6th International and 8th Iranian Congress of Endocrinology & Metabolism Updates

21st -23rd May 2025
Abbassi Hall, Abbassi Hotel, Isfahan, Iran

Plenary Lectures

Current Status of Congenital Hypothyroidism in Iran

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The Future of GLP-1 Receptor Agonist Medications: Dual and Triple Agonists

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The concept of incretins was first introduced over a century ago, with early studies demonstrating that oral glucose induces a greater insulin response than intravenous glucose-a phenomenon now known as the incretin effect. This effect is mediated primarily by gut-derived hormones, notably glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

Approximately sixty years after the initial theory, landmark studies confirmed that the enhanced insulin secretion following oral glucose is attributable to these incretin hormones. Two decades later, the discovery of Exendin-4, a GLP-1 receptor agonist derived from the venom of the Gila monster, marked a breakthrough in diabetes therapy by demonstrating significant glucose-lowering effects.

This discovery paved the way for the development of GLP-1 receptor agonists, which have since revolutionized the management of type 2 diabetes and obesity. Beyond glycemic control, large cardiovascular outcome trials have shown that GLP-1 receptor agonists significantly reduce major

adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death, and also promote weight loss, lower blood pressure, and improve lipid profiles.

Current research focuses on optimizing the pharmacokinetics of these agents, with newer formulations allowing for once-weekly or even less frequent dosing, and the development of oral preparations for greater convenience. Furthermore, next-generation multi-agonists-combining GLP-1 activity with GIP or glucagon receptor agonism-are being investigated for their potential to further enhance glucose lowering, weight reduction, and provide additional benefits for cardiovascular, renal, and hepatic health.

Emerging data also suggest possible neuroprotective effects, with ongoing studies exploring their role in conditions such as Alzheimer's and Parkinson's disease. Efforts to minimize adverse effects and improve tolerability continue to drive innovation in this rapidly evolving field.

Together, these advances illustrate the expanding therapeutic universe of GLP-1 receptor agonists and incretin-based therapies, heralding a new era in the management of metabolic and cardiovascular diseases.

New Insulin Formulations and Their Clinical Applications

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Basal insulin continues to play a vital role in treating both type 1 and type 2 diabetes (T1DM & T2DM). Over the last 20 years, innovations have led to the development of long-acting basal insulin analogues with more consistent pharmacokinetic profiles, enhancing both safety and efficacy by notably reducing nocturnal hypoglycemia. Two major once-weekly basal insulins include ***insulin icodec*** and ***insulin efsitora alfa*** (BIF). Efsitora alfa is a novel basal insulin comprising a single-chain variant of insulin fused with a human IgG2 Fc domain. Icodec is a C20 acylated insulin analogue with three amino acid substitutions: TyrA14Glu, TyrB16His, and PheB25His. Phase 2 and 3 trials (QWINT for efsitora and ONWARDS for icodec) confirm that once-weekly insulins achieve glycemic control comparable to once-daily analogues with similar hypoglycemia risk.

Other weekly basal insulins in development include GZR4 and GZR101, the latter being a premixed formulation containing ultra-long-acting basal GZR33 and fast-acting insulin aspart.

Smart insulin, also known as glucose-responsive insulin (GRI), refers to insulin that self-regulates in response to blood glucose levels. Three primary mechanisms are being explored:

1. Glucose-binding proteins, such as concanavalin A (ConA), which bind glucose and mannose reversibly. These systems aim to sequester insulin during normal glucose levels and release it during hyperglycemia via competitive glucose binding.

2. Phenylboronic acid (PBA), which binds glucose reversibly and can trigger insulin release using smart matrices (e.g., gels, micelles, or capsules) through mechanisms like swelling or dissociation.

3. Glucose oxidase (GOx) systems convert glucose and oxygen to gluconic acid, which, when combined with pH-responsive materials, triggers insulin release through swelling/deswelling mechanisms.

4. Glucose-responsive microneedle patches deliver insulin via vesicles made from hypoxia-sensitive hyaluronic acid conjugated with 2-nitroimidazole. Under hyperglycemic conditions, enzymatic oxidation of glucose creates a hypoxic microenvironment, triggering vesicle dissociation and the release of insulin, offering a potential painless, smart insulin delivery system.

Among these, GOx-based systems show the most in vivo promise. Animal studies have demonstrated glucose-sensitive insulin release lasting 24 hours to 14 days.

Notable examples:

- MK-2640 (binds MRC1 receptor)
- NNC2215, BIOD-123 (ultra-rapid insulin)

Oral insulin (ORMD-0801) is delivered in an enteric-coated capsule to protect insulin from degradation in the GI tract. Nanotech approaches are also under development.

Hypopituitarism in 2025: Emerging Insights and Innovations

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Hypopituitarism remains a dynamic field in endocrinology, with 2025 marked by advances in precision diagnostics, novel therapies, and deeper mechanistic insights. Recent studies highlight immune checkpoint inhibitor (ICI)-induced hypophysitis as a growing concern, driven by expanded use of combination immunotherapies (e.g., anti-CTLA-4 + anti-PD-1). Up to 20% of ICI recipients now develop pituitary dysfunction, with thyrotroph and corticotroph deficiencies predominating. Biomarkers like anti-pituitary antibodies (APA) and pituitary-specific T-cell clones are being validated for early detection

In traumatic brain injury (TBI), advanced neuroimaging (7T MRI) and machine learning algorithms now predict pituitary damage with >90% accuracy, enabling preemptive hormone screening. Longitudinal data reveal GH deficiency persists in 30% of TBI survivors at 5-year follow-up, correlating with poor neurocognitive recovery, spurring advocacy for mandatory endocrine monitoring in TBI guidelines.

Gene-editing therapies show promise in preclinical models: CRISPR-Cas9 targeting PROP1 mutations restored pituitary function in congenital cases . Meanwhile, stem cell-derived pituitary organoids are entering Phase I trials, aiming to regenerate hormone-secreting cells.

Clinically, personalized hormone replacement is gaining traction. Subcutaneous pulsatile GH pumps, synchronized with circadian rhythms, improve metabolic outcomes compared to daily injections. For adrenal insufficiency, dual-release hydrocortisone formulations mimic physiological cortisol rhythms, reducing cardiovascular risks.

Finally, the gut-pituitary axis has emerged as a research frontier. Dysbiosis-linked inflammation exacerbates pituitary dysfunction in animal models, prompting trials of probiotics and fecal transplants to augment traditional therapies.

Conclusion: Hypopituitarism management is shifting toward proactive screening, biologics, and regenerative medicine, with multidisciplinary care essential to address its multisystemic impact.

Updates on Acromegaly Management : Diagnosis, Remission and Treatment

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Acromegaly caused by a GH-secreting pituitary adenoma can deleteriously affect QOL and mortality if not diagnosed early and properly treated. In patients presenting with typical clinical manifestations or Several acromegaly-related conditions or any pituitary mass, should raise suspicion for the diagnosis of acromegaly.

IGF-1 is used for screening as it does not vary with sleep patterns, exercise, or throughout the day like GH. In patients with typical signs and symptoms of acromegaly, IGF-1 levels >1.3 times the upper limit of normal for age confirm the diagnosis without the need for further testing . In patients with equivocal results, repeat the IGF-1 measurement or perform an OGT, may also be useful and BMI-based GH nadir cutoffs can be considered for diagnosis.

In severe acromegaly comorbidities, high surgical risk and tumours with Cavernous sinus invasion without chiasmal compression, when significant debulking is not feasible, preoperative treatment with SRLs is indicated.

Early postoperative assessment at 1 day after surgery predicted long-term remission. Generally, IGF-I normalization measured 12 weeks after surgery defines surgical success.

For patients who did not achieve postoperative remission and treated with adjuvant SRL, IGF-I should be assessed 3 months after initiation/dose adjustment. For patients who have achieved a complete or partial biochemical response on injectable SRLs, new formulation of octreotide, oral octreotide, can be used. Second-generation SRL, Pasireotide, effective in patients not controlled with maximal doses of First -generation SRLs especially those with normal glucose metabolism.

Although first-line medical treatments are SRLs, Cabergoline monotherapy, is recommended only for patients with mild (<1.5 ULN) elevations of IGF-I levels and symptoms. Pegvisomant useful for patients are resistant to SRL, as well as patients with hyperglycemia. GH assessment is not informative in follow-up of pegvisomant and cabergoline and IGF-I should be assessed.

Male Hypogonadism

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Hypogonadism in males refers to a decline in one or both primary functions of the testes: sperm production and testosterone secretion. This condition may result from a disorder of the testes (primary hypogonadism) or dysfunction of the pituitary or hypothalamus (secondary hypogonadism). A failure to initiate or complete puberty suggests inadequate testosterone secretion.

Hypogonadism is suspected in individuals presenting with sexual symptoms, osteoporosis, prolonged use of sustained-release opioids or high-dose glucocorticoids, incomplete virilization, or small testes upon examination. However, men experiencing acute or subacute illness should not be assessed for hypogonadism, as such conditions may induce transient functional secondary hypogonadism.

Testosterone replacement therapy (TRT) remains the cornerstone of symptomatic hypogonadism management, with available options including transdermal gels and patches, injectable esters (cypionate, enanthate), testosterone undecanoate injections, and orally administered testosterone undecanoate (which undergoes lymphatic absorption, bypassing first-pass liver metabolism). For secondary hypogonadism, alternatives such as human chorionic gonadotropin (hCG) or gonadotropins may preserve fertility by stimulating endogenous testosterone production and spermatogenesis.

Diagnosing hypogonadism requires measuring morning serum total testosterone levels between 8 and 10 AM on at least two separate days. Assessing serum free testosterone is beneficial only when abnormalities in testosterone binding to sex hormone-binding globulin (SHBG) are suspected. Common conditions affecting SHBG levels include obesity (which reduces SHBG concentrations) and aging (which increases SHBG concentrations). If total testosterone levels are subnormal, repeat testing between 8 and 10 AM is advised, along with measurements of serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to distinguish primary from secondary hypogonadism. Additionally, semen analysis should be performed in patients seeking fertility evaluation or diagnosed with infertility.

GH-IGF-1 System and Carcinogenesis

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Over 70 years, hundreds of studies across more than 20 cancer types have amassed a persuasive body of evidence implicating GH and cancer. Autocrine/paracrine GH action, rather than endocrine, is suggested to promote age-associated cancer development. GH signaling directly orchestrates several hallmark tumor-supportive mechanisms at or in the tumor microenvironment (TME).

Strong evidence for the involvement of GH and GHR exists in various cancers, including breast, colorectal, liver, prostate, and gastric cancers. Expression of GH and GHR is reported in many cancer cell lines and patient samples. GH and IGF1 are also implicated in driving resistance to radio- and chemotherapy in some cancers.

Notably, conditions with reduced GH signaling, such as Laron Syndrome (LS), are associated with a major reduction in cancer and diabetes risk in humans.

Targeting GH action is considered an effective and highly feasible approach to enhance the efficacy of multiple types of anticancer therapies. Pegvisomant (Somavert), the only FDA-approved

GHR antagonist for acromegaly, has shown reduced proliferation, increased apoptosis, and inhibited tumor growth in various preclinical models. Systemically blocking GH action can also have indirect benefits via reduction of IGF1 and improving insulin sensitivity. Other potential therapeutic strategies include GHRH antagonists and Fasting Mimicking Diet (FMD).

Cushing's Syndrome: Recurrent and Refractory Cases

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Management of Complicated Diabetes Cases

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Hypoparathyroidism Updates: Management and Emerging Therapies

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Hypoparathyroidism is a rare endocrinological disease that results in hypocalcemia, hypercalciuria and hyperphosphataemia.The underlying aetiology is divided into two major categories:postsurgical and non-surgical. Postsurgical causes comprise up to 75-80% of all cases.

Chronic postsurgical hypoparathyroidism may be predicted by serum PTH <10 pg/mL in the first 12-24 hours after surgery.

Conventional therapy (supplementation with oral calcium salts and active vitamin D)is recommended as first –line therapy. Patients with persistent symptomatic hypocalcaemia, hyperphosphataemia, hypercalciuria, complications of hypoparathyroidism or poor quality of life ,those unable to tolerate large doses of calcium and active vitamin D should be considered for PTH replacement therapy.

Research Lectures

Telehealth-Enhanced Diabetes Self-Management Education and Support (Telehealth DSMES): A Novel Approach to Improve Glycemic Control, Quality of Life, and Access to Care

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Introduction: With approximately 589 million people worldwide affected by diabetes, achieving therapeutic goals remains challenging despite advances in medical treatments and technology. Pharmacotherapy alone is insufficient for optimal diabetes control, emphasizing the need for behavioral optimization and psychosocial support. Telehealth DSMES offers a scalable, patient-centered solution by integrating digital tools to deliver core DSMES components remotely. This approach addresses critical gaps in traditional DSMES, such as limited access to educators, geographic barriers, and time constraints. Telehealth DSMES enables tailored education on pathophysiology, insulin injection techniques, oral medication management (dosing, timing, and administration), blood glucose monitoring, complication prevention, and problem-solving skills through virtual platforms, ensuring sustained engagement and empowerment.

Materials & Methods: Telehealth DSMES programs deliver evidence-based content via remote platforms, including:Pathophysiology Education : Simplified explanations of diabetes mechanisms using interactive tools. Insulin Injection Training: Virtual demonstrations and real-time feedback on injection techniques.

Oral Medication Management : Guidance on optimal dosing, timing, and adherence strategies.

Problem-Solving Skills : Case-based scenarios to address hypoglycemia, meal planning, and stress management.

Psychosocial Support : Tele-counseling to improve self-efficacy, coping mechanisms, and emotional well-being. Programs are personalized to cultural, linguistic, and literacy needs, leveraging

interprofessional teams (endocrinologists, dietitians, diabetes educators) during critical junctures: at diagnosis, annually or when treatment goals are unmet, during complicating factors (e.g., CKD, stroke), and during transitions in care. Outcomes are measured via HbA1c reductions, quality-of-life metrics, and healthcare utilization rates.

Results and Conclusion: Clinical trials demonstrate that Telehealth DSMES reduces HbA1c by ≥0.6% over 6–12 months, comparable to in-person DSMES. Key advantages include: Improved Access, Cost-Effectiveness, Psychosocial Benefits, and Scalability.

Telehealth DSMES represents a paradigm shift in diabetes management, combining clinical rigor with digital innovation. To maximize impact, healthcare systems must:

Prioritize Telehealth DSMES : Integrate it into national diabetes care guidelines.

Invest in Infrastructure : Expand broadband access and digital literacy training for patients and providers.

Develop Hybrid Models : Combine telehealth with in-person follow-ups for complex cases (e.g., insulin pump users).

Policy Reforms: Reimburse virtual DSMES sessions and incentivize provider participation. By adopting Telehealth DSMES, stakeholders can reduce the global diabetes burden, empower patients, and achieve equitable, high-quality care.

Redefining Metabolic Syndrome: Predictive Value for Mortality Events in Over 17 Years of Follow-Up

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Background: Metabolic syndrome (MetS) is a well-established contributor to elevated cardiovascular and mortality risk. Although waist circumference (WC) is commonly used to define central obesity in MetS, its dependency on body weight may compromise its precision. The weight-adjusted waist index (WWI) has emerged as a novel anthropometric index that more accurately reflects visceral adiposity, independent of weight.

Objectives: This study investigated whether replacing WC with WWI in the MetS definition enhances the long-term prediction of mortality outcomes.

Methods: We utilized data from 6,504 adults aged 35 and older, who were free from cardiovascular disease at baseline, during a 17-year follow-up period. Participants were categorized using both the standard MetS criteria and a modified version which incorporated WWI in place of WC. We used Cox regression to evaluate associations with mortality outcomes and employed Kaplan-Meier and ROC analyses to assess the predictive value of both definitions.

Results: During the follow-up period, 197 cardiovascular and 524 all-cause deaths were documented. The modified MetS definition showed stronger predictive associations with mortality outcomes compared to the classic version—CVD mortality (HR: 2.77 vs. 2.07) and all-cause mortality (HR: 1.90 vs. 1.44). ROC analysis also showed the better specificity and the more overall accuracy for the WWI-based model. Kaplan-Meier curves also showed greater survival discrimination in the modified definition, despite a slightly lower average survival time.

Conclusion: Replacing WC with WWI in the MetS criteria enhances its capacity to predict long-term mortality, highlighting WWI's clinical value for this risk assessment. These findings should be tested in different populations to make sure they are reliable.