



**CALIFORNIA CHAPTER OF THE
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS**

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Editor: Herbert I. Rettinger, MD, FACE

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PRESIDENT'S MESSAGE

Dear Colleagues:

On November 9-11, 2007, the California chapter of AACE held its 7th Annual Meeting (this year in the LA area). The quality of faculty was outstanding and typical of national meetings. We had over 110 members from the Western Consortium of states attend along with an excellent turnout from our endocrine fellows in training. The attendee feedback was extremely positive and one third of those attending took advantage of the opportunity to wear a subQ CGMS for 36 hours. The Saturday afternoon highlight was a 2-hour session on thyroid cancer that offered varying opinions by Ian Hay, Orlo Clark and Alan Waxman. The Saturday eve social event was the best ever and I think everyone agreed that it was an outstanding weekend with just the right mix of didactic information and social camaraderie. Special thanks to the Program Committee led by Herb Rettinger.

Preparations are underway for next year's meeting in early November, to be chaired by Mike Bush, and located for the first time in "The OC".

I wish you all a very Healthy and Happy 2008.

Laurence A. Gavin, MD, FRCP, FACP, FACE,
President, California Chapter of AACE

Lipid Metabolism

Dr. Thomas Dayspring kicked off the seventh annual CA-AACE meeting and symposium with a provocative and fast-paced review of lipid metabolism. Transportation of lipids within lipoproteins represents a very dynamic process that is not always reflected well in a standard lipid profile. In atherosclerosis, there is a relative and absolute increase in beta-lipoprotein particles even when total blood cholesterol or LDL-C is normal.

Apo-B represents a marker of the number of atherogenic lipoproteins as there is one molecule of Apo-B on each beta-lipoprotein particle (chylomicrons, VLDLs, IDLs & LDLs). Apo-B thus represents a surrogate of LDL particle concentration (LDL-P). LDL-C or non-HDL are the lipid concentration estimates of Apo-B or LDL-P. This relationship weakens when LDL-C is <100 and the predominant LDL species are small TG-rich or otherwise cholesterol depleted. Apo-A1 is a surface protein enwrapping HDL; HDLs can lipidate (acquire cholesterol) at any tissue but do so primarily at the proximal small bowel and liver. Small HDL molecules initiate lipidation and then mature into larger species. An increase in HDL from 20→40 is due to increase in number of these small HDL particles; at levels > 40, HDL molecules are larger and fluffier (lipid-laden) and less efficient in delipidation. HDL molecules are thus in a continual state of flux, not reflected in standard lipid testing. Apo-A1 levels should ideally be in 130-140 range.

An increase in the Apo B/Apo A-1 ratio (>.75) is strongly associated with cardiovascular disease risk. Dr. Dayspring explained that the number of LDL particles (LDL-P) was more strongly related to cardiovascular disease than LDL size or LDL-C. The dyslipidemia of diabetes and the metabolic syndrome is an Apo-B mediated process often related to triglycerides (ideal level <70). Treatment should be aimed at normalizing non-HDL cholesterol; once at goal, then Apo B or LDL-P should be pursued to promote vascular health. He emphasized that particle size no longer seems as relevant as particle number (LDL-P can now be run by many labs) in determining a lipid-related cardiovascular risk.

Submitted by Vas Narayan, M.D., 2nd year Endocrine Fellow, UCLA/VA.

Managing Osteoporosis: Beyond DXA

Michael Kleerekoper gave a wonderful talk on osteoporosis, defined as a skeletal disorder characterized by compromised bone strength, predisposing to an increased risk of fracture. Contributors to bone strength include not only bone density, but also bone turnover, mineralization, and architecture.

Bone turnover has been determined to be an independent risk factor for fracture. It is regulated by many genes and involves the breakdown of cross-linked collagen into individual components, some of which may be measured in the serum and used as bone turnover markers (BTM). Resorption markers include N-telopeptide and C-telopeptide, while markers of formation include P1NP, P1CP, TRAPc5B, and BSAP. Several clinical studies, including McClung (*NEJM 2006*) with denosumab (an osteoclast ligand antibody), and Black (*NEJM 2007*) with zoledronic acid, have demonstrated that without active therapy for osteoporosis, bone density continues to decline, while there is no change in BTMs; active therapy, however, results not only in an increase in bone density, but also a decline in N- and C- telopeptides (serum or urine).

He stressed that while BTMs should not be used to diagnose osteoporosis, it has great utility for early and reliable feedback for the effectiveness of osteoporosis therapy, as well as monitoring of “drug holidays”. One approach measures bone density via DXA as well as a BTM at baseline. Approximately 3 months after osteoporosis therapy is initiated, BTM should be rechecked; success of therapy is marked by a 30-50% decline. If not, causes for failure of therapy should be sought, such as medication compliance, secondary causes of osteoporosis, and possible need for treatment changes. If the appropriate decline occurs, treatment should be continued, and a repeat DXA and BTM should be checked at the 2-year mark. If lack of further bone loss is confirmed by the repeat DXA, the patient may be a candidate for a “drug holiday”, where treatment is temporarily held and BTM is measured at 3, 6,

and 12 months; therapy should be restarted as soon as a rising BTM is noted. Dr. Kleerekoper reminded us that BTMs may exhibit a diurnal pattern; levels should therefore be checked in the morning after an overnight fast. In addition, assays are not necessarily standardized between manufacturers, which may allow for variability in results.

Submitted by Sonia Ralli Grewal, MD, 1st year Endocrine Fellow, UCI.

Cushing's Syndrome

Dr. Lawrence Crapo gave a stimulating talk on Cushing's syndrome (CS). It is often difficult to diagnose as the clinical features can be deceptive and nonspecific (obesity, weight gain, hirsutism, irregular menses, hypertension and diabetes). Discriminate features include osteoporosis, muscle weakness and ecchymosis, while cardinal features include Cushingoid appearance and wide purple striae.

Subclinical Cushing's syndrome (SCS), defined as biochemical evidence of mild CS in setting of adrenal incidentaloma or selective screening of CS, has a prevalence of 2.9-18% with the wide range due to the variable definition in each study. The debate of whether patients with SCS and adrenal incidentaloma should have adrenalectomy lies in the variable clinical features, lack of data on long term morbidity and mortality in these patients, the rarity of progression to overt CS, and the paucity of data relating SCS with CV risk factors including glucose, lipid abnormality and hypertension. The incidence of SCS discovered on selective screening has reported to be low.

He suggested that LNSC (late night salivary cortisol) is not a reliable test for screening given the high prevalence of false positives. Definitive diagnosis of CS may be difficult. There is considerable overlap in the lab results of patients with CS and those without. Therefore, there is no test that will be able to provide 100% diagnostic accuracy. Daily urinary free cortisol (UFC) originally reported excellent sensitivity and specificity; however, more recent studies have shown wide variation in sensitivity and specificity (stress and depression may give false positive results). Dexamethasone suppression test, either with the overnight suppression (ONDST) or 2-day low dose (LDDST), is also subject to variations in sensitivity and specificity, and most recent studies show significant limitations with low specificity. Late night salivary cortisol (LNSC) and plasma cortisol (LNPC) have been evaluated in many studies with varying sensitivities and specificities due to variation in cut off values. The combined Dexamethasone/CRH test (Dex/CRH) again shows a wide range of diagnostic accuracy.

ACTH-dependent cases (80% of etiologies, and ACTH >15 pg/ml) include Cushing's disease (CD) (85%), ectopic ACTH syndrome (EAS) (15%), or ectopic CRH syndrome (rare). ACTH-independent cases (20% of etiologies, and ACTH <5 pg/ml) include adrenal tumor (95%) or nodular adrenal hyperplasia (5%). High dose dexamethasone suppression test (HDDST) and CRH test may be used to differentiate CD from EAS, however, Dr. Crapo cautioned that considerable overlap exists. Inferior Petrosal sinus sampling (IPSS) is the gold standard for distinguishing CD from EAS; however, this test is invasive and often difficult to perform.

Tumor localization employs use of CT scan or MRI of the adrenals for ACTH-independent CS and MRI of the pituitary, lung or abdomen for ACTH-dependent CS. Somatostatin receptor scintigraphy (SRS) may be useful for localization of ectopic tumors. FDG-PET scan is not currently recommended due to lack of studies to substantiate its utility in evaluation of CS.

Submitted by Emily Tan, M.D., 2nd year Endocrine Fellow, UCLA/VA.

Thyroid Cancer

Use of I-131 for treatment PTC:

Dr. Ian Hay (Mayo Clinic) pointed out that PTC: represented more than 80% of clinically recognized cases of follicular cell-derived carcinomas; is a disease of people in 40s, and usually presents with a mean size at diagnosis of 2.1+/- 1.6cm. The newer thinking at Mayo Clinic is to use a selective approach to RRA (radioactive remnant ablation); its use is restricted to those patients with high risk PTC (metastasis, age, completeness of resection, invasion, size - MACIS score of 6 or greater or those with Follicular or Hurtle cell carcinoma). The preferred primary surgical treatment for FNA-diagnosed PTC remains total or near-total thyroidectomy. He also recommends a pre-operative US of the neck with identification of metastatic nodes that will allow the planning of an appropriate nodal resection at the time of the initial neck exploration. This may then include central node dissection with a sampling of level VI nodes. Radioiodine therapy should not be used as an alternative to an inadequate primary surgery.

In low risk patients with PTC (MACIS score <6) there was little difference in outcome, mortality rate (1% in 40 years) and recurrence between those having surgery alone or surgery followed by I-131 treatment. Thus I-131 should be given to patients with MACIS score > or equal 6 and to those with Hurtle or Follicular cell thyroid cancer.

The role of nuclear Medicine in the Management of Thyroid cancer

Dr. Alan Waxman from Cedars-Sinai suggested I-131 tx for patients with >15mm of tumor size (smaller if unfavorable histology, or lymphatic or vascular invasion), multifocal presentation or for tumors with capsular invasion. Elderly patients, patients with Struma Ovarii and patients with metastasis require aggressive therapy. He pointed out that I-131 is not contraindicated in the pediatric population.

He recommends 100 mCi for treatment of the thyroid bed and doses up to 200 mCi for those with mets outside the neck nodes. Patients with local nodular mets or capsular invasion may be best served with 150-175 mCi. Post treatment scans can be done within 5-10 days under most circumstances.

He suggested that a PET positive scan indicates poor prognosis as uptake increases as tumor becomes less differentiated.

Surgical Insight

Dr. Orlo Clark added insight from a surgical standpoint. DTC has the 2nd highest mortality in endocrine tumors after ovarian. Initial assessment of the tumor is important and it can be assessed using MACIS, AMES, AGES, or TMN. He pointed out that 7% papillary cancer, 14% follicular thyroid cancer, 21% Hurtle Cell cancer and 28% of those with medullary cancer die within 10 years after diagnosis of their disease.

Patients at higher risk have:

- Distant metastasis
- Locally invasive tumor
- Large tumor size
- men > women
- high tumor grade
- Familial PTC (3x more aggressive)

- Older age
- multifocal
- Recurrent or persistent tumor
- failure to suppress TSH
- Inadequate operation
- failure to use I-131 when needed

He reported that 80% of patients with PTC usually have one of the following mutations: BRAF (40% of papillary tall cells and tumors with lymph nodes metastasis); RET/PTC (present in 80% PTC in children); RAS; TPK.

Dr. Clark suggested diagnostic lobectomy as a treatment option for FNA that is suspicious for malignancy. He also recommended US as part of pre-op evaluation as this helps determine extent of surgery. If tumor size is > or equal to 1cm, total thyroidectomy has better outcomes. For smaller tumors, a lobectomy may be sufficient. Stimulated thyroglobulin levels plus ultrasound of the neck may eventually replace whole body scans.

Submitted by Jhanna Nariyants, M.D., 2nd year Endocrine Fellow, UCSD.

PCOS

Dr. Ricardo Azziz (Cedars-Sinai) gave a stimulating talk on polycystic ovary syndrome (PCOS), the most common endocrinopathy of reproductive age women. There are many criteria formulated by various groups including the NIH, Rotterdam and Androgen Excess Society (AES) to characterize the phenotypes of PCOS. The NIH (1990) include 3 criteria: hirsutism/hyperandrogenism, ovulatory dysfunction and polycystic ovaries. The Rotterdam criteria (2003) only require 2 out of the 3 criteria, while the AES (2006) does not require ovulatory dysfunction.

The role of obesity in PCOS has been controversial. It was concluded that obesity itself does not drive the epidemic of PCOS, but can minimally increase its risk.

The most bothersome aspect of PCOS to patients is likely hirsutism (evaluated using a modified Ferriman/Gallwey scoring system) and hyperandrogenism. Dr. Azziz cautioned that there are other disorders associated with hirsutism and hyperandrogenism and one should rule out: non-classical adrenal hyperplasia, androgen secreting tumors, drug-induced hirsutism and syndromes of severe insulin resistance (i.e. HAIRAN - HyperAndrogenism, Insulin Resistance, Acanthosis Nigricans).

Since vaginal bleeding does not necessarily equal ovulation (especially in the presence of hirsutism), a progesterone level should be checked at day 22-24 in the cycle. Sonographic evidence for polycystic ovaries involves specific criteria that can change dramatically if the patient is on oral contraceptives.

Metabolic evaluation of PCOS should include the following: FBS (or other testing to r/o T2DM), fasting insulin level, and a lipid profile (to r/o dyslipidemia).

Treatment of PCOS should include a combination therapy approach to address the dermatologic issues (hirsutism, acne and alopecia), ovulatory issues (dysfunctional uterine bleeding/amenorrhea or endometrial hyperplasia/cancer), infertility issues and metabolic issues (dyslipidemia, obesity and glucose intolerance/insulin resistance). These may include: electrolysis, laser hair removal, shaving, chemical depilation and bleaching. Plucking and waxing is not recommended. Androgen blockage can be achieved with spironolactone - caution is advised since it is a known teratogen. Oral contraceptives should be considered concurrently with spironolactone if there is concern for potential pregnancy.

Oral contraceptives also help in regulating menses and decreasing free testosterone by: (1) increasing SHBG and (2) decreasing LH secretion. In conclusion, PCOS is a common and chronic condition that requires a combination therapy approach.

Submitted by Sandra Kwak, M.D., 2nd year Endocrine Fellow, UCI

OBESITY

Dr Michael Bush discussed the treatments available for obesity noting that endocrinologists understand the implications and the mechanisms of obesity better than other specialists. Our environment has become very adipogenic secondary to the abundance of food and the small percentage of people that exercise regularly. Diet is an important aspect in management, but adherence is usually poor. Most effective is a diet combined with behavior modification therapy and perhaps the use of pharmacological agents. A 5% drop in weight/yr should be an attainable goal.

Medications such as sibutramine and orlistat have been used with success especially with behavior modification. Weight loss of approximately 8 lbs can be expected with treatment. Dr Bush noted that in very large doses, increased adrenergic side effects were noted. Orlistat interferes with breakdown of triglycerides into glycerol and fatty acids; a 60mg is available over the counter. Adding Orlistat after 1 year of sibutramine did not produce any significant change.

Off label uses of drugs for weight loss were also mentioned including bupropion, topamax, zonegran, pramlintide and exenatide. Endocannabinoid receptor inhibitors have been studied but rejected this year by the FDA.

Dr Bush touched on frontiers of endocrinology and obesity including gastrointestinal neuroendocrinology and the actions of leptin, ghrelin and PYY.

Submitted by Monica Schwarcz, M.D., 2nd year Fellow Harbor-UCLA.

Bill Zigrang gave a talk on getting paid in difficult times. He pointed out a complete endocrine 'patient encounter form' that contained all the information needed for Medicare payment. This can be downloaded and personalized from the CALAACE web site at calaace.com. (user = aace / password = ca)

Editor's Note: If you have managed-care contracts tied to current Medicare payment schedules, consider revising them to a set dollar amount or to a prior year fixed schedule. There is a good chance that M/C payments will decrease and, therefore, your reimbursement along with it.