Annual Conference of Endocrine Society of India (ESICON 2019)

21ST-24TH NOVEMBER, 2019 | HOTEL LE MERIDIEN, NAGPUR

PPAR TARGETS: FUTURE OF GLITAZONES/GLITAZARS

Brig (Dr) Narendra Kotwal, New Delhi

- Peroxisome proliferator-activated receptor (PPAR) agonists work as integrators of inflammatory and metabolic signaling networks; work as lipid sensors; repress pro-inflammatory gene expression; fine-tune post-translational modifications and exert antiatherogenic effects.
- Potential of PPAR agonists is well-established in therapeutic areas related to lipid and glucose metabolism and inflammation such as type 2 diabetes mellitus, obesity, dyslipidemia and NAFLD and/or NASH.
- PPAR-γ ligand may prevent loss of β-cell mass.
- PPAR-γ activation reduces insulin resistance, preserves pancreatic β-cell function, improves cardiovascular risk profile.

PPAR agonists play significant roles in several diseases including primary biliary cholangitis, gout, non-small cell lung cancer, neurological diseases and ulcerative colitis.

ALPHA BETA CROSSTALK: BETA TO ALPHA CELLS AND BACK!

Dr Madhukar Mittal, Jodhpur, Rajasthan

- Biological crosstalk – Components of one signal transduction pathway affect another in a number of ways, most common form being crosstalk between proteins of signaling cascades.
- There is a crosstalk between cells that control body's response to sugar and understanding the conversation can help us understand and treat diabetes.
- In type 1 diabetes mellitus, there is almost complete destruction of β-cells; α-cells are present but their function is impaired. In type 2 diabetes mellitus, β-cell number reduction is progressive and α-cell numbers may actually be increased.
- Artemisinins inhibit ARX function and impair α-cell identity. Artemisinins increase β-cell mass in zebrafish and rodent models. They target $GABA_A$ receptor signaling.
- Glucagon-like peptide-1 (GLP-1) receptor agonists exert some of their glycemic effects through reduction in endogenous glucagon. GLP-1 treatment reduces glucagon secretion: by action on pancreatic α-cells, and by stimulation of β-cells, and the paracrine effects of the secreted insulin on adjacent α-cells.
- There are significant structural and functional differences in rodent islets and human islets.
- Structure of human islets permits greater role of paracrine and autocrine interactions in regulating islet cell function.
- This is an ever-expanding area of research with knowledge gaps, and has a potential role in the management of diabetes.

Deciphering α-β crosstalk has potential for curative therapies for diabetes.

SOLITARY THYROID NODULE: WHAT'S NEW IN APPROACH?

Dr Bipin Kumar Sethi, Hyderabad, Telangana

- High resolution ultrasound can detect thyroid nodules in 19-68% individuals. Approximately 1 in 2 people may have incidental thyroid nodules.
- The frequency is higher in the elderly and in females.
- Indeterminate nodules continue to challenge and tease those who wish to separate the chaff from the grain.
- There remains a significant percentage of nodules with ambiguity.
- Commercially available molecular markers: *Afirma* – relies on mRNA microarray sequencing and has high sensitivity/NPV and low specificity/PPV; *ThyroSeq GC* is a DNA- and RNA-based next-generation sequencing (NGS) with high specificity/PPV and high sensitivity/NPV; *ThyGenX + ThyraMIR combination* – overall performance is moderate.

- Artificial intelligence algorithms decrease the subjectivity of medical image interpretation.
- More often one "errs" in favor of surgery than uncertainty.

Newer techniques refine the accuracy but do not entirely eliminate the uncertainty and are currently in "not for you" category.

ADRENAL INSUFFICIENCY: CHANGING CONCEPTS IN MANAGEMENT

Prof (Dr) Paul M Stewart, UK

- Morbidity and increased mortality in patients with adrenal insufficiency is unacceptable. Management of adrenal crisis is currently inadequate.
- Morbidity is related, in part, to excessive daily doses of glucocorticoids.
- Glucocorticoid replacement in the treatment of adrenal insufficiency – Current practice: According to a survey of current practice in glucocorticoid replacement therapy in patients with adrenal insufficiency, glucocorticoid replacement therapy consisted primarily of hydrocortisone.
- Patients with adrenal insufficiency are not sufficiently equipped with emergency kits. Recent studies show that subcutaneous administration of drug is effective and patient acceptance is high.
- Subcutaneous administration of 100 mg hydrocortisone shows excellent pharmacokinetics for emergency use; it has a good safety profile and is preferred by patients over intramuscular injection (Hahner S, et al. Eur J Endocrinol. 2013;169(2): 147-54).
- Adrenal suppression after glucocorticoid treatment is dose- and duration-dependant. Suppression of the adrenal response is common after short-term, high-dose glucocorticoid treatment (Henzen C, et al. Lancet. 2000;355(9203):542-5).
- Evidence suggests that circadian rhythm is important. There are deleterious consequences of 'late pm' excess. Elevated evening levels of cortisol are associated with glucose intolerance, abdominal obesity, coronary atherosclerosis, insomnia and reduced sleep quality.
- Management of adrenal suppression is challenging and more studies are required.

Newer preparations mimicking physiology are highly desirable. Endocrinologists need to take ownership of iatrogenic adrenal insufficiency.

CAH: NEWER INSIGHTS IN ETIOLOGY AND MANAGEMENT

Prof (Dr) Richard Auchus, US

- 11-oxygenated 19-carbon ($11oxC_{19}$) steroids are elevated in both men and women with classic 21-hydroxylase deficiency (21OHD). $11oxC_{19}$ steroids are specific biomarkers of adrenal-derived androgen excess (Turcu AF, et al. Eur J Endocrinol. 2016;174(5):601-9).
- Potential therapies for management of congenital adrenal hyperplasia (CAH) – Modified-release hydrocortisone; Hydrocortisone subcutaneous infusion pump; Super-androgen receptor antagonists: P450 17A1 inhibitor – Abiraterone acetate, CRH receptor antagonist – NBI-77860, NBI-74788, SPR-001 = Tildacerfont and ACAT1 (SOAT1) inhibitor – ATR-101 (Nevanimibe).
- Abiraterone for 21OHD – Abiraterone acetate is a potent P450 17A1 inhibitor that is FDA-approved for the treatment of prostate cancer with prednisone to prevent hypertension and hypokalemia. The concept is to add abiraterone acetate to replacement hydrocortisone to control androgen excess and mitigate the consequences of chronic supraphysiologic glucocorticoids.

Abiraterone acetate at 250 mg/day with hydrocortisone 20 mg/day for 1 week normalizes androgens in the majority of adult women with classic 21OHD, without causing hypertension or hypokalemia.

PREVENTION OF TYPE 2 DIABETES: GLOBAL PERSPECTIVE

Dr Ashok Kumar Das, Puducherry

- Triad of modalities in preventing type 2 diabetes – Diet, exercise and medication.
- Lifestyle intervention can prevent type 2 diabetes onset. Several randomized trials have shown that interventions – lifestyle, medications – can decrease the rate of onset of diabetes. These include Da Qing Study, Finnish Diabetes Prevention Study and Diabetes Prevention Program for lifestyle interventions; and Diabetes Prevention Program (metformin), The Stop-NIDDM and ACT NOW (pioglitazone) for medications.
- ACT NOW - Pioglitazone reduced the risk of type 2 diabetes mellitus by 72% vs. placebo. Pioglitazone reduced fasting glucose, 2-hour glucose and HbA_{1c}.
- ADA 2019 nutritional recommendations – The eating patterns that may be helpful for those with prediabetes include a Mediterranean eating plan and a low-calorie, low-fat eating plan. Higher

intakes of nuts, berries, yogurt, coffee and tea are associated with reduced diabetes risk.

- ADA 2019 pharmacological recommendations – Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years and women with prior gestational diabetes mellitus. Metformin has the strongest evidence base and demonstrated long-term safety as pharmacologic therapy for diabetes prevention.

We must identify patients at high risk (prediabetes). Modest lifestyle changes are most effective. Increase opportunities for community programs to support prevention. Delaying or preventing type 2 diabetes is cost-effective and will help turn the tide on the diabetes epidemic.

APPROACH TO ADAM

Dr KVS Hari Kumar, Panchkula, Haryana

- Androgen deficiency in aging male (ADAM) is functional hypogonadism and is a diagnosis of exclusion.
- Sexual symptoms (erectile dysfunction and reduced sexual thoughts) are significant symptoms for the diagnosis.
- Diagnosis is based on the demonstration of low levels of total testosterone done at least twice along with symptoms.
- Other hormonal panel aids in the exclusion of other causes.
- Free testosterone has limited role in the diagnosis.
- Testosterone therapy is not approved by US FDA for ADAM and is considered as off-label use only.
- Prostate and breast carcinoma are absolute contraindications for testosterone therapy and beware of the risks involved with therapy.
- Anabolic steroids and other compounds have limited benefit.

Testosterone offers moderate benefit on sexual symptoms and modest benefit on body composition, bone density and cognition. Individualized testosterone therapy is recommended by guidelines from the Endocrine and Geriatric societies.

GRAVES' DISEASE: PREDICTORS OF REMISSION

Dr KM Prasanna Kumar, Bengaluru, Karnataka

- Hyperthyroidism relapses in the majority of patients with Graves' disease treated with antithyroid drug (ATD).
- Among different clinical and laboratory features, age at onset of hyperthyroidism, goiter size and TSH-receptor antibody (TRAb) level are particularly helpful in identifying those patients who are more prone to undergo a remission of hyperthyroidism, after medical treatment.
- Remission is independent of the type of ATD (methimazole, propylthiouracil and carbimazole).
- Graves' patients with the G allele in exon 1 of the CTLA-4 gene, were required to continue ATD treatment for longer periods to achieve remission.
- Children with hyperthyroidism often require prolonged courses of antithyroid medication to achieve remission, and long-term compliance is problematic.

Age at onset of hyperthyroidism, goiter size and TRAb level help identify patients more prone to undergo a remission of hyperthyroidism.

The most relevant predictor of Graves' disease outcome seems to be serum level: TRAb at the time of Graves' disease diagnosis <2.5 times the upper reference limit, TRAb normalization during ATD and TRAb normalization timing each may predict positive outcomes.

OBESITY AND FERTILITY

Dr Sarita Bajaj, Prayagraj, Uttar Pradesh

- Obesity in men and women is associated with impaired reproductive function.
- Preconceptional counseling for obese couples should address the reproductive and maternal-fetal consequences of obesity.
- Lifestyle modification is the first-line treatment for obesity, followed by adjunctive medical therapy.
- Elimination of tobacco, alcohol and stress management may be of more immediate benefit in achieving conception. Bariatric surgery is an important adjuvant to lifestyle modification and medical therapy for weight loss, but pregnancy in women should be deferred for 1 year post-op.
- The excess reproductive morbidity associated with obesity may increase with longer duration, making the current trends among children and young adults particularly critical in terms of their future reproductive potential.
- Conveying the impact of these lifestyle changes on future progeny can serve as a powerful tool for obese people to modify their behavior.

Reproductive urologists and endocrinologists must learn about the importance of paternal preconception health.

STEM CELL THERAPY IN DIABETES

Dr Ganapathi B, Bengaluru, Karnataka

- Stem cell therapies for type 1 diabetes are novel.
- The use of stem cells in the generation of a renewable source of β-cells remains a promising reality.
- A meta-analysis of the clinical efficacy of stem cell therapy for diabetes mellitus revealed the following: (1) remission of diabetes mellitus is possible following stem cell therapy; (2) stem cell transplantation can be a safe and effective approach for therapy of diabetes mellitus; (3) available data indicate that the most promising therapeutic outcome was shown in mobilized marrow $CD34^+$ hematopoietic stem cells (HSCs); (4) patients with previously diagnosed diabetic ketoacidosis are not good candidates for the applied approaches stem cell therapy; (5) stem cell therapy at early stages after diabetes diagnosis is more effective than intervention at later stages and (6) well-designed large scale randomized studies considering the stem cell type, cell number and infusion method in diabetes patients are urgently needed (El-Badawy A, El-Badri N. PLoS One. 2016;11(4):e0151938).
- Autologous umbilical cord blood transfusion in children with type 1 diabetes is safe but has yet to demonstrate efficacy in preserving C-peptide (Haller MJ, et al. Diabetes Care. 2009;32(11):2041-6).
- A major issue that needs to be addressed is the *in vitro* maturation of insulin-positive cells.

Even with an abundant supply of stem cell-derived β-cells with robust glucose-responsiveness, many issues still need to be addressed and resolved before this approach becomes a therapeutic option.

THYROID STORM

Dr RV Jayakumar, Cochin, Kerala

Thyroid storm is an important endocrine emergency. Suspect the condition in any severely ill patient with tachycardia, high fever and a thyroid swelling. Early treatment with antithyroid drugs, iodine, steroids, β-blockers and supportive measures reduces mortality. Treatment of the precipitating factors is also important. Once treated for the acute problem, don't forget the long-term management of thyrotoxicosis.

Remember 5 B's in management *- Block Synthesis - Antithyroid drugs; Block Releasers - Iodine; Block T4 to T3 conversion - Propylthiouracil (PTU), Steroids; Beta-blockers - for symptomatic relief; Block enterohepatic circulation - Cholestyramine.*

ECTOPIC ACTH-PRODUCING CUSHING'S SYNDROME

Prof Nihal Thomas, Vellore, Tamil Nadu

- This is an important differential diagnosis for adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome. It has a more rapid and fulminant onset with significantly higher levels of ACTH, serum hypercortisolemia and urine free cortisol levels when compared with pituitary-dependent Cushing's syndrome.
- Intrathoracic origin for ectopic ACTH-producing tumors is the most common; particularly thymic, bronchial carcinoid and bronchogenic carcinoma.
- Opportunistic infections which are secondary to immune suppression are more common and can be lethal if not treated aggressively.
- Thymomas are frequently malignant and clinical remission postoperatively is uncommon.

In patients with severe clinical symptoms of Cushing's, control of hypercortisolemia with medical management, particularly ketoconazole, and in refractory cases, early adrenalectomy may precede the excision of the primary tumor.

TYPE 2 DIABETES MELLITUS IN INDIANS – NOVEL INSIGHTS

Prof (Dr) SV Madhu, New Delhi

- The burden of type 2 diabetes mellitus continues to rise.
- The way our body handles meal-related surges in lipids and the associated postprandial triglyceride dysmetabolism appears to be a major determinant of our risk of developing type 2 diabetes mellitus.
- We have obtained unequivocal evidence that postprandial hypertriglyceridemia leads to the development of insulin resistance, glucose intolerance and type 2 diabetes mellitus in a diet-induced rat model of type 2 diabetes mellitus.
- Polymorphisms of RAGE gene have significant effects on advanced glycation end products (AGEs) level and PON1 activity in diabetic subjects as compared to healthy individuals.
- Transcriptional expression of RAGE mRNA in peripheral blood mononuclear cells (PBMCs) has

been found to be significantly higher in diabetic patients than in controls.

- Role of arginine vasopressin pathways in chronic stress coping is being increasingly recognized.
- A chronically hyperactive and dysregulated HPA axis is associated with enhanced diabetes risk.
- Other novel risk factors for type 2 diabetes mellitus include circadian disruption and environmental pollutants. Shift work is associated with metabolic and genetic dysregulation among Indians.
- Postprandial triglyceride dysmetabolism appears central to the pathogenesis of type 2 diabetes mellitus.
- Genetic/molecular studies can also help in understanding the underlying pathogenetic mechanisms of type 2 diabetes risk.
- Longitudinal studies throw up challenges to traditional concepts and widen the scope of our understanding of the disease.
- We need to develop culturally sensitive diabetes management recommendations that allow women to remain integrated in protective social and family roles while still successfully managing blood sugar.

There is a strong inverse link of stress coping capabilities with diabetes risk. Hence, there is a need to focus on strategies to improve stress coping.

NONGLYCEMIC EFFECTS OF SGLT-2 INHIBITORS

Dr Shashank Joshi, Mumbai, Maharashtra

- Nonglycemic benefits with sodium-glucose cotransporter-2 (SGLT-2) inhibitors – Metabolic benefits, weight/fat loss benefits, cardiovascular (CV) benefits and renal benefits.
- Cardiovascular disease (CVD) mortality in type 2 diabetes mellitus has remained a significant challenge over the years, and targeting vasculo-metabolic axis is key to sustained improvement in health outcomes.
- Personalized medicine approach and guidelines suggest the preferential use of SGLT-2 inhibitors, for compelling reasons of atherosclerotic CVD (ASCVD), heart failure (HF) or chronic kidney disease (CKD), weight loss or lower risk of hypoglycemia. Agents with proven CVD benefit are recommended for patients with ASCVD.
- SGLT-2 inhibitors have demonstrated consistent CV benefits, including reductions in CV death, HF hospitalizations and nephropathy in type 2 diabetes mellitus with CVD.
- Start early with SGLT-2 inhibitors for cardiorenal protection.
- CREDENCE is the first dedicated kidney outcome trial which showed 30% reduction in primary outcomes like end-stage kidney disease, doubling of serum creatinine or renal or CV death with SGLT-2 inhibitor therapy.

Optimize clinical considerations of risk-benefit for each antidiabetic agent, in principle of individualized approach for every patient.

FERTILITY PRESERVATION IN PATIENTS UNDERGOING CANCER TREATMENT

Prof Jubbin Jagan Jacob, Ludhiana, Punjab

- Better survival among adolescents and young adults with cancer means that fertility issues become important among survivors.
- Current recommendations from American Society of Clinical Oncology suggest that counseling of all adults in reproductive age group and parents of children undergoing cancer therapy for reproductive and fertility issues be undertaken. For post-pubertal males, the best option for fertility preservation remains cryopreservation of semen for use subsequently. Gonadotropin-releasing hormone (GnRH) analogues are not recommended as they do not have much success.
- GnRH analogues work by shutting down the hypothalamic-pituitary-gonadal axis and this, in turn, reduces gonadotoxicity by: a) Reduction in recruitment of active gametes. b) Reduction in blood supply to the gonad reducing the exposure of the gonad to toxic drugs. For prepubertal people, the only option is gonadal shielding when being administered radiation. Other avenues for fertility preservation are currently experimental only.

For post-pubertal females, embryo preservation gives the highest chance of success followed by oocyte cryopreservation. However, when both these avenues are not possible then the use of GnRH analogues is an option.

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