I’m going to particularly focus my talk this morning on the medical management of primary hyperparathyroidism. And I have no disclosures.

Just to give a general overview primary hyperparathyroidism is an extremely common endocrine disorder affecting 1 to 500 to 1 in 1000 people. It’s a hypercalcemic state by definition and it results from excessive secretion of parathyroid hormone. 80% of patients with primary hyperparathyroidism have a single parathyroid adenoma and about 20% have parathyroid hyperplasia, which can be associated either with a other syndrome, some of the MEN syndromes or just happen individually. Very rarely we see parathyroid carcinoma.

As I hope most people here know, most cases of primary hyperparathyroidism in this day and age are asymptomatic and are diagnosed simply when patients are found to have hypercalcemia on a routine chemistry panel. However patients still can have some of the skeletal and renal complications described in the past.

The diagnosis is established with lab tests. Patients need to be hypercalcemic although calcium can dip into the upper end of normal range and sometimes needs to be repeated to confirm the diagnosis. And it should be associated either with an increased PTH or an inappropriately normal PTH so if you have a patient who has a serum calcium of 10.8 it is not appropriate for them to have a PTH at 60 or
at the upper end of normal, that patient if they do not have primary hyperpara should have a PTH in the low end of normal.

Just so we are all again on common ground, I just want to emphasize that surgery is the treatment of choice for primary hyperparathyroidism in anybody who has symptomatic disease, in anybody who has asymptomatic disease and meets surgical criteria and I will review that this morning, and it must be done by an experienced and skilled surgeon. So the general surgeon who sees 1 or 2 cases or primary hyperparathyroidism a year is not the person you want operating on your patient. This is a patient that should be referred to a major medical center. We are very lucky here in Pittsburgh, we have not one but a whole group of endocrine surgeons who are experienced but clearly complications and outcomes are directly related to the number of cases that are done per year.

There was a workshop on primary hyperparathyroidism, the most recent one in 2008, the results of which were published in 2009 and I’m really going to base most of my recommendations on that today. So the learning objectives then are we are going to go over the guidelines for parathyroid surgery in asymptomatic patients. The management guidelines for patients who do not undergo surgery and focusing on that I’m going to particularly emphasize the role of the antiresorptive agents in preventing the skeletal complications of primary hyperpara and the role of Cinacalcet in normalizing PTH and calcium and whether that plays a role in the skeletal complications.
So what are the surgical criteria for asymptomatic primary hyperparathyroidism? Well to begin with the serum calcium should be greater than 1 mg/dl above the upper limit of normal. So that requires that you know the upper limit of normal for your assay. It ranges generally somewhere between 10.2 and 10.5 depending on which lab you use and this should be a corrected serum calcium, which means you should never be measuring the serum calcium without an albumin, every calcium should be corrected.

In previous recommendations a 24 hour urine calcium was used as a guideline for surgery and that is no longer recommended because there is not really a very good correlation between total 24 hour urine calcium and the incidence of renal calculi in these patients. There are some physicians however who still feel that a urine calcium greater than 400 mg per day is an indication for surgery, and as I’ll mention in a minute it’s important in the baseline evaluation of patients with primary hyperpara that you do get a 24 hour urine calcium.

Instead we’ve switched over to using a creatinine clearance, a calculated clearance of less than 60 as an indication of renal insufficiency due to chronic hypercalcemia. Bone mineral density should be done in all patients with primary hyperpara, it should be done at 3 sites, it should be done at the hip, the spine and this is probably the one indication where you should be getting a forearm bone density as well because often patients with longstanding hyperparathyroidism have as much cortical as trabecular bone loss and will often present with a lower bone density in the forearm than the other two sites. So a bone density T score of less than -2.5 at any site or a previous fragility fracture is an
indication for surgery in these patients. And in the younger patient, the premenopausal woman and a male less than 50 we would use a Z score rather than T score. And the age less than 50 has been a longstanding recommendation, the feeling being that we don’t want patients to live for 30, 40 years with chronic hypercalcemia.

Other things you need to consider in these patients are vitamin D deficiency. Vitamin D deficiency is extremely common in general populations, particularly in patients with primary hyperparathyroidism for reasons we don’t fully understand but it certainly may worsen their clinical picture. A 25, not a 125 but a 25 hydroxy vitamin D should be measured in all patients with primary hyperparathyroidism and it should be treated before making surgical or medical decisions. I use a cutoff of 30 as where I like their vitamin to be, some people would recommend somewhere around 20, but you need to replace vitamin D. There is always concern that if you replace vitamin D that you are going to worsen the hypercalcemia and really put these patients into hypercalcemic crisis. There have been a number of studies that have done that have looked at this and even in studies where they’ve given 50,000 units of vitamin D a week these patients do not become suddenly hypercalcemic.

In general primary hyperparathyroidism is not a disease of acute onset. I feel in most patients there is not a huge rush to decide what you are doing, so it’s fine to take your time in replacing the vitamin D in these patients. I often give 1 to 2,000 units a day and then monitor their vitamin D levels over
time. For some patients the calcium will go up a little bit and it might just tip them over that limit where they become surgical candidates.

I mentioned a 24 urine calcium before, while it’s not a surgical criteria it is essential that you get it to rule out FHH. You do not want to send a patient with FHH to surgery because surgery will not – is not indicated in those patients. So someone who has a very low urinary excretion of calcium probably does not have hyperpara. And renal imaging would only be indicated if you suspect that they have renal calculi, and we usually recommend starting simply with an ultrasound and then proceeding to CT if anything is seen on ultrasound.

Okay, now we’ll move onto how frequently you should monitor the patient. So the recommendation is that you get a serum calcium annually. I get it more often if I’m actively replacing vitamin D but once the patient is stable annually is probably adequate. We know looking at studies that have followed patients without surgery over time that while some patients will progress to develop and meet surgical criteria in general both calcium and PTH levels are relatively stable over time, so there is no real need to measure them more frequently. Once you’ve established the baseline 24 hour urine calcium and creatinine it is not recommended to repeat it unless clinically indicated. It is recommended to follow a serum creatinine annually and with that a creatinine clearance.

Bone density I think should be measured every 2 years, in the rare patient you might get it every year if they are sort of borderline and you are worried. But again if you look at longitudinal studies over
time about 10 to 20% of primary, patients with primary hyperparathyroidism will lose enough bone to meet surgical criteria over time, so it’s not something that you don’t want to monitor, but this does happen slowly so usually every 2 years is indicated, and again all 3 sites should be monitored, the hip, the spine and the forearm. Abdominal x-rays and ultrasound again are not indicated unless the patient has evidence of renal calculi or some other process going on.

So if you have a patient who has moderate to low bone density who is not undergoing surgery and usually this would be a patient who either refuses or who cannot undergo surgery because if they have very low bone density they do meet the surgical criteria, what is the effectiveness of using the antiresorptive agents in these patients as we would in say a typical postmenopausal patient with osteoporosis? There have been no large controlled trials done in this and there is absolutely no fracture data. To do a fracture study you need to study somewhere between 2000 and 5000 patients. The largest studies with primary hyperparathyroidism may go somewhere between 75 to 125, there is just no single institution or group of institutions that have enough patients with primary hyperpara to do the long term fracture studies.

But a number of small studies have been done that show them to be quite effective, and Alendronate is the agent that has been evaluated most extensively of all the bisphosphonates, but really all the bisphosphonate studies have pretty much similar data. Alendronate and the bisphosphonates suppress markers of bone turnover as you would expect in a typical osteoporotic patient. They’ve been shown to increase hip bone density anywhere from 4 to 5% and lumbar spine bone density
anywhere from 3 to 9% depending on the duration of therapy. With initiation of bisphosphonate therapy a lot of the studies showed an early decrease in serum calcium and an increase in PTH and there was some concern over this but in retrospective evaluation of this data many of the subjects in these studies were somewhat vitamin D deficient and this has not panned out to be a clinical issue. I’ll show you some of that. And usually it’s very transient.

Estrogen, another big antiresorptive agent, has also been shown to be quite effective and it’s interesting because postmenopausal females are the most common group of women, of patients to get primary hyperparathyroidism. So estrogen also suppresses markers of bone turnover, it’s been shown to increase hip and lumbar spine bone density as well as forearm significantly compared to placebo. Estrogen has also been associated with a small decrease in total serum calcium; however when you look closely there is no change in ionized calcium and no change in PTH and it’s thought that this change in serum calcium really just reflects a change in binding proteins as a result of the estrogen with no real clinical significance.

There have been two studies that have done that have looked at the role of parathyroidectomy which is extremely effective in increasing bone density and shown that estrogen is actually somewhat equivalent to parathyroidectomy in increasing bone density.

So these are the graphs from one of the many small bisphosphonate studies, and this is an old trial that was published in 2004 and this was a group of patients with hyperparathyroidism that either
received Alendronate for 12 months and then an extension for 12 months, or received placebo for the first 12 months and then Alendronate for the second 12 months. And you can see, this is the percent change in bone density looking at the lumbar spine, the hip, the femoral neck or the radius that whenever the subjects received Alendronate they had a significant increase in bone mineral density and we presume from our other large fracture studies in osteoporotic women that this correlates to a reduction in fracture; but again this has never been shown.

These show the changes in serum calcium and PTH that were seen in this study, and the placebo group is here in the squares and obviously they were stable for the first year. When they got Alendronate they have this little fall in serum calcium. When the Alendronate group started in the other treatment group they also had this small fall in calcium, but in both these groups within a few months it normalized. And again you can see there is an increase in PTH in the group that received Alendronate during the first year and an increase in the group that received it during the second, again not sustained and not to be thought of any clinical significance.

Given the ongoing concerns and debate over hormone replacement therapy in postmenopausal women the bisphosphonates are really the first line therapy to treat the skeletal complications of patients with primary hyperparathyroidism who do not undergo surgery, the duration of therapy that is needed is completely unclear as it is in the osteoporotic postmenopausal population at this time.
So how about Cinacalcet’s role in both normalizing PTH and calcium and potentially treating the skeletal complications as well? So this is a drug that I think people are a little bit less familiar with. Cinacalcet is a calcimimetic agent, it is not a true ligand but a sensitizer. It increases the sensitivity of the calcium sensing receptor in the parathyroid to extracellular calcium and by doing this it inhibits PTH secretion, it inhibits gene transcription and it inhibits parathyroid cell proliferation. It was mostly recently approved in the U.S. for treatment of severe and symptomatic hypercalcemic due to primary hyperparathyroidism. Previously it was only approved for the treatment of secondary hyperparathyroidism in patients with renal failure. Now that of course didn’t stop us from using it off label, but it’s nice to know that it is now approved which improves insurance approval.

So there have been a number of small studies done on Cinacalcet, the initial studies were done, there were 2 week dose escalation studies that shown that different doses given twice daily decreased serum calcium in 2 weeks by about 16%, with about a 30 to 50% decrease in PTH. And these studies have basically been done by various members of the same group.

They went on to do a large double blind placebo controlled trial, 52 week study, in 78 patients. So again for a parathyroid – primary hyperpara study this was relatively large. And they showed in 52 weeks that there was significant lowering or normalization of serum calcium in 78%, or 73% of the patients. It’s really interesting, this was associated with a decrease in PTH, but as I’ll show you graphically the PTH did not decrease into the normal range, it only decreased by 13%. There was an expected increase in serum phosphorus, although it was still in the normal range for most patients.
And interesting despite the normalization of calcium and the decrease in PTH there was no change in 125 vitamin D levels. No change in urinary calcium excretion, no change in markers of bone turnover and at one year there was no significant change in bone density. At the end of the one year trial there was an open label extension that extended out to 5 years, and that data was recently published and showed that in about 80% of the subjects treated over 5 years there was maintenance of normal serum calcium but again no affect on bone mineral density. The Cinacalcet was fairly well tolerated, the most common side effects were nausea and some musculoskeletal symptoms.

This graphically shows the results of the serum calcium. The patients that got placebo remained hypercalcemic, the patients that got Cinacalcet dropped into the normal range and the patients who got – all had high PTHs to begin with, and this came down with the treatment although did not normalize.

So to summarize, surgical monitoring criteria for asymptomatic primary hyperparathyroidism were updated in 2008, the medical options should be considered for those who do not meet surgical criteria or who cannot undergo parathyroidectomy. The bisphosphonates and estrogen effectively decreased bone turnover and increased bone density although neither significantly lowered serum calcium nor have a sustained effect on PTH. Therefore they are the treatment of choice for those in whom skeletal complications are the primary concern. Cinacalcet can be considered for patients in whom hypercalcemia is the primary concern for long term lowering of calcium and PTH; however it does not appear to have a beneficial effect on bone density. It is really important to replace vitamin D
before making a therapeutic decision and it’s really prudent to avoid situations that can worsen hypercalcemia such as dehydration, Hydrochlorothiazide therapy and immobilization. So I don’t know if I have any time for questions or – okay, thank you.