, Nawabshah
10. **Dr. Talha Khalil**
    Ghazi Medical College, Dera Ghazi Khan
11. **Dr. Hareem Farooq**
    Govt. Abdul Qayyum Hospital, Sahiwal
12. **Dr. Afzal Hussain**
    PSRD Hospital, Icchra, Lahore
13. **Dr. Sikandar Hayat**
    Sikandar Hospital, Wapda Town, Gujranwala
14. **Dr. Salman Saeed**
    Independent University Hospital, Faisalabad
15. **Prof. Dr. Zahid Askar**
    Khyber Teaching Hospital, Peshawar
16. **Dr. Wali Muhammad Khan**
    Lady Reading Hospital, Peshawar
17. **Dr. Ihsan Ullah**
    Saidu Teaching Hospital, Swat
18. **Dr. Syed Ishtiaq Hussain Shah**
    Saidpur Road, Rawalpindi
19. **Dr. Sajid Razzaq**
    Poonch Medical College, Rawlakot, Azad Kashmir
20. **Dr. Shoukat Hayat**
    Abbas Institute of Medical Sciences (AIMS), Muzaffarabad, Azad Kashmir

Photo Quiz



Question

What is the primary cause of the manifestation shown here?

- Eisenmenger syndrome
- Gout
- Raynaud phenomenon
- Tobacco smoking