What's Inside

MESSAGE FROM THE PRESIDENT

To all CA AACE chapter members:

I hope that all of you and your families are safe and well in the face of, unfortunately, rising COVID case numbers and infection rates in our state. I hope that your practices are not hindered in too great of a manner. For those who were able to log on to and attend the Medicare and telemedicine webinar that was given in May for our chapter by Dr. Arthur Lurvey, I hope that you found this valuable. This will be my final letter to you all as your chapter's president because, in September, our officer positions and chapter Board of Directors will be turning over as per our chapter bylaws, and my term will come to an end.

This brings me to the primary purpose of this letter which is to remind everybody, as per e-mail invitations that have already been sent out by our Association Management Company, W.J. Weiser, that our annual chapter meeting is approaching in September. As you all, hopefully, know by now per those invites, our meeting will be held in a virtual fashion. Our Annual Meeting program committee, chaired by Drs. Patricia Wu and Adrienne Nassar, is busy creating what I believe will be allow for continued delivery of the educational experience that you have all come to expect from our annual gathering but in a virtual and safe format that is mandated by our COVID situation. This meeting will be held during the same weekend in September, with the same agenda of talks, and, hopefully, with the same speakers as were to be held live. Registration fees are to be halved (a change from the original e-mail invite) out of respect for financial constraints possibly being experienced by some members. At our Business Meeting held on the Saturday morning, the results of the deliberations by our chapter's Nominating Committee, vis a vis officer and Board turnover, will also be displayed for membership approval.

With that said, I hope to "see" everybody in September. CME and MOC credits will still be offered. If there are any questions or concerns that arise before then, please feel free to reach out to me, as always. My e-mail address is Levine.Matthew@scrippshealth.org.

Matthew J. Levine, MD, FACE
President, CA Chapter of AACE
Scripps Clinic, Division of Diabetes/Endocrinology
Endocrinology Fellowship Director, Scripps Clinic/Scripps Green Hospital

NEW LEADERSHIP

Officer positions for the years 2020 - 2022 as selected by the Nominating Committee and approved by the Board of Directors are as follows:

- PRESIDENT
  Jane Weinreb, MD
- VICE PRESIDENT
  Dianne Cheung, MD, FACE
- TREASURER
  Jennifer Han, MD, FACE
- SECRETARY
  Priya Shah, MD, FACE
- IMMEDIATE PAST PRESIDENT
  Matthew Levine, MD, FACE

Board of Directors 2020 - 2022

- Renil Rodriguez-Martinez, MD
- Jody Hawkins, MD, FACE
- Patricia Wu, MD, FACE
- Jaiwant Rangi, MD
- Chris Guerin, MD, FACE
- Vasanthi Narayan, MD

Contact Us

California Chapter of AACE
Two Woodfield Lake
1100 E Woodfield Road
Suite 350
Schaumburg, IL 60173

(847) 517-7225

ca-aace@wjweiser.com

Follow us on Facebook

Follow us on Twitter

Follow us on Instagram

CALIFORNIA AACE 2020 ANNUAL MEETING - **VIRTUAL**!

We are holding our 20th Annual Meeting and Symposium for the California Chapter of AACE virtually this year! The meeting will take place on **September 12 - 13, 2020**. The agenda promises to be very educational and exciting and we hope to see you there!

REGISTRATION

Endocrinologists, MDs / DOs, advanced practice clinicians, and other healthcare professionals interested in the treatment of endocrine disease will benefit most from the CA AACE Annual Meeting.

Registration prices have been reduced to help accommodate the difficulties many are facing during this time.

AACE Member Physician $50

Non-AACE Member Physician $50

Nonphysician Provider (APA, NP, PA).....$50

Fellows Program Director $0

Fellow, Resident, or Medical Student.....$0

We hope you'll join us. Register online today. Registration will remain open until Tuesday, September 8 at noon.

INDUSTRY SUPPORT

The California Chapter of AACE would like to acknowledge and thank the following organizations and companies that have provided or pledged support for this educational activity.

Thank You to Our 2020 Promotional Partners

PLATINUM LEVEL

AstraZeneca Lilly Rhythm PHARMACEUTICALS

GOLD LEVEL

veracyte

PROGRAM COMMITTEE

Adrienne A. Nassar, MD, FACE (Program Co-Chair)

Patricia Shen-Chi Wu, MD, FACE (Program Co-Chair)

Karen E. Earle, MD

Matthew J. Levine, MD, FACE

Tina Mosaferi, MD

Zoe Quandt, MD, MS

Renil M. Rodriguez Martinez, MD

Priya K. Shah, MD, FACE, ECNU

Lauren H. Stieger Clarine, DO

Jane E. Weinreb, MD

Register online at endoconnection.com/ca

PROGRAM FACULTY

Richard J. Auchus, MD, PhD
Michigan Medicine Temporary Metabolism, Endocrinology and Diabetes - Taubman Center

Timothy S. Bailey, MD, FACP, FACE, ECNU
AMCR Institute

Pauline Camacho, MD, FACE
Loyola Medicine

Raymond Douglas, MD, PhD
Beverly Hills, California

Sergio Fazio, MD, PhD
OHSU Knight Cardiovascular Institute Cardiology Clinic, Beaverton

Michael Greger, MD, FACLM
NutritionFacts.org

Chris K. Guerin, MD, FACE
AMCR Institute

Bryan McIver, MD, PhD
Moffitt Cancer Center

Sunder Raj D. Mudaliar, MD, FACE
UC San Diego

Rashmi S. Mullur, MD
UCLA Health

Adrienne A. Nassar, MD, FACE
Kaiser Permanente

Roger L. Sur, MD
UC San Diego

Patricia Shen-Chi Wu, MD, FACE
Kaiser Permanente

PROGRAM DISCLAIMER

The material presented during the California Chapter of AACE annual meeting is being made available by the California Chapter of AACE for educational purposes only, and does not necessarily represent the only or best method or procedure appropriate for the medical situations discussed. The opinions and views expressed represent the opinions of the presenters and not necessarily those of the California Chapter of AACE, AACE, or its governing body. Therefore, the California Chapter of AACE and AACE disclaim any and all liability for injury or other damages resulting to an individual attending this meeting or to any third party for claims based upon the use of techniques and/or products presented by any party at this meeting.

California Chapter of AACE

20TH ANNUAL MEETING & SYMPOSIUM
SEPTEMBER 12 - 13, 2020

Virtual Meeting

SCHEDULE AT A GLANCE

Speakers and times are subject to change

SATURDAY, SEPTEMBER 12, 2020

8:00 a.m. - 8:10 a.m.	**Welcoming Remarks**
8:10 a.m. - 8:20 a.m.	**Pre Meeting Assessment**
8:20 a.m. - 9:15 a.m.	**2020 AACE/ACE Postmenopausal Osteoporosis Treatment Guidelines Updates**
9:15 a.m. - 10:10 a.m.	**Lipid Updates / Management**
10:10 a.m. - 11:10 a.m.	**Industry Sponsored Symposium***
11:10 a.m. - 12:05 p.m.	**Thyroid Eye Disease**
12:05 p.m. - 12:25 p.m.	**Annual Business Meeting**
12:25 p.m. - 1:25 p.m.	**Industry Sponsored Symposium***
12:25 p.m. - 1:25 p.m.	**Fellows Luncheon / Meeting**
1:25 p.m. - 2:20 p.m.	**Personalized and Precision Approaches to Thyroid Cancer Treatment: Making the Punishment Fit the Crime**
2:20 p.m. - 4:55 p.m.	**Nutrition Symposium**
2:20 p.m. - 3:00 p.m.	**Evidence Based Weight Loss**
3:00 p.m. - 3:40 p.m.	**Plant Based Diets for DM & CVD Reversal: Fad or Fabulous?**
3:40 p.m. - 3:45 p.m.	**Break**
3:45 p.m. - 4:25 p.m.	**Common Supplements Use by Endocrinology Patients: Facts and Myths**
4:25 p.m. - 4:55 p.m.	**Q & A**

SUNDAY, SEPTEMBER 13, 2020

8:00 a.m. - 8:10 a.m.	**Pre Meeting Assessment**
8:10 a.m. - 9:00 a.m.	**Neuroendocrine Tumor Imaging**
9:00 a.m. - 9:50 a.m.	**Diabetes Technology Update**
9:50 a.m. - 10:50 a.m.	**Industry Sponsored Symposium***
10:50 a.m. - 11:40 a.m.	**The Deadly Triad - Diabetes, CVD and CKD. Can the Newer DM Medications Help?**
11:40 a.m. - 12:30 p.m.	**Dietary Management of Nephrolithiasis**
12:30 p.m. - 12:40 p.m.	**Post Meeting Assessment**
12:40 p.m. - 12:45 p.m.	**Closing Remarks / Adjournment**

**Not CME Accredited*

Register online at endoconnection.com/ca

CA AACE 2019 ANNUAL MEETING SYNOPSES OF PRESENTATIONS

Special thanks to the Endocrine Fellows from UCSF, UCSD, UCI, Scripps and UCLA!

Fellows will be able to join our annual meeting for free! Please email jhan@mednet.ucla.edu for further information to attend for FREE!

Also thanks to all the attendees for making this an amazing conference! We cannot wait to see everyone VIRTUALLY this September 12 - 13, 2020.

Please visit the CA AACE Meeting Page for registration!

Jennifer Han MD, FACP, FACE
CA AACE Newsletter Chair

LIST OF PRESENTATIONS

The Path to Preventing Type 1 Diabetes

Speaker: Sandra Weber, MD

Synopsis written by: Jane Rhyu, MD (UCLA)

The traditional model of the natural history of type 1 diabetes (T1DM) describes an underlying genetic predisposition followed by an insult leading to beta cell injury and insulitis and development of cellular T cell autoimmunity and autoantibodies. The model then describes loss of first phase insulin with progression to prediabetes, followed by T1DM. The Diabetes Prevention Trial - Type 1 (DPT-1), which started in the early 1990's, has provided further insight into the natural history of T1DM. The study shows that once two or more autoantibodies form, the majority of patients develop T1DM over the course of six years. ICA and GAD antibodies are present in up to 80% of patients with T1DM, with other antibodies being present in lower frequency.

Trial Net thus redefines T1DM as a disease of islet autoimmunity. In the newer model, T1DM starts with a genetic predisposition, followed by immune activation when beta cells are attacked, and subsequent immune response with formation of one autoantibody. Trial Net defines stage 1 as the presence of two or more autoantibodies with normal blood glucose, at which time the destructive process of the beta cell has already begun with eventual progression to T1DM. Stage 2 is defined as prediabetes, and stage 3 is defined as overt T1DM. Notably, the earlier in life the antibodies develop, the faster the development of T1DM. Puberty appears to be an important cut point, after which T1DM progression is more prolonged. The incidence of T1DM is projected to continue to rise in a linear fashion, highlighting the importance of preventing or delaying onset of this disease.

Pathogenesis of T1DM involves genetics, environment, and the immune system. Treatment targeting genetics would be difficult as T1DM involves polymorphisms in multiple genes, with HLA alleles (DRB1, HLA-DQB1, and HLA-DQA1) conferring the greatest risk. Interestingly, HLA DQB1*0402 is protective against T1DM. However, even if genetic treatments were to advance with ability to confer a protective mutation, it would be difficult to target somatic mutations in multiple cell lineages. Myriad studies also have investigated environmental triggers, given that T1DM patients have no family history in 85-90% of cases. More than 200 studies have been performed in the NOD diabetes mouse model. However, TRIGR (Trial to Reduce IDDM in the Genetically at Risk) modeled a trial after a NOD mouse study that showed a protective effect from T1DM by using hydrolyzed weaning formula. TRIGR showed no difference in T1DM risk in infants randomized to weaning to hydrolyzed casein formula versus regular intact cow's milk over 11.5 years. The TEDDY trial (The Environmental Determinants of Diabetes in the Young) prospectively followed over 8,000 children with increased genetic risk of T1DM. The study showed that GI viral infections at age 4 years or younger were associated with increased risk of islet autoimmunity. Other studies have shown in-utero exposure to rubella and mump and early neonatal exposure to mumps, rotavirus, and CMV to be linked to T1DM. 30% of patients with congenital rubella develop T1DM with an incubation period of 5-20 years. These studies emphasize the importance of vaccination, and T1DM has notably not been associated with MMR vaccination. Studies on immune modulation after T1DM onset have also shown that cyclosporine A, rituximab, and abatacept can prolong insulin production.

The focus of T1DM prevention is now shifting towards immunomodulation of patients with beta cell injury and autoantibodies at the time of euglycemia. By the time T1DM prediabetes develops, delay or prevention trials have not yet been successful. Moreover, drugs introduced prior to development of clinically evident disease may be both more effective and less toxic. Trial Net is the first trial to show that immune therapy can be used to delay onset of T1DM. Trial Net was established in 2001 and enrolls 15,000 subjects/year at increased risk for diabetes. 10-12% of patients per year develop T1DM. As part of the Trial Net intervention, 76 high risk, autoantibody positive, non-diabetic relatives of patients with T1DM were randomized at the mean age of 13-14 years to a single 2 week treatment with teplizumab, an anti-CD3 monoclonal antibody. Treatment with an anti-CD3 mAb had been shown to reverse diabetes in 80% of diabetic NOD mice with long-lasting effect that did not require continued treatment. In the study, 43% of patients treated with teplizumab developed T1DM versus 72% of those patients receiving placebo. The delay in median time to diabetes in the teplizumab group was 2 years. There was a decrease in lymphocyte count in the teplizumab group within the first 8 days of treatment without significant adverse effect. Interestingly, various subgroups and certain HLA-types had a particularly robust response to teplizumab, and can be potentially identified at screening in the future. Trial Net is also developing a new biomarker for the active rate of beta cell death called beta cell-derived insulin encoding DNA (INS DNA), which can be measured in the circulation. Through studies on early immunomodulation and improved biomarkers for T1DM, the hope is to monitor and improve beta cell health status during prevention and intervention studies.

Thyroid Nodule Evaluation in the Era of Multiple Diagnostic Options

Speaker: Susan J. Mandel, MD, MPH

Synopsis written by: Preethika S. Ekanayake MD (UCSD)

Dr. Susan Mandel MD from University of Pennsylvania discussed the patient specific and nodule specific factors that play into making an informed, patient-centered decision about when to consider performing Fine Needle Aspiration (FNA) for thyroid nodule. In the last 20 years, there has been an increase in detection of thyroid cancer in developed areas in the world, but this increase is mainly attributed to detection of thyroid cancers that are <2cm, predominantly attributable to increased FNAs being performed by clinicians for nodules incidentally detected on imaging studies.

Currently there are several very well validated systems

in place look at constellation of sonographic patterns such as composition, echogenicity, shape, margins, echogenic foci. Two systems discussed were the American Thyroid Association's pattern-based atlas to predict risk of malignancy, and the American College of Radiology's TI-RADS guidelines 2017, which is a sum of points-based classification system for 5 ultrasound features mentioned above (composition, echogenicity, shape, margins, echogenic foci). Both systems help guide clinicians and patients to decide when to perform a FNA for an incidentally found thyroid nodule based on constellation of sonographic characteristics present within the nodule. Patient comorbidities, age, family history of thyroid cancer and personal history of neck radiation also factor into the decision to proceed with FNA in the ATA system but not in TI-RADS.

Notably, ACR's TIRADS has a higher threshold to observe the same nodules that ATA classified as "intermediate suspicious" (TI-RADS 4) until they are greater than or equal to 1.5cm in size, in contrast to the ATA recommendation for FNA when these nodule size exceeds 1cm. Similarly ACR-TIRADS recommend FNA for "low suspicious" nodules (TI-RADS 3) if size is greater than or equal to 2.5cm, in contrast to ATA recommendation for the same type of nodules to be biopsied at greater than 1.5cm. ACR-TIRADS also recommends observation or FNA when size greater than 2cm for those nodules classified as "very low" suspicion by ATA (TIRADS 2). Both TIRADS and ATA recommend biopsy for "high suspicion" (TIRADS 5) when nodule size is equal to or greater than 1cm.

Dr. Mandel quoted a Korean study by *Ha et al* published in *Radiology 2018* which compared the biopsy rate and diagnostic accuracy of ATA and ACR TI-RADS applied to 2000 nodules greater than 1cm and found that ATA driven biopsies had higher sensitivity (91%) but lower specificity (33%) due to the lower FNA size cutoffs. However when ATA guidelines were modified by delaygin biopsy of those "low suspicious" (i.e. TI-RADS 3) nodules until they are at least 2cm or greater, and avoiding biopsy of "very low suspicious" (i.e TI-RADS 2) all together, led to an increase in ATA specificity to 50% from 33% without affecting sensitivity (89% sensitivity for ATA with modifications compared to 91% for ATA without TI-RADS modifications applied). Italian study by Grani et al published on Journal of Clinical Endocrinology Metabolism 2019, looking at 502 nodules over 1cm showed that by applying ACR TI-RADS, clinicians were able to avoid FNA 53% of time with false negative rate of 2.2%, whereas application of ATA atlas avoided FNA 44% of the time with false negative rate of 3.1%.

The second half of Dr. Mandel's talk discussed the Bethesda classification for thyroid cytology after FNA, and how to utilize the same sonographic characteristics per ATA and/or ACR TI-RADS for future management, decision making when cytology back as nondiagnostic (Bethesda I), benign (Bethesda II), AUS/FLUS (Bethesda III), or Follicular neoplasm (Bethesda IV). Bethesda V, VI, which are suspicious for malignancy and malignant carry 50-99% risk of cancer, can proceed directly to surgery. However using sonographic characteristics when cytology showing Bethesda classes I-IV can be of utility to guide management. For an example, nondiagnostic cytology results on an already biopsied nodule with 1 or fewer suspicious US features, can be followed rather than re biopsy as cancer rates are less than 2% when overlaying cytology with sonographic pattern. However, nondiagnostic cytology on a nodule that has high suspicion pattern per ATA atlas or ACR-TIRADS 5, ATA 2015 guidelines recommend surgical consideration. Moreover, important to note that benign cytology on a nodule with 3 or more individual ultrasound features (ATA high suspicion or TIRADS 4) should warrant repeat US and FNA within 12 months given higher false negative rates despite benign cytology. Growth is not a good predictor of missed malignancy in cytologically benign nodules if the sonographic pattern is not suspicious.

For Bethesda class III and IV (AUS/FLUS or follicular neoplasm), the use of sonographic pattern also greatly modifies associated cancer risk. For an example, Bethesda III/IV nodule that appear to be spongiform, does not be re-biopsied as it likely did not need a FNA to begin with. However, most nodules that underwent appropriate FNA with resulting cytology diagnosis of AUS/FLUS or follicular neoplasm, carries an overall risk of 26% of cancer, and this risk amplifies based on the number of concerning sonographic patterns present. This is where molecular testing is of use. To summarize, in nodules with Bethesda III/IV cytology after first FNA, the absence of molecular finding on a repeat FNA decreases cancer risk, preventing the need for unnecessary surgery; and the presence of molecular findings increases cancer risk, which would necessitate surgery. Commonly used commercially available molecular tests with multicenter blinded study validation are Afirma Gene sequence classifier 2017 and ThyroSeq v3, While negative predictive value is high in 98%, positive predictive value is around 55-65%. However, by using highly validated sonographic patterns, combined with molecular markers, and patient characteristics and comorbidities, endocrinologists can guide their patients toward the best option for management of thyroid nodules without the need for unnecessary FNAs or unnecessary lobectomy/thyroidectomy.

Menopause Hormone Therapy: WHI or WHI Not, Lessons from the Past Decade

Speaker: Chrisandra Shufelt, MD, MS, FACP, NCMP

Synopsis written by: Karen C. Wu M.D. (UCSF)

The idea of using hormone therapy (HT) for cardioprotection stemmed from the hypothesis that the decline in estrogen level during menopause is associated with accelerated cardiovascular disease (CVD), therefore replacing estrogen would reverse this. This hypothesis was also supported by both animal and observational studies that found women on HT had ~40-50% lower rates of CVD. It will not until the 1990's however, when this was tested in a double-blind placebo-controlled randomized clinical trial. The Women's Health Initiative (WHI), was designed to try to answer this question – does HT prevent heart disease as well as other

chronic diseases? The WHI was made up of 2 separate trials of conjugated equine estrogen (CEE) alone or placebo if women had a hysterectomy (~10,000) or CEE in combination with medroxyprogesterone acetate (MPA) in women had an intact uterus (~16, 000). The choice for the type and dose of HT used in the WHI was based on most commonly available HT formulation at the time of study initiation. To most people's surprise, the result of the WHI is not concordant with the observational studies in its primary outcome, showing a higher relative risk in coronary heart disease in those randomized HT. One speculation is that women enrolled in the WHI, by design women with severe symptoms of menopause were not enrolled resulting in the average age of 62 years compared to the average age of menopause in the United States of 51 years. Furthermore, when the data was stratified by age, the absolute risk of all adverse outcomes were lower in the younger age group, 50-59 years at enrollment. This finding gives rise to the "timing hypothesis" and the current recommendation that HT may be appropriate treatment for menopausal symptoms when initiated in women below 60 years of age or within 10 years of onset of the menopause. Subsequent studies have also suggested that other formulations, including oral or transdermal estradiol, may be less thrombogenic and may carry less CVD risk.

After a decade of debate, the North American Menopause Society have put out an updated Position Statement in 2017, revising the previous recommendation of "lowest dose for the shortest period of time." The newest statement focuses on appropriate, duration and route of administration for appropriate symptoms. Basically, treatments should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation. Factors such as severity of vasomotor symptoms, years since menopause, 10-year cardiovascular disease risk calculation, risks of breast/endometrial cancer, history and risks of thromboembolic events, history of stroke, and others should be taken into consideration when determining appropriate therapy. Those who are high risk candidates for HT with vasomotor symptoms, non-hormonal therapy such SSRI/SNRIs and gabapentin should be considered. Topical vaginal estrogen is generally recommended for genitourinary syndrome of menopause, as achievement of systemic levels or stimulation of the endometrium do not occur. Lastly, both compounded bioidentical HT and over-the-counter supplements/herbal therapies cannot be recommended at this point due to safety concern, consistency in dosing and insufficient evidenced-based data.

Testosterone Replacement Therapy

Speaker: Alvin M. Matsumoto, MD

Synopsis written by: Pratik Shah, MD (UCI)

The work up of hypogonadism should include using accurate assays with harmonized reference ranges, recognizing potentially reversible or treatable functional causes of hypogonadism, emphasizing free testosterone levels (including borderline low total testosterone) and identifying situations such as opioid-induced and anabolic steroid withdrawal induced hypogonadism.

The symptoms of hypogonadism are non-specific and may be divided into three categories: sexual, psychological and physical. Sexual symptoms include poor sexual development, small testes (<6 cc volume), decreased libido, decreased frequency of morning erections and infertility. Psychological symptoms include decreased energy, concentration, sleep, memory and mood. Physical symptoms include gynecomastia, decreased male hair and decreased bone mineral density.

Before checking a total testosterone level, it is important to consider that a transient decrease in testosterone levels can be seen in the setting of recent illness, due to medications or due to energy deficit. Low sex hormone binding globulin (SHBG) can also lead to low levels of total testosterone which are not caused by hypogonadism. Comorbid illnesses, depression and medications should be ruled out as potential causes of symptoms of hypogonadism.

Secondary hypogonadism can be divided into organic and functional causes. Organic causes include hypothalamic/pituitary tumors, pituitary stalk disease, hypopituitarism, hemochromatosis and Kallmann syndrome. Functional causes include opioids, central nervous system acting drugs, glucocorticoids, hyperprolactinemia, chronic illness, wasting, organ failure, malnutrition, morbid obesity, excessive exercise, androgens, progestins, estrogens, gonadotropin releasing hormone (GnRH) agonists and aging (associated with age-related comorbidities). An MRI of the sella is not always necessary if the working diagnosis is due to a functional rather than organic cause, if hypogonadism is only mild and if there are no clinical manifestations of panhypopituitarism.

In practice, one should use total testosterone assays which are CDC-certified with a harmonized reference range (264-916 ng/dl). Samples should also be drawn in the morning as levels are lower the rest of the day with up to 30% day to day variability and drawn while fasting as levels may decrease after a high carbohydrate meal. Because of the variability in testosterone concentrations, low levels should be confirmed by repeating a morning, fasting testosterone level. When free levels of testosterone are checked, it is important to use an assay which measures free testosterone by equilibrium dialysis to give the most accurate results; calculated free testosterone provides a good estimate of free testosterone by equilibrium dialysis.

The first goal of treatment of hypogonadism should be to encourage weight loss, exercise, better blood glucose control, treatment of sleep apnea and to discontinue or reduce culprit medications such as opioids. If symptoms continue to worsen and functional causes are unable to be treated, then treatment with testosterone can be considered which may indirectly lead to increased motivation and energy to exercise to lose weight, etc.

Testosterone replacement has shown efficacy to improve sexual function (increased libido, erectile function and sexual activity), improved bone mineral density and possibly improved mood. Use should be cautioned if a patient has had a cardiovascular or thrombotic event within 6 months of treatment. Erythrocytosis is the most common adverse

effect but there is lack of evidence for testosterone effects on cardiovascular events, prostate cancer, and in reducing fracture risk. Patients should be monitored by checking testosterone and hematocrit at 3-6 and 12 months. If Hct >54, then it is recommended to stop testosterone, evaluate for hypoxia and restart testosterone at a reduced dosage. Testosterone gel formulations have large variability in testosterone levels and repeat levels should be checked while focusing on clinical response of the patient rather than focusing on the "number". Prostate cancer monitoring should be performed in ages >55 via shared decision making and in accord with usual screening guidelines. If prostate specific antigen (PSA) is >4 ng/ml or increases >1.4 ng/ml in 12 months, then the patient should be referred to urology for further evaluation.

Nuances in Medical Management of Transgender Care

Speaker: Madeline B. Deutsch, MD, MPH

Synopsis written by: Uzoma Mba, MD (Scripps)

When initiating hormone therapy it is important to evaluate psychosocial support and any co-existing medical or mental health conditions. It is no longer necessary to have a clearance letter from a mental therapist. It's important to discuss age adjusted expectations, patient's long term goals from hormones, and the expected time it will take to achieve these goals. The goal is to get hormones into the desired sex physiological range with interval laboratory evaluation every 6 -12 months.

The goals of feminizing hormones are to decrease erectile function, decrease testicular size, decrease or even eliminate ejaculatory fluid and sperm count. Some other hormonal effects are a decrease in libido, emotional lability, and changes in social functioning. The effects will vary from person to person, so providers should avoid generalized stereotypes and discuss these possible changes with patients. Estrogen and androgen blockers, such as Spironolactone, are some of the most commonly used. Progesterone is sometimes used based on anecdotal evidence for breast augmentation, but this can cause weight gain and mood changes. Bicalutamide, an androgen blocker, has also been used, but should be avoided as this can cause liver function test abnormalities and there is no standardized way of monitoring levels. Tobacco smoking on oral estrogen is a risk factor for thromboembolism, as it causes an imbalance in protein C and S, and should always be avoided. Transdermal estrogen is the only estrogen where this does not occur. Some people have proposed putting all patients on 81 mg of Aspirin to decrease risk of thromboembolism, but this is not an accepted practice as the risk of gastrointestinal hemorrhage has not been established.

The goals of masculinizing hormones are cessation of menses, infertility, an anovulatory state, and the development of masculinizing features such as coarse terminal hair. Some unexpected effects are increasing libido, vaginal dryness and atrophy, and possible changes in emotional and social functioning. Acne is also a significant adverse effect and is expected to peak at 1 year of therapy. In order to decrease some of the unwanted side effects it is very important to avoid supra-physiological testosterone levels. Despite the effects of masculinizing hormones, options for contraception are still needed such as OCPs (oral contraception pills) or Copper IUD which is more widely accepted for its lack of estrogen. Patients with PCOS (polycystic ovarian syndrome) are eligible for treatment with masculinizing therapy and it is not a contraindication to hormonal therapy but patients should be closely monitored for glucose intolerance.

Overall, taking care of a transgender patient requires a careful review of all concurrent medical conditions. There are multiple aspects of hormonal therapy that have not been well established due to lack of trials or guidelines. One such example is the lack of a cardiovascular risk calculator for patients on hormonal therapy of the opposing sex. Multiple papers have attempted to create a method to risk stratify but none have established any clinical significance. Therefore, in these circumstances, a shared decision making is recommended. Other concurrent medical conditions that must not be ignored are the the higher incidence of prolactinomas seen in transgender women and the clear hormonal component of migraines. Endocrine Society recommends "watchful waiting" in asymptomatic prolactinomas, with screening only indicated if symptoms arise. In the case of migraines, hormone treatment must be started at a low dose and slowly titrated. It is also important to know there is no need to stop hormonal therapy in the perioperative period.

There are multiple resources that can be used to help guide treatment such as transcare.ucsf.edu and Fenway Healthcare Boston.

Surgical Management of Transgender Care

Speaker: Marci L. Bowers, MD

Synopsis written by: Uzoma Mba, MD (Scripps)

Transgender surgery has been a part of history for many years, Examples can be seen in biblical eunichs and in 855 A.D. with Pope Joan/John. One of the pioneers in transgender surgery in the modern world was Georges Burou who in the 1950s developed the "penile inversion" in Casablanca. Later in the 1970s, Trinidad, Co. became the "sex change capital of the world".

Transgender surgery allows for reduction in teen suicide with a decrease in antisocial and destructive behaviors. It is estimated that nearly 50% of transgender patients have attempted suicide at least once in their lifetime. Many patients do not choose surgery due to its high cost and risk for complications although in 2014 Medicare has allowed insurance coverage.

Testosterone and estrogen are the mainstay of hormone

therapy. Gender affirmation surgery has multiple aspects and includes facial feminizing surgery, body modification surgery (changes in fat distribution and breast augmentation or mastectomy), and genital reassignment surgery (valvuloplasty, phalloplasty, metoidioplasty). After surgery, patients can expect to be able to walk within 36 hours and be discharged from the hospital in 72 hours. Usually patients are able to return to work in 6 weeks with a full recovery including sexual intercourse within 3 months.

Focal Feminization surgery includes rhinoplasty, forehead contouring, jaw reconstruction, cheek and chin augmentation, tracheal shaving to decrease thyroid cartilage (as this grows in response to testosterone), and dental feminization. Genital reassignment and vaginoplasty are accomplished by removing the testicles and reassigning the embryological homologous structures. In this procedure. the glans becomes the clitoris, the urethra becomes the labia minora, and the scrotum and penile skin become the vagina. The aim for vaginal depth is 15cm. In this procedure, the Cooper's glands and prostate gland are retained. Since the prostate is retained, prostate exams are still possible and should be done through the vagina. 90% of patients can still orgasm but will require lubrication for intercourse.

Masculinizing surgery goals are to achieve proper function, appearance, and ability to stand to urinate. It continues to be a multistage process and can be very expensive. Surgery involves thyroid cartilage augmentation, mastectomy, chest surgery, phalloplasty, and metoidioplasty. The process begins by enlarging the clitoris with testosterone, which grows an average of 5 cm after being on androgens for 2 years. Phalloplasty and metoidioplasty continue to be high risk procedures, as they have nearly 100% and 30% rate of complications respectively.

As surgical management develops, ethical dilemmas in transgender youth continue. One of the main concerns is the appropriate age when hormonal treatment should be initiated; if hormonal treatment is begun in the pre-pubertal age then patients can remain in Tanner Stage 2 which can ultimately limit their surgical options in the future since it is difficult to use infantile genitalia to re-create adult genitalia. Another ethical concern is the appropriate timing of surgery, or the ability to obtain informed consent in a minor for a procedure that can lead to infertility or lack of orgasmic experience.

Salivary Hormone Testing: Validity and Interpretation

Speaker: Hershel Raff, PhD, FAAAS, FAPS - Medical College of Wisconsin

Synopsis written by: Sukhmani Singh, MD (UCSF)

Spontaneous Cushing's syndrome can be broadly classified into endogenous and exogenous hypercortisolism; endogenous hypercortisolism resulting from secretion of too much cortisol from the adrenal gland regardless of the cause and exogenous hypercortisolism resulting from pharmacologic doses of glucocorticoid therapy. Endogenous hypercortisolism can be further divided into ACTH-dependent and ACTH-independent causes with pituitary and adrenal adenomas accounting for the bulk of cases.

Screening for Cushing's syndrome is typically prompted by signs of central obesity with facial rounding and plethora, increased supraclavicular and dorsocervical fat, violaceous striae, cutaneous wasting with ecchymoses and proximal myopathy. Individuals with metabolic syndrome, hypogonadotropic hypogonadism, incidental adrenal mass and osteoporosis particularly in those under age 65 with signs and symptoms of hypercortisolism lower the threshold for screening. Although Cushing's syndrome has been thought of as an uncommon disorder, multiple epidemiologic studies have shown that the incidence of Cushing's syndrome is much higher than previously thought. Studies have cited a prevalence of 0.5-8% in patients with resistant hypertension, up to 3% in poorly controlled or newly diagnosed type 2 diabetes and 7.4% in patients with a combination of obesity, type 2 diabetes and hypertension. Though the prevalence may be higher than previously thought, the presentation of Cushing's syndrome may be more nuanced, with patients presenting with a more subclinical picture.

The screening test of choice has often been the low dose dexamethasone suppression test (LD-DST) and 24 hour urine free cortisol; however, given the ease and accuracy of late night salivary cortisol it should be considered among the initial tests of choice. Late night salivary cortisol targets the circadian nadir of cortisol secretion, thus being able to differentiate normal individuals from those with Cushing's syndrome. Initial studies showed a 95% sensitivity rate for salivary cortisol testing with repeat studies and meta-analysis supporting this with sensitivity noted to be 95% and specificity 97%. Studies of low-dose dexamethasone suppression tests where a cut-off of 1.8 ug/dL is utilized indicate that the false negative rate is high enough to recommend that LD-DST not be used as the sole criterion for excluding a diagnosis of endogenous hypercortisolism, particularly if the suspicion for Cushing's syndrome is high. The clinician should also be mindful of drugs that alter dexamethasone metabolism and consider adding a dexamethasone level when testing. 24 hour urine cortisol is not without issues either; it does not perform as well as late night salivary cortisol with sensitivity ranging 81-84% and specificity ranging 54-69% (14) and is not a reliable test in those with renal dysfunction.

With this in mind, a suggested diagnostic strategy to test for hypercortisolism is to obtain 2 late night salivary cortisol measurements by immunoassay or LC-MS. If there is a high clinical index of suspicion and the results are high-normal repeat the test as there are individuals who demonstrate periodic hormonogenesis. If the results are 2-20 times above the upper limit of normal, one may want to perform confirmatory testing with a dexamethasone suppression test. However, if the results are over 20 times the upper limit of normal, one should test for contamination by measuring salivary cortisone. As the salivary gland expresses 11-β hydroxysteroid dehydrogenase, cortisone should normally exceed the concentration of cortisol. If this balance is reversed, consider contamination of

salivary with hydrocortisone, which could occur from and individual handling the sample after administering topical hydrocortisone cream. If the late night salivary cortisol is less than the upper limit or normal and a dexamethasone suppression test is normal Cushing's syndrome is extremely unlikely.

Late night salivary cortisol is also a very useful approach to follow patients after transsphenoidal surgery for Cushing's disease. Multiple studies have confirmed that late night salivary cortisol is a sensitive index of recurrence. The ease of use and high reliability make late night salivary cortisol an excellent test in the endocrinologist's toolkit for screening and diagnosis of Cushing's syndrome.

New Data for Treatment of Type 1 DM

Speaker: Bruce Buckingham, MD

Synopsis written by: Tejaswi Kompala (UCSF)

Dr. Buckingham provided an update on how clinicians should incorporate CGM data into their traditional A1c-focused thinking, and also discussed updates and nuances specific to each of the leading automated insulin delivery systems.

Metrics for Assessing Risk of Long-Term Complications; CGM data compared to A1c

Our previous data about A1c and risk for complications really hinged on A1c as a surrogate marker for glycemic control. Now with the increased information provided by CGM, time-in-range metrics serve as a more meaningful metric. Hemoglobin A1c is influenced by numerous clinical factors, and in a typical adult diabetes practice, 14-25% of A1c measurements are misleading.

Continuous glucose monitoring data now allows us to think about Time in Range (TIR), typically defined as blood glucoses between 70-180mg/dl. TIR has high correlation with mean glucose; each increase in TIR by 10% correlates with an A1c decrease of 0.6%. Clinical targets for CGM data have been defined (Battelino, Diabetes Care 2019) for the adult population with Type 1 and Type 2, for older/high risk patients, and for pregnancy as well. For the adult with Type 1 DM, the proposed target for TIR is >70%.

Updates on Automated Insulin Delivery systems

Medtronic 670G, which was FDA approved in 9/2016, was the first commercial "hybrid" closed-loop device. Data from the 30,000 patients using the 670G have now been published, which demonstrated increase in TIR from 62% to 70%; patients with the highest A1c values had the biggest benefit in A1c reduction. Dr. Buckingham noted the importance of managing expectations related to device use; fingersticks are still required for boluses, and daytime diabetes tasks are still equally present. Medtronic is adjusting the algorithm so users can remain in auto-mode more of the time, with fewer auto-kickouts to manual mode.

A trial regarding **Tandem Control IQ** use by 48 kids at home and while skiing, demonstrated improvements in TIR, hypoglycemia and particularly overnight hyperglycemia. A separate study, the International Diabetes Closed-Loop Trial, is a randomized (2:1) multicenter controlled trial with 168 subjects that will be published shortly. The trial evaluates the Tandem Predictive Low Glucose Suspend (PLGS) System Algorithm. This system uses the last 4 glucose readings to make a prediction, driving automatic adjustments to basal rates and correctional doses.

Insulet Omnipod now also has a hybrid closed loop system using the Dexcom CGM sensor. The algorithm is on the pod, and adapts every three days when the pod is changed. Studies in children 2-6yo identified improvements in hypoglycemia <70mg/dl, and improvements in TIR.

The **Bionic Pancreas**, with pumps for insulin and glucagon, operates solely based on blood glucose and has also demonstrated improvements in TIR and hypoglycemia (Lancet 2017). **Full Closed Loop** systems – that don't require meal or correction boluses – are also being developed. Coformulations with insulin and amylin will be studied.

Dr. Buckingham concluded with his vision of the future: full closed-loop devices that won't require carb counting or premeal bolus delivery. Next steps will be more adaptability of insulin delivery to the unique and dynamic needs of the individual, incorporation of accelerometer and heart rate monitoring data, and better integration into consumer devices.

Metabolic Complications of Surgery

Speaker: Umesh Masharani, MBBS

Synopsis written by: Stephanie Kim, MD (UCSF)

Obesity increases all-cause mortality, cardiovascular mortality and cancer, while bariatric surgery lowers all-cause mortality, the incidence of diabetes, myocardial infarction, stroke and cancer, as shown by the Diabetes Prevention Program (DPP, weight loss following intensive lifestyle interventions) and the Swedish Obesity Study (SOS, weight loss following bariatric surgery). Types of bariatric surgery include biliopancreatic diversion with duodenal switch, Roux-en-Y, adjustable gastric band, and sleeve gastrectomy. Trends in the types of bariatric surgery performed in the United States from 2008-2016 show an increase in sleeve gastrectomy and a decrease in the other types of procedures.

Micronutrient and macronutrient consequences

Vitamin B12 levels decline in patients who have undergone bariatric surgery due to a decrease in intrinsic factor levels, food bound B12 not being released due to the lack of hydrochloric acid or pepsin, and B12 binding protecting intrinsic factor and after gastric bypass, intrinsic factor is sensitive to proteolysis by pepsin and trypsin. These patients also encounter iron deficiency post-operatively as the absorption of ferrous ascorbate is decreased.

Bariatric surg and skeletal health

Complications include a significant decline in bone mineral density (both at the femoral neck and lumbar spine) in post-bariatric surgery patients, as well as an early and sustained increase in bone turnover. Mechanisms for this include decreased loading, decreased muscle mass, vitamin D deficiency, decrease in calcium absorption, and changes in hormones, including ghrelin and leptin. The intestinal calcium absorption capacity decreases and due to the reduction of gastric acid post-operatively, calcium citrate, rather than carbonate, should be used for better absorption. Fracture risk is increased at typical osteoporotic sites 2-5 years after surgery and can be further impacted by menopause though this is unknown. These patients may also be at risk for deficiencies in thiamine, folate, fat soluble vitamin, protein and trace minerals.

Gastric bypass associated hypoglycemia

Why do patients present with hypoglycemia following gastric surgery? Service, et al proposed that this was due to Nesidioblastosis, or hyperplastic islet cells, though this was later challenged by Meier, et al. Late dumping syndrome is a complication of gastric surgery. Additionally, the rapid delivery of carbohydrates into the bowel results in rapid rise in glucose and insulin, and hyperinsulinemia leads to subsequent hypoglycemia. Furthermore, GLP1 and GIP may play a role in insulin stimulation.

In terms of prevalence, a Swedish nationwide cohort study of nondiabetic bariatric surgery patients were compared to referent normal, 0.2 % of gastric bypass patients affected by hypoglycemia compared to general population rate of 0.04%; in contrast, the incidence of insulinomas is 3 -10 cases/ million/yr.

Evaluation of hypoglycemia post-gastric surgery- differentiating gastric bypass hypoglycemia and insulinoma

If there were hypoglycemic symptoms before bariatric surgery, then the patient may have had an insulinoma. Gastric bypass hypoglycemia typically occurs 2-4 hours after meals, whereas insulinoma hypoglycemia occurs with fasting and exercise. Additionally, gastric bypass hypoglycemia is typically precipitated by rapidly absorbed carbohydrates. Gastric bypass associated hypoglycemia typically occurs 1-2 years post-surgery whereas insulinoma symptoms occur early after surgery. Testing includes home glucose monitoring. If patient's history is consistent with gastric bypass hypoglycemia and the fingerstick glucose levels are low only postprandially, ask the patient to modify diet. If the patient reports that fasting will cause hypoglycemia, then consider a supervised fast.

Treatments include reducing peaks of postprandial glucose excursions (diet, acarbose, SGLT2 inhibitors), reducing incretin effect (GLP1 receptor antagonist), reducing insulin secretion (diaxozide, octreotide), reducing insulin signaling (insulin receptor antibody that blocks insulin signaling) and surgical reversal. Dietary modification includes avoiding rapidly absorbable carbohydrates, a high fiber and protein rich foods, 6 small meals, and pectin.

Treatment with Anti-PD-1/PD-L1 and Anti-CTLA Drugs: Endocrine Side Effects

Speaker: Laurence Katznelson, MD

Synopsis written by: Stephanie Kim, MD (UCSF)

Two classes of drugs include anti-PD-1/PD-L1 monoclonal antibodies and anti CTLA-4 monoclonal antibodies. These drugs work by "releasing the brakes" at immune checkpoints, allowing for T-cell activation and decreasing peripheral tolerance in the immune system. While they can be very effective at treating malignancy, they also allow for development of autoimmune side effects called immune related adverse events (irAE).

Ipilimumab is the only FDA approved anti CTLA-4 monoclonal antibody. It is associated with hypophysitis and thyroid dysfunction. Pembrolizumab, nivolumab and cemiplimab are the FDA approved anti PD-1 monoclonal antibodies. Atezolizumab, avelumab and durvalummab are the FDA approved anti PD-L1 monoclonal antibodies. Anti-PD-1 and anti-PD-L1 antibodies are associated with development of thyroid dysfunction and autoimmune diabetes mellitus.

Hypophysitis occurs in 0-17% of patients treated with ipilimumab. It is more common in older patients and men. It usually occurs in the first 10 weeks since initiating treatment with ipilimumab or combination ipilimumab and nivolumab. Clinically, patients often report headache and fatigue. Labs frequently reveal central adrenal insufficiency and often reveal central hypothyroidism and hyponatremia. Gonadotroph function can also be affected. Growth hormone is less likely to be impacted and patients do not develop diabetes insipidus. Imaging is either normal or consistent with an enlarged pituitary gland. High dose steroids do not seem to affect resolution of hypophysitis nor pituitary function and may be associated with a worsened survival response.

Diabetes mellitus occurs in about 1 % of individuals treated with anti-PD-1/PD-L1 monoclonal antibodies alone or in combination with anti CTLA-4 monoclonal antibodies. Onset is variable and can occur months after initiating treatment. Beta cell autoantibodies are present in about half of these individuals.

Thyroid dysfunction can occur with both types of immune checkpoint inhibitors but is more common with anti-PD-1/ PD-L1 monoclonal antibodies.

Adrenal insufficiency is uncommon and is more common with anti-PD-1/ PD-L1 monoclonal antibodies.