Most patients with papillary thyroid cancer (PTC) present with disease confined to the thyroid; however, neck nodal metastases (NNM) may be found in up to 40 percent of patients at the time of initial surgical resection. Despite potentially curative primary operative intervention, approximately 15 percent of patients with PTC are also later found to have NNM — discovered months to years after the initial operation. Recent advances in neck ultrasound and thyroglobulin-directed detection of small NNM presents the endocrinologist with a dilemma in terms of best management.

Ian D. Hay, M.D., Ph.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Rochester, Rochester, Minnesota, says: “It is being increasingly recognized that radioiodine remnant ablation rarely prevents the later discovery of postoperative NNM in PTC. Reoperative, compartment-oriented surgery, recommended by most management guidelines for the treatment of recurrent NNM, unfortunately produces a biochemical remission in only 30 to 50 percent of cases.

“Our group first used ultrasound-guided percutaneous ethanol ablation (UPEA) in the management of recurrent NNM in PTC in 1993, and in 2002 we reported that it was a safe, effective and considerably less expensive alternative to operative management. In 2013, we reported on the long-term efficacy of UPEA in the initial control of 37 recurrent NNM in 25 patients with advanced localized disease (pTNM stages III or IVA) who had previously been treated by both primary definitive surgery and postoperative RAI therapy.” Of the 25 ablated patients:

- 10 (40 percent) had only central nodes ablated
- One had both central and lateral nodes treated
- 14 (56 percent) had lateral nodes only

Robert A. Lee, M.D., of the Department of Radiology at Mayo Clinic in Rochester, explains: “The largest diameter of treated nodes ranged from 4 to 21 mm (mean, 14). See Figure 1.

Figure 1. Neck ultrasound images with Doppler flow image on right show recurrent metastatic papillary thyroid cancer in a hypervascular right neck lymph node (arrows) with a calculated lymph node volume of 168 mm$^3$ prior to ethanol ablation.
UPEA was typically performed in two sessions on consecutive days. Seven of 25 patients (28 percent) had further sessions (average one more), typically three to six months later, to completely eliminate Doppler flow in the NNM (Figure 2). The volume of ethanol injected per session ranged from 0.1 to 1.4 mL, and the average injection was 0.5 mL.

**Efficacy of UPEA**

Dr. Hay highlights: “In this series of 37 NNM treated by UPEA, tumor perfusion, as evidenced by Doppler blood flow, was eliminated in each ablated node after successful therapy (Figure 2). After a mean follow-up of 65 months (range, 5 to 157), 17 ablated NNM (46 percent) completely disappeared on ultrasound rescanning. During follow-up, six of the 25 patients (24 percent) developed 18 new NNM; 15 of the 18 (83 percent) were managed successfully by UPEA, rather than by neck re-exploration. Serum thyroglobulin (Tg) levels were meaningfully followed in the 22 patients without Tg autoantibodies. Optimal Tg values of < 0.2 ng/mL on thyroid hormone suppressive therapy (THST) were found at last follow-up in 12 of the 22 (55 percent). Intermediate Tg levels of 0.3 to 2.4 ng/mL were seen in six (27 percent) without demonstrable disease; and unacceptable serum Tg values of > 2.5 ng/mL were seen in four (18 percent) who had persistent PTC in NNM, which was biopsy proven in all four cases.”

**Complications**

Dr. Lee notes: “Most patients experienced brief discomfort at the UPEA site. In all of these patients, the discomfort resolved after several minutes. None of the 25 patients undergoing UPEA of the initial 37 NNM experienced, as a consequence of their UPEA, transient or permanent hoarseness or vocal cord paralysis.”

**Treatment goals**

Dr. Hay explains, “Our treatment goals are, in order of importance:
1. Elimination of significant nodal blood flow (“tumor perfusion”) by Doppler ultrasonography
2. Reduction in volume of treated NNM, ideally to the point of disappearance on rescanning
3. When possible, concomitant reduction in circulating serum Tg levels on THST

![Image of ultrasonic images of lymph nodes after ethanol ablation](Image)

**Figure 2.** Neck ultrasound images of the same patient shown in Figure 1 (Doppler flow image on right). Ten months after ultrasound-guided percutaneous ethanol ablation, the treated lymph node (arrow) is now small and hypovascular with a calculated lymph node volume of 12 mm$^3$. 
Hypophosphatasia

Hypophosphatasia (HPP) is an inborn error of metabolism with highly variable clinical severity caused by loss of function mutations in the gene encoding tissue nonspecific alkaline phosphatase (TNSALP). The prevalence of the severe form is estimated to be between 1/100,000 and 1/300,000. The prevalence of the mild forms is likely much more frequent.

Clinical manifestations

HPP has been classified into five categories depending on the age at diagnosis. Peter J. Tebben, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition and the Division of Pediatric Endocrinology and Metabolism in the Department of Pediatric and Adolescent Medicine at Mayo Clinic’s campus in Rochester, Minnesota, says: “In general, the younger the age at diagnosis, the more severe the disease. Disease severity can range from death in the perinatal period to dental problems or fractures in adulthood.”

Categories include:

- Perinatal HPP presents with clinical features noted at birth or before based on a prenatal ultrasound. Clinical exam will reveal obvious skeletal abnormalities including chest wall deformities, as well as short or bowed long bones. The skeleton is hypomineralized, which is readily identified on X-ray. This form of HPP is almost universally fatal shortly after birth.
- Infantile HPP is diagnosed by 6 months of age. Characteristic changes of rickets are seen on X-ray, and fractures are often present. Infants fail to grow appropriately and some will experience vitamin B-6 responsive seizures. Hypercalcemia and nephrocalcinosis have also been described. Mortality in the infantile form of HPP is substantial.
- Childhood HPP is diagnosed when disease manifests after 6 months of age. Children often have a delay in gross motor milestones and a static myopathy. A common feature of childhood HPP is premature loss of deciduous teeth (before 5 years of age) with the root intact. Radiographs reveal changes of rickets and often a radiolucent band extending from a central compartment node dissection or a unilateral modified radical neck dissection.

Conclusion

Dr. Hay concludes: “It is our opinion that UPEA should be more generally incorporated into the management of NNM in advanced localized PTC not amenable to conventional retreatment with surgery, radioiodine or external irradiation. Moreover, our 25 patients, by avoiding 40 further neck explorations, on average saved themselves at least $61,000 in medical charges.”
the growth plate into the metaphysis.

- Adult HPP may manifest with recurrent or slow-to-heal metatarsal fractures or subtrochanteric femoral pseudo fractures. A recent review of Mayo Clinic patients diagnosed with HPP in adulthood demonstrated they often present with nonspecific musculoskeletal complaints. Many adults with HPP will report having had symptoms during childhood, but the diagnosis was not made until later in life.

- Odontohypophosphatasia, the least severe form of HPP, is diagnosed when dental abnormalities are present but no other skeletal disease, such as rickets or osteomalacia, is identified.

**Laboratory findings**

The hallmark laboratory finding in HPP is a low blood level of alkaline phosphatase activity. Dr. Tebben explains, “Because the abnormal alkaline phosphatase gene located on chromosome 1 encodes the tissue nonspecific form of alkaline phosphatase (bone, liver, kidney), measuring bone-specific alkaline phosphatase is typically not necessary. However, a low total alkaline phosphatase is not pathognomonic, as this finding can be associated with other disorders. In adults, prior treatment with anti-resorptive therapy is a common cause of low alkaline phosphatase. However, in the context of the appropriate clinical setting, a low alkaline phosphatase is strong evidence for a diagnosis of HPP.”

Dr. Tebben explains: “When interpreting the result of an alkaline phosphatase measurement, it is crucial to utilize the appropriate age and gender-specific reference ranges. Children have significantly higher alkaline phosphatase concentrations compared with adults, and the diagnosis can therefore be overlooked if an adult reference range is applied. Additional laboratory tests that are supportive of the diagnosis include hypercalcemia, hyperphosphatemia and hypercalciuria, particularly in the infantile and childhood forms. Phosphoethanolamine and pyridoxal 5’-phosphate are substrates for alkaline phosphatase and are elevated in patients with HPP. Pyridoxal 5’-phosphate is a product of vitamin B-6, and patients taking supplements containing vitamin B-6 should discontinue them two weeks prior to measurement.”

**Radiographic findings**

Severely hypomineralized bone is seen in patients with perinatal and infantile forms of the disease. Childhood HPP will exhibit metaphyseal changes of rickets and bands of radiolucency extending from the growth plate into the metaphysis. In adults, metatarsal fractures, pseudo fractures in the femur and calcium pyrophosphate deposition disease are commonly identified. Enlarged pulp chambers can be seen on dental X-rays.

**Histologic findings**

Bone histology varies depending on the age of presentation and severity of disease. Robert A. Wermers, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: “Infantile HPP demonstrates severely defective skeletal mineralization, with osteoid composing the majority of the bone tissue. On the other hand, patients with childhood and adult HPP with less severe manifestations may have no evidence of a mineralization defect. Iliac crest bone biopsies from more-severe forms of childhood and adult HPP will generally demonstrate osteomalacia, with areas of unmineralized osteoid and absence of tetracycline label uptake. However, findings of osteomalacia can be patchy, with accumulated osteoid on some surfaces, whereas other bone surfaces show normal mineralization. Cortical and trabecular bone volumes are normal in adult HPP.”

**Treatment**

There is no Food and Drug Administration-approved treatment for HPP. Dr. Tebben notes: “In the perinatal and infantile forms, therapy has largely been supportive. Vitamin B-6 may be helpful for seizures in patients with infantile HPP. Recently, recombinant tissue nonspecific alkaline phosphatase modified to target and anchor to bone has been developed and tested in infants and children with severe HPP. Improved biochemical, radiographic and clinical parameters were observed. Long-term outcomes are yet to be reported. The utility of treatment in less severely affected individuals is unknown.”

**Conclusion**

HPP can manifest with a broad range of symptoms and severity. During infancy and childhood, the diagnosis can readily be made based on clinical, radiographic and basic laboratory findings. Dr. Wermers summarizes: “Adults often present with more nonspecific symptoms, and a low alkaline phosphatase should prompt consideration of HPP. Recognition of adult HPP is important, as the most commonly utilized medications for osteoporosis (anti-remodeling agents) could further impair skeletal mineralization and should be avoided.”
The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, has had a major role in decreasing cardiovascular risk over the past three decades. Statins have become one of the most prescribed medication classes in modern medicine. However, the efficacy of statins is limited in part by statin discontinuation.

Juan P. Brito Campana, MBBS, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “In some cohorts, half of all patients discontinue statin therapy within two years of their prescription. Discontinuation is frequently due to the development of musculoskeletal complaints. The incidence of these complaints is between 1 percent and 5 percent in randomized controlled trials and 10 percent in large observational studies. The key challenge for the clinician is to find a way to preserve the cardiovascular benefits of statins in patients experiencing musculoskeletal side effects attributed to statins.”

**A practical definition**

Statin-associated musculoskeletal syndrome (SAMS) comprises musculoskeletal symptoms or signs (muscle or tendon discomfort, pain, or impaired function) that develop while the patient is taking statins, decrease the health-related quality of life of the patient and resolve after statin discontinuation. Most complaints are not associated with abnormalities of creatine kinase (CK), which is an imperfect marker of muscle damage.

**Risk factors for SAMS**

Vinaya Simha, MBBS, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: “A systematic review of 27,548 patients found a greater incidence of SAMS (odds ratio=9.97; 95 percent confidence interval, 1.28 to 77.92) in patients receiving intensive-dose statin therapy compared with standard-dose therapy. In addition, the risk of SAMS may depend on the type of statin used.

“An article published in *Cardiovascular Drugs and Therapy* in 2005 about the Prediction of Muscular Risk in Observational conditions (PRIMO) study reported different rates of SAMS with fluvastatin 40 mg (5 percent), pravastatin 40 mg (11 percent) and simvastatin 40 to 80 mg (18 percent). A meta-analysis including 71,108 people, 36,062 on statins and 35,046 on placebo, reported the greatest risk of SAMS with atorvastatin and the least risk with fluvastatin.

“Different rates have been attributed to pharmacological differences between statins. For example, rosvastatin and pravastatin are primarily metabolized by cytochrome 2C9, a site with fewer drug-drug interactions than cytochrome 3A4, which metabolizes simvastatin, lovastatin and atorvastatin. Drugs inhibiting glucuronidation, such as gemfibrozil, or drugs affecting cytochrome 3A4 activity, such as amiodarone, protease inhibitors, niacin, azole antifungals, macrolides and nondihydropyridine calcium channel blockers, affect the clearance and increase the blood levels of statins.” Other important risk factors for SAMS are:

- Age > 65 years
- Family or personal history of SAMS
- Unexplained muscle cramps
- Hypothyroidism
- Vitamin D deficiency
- Rare hereditary metabolic muscle diseases

**Establishing the diagnosis of SAMS**

Dr. Simha highlights: “The clinician needs to consider whether the patient complaint represents SAMS or an alternative diagnosis. After excluding alternative diagnoses, clinicians should determine the extent to which the musculoskeletal symptoms experienced affect the quality of life of the patient. This would
include disruptions or impairments during work, recreation or sleep attributed to SAMS.”

Assess and consider the potential benefit from statins
Clinicians and patients should review the potential value of statins. Using state-of-the-art risk communication tools, such as the Statin/Aspirin Choice Decision Aid available at http://statindecisionaid.mayoclinic.org, clinicians can explain to patients what the cardiovascular risk reduction means so that patients can consider whether the pursuit of this reduction is worth the work and potential side effects associated with therapeutic trials of other statins (Figure).

Dr. Brito notes: “Patients at very low cardiovascular risk will likely opt to focus their health efforts in areas other than lowering-lipid fractions and cardiovascular risk. Clinicians should reassure these patients because some might have been mistakenly informed that they were at high risk of cardiovascular events. Patients at high cardiovascular risk who value the risk reduction afforded by statins and are willing to run the risk of SAMS to find the right statin will proceed with restarting statins. Patients at high risk who are less willing to experience SAMS may instead choose to focus on other ways to reduce cardiovascular risk.”

Restarting statins
If the diagnosis of SAMS was correct and there were no risk factors to modify, SAMS will likely recur after the same statin is resumed at the same dose. Dr. Simha suggests: “Two modifications may reduce the risk of recurrence of SAMS: switching to another statin and decreasing the dose. The statins with the lowest rates of SAMS include pravastatin, fluvastatin and rosuvastatin. Using a low dose — either by reducing the daily dose or by reducing the frequency of administration — of any of these could achieve the goal of SAMS-free adherence to statins.”

Conclusion
Dr. Brito concludes: “Instead of taking a purely technical approach, we suggest that clinicians engage the patient in a dialog about the promised quantified benefits of statins in light of their potential to cause SAMS. Patients should recognize there are other interventions also capable of reducing their cardiovascular risk that they may have already implemented or may be available to them to use instead of statins. For patients who value the risk reduction with statins, clinicians should prescribe therapeutic trials with statins associated with low risk of SAMS and administered at lower doses or frequency. A close partnership with the patient may lead to a greater proportion of patients who are able to achieve their goals with therapies that do more good than harm.”

For more information
SAMS affecting patient’s quality of life

Reassess need for statin therapy

Patient and provider opt for individualized discussion on potential value of statins and shared decision-making on statin therapy to lower cardiovascular risk (CV)

Reassess need for statin therapy

Reassess statin tolerance after treatment of other identified conditions

Recurrence of symptoms

Patient decides to re-try statin therapy

Does the patient want and need statins?

Patient decides to pursue non-statin options to decrease cardiovascular risk

Other underlying causes for musculoskeletal pain: (e.g. inflammatory and hereditary myopathies)

Predisposing causes for SAMS: (e.g. hypothyroidism, vitamin D deficiency, concomitant medications, hepatic and renal insufficiency)

Reassess statin tolerance after treatment of other identified conditions

Recurrence of symptoms

Modify statin therapy

Lower dose of previously tried statin

A different statin (pravastatin, fluvastatin)

Decreased frequency (e.g., rosuvastatin 1-2 times/week)

Recurrence of symptoms

Consider non-statin therapies (no proven benefit): ezetimibe, bile-acid binding resins, niacin, stanol esters

Baseline CV risk score

CV risk score after nonstatin treat-to-risk therapies (smoking cessation and aspirin)

CV risk reduction with statin therapy

The risk of heart attack in the next 10 years for 100 people like you

The risk of heart attack in the next 10 years for 100 people like you

The risk of heart attack in the next 10 years for 100 people like you who do take statins

82 People DO NOT HAVE a heart attack

91 People DO NOT HAVE a heart attack

91 People DO NOT HAVE a heart attack

9 People DO HAVE a heart attack

2 People AVOID heart attack

7 People DO HAVE a heart attack

18 People DO HAVE a heart attack

Figure. Flow diagram of an approach to the patient with statin-associated musculoskeletal syndrome (SAMS). The sample decision aid in the algorithm applies to a 62-year-old Caucasian man who smokes tobacco and has a total cholesterol of 200 mg/dL and a HDL-cholesterol of 40 mg/dL. He does not have diabetes mellitus or hypertension.
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Mayo Clinic Nutrition and Wellness in Health and Disease
Sept. 18-19, 2014, in San Francisco
Nutrition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. This course — designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness staff — will provide a full-spectrum, in-depth overview of situations that clinicians encounter in the ambulatory setting, including obesity in adults and children, weight management strategies, healthy diets, obesity-associated medical conditions, bariatric surgery and pre- and post-surgery medical management, ambulatory nutrition topics in the news, and a healthy cooking demonstration, in addition to physical activity and wellness. Current clinical topics will be highlighted through presentations with teaching pearls, interactive case studies and panel discussions. The course will be held at Marriott Marquis in San Francisco.

18th Mayo Clinic Endocrine Course
Feb. 16-20, 2015, in Riviera Maya/Cancun, Mexico
Designed for endocrinologists and interested internists and surgeons, the 18th Mayo Clinic Endocrine Course will address gaps in medical knowledge and barriers in clinical practice in order to improve the outcomes of patients with endocrine and metabolic disorders. This course will span the full range of endocrinology, through lectures, debates, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast round-table discussions and small-group discussions with experts. Attendees will have plenty of opportunity for interaction with the course faculty, who are selected from Mayo Clinic for their expertise and clinical acumen. The course will be held at The Fairmont Myakoba in Qintana Roo, Mexico. To ensure accommodations at the discounted rate, please make your reservations directly with the hotel by calling 800-441-1414 (toll-free). Identify yourself as a participant of the Mayo Clinic Endocrine Course.

The 39th Samuel F. Haines Visiting Professor Antonio Bianco, M.D., University of Miami Miller School of Medicine; Chief, Division of Endocrinology, Diabetes, and Metabolism, with members of the Thyroid Core Group at Mayo Clinic in Rochester. Seated left to right: Diana S. Dean, M.D., John C. Morris III, M.D., Antonio Bianco, M.D., Rebecca S. Bahn, M.D. Standing left to right: M. Regina Castro, M.D., Marius N. Stan, M.D., Mabel Ryder, M.D., Ian D. Hay, M.D., Ph.D., Jolanta M. Durski, M.D., Stefan K. Grebe, M.D., Ph.D., Michele M. Merton, R.N., C.N.P., George G. Klee, M.D., Ph.D., Vahab Fatourechi, M.D., and Hossein Gharib, M.D.