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Section 3: Diabetes and Metabolic Disorders

Section Editor: Siddharth N Shah

Associate Editors: Ragini M Rohatgi, Naveen Mittal

JAYPEE BROTHERS

ARTICLE 1

Cardiovascular Manifestations in Newly Diagnosed Hyperthyroid Patients and their Outcome with Anti-thyroid Treatment

Sonawale A, Chichkhede A. Cardiovascular manifestations in newly diagnosed hyperthyroid patients and their outcome with anti-thyroid treatment.

J Assoc Physicians India. 2018;66(6):22-6.

Abstract

Objectives: To evaluate the incidence of cardiovascular abnormalities in newly identified hyperthyroid patients and their outcome with anti-thyroid therapy.

Methods: A total of 96 patients who were newly diagnosed to have hyperthyroid disease were screened and out of them, 40 patients who presented with cardiovascular symptoms and sign were included in study (30 females, 10 males). Hyperthyroid patients were re-evaluated after antithyroid therapy. Findings in patients were compared at presentation, and after 3 months of treatment. All had undergone a structured cardiovascular history and examination, including measurements of blood pressure (BP) and pulse rate. All had resting 12-lead electrocardiogram and 2D ECHO.

Results: Cardiovascular symptoms and signs, as well as abnormal hemodynamic and dysrhythmias, especially supraventricular, were frequent among patients with hyperthyroidism. Palpitation and atrial fibrillation (AF) were more recurrent in overt hyperthyroid subjects than those with subclinical hyperthyroidism and remained more prevalent after 3 months of antithyroid treatment in that subject who had persistently high serum T3 and T4 level.

Conclusion: Cardiovascular abnormalities are one of the most common presentations in patients with hyperthyroidism and they respond very well to treatment before the structural changes occur in the cardiovascular system.

"Every hour of useful work is precious"

– William Lyon Mackenzie King

COMMENT

What is the incidence of cardiovascular abnormalities in newly diagnosed hyperthyroid patients? How many of them improve with antithyroid treatment? These are two questions which are discussed in this paper.

The thyroid hormone acts on all organ systems; but the heart responds to even minimal changes in thyroid hormone level. Overt hyperthyroidism leads to hyper-dynamic circulatory state (high cardiac output with lesser systemic vascular resistance), and leads to faster heart rate, enhanced left ventricular systolic and diastolic function and increased chances of supraventricular tacharrhythmias.

About 40 patients (30 females, 10 males) who came with cardiovascular symptoms and sign were included in this study. Hyperthyroid patients were given treatment with anti-thyroid drugs

for 3 months and then re-evaluated. Findings in patients were compared at presentation, and after 3 months of treatment.

Palpitation was the most common cardiovascular symptoms, followed by dyspnoea, followed by chest pain, cough and pedal edema. After 3 months of treatment, patients became clinically and biochemically euthyroid and symptoms reduced. Successful management of the hyperthyroidism has led to reversal of these symptoms.

Atrial fibrillation(AF) was found in 15% of patients with hyperthyroidism, as compared with 4% incidence in the general population.

At the start of treatment 12 of 40 patient (30%) show abnormal ECHO findings. Diastolic dysfunction was the most common finding, with one patient having systolic dysfunction. These 2D ECHO findings which improved after restoration of euthyroid state were functional rather than structural. But the structural abnormalities like dilated cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy and pulmonary hypertension persisted. The above findings suggest that once the structural changes have occurred in heart, they do not show much improvement much even if patients become euthyroid.

So this study shows that cardiovascular system involvement was seen in 40% of hyperthyroid patients.

Clinical symptoms and signs such as tremors, tachycardia, atrial fibrillation showed significant improvement with antithyroid treatment. Hyperthyroid patients who became euthyroid with treatment had significant relief in their symptoms as well as ECG abnormality but some 2D ECHO abnormalities persisted.

Key Messages

- ***Cardiovascular system involvement is observed in 40% of hyperthyroid patients.***
- ***Patients who become euthyroid with treatment have significant relief in their symptoms as well as ECG abnormality, but some 2D ECHO abnormalities persist.***

JAYPEE BROTHERS

ARTICLE 2

Prevalence and Clinical Use of Anti-thyroid Antibodies in RA Patients: A Prospective Case-control Study

Haridas V, Haridas K. Prevalence and clinical use of anti-thyroid antibodies in RA patients: a prospective case-control study. ***J Assoc Physicians India. 2018;66(5):14-6.***

Abstract

Aim: To evaluate the prevalence of anti-thyroid antibodies in a cohort of rheumatoid arthritis (RA) patients from south India and their clinical use.

Methods: The prospective case-control study, conducted for 3 consecutive months in a tertiary care hospital based in India, evaluated 103 RA patients (active group) and 36 age-matched healthy controls without the disease. Both the control and active groups were compared for thyroid autoantibodies, and the clinical evaluation included assessment of swollen joint counts (SJC), tender joint counts (TJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), pain scale, disease activity score (DAS), rheumatoid factor (RF), anti-nuclear antibody (ANA) and anti-cyclic citrullinated peptide (anti-CCP). The active group subjects were further subdivided into RA patients with and without hypothyroidism, and were compared for normal and abnormal levels of thyroid autoantibodies and the variations were statistically analysed.

Results: The corresponding mean age of the subjects belonging to the active and control groups were 47.09 ± 11.29 and 41.03 ± 11, with a female to male ratio of 1:0.12 and 1:0.29 respectively. Among the various thyroid autoantibodies compared between the active and control groups, a significant correlation

(p = 0.00936) was observed for anti-TTG antibodies. Also, the study has noted a significantly elevated level of anti-TPO antibodies in RA patients with hypothyroidism compared to the group without hypothyroidism (p = 0.0074).

Conclusion: A significantly increased level of anti-TPO antibodies was noted in RA patients with hypothyroidism.

"I'm always trying to find brain food and indulge in knowledge that's gonna be useful"

– Big Boi

COMMENT

The increased prevalence of thyroid diseases in patients suffering from rheumatoid arthritis (RA) is known. The association may be due to sharing of some common genes, such as CD40, CTLA4, HLA gene complex, and PTPN22, which may increase the risk of disease development.

This study has looked for the prevalence of anti-thyroid antibodies in a cohort of RA patients from south India.

What they found: This study has found increased titer of anti-thyroid peroxidase (anti-TPO) antibodies in RA patients with hypothyroidism compared to those without the disease (p = 0.0074).

Anti-tissue transglutaminase antibody (anti-TTG) was also higher in subjects with RA compared to controls. There is no study looking for prevalence and clinical use of anti-thyroid antibodies in RA patients from Indian settings, hence the present study can be considered as first of its kind evaluating the association.

The present study has reported a significantly elevated level of anti-TPO antibodies in RA patients with hypothyroidism.

Key Message

- ***A significantly increased level of anti-TPO antibodies are found in rheumatoid arthritis patients with hypothyroidism.***

ARTICLE 3

Subclinical Hyperthyroidism

Biondi B, Cooper DS. Subclinical Hyperthyroidism.
N Engl J Med. 2018;378:2411-9.

Abstract

It is characterized by normal serum level of thyroid hormones and subnormal serum thyrotropin levels (<0.4 mU/L). It is due to excess endogenous thyroid hormone or intake of thyroid hormone. When serum thyrotropin levels are <0.1 mU/L it becomes overt. Even before becoming overt it can cause complications like cardiovascular (atrial fibrillation, coronary artery disease, and heart failure), bone fractures, and dementia in elderly. Treatment of this condition is recommended by experts for those >65 years and for postmenopausal women specially when levels are less than 0.1 mU/L. It may be treated with methimazole in those less than 65 years, radioiodine in those where it is caused by toxic multinodular goiter or toxic adenoma or surgery in those with large goiter and compressive symptoms.

In overt hyperthyroidism serum levels of free T3, T4 or T3 alone are elevated and serum thyrotropin levels are suppressed. In subclinical hyperthyroidism levels of free T3 and T4 are normal and thyrotropin levels are reduced.

JAYPEE BROTHERS

"The journey of a thousand miles begins with one step"

– Lao Tzu

COMMENT

Subclinical hyperthyroidism (SCH) is a condition where levels of free T4 and T3 are normal, but thyrotropin levels are suppressed (≤0.4 mU/L). Whereas, in overt hyperthyroidism, serum levels of free T4 and triiodothyronine (T3) are elevated, and serum thyrotropin levels are suppressed. The diagnosis of SCH is based on laboratory results.

The common endogenous causes SCH are Graves' disease, multinodular goiter and toxic adenoma. Exogenous SCH results from excessive intake of levothyroxine.

Subclinical hyperthyroidism may progress to overt hyperthyroidism, especially if serum thyrotropin levels are less than 0.1 mU per liter. Even if it does not progress to overt hyperthyroidism, SCH may lead to adverse outcomes, including cardiovascular disease (e.g. atrial fibrillation, heart failure and coronary heart disease), osteoporosis, fractures, and dementia, particularly in persons more than 65 years of age.

Older patients with SCH are mostly asymptomatic, where as younger persons show mild adrenergic symptoms. On physical examination, you may find an enlarged or nodular thyroid or Graves' ophthalmopathy, but adrenergic signs of thyroid over activity like tachycardia, tremors may be absent.

If a diagnosis of SCH is made, further evaluation should be done after 2–3 months, at which time testing should be repeated. Subnormal serum thyrotropin levels are transient in half of patients, most often in those with mild disease (TSH between 0.1 to 04 mU/L). If a subnormal serum thyrotropin level persists, further investigations are indicated to determine the cause.

For finding the etiology, clinical examination of thyroid coupled with thyroid Scintigraphy with technetium (Tc) is the best. It will tell you if your patient is having Graves' disease, multinodular goiter or toxic nodule. Thyroid ultrasound can be done if nuclear medicine facility is not available.

Whether to treat and which form of treatment (medical, surgical or radioiodine) should be given? It depends on the underlying diagnosis, the degree of thyrotropin suppression, patient age, and any coexisting conditions. Anti-thyroid drugs are the preferred treatment in patients with Graves' disease, because it leads to remission in 50 % of cases. Radioiodine should be given in patients with toxic nodular disease. Surgery is the treatment of choice in patients with large goiter, causing obstructive symptoms (dysphagia,dysphonia and dyspnea).

Key Messages

- ***Graves's disease is most common cause of subclinical hyperthyroidism, followed by multinodular goiter and toxic adenoma.***
- ***Anti-thyroid drugs are the first line of treatment in patients with Graves' disease, whereas radioiodine is preferred in patients suffering from toxic nodular disease. Patients with large goiter that is causing obstructive symptoms should undergo surgery.***

ARTICLE 4

Hyponatremia, Falls and Bone Fractures: A Systemic Review and Meta-analysis

Corona G, Norello D, Parenti G, et al. Hyponatremia, falls and bone fractures: A systemic review and meta-analysis. ***Clin Endocrinol (Oxf). 2018;89(4):505-13.***

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Abstract

Objective: To perform a meta-analysis based on published studies that compared falls and bone fractures between patients with and without hyponatremia.

Context: There is evidence suggesting that hyponatremia is associated with an increased risk of falls and bone fractures.

Design: An extensive Medline, Embase and Cochrane search was performed to retrieve all studies published up to 30 April, 2017, using the following words: "Hyponatremia" or "hyponatremia" and "falls" and "bone fractures". A meta-analysis was performed including all studies comparing falls and bone fractures in subjects with or without hyponatremia.

Patients and Results: Out of 216 retrieved articles, 15 studies satisfied inclusion criteria encompassing a total of 51,879 patients, of whom 2,329 were hyponatremic. Across all studies, hyponatremia was associated with a significantly increased risk of falls [MH-OR = 2.14 (1.71; 2.67)]. This result was confirmed when only hospitalized patients were considered [MH-OR = 2.44 (1.97; 3.02)]. A meta-regression analysis showed that the hyponatremia-related risk of falls was higher in those studies considering a lower serum [Na^+] cutoff to define hyponatremia. Interestingly, the estimated risk of falls related to hyponatremia was already significantly higher when a serum [Na^+] cutoff of 135 mmol/L was considered [MH-OR = 1.26 (1.23; 1.29)]. The presence of hyponatremia was also associated with a higher risk of fractures, particularly hip fractures [MH-OR = 2.00 (1.43; 2.81)].

Conclusion: This study confirms that hyponatremia is associated with an increased risk of falls and bone fractures. The clinical, social, and economic relevance of such association is strengthened by the increased incidence of hyponatremia in older people.

"Efficiency is doing things right; effectiveness is doing the right things"

– Peter Drucker

COMMENT

We have commonly seen that elderly people fall more frequently and have higher chances of getting fracture. Hyponatremia is a common abnormality seen in elderly. Is there an association between hyponatremia and falls/fractures? This question is reviewed in this meta-analysis.

It is known that acute severe hyponatremia can cause severe brain damage due to cerebral edema and can be lethal if not properly treated. What is the effect of mild hyponatremia?

This study has shown that hyponatremia is inversely associated with an increased risk of falls. Interestingly, the association was significant when a cutoff of 135 mmol/L was considered for serum sodium. In addition, among patients who had a fall, those with hyponatremia had a further higher risk of bone fracture.

In addition, literature has shown that chronic hyponatremia represents a poor prognostic factor in congestive heart failure, cirrhosis, pneumonia, hospitalized patients, in transplantation recipients, and also in cancer patients.

What is the mechanism of fall with hyponatremia? It is not completely understood. However, several problems, associated with hyponatremia, have been previously considered possible risk factors for falls. Among them, the use of diuretics or antidepressants, hypothyroidism, and central nervous system disorders represent the common conditions. So hyponatremia could represent the possible link between these factors and the higher risk of falls. In addition, even mild and apparently asymptomatic hyponatremia is associated with gait disturbances, attention deficit and cognitive decline, which are associated with an increased risk of falls. Noteworthy, it has been demonstrated that correction of hyponatremia is associated with gait stability improvement, suggesting that the risk of falls can be reduced by increasing serum sodium.

What is the cellular mechanism of osteoporosis in hyponatremia? Experimental data suggest that chronic hyponatremia increases the number and the activity of osteoclasts, which contribute

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to the mobilization of sodium from the bone. In particular, it has been shown that osteoclast activation is mainly the result of low sodium-induced oxidative stress.

So what is message from this study? If you see mild hyponatremia in an elderly patient (serum sodium between 125 mEq/L and 135 mEq/L), do not neglect it. Recognition and management of age-related hyponatremia and its associated conditions might contribute to the prevention of falls and bone fractures, ultimately resulting in reduction of healthcare costs.

Key Message

- ***Hyponatremia can cause a fall and fracture especially in elderly people. Even if you see a mild hyponatremia, try to find the etiology and correct it. You may be able to prevent the fall and hence bone fracture.***

ARTICLE 5

Advances in the Management of Cushing's Syndrome

Feelders RA, Newell-Price J, Pivonello R, et al. Advances in the management of Cushing's syndrome.
Lancet Diabetes Endocrinol. 2018;7(4):300-12.

Abstract

Cushing's syndrome, also known as hypercortisolism, is directly linked to multisystem morbidity. Left undiagnosed or treated suboptimally, it can even increase risk of fatality. In case surgery fails to work, an alternate option is medical therapy. This can be classified into—pituitary-directed drugs, steroid synthesis inhibitors, and glucocorticoid receptor antagonists. Each of these drug categories has experienced tremendous advancements and new developments in the last decade. In up to 40% of patients, the production of cortisol hormone can be controlled successfully. This can be done by simply targeting dopamine and somatostatin receptors on corticotroph adenomas, using either cabergoline or pasireotide, or both. Upon examining the corticotroph adenomas, one chances upon potential new targets such as the epidermal growth factor receptor, cyclin-dependent kinases, and heat shock protein 90. Currently, research is going on to evaluate the new inhibitors of steroidogenesis, namely osilodrostat and levoketoconazole, in multicenter trials. In addition, a new selective glucocorticoid receptor antagonist is also under investigation, known as CORT125134.

We collectively summarize the long list of drug therapies available for various forms of Cushing's syndrome. However, that is not all. Our focus lies on emerging drugs and newest drug targets that carry the potential of providing new and effective tailor-made pharmacotherapy options for patients with Cushing's syndrome.

"The best way out is always through"

– Robern Frost

COMMENT

In all patients with Cushing's syndrome, physician should try to completely normalize cortisol production to improve symptoms and prevent mortality. The firstline treatment of Cushing's syndrome is surgery. But medical treatment is an important option for patients with Cushing's syndrome who cannot be cured by surgery or in whom surgery is contraindicated.

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Medical therapy can be divided into pituitary-directed drugs, steroid synthesis inhibitors, and glucocorticoid receptor antagonists.

Among the pituitary-directed therapies, blockage of dopamine and somatostatin receptors present on corticotroph adenomas with cabergoline or pasireotide, or both, controls cortisol production in up to 40% of patients. One should know, new potential compounds for treatment of Cushing's disease include retinoic acid, somatostatin–dopamine chimeric ligands, the epidermal growth factor receptor, cyclin-dependent kinases, and heat shock protein 90 inhibitors.

Steroidogenesis enzyme inhibitors are going to be effective in all forms of Cushing's syndrome, as they block various steps of the steroidogenic pathway. The available agents are ketoconazole, metyrapone, mitotane and etomidate. New Steroidogenesis inhibitors are osilodrostat and levoketoconazole. Blockade of the ACTH receptor might become a new approach in future.

Finally, glucocorticoid receptor antagonist (mifepristone) can be effective. CORT125134 is a new selective GR antagonist without anti-progestogen effects.

Cushing syndrome can result in many complications like—hypertension, dyslipidemia, diabetes mellitus, accelerated atherosclerosis, venous thromboembolism, infections and osteoporosis. In Cushing's syndrome, major cause of death is cardiovascular complications. So in patient of Cushing syndrome, these complications should also be managed according to standard guidelines.

Key Messages

- ***The firstline treatment of Cushing's syndrome is surgery.***
- ***Medical therapy is an important alternative for patients with Cushing's syndrome who cannot be cured by surgery or in whom surgery is contraindicated.***
- ***Medical therapy can be divided into pituitary-directed drugs, steroid synthesis inhibitors, and glucocorticoid receptor antagonists.***

ARTICLE 6

Autoimmune Polyendocrine Syndrome

Husebye ES, Anderson MS, Kämpe O. Autoimmune Polyendocrine Syndrome.
N Engl J Med. 2018;378:1132-41.

Abstract

Autoimmune polyendocrine syndromes (APSs) include conditions having involvement of multiple endocrine glands due to immune phenomenon. These patients often have alopecia, vitiligo, celiac disease, and autoimmune gastritis which are due to involvement of nonendocrine organs. They are divided into the less common monogenic form called the autoimmune polyendocrine syndrome type 1 (APS-1) and the more common polygenic form called autoimmune polyendocrine syndrome type 2 (APS-2). They are slow in onset. Have circulating autoantibodies. There is lymphocyte infiltration of the affected organ which causes its failure. These can manifest from infancy to old age. The occurrence is due to a combination of genetic susceptibility and also there is role of environmental factors.

Autoimmune polyendocrine syndrome type 1 has prevalence of 1 in 100,000. It has two of the three major components of chronic mucocutaneous candidiasis, hypoparathyroidism, and Addison's disease. Other features are diarrhea, ovarian insufficiency, and enamel hypoplasia.

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Autoimmune polyendocrine syndrome 2 is much more common, they have at least two of the three endocrinopathies type 1 diabetes mellitus, Addison's disease, and autoimmune thyroid disease. The inheritance of APS-2 is complex although genes related to the disease have been identified. It occurs in young adults usually later than APS-1.

The treatment of these conditions is mainly hormone replacement therapy and treatment of complications. Patients of APS can have other organ-specific autoimmune disease also.

"Keep your face to the sunshine and you can never see the shadow"

– Helen Keller

COMMENT

Autoimmune polyendocrine syndrome (APS) is a group of clinical conditions which are characterized by functional impairment of multiple endocrine glands. APS are broadly classified into 2 types—Type 1 and Type 2 APS.

Autoimmune polyendocrine syndrome type 1 (APS-1) is an autosomal recessive disorder caused by mutation in the *AIRE* gene found on chromosome 21. Classically it develops very early in life, often in infancy. Chronic mucocutaneous candidiasis is often the first manifestation. Hypoparathyroidism usually develops next, followed by adrenal insufficiency. Gonadal failure affects women more than men.

Diagnosis of APS-1 is made clinically when two of the three component (candidiasis, hypoparathyroidism and adrenal insufficiency) disorders are found in an individual. Autoantibodies to type 1 interferons, namely interferon-ω and interferon-α, are present in almost all patients.

Regarding treatment of APS-1, replacement of deficient hormones (e.g. adrenal, pancreas, ovaries/testes) is required. Chronic mucocutaneous candidiasis is managed with oral mycostatin and oral amphotericin B.

Autoimmune polyendocrine syndrome type 2 (APS-2) is more common than APS-1 with a prevalence of 1 in 1000. APS-2 has its onset in adulthood and shows familial, multigenerational inheritance.

The presence of two or more of following disorders in same patient defines the presence of APS-2—primary adrenal insufficiency, autoimmune thyroid disease, type 1 diabetes mellitus (T1DM) or primary hypogonadism.

Circulating antibodies can precede the development of clinical disease by many years. Some of examples are—antibodies to thyroid peroxidase in autoimmune thyroid disease, to glutamic acid decarboxylase in T1DM, and to 21-hydroxylase in autoimmune Addison's disease.

While treating patients of APS-2, focus should be on replacement of missing hormones. One should remember that a patient with APS-2 is at increased risk for the development of another organ-specific autoimmune disease.

Early recognition of the clinical features of these disorders and to initiate therapy is important to improve the outcome.

Key Messages

- ***Diagnosis of APS-1 is made clinically when two of the three component (candidiasis, hypoparathyroidism and adrenal insufficiency) disorders are found in an individual.***
- ***The presence of two or more of following disorders in same patient defines the presence of APS-2: primary adrenal insufficiency, autoimmune thyroid disease, type 1 diabetes mellitus or primary hypogonadism.***
- ***Early recognition of the clinical features of these disorders and to initiate therapy is important to improve the outcome.***

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ARTICLE 7

Cinacalcet: A Viable Therapeutic Option for Primary Hyperparathyroidism in the Elderly

Abusahmin H, Surya A, Aldridge A, et al. Cinacalcet: a viable therapeutic option for primary hyperparathyroidism in the elderly. ***Indian J Endocrinol Metab. 2018;22(4):485-8.***

Abstract

Objective: Parathyroidectomy is usually curative in primary hyperparathyroidism (PHPT), but its utility would be limited if patients are elderly who may either refuse surgery or may have advanced frailty and multimorbidity. We evaluated the effectiveness of cinacalcet, an allosteric modulator of calcium-sensing receptor in PHPT in an elderly cohort of patients.

Methods: A prospective analysis of 29 patients who had PHPT and despite fulfilling criteria for surgery were unable to undergo parathyroidectomy either due to self-refusal (n = 12) or due to advanced multimorbidity (n = 17). All patients completed treatment with cinacalcet for at least for 6 months. Analyses were performed as per age (<75 and ≥75 years) and Charlson comorbidity index (CCI) score (≤5 and >5).

Results: Our patients were the elderly (77 ± 12.7 years). In the whole group, complete normocalcemia was observed in 72.4% of patients {mean reduction: −0.55 mmol/L [confidence interval (CI) 0.4–0.7; p < 0.0001]} and parathormone (PTH) normalized (≤6.9 pmol/L) in 33.4% of patients [mean reduction: −5.5 pmol/L (CI −11.6–0.6; p = 0.0015)]. In subgroup analysis, the severity of hypercalcemia was found to be higher patients with age <75 years and also in patients with CCI score >5. Cinacalcet lowered adjusted calcium in both age groups (p <0.0001) with a greater reduction (20.5% vs. 16.2%; p <0.0001 for both) in patients with CCI score >5. PTH fell in both age groups but significantly [−6.7 pmol/L (CI −14.9–1.5); p = 0.008] in ≥75 years category and likewise, the drop was greater in patients with higher CCI scores [−7.1 pmol/L (CI −15.8–1.6); p = 0.009] versus [−4.5 pmol/L (CI −3.9–5.10); p = 0.001]. Patients with age <75 years and with CCI score ≤5 needed higher doses of cinacalcet to achieve biochemical targets.

Conclusion: Cinacalcet is a viable and valuable treatment strategy for elderly patients with multiple comorbidities who suffer from PHPT but either cannot or refuse to undergo parathyroidectomy.

"Know what you do not know"

– Gautama Buddha

COMMENT

Primary hyperparathyroidism (PHPT) is a common endocrinological disease, characterized by overproduction of parathyroid hormone (PTH) and elevated serum calcium. The goal of therapy in patients with PHPT is to normalize serum calcium and PTH levels, and to improve the associated clinical manifestations. Parathyroidectomy is the only intervention which will cure the disease. However, there are patients whose PHPT is unresolved by surgery, or in those who have contraindications for surgery or who refuse the procedure.

What to do with these patients? Ask them to take more fluid, don't get dehydrated. What about specific drug?

Calcium-sensing receptors (CaSRs) was discovered on cell membrane of parathyroid glands. It regulates PTH secretion according to extracellular calcium concentrations. Cinacalcet hydrochloride is an allosteric modulator of CaSRs which increases sensitivity to extracellular calcium and leads to downregulation of PTH secretion. Treatment with cinacalcet has proven to be a reasonable alternative for parathyroidectomy.

Cinacalcet was approved by the European Medicines Agency for the treatment of hypercalcemia in patients, suffering form PHPT for whom parathyroidectomy is not done.

In this study authors have evaluated the effectiveness of cinacalcet in an elderly cohort of

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patients who were either refused surgery or were not medically fit to undergo surgery.

What they found: Cinacalcet administered in doses of 30–90 mg normalized serum calcium in most patients with additional modest benefits seen in serum PTH, phosphate, and ALP concentrations. In this study, most of the patients were precluded from surgery on the grounds of multimorbidity, in contrast to previous observational study participants most of whom were deemed fit for surgery and only received cinacalcet following unsuccessful operations or parathyroid gland localization.

Further more patients who were more sick had greater hypercalcemic severity at onset which may be a reflection of a more severe form of PHPT (serum calcium relating to higher PTH levels) or particular comorbidities may have been a contributory factor. Interestingly, this cohort of the patient's achieved a greater reduction in adjusted calcium and PTH levels in comparison to patients with lower comorbidity scores, suggesting that cinacalcet is very effective when advanced multimorbidity coexist with PHPT and limits surgical options.

So this study shows the cincalcet is a viable treatment strategy for the elderly who either cannot or refuse to undergo surgery.

Key Message

- ***Cincalcet is a viable treatment strategy for the elderly who either cannot or refuse to undergo surgery.***

ARTICLE 8

Genital Infections with Sodium-glucose Cotransporter-2 Inhibitors: Occurrence and Management in Patients with Type 2 Diabetes Mellitus

Unnikrishnan AG, Kalra S, Purandare V, et al. Genital Infections with Sodium Glucose Cotransporter-2 Inhibitors: Occurrence and Management in Patients with Type 2 Diabetes Mellitus.
Indian J Endocrinol Metab. 2018;22(6):837-42.

Abstract

Diabetes is a metabolic disorder characterized by hyperglycemia and is associated with several comorbidities and complications. Genital infection is one such complication that is often associated with diabetes mellitus (DM). Even though abnormalities in immune system, high urine glucose, and bladder dysfunction are important contributors for the increased risk of genitourinary symptoms, yet the possible role of pharmacologically induced glucosuria cannot be completely overlooked in such patients. There are various classes of medications to control blood glucose levels. A new therapeutic option to manage hyperglycemia is to increase renal glucose excretion by inhibiting sodium-glucose cotransporter-2 (SGLT-2) glucose transport proteins. SGLT-2 inhibitors represent a novel class of oral antidiabetic drugs which are associated with drug induced glucosuria. Currently, canagliflozin, dapagliflozin, and empagliflozin are the three SGLT-2 inhibitors approved for therapy in Type 2 Diabetes mellitus (T2DM). Safety studies with these three SGLT-2 inhibitors have reported events of mild moderate genital infections in patients on SGLT-2 inhibitors therapy. However, most of the reported infections responded to standard treatment. Apart from SGLT-2 inhibitors, factors including personal hygiene, menopause, and circumcision might have a possible role in reported events of genital infections among T2DM patients on SGLT-2 inhibitors therapy. The present review identifies the occurrence of genital infections in diabetic patients on SGLT-2 inhibitors therapy, factors affecting the incidence of genital infections, and management strategies in patients with T2DM on SGLT-2 inhibitors therapy.

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"The secret to winning is constant, consistent management"

– Tom Landry

COMMENT

Patients with diabetes are at a 2-fold higher risk of developing infections as compared with nondiabetic individuals.[1]

In the US Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (2008) survey, it was found that women and men with type 2 diabetes mellitus (T2DM) had 1.9 and 2.3 times higher chances of experiencing at least one episode of vaginitis and balanitis infection, respectively, compared with women and men without diabetes. *Candida albicans* is the most common pathogen causing balanitis in men, and *Candida glabrata* is responsible for a maximum number of genital mycosis infections in women (Table 1).

The predisposing factors for genital infections are hyperglycemia and glucosuria, decreased humoral and cellular immunity, poor hygiene, topical corticosteroid use, pharmacologically induced glucosuria, pregnancy, postmenopausal status, estrogen, and oral contraceptive use.

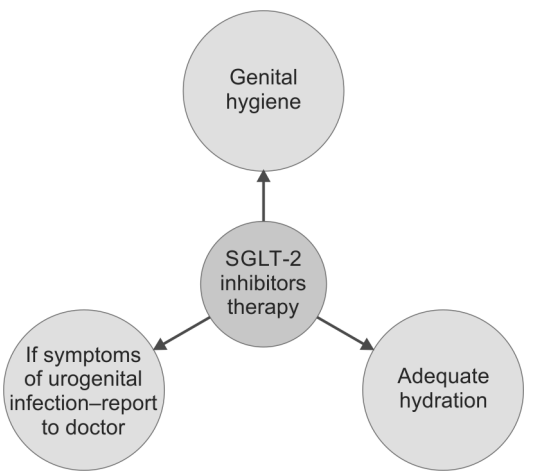
The sodium-glucose cotransporter-2 (SGLT-2) inhibitors are responsible for pharmacologically induced urinary glucose concentration (renal glucosuria) (Fig. 1). A double-blind, parallel group, placebo-controlled study with 546 adults reported higher incidence of genital infections in the dapagliflozin group [2.5 mg, (8%); 5 mg, (13%); 10 mg, (9%)] than in the placebo group (5%). A single efficacy study in which patients received 100 and 300 mg of canagliflozin demonstrated early onset of genital infection symptoms in 14.5% and 14.4% patients, respectively. Safety data pooled from four randomized, placebo-controlled Phase III trials (n = 2,477 patients) showed that patients on empagliflozin therapy had a higher incidence (empagliflozin 10 mg: 4.2%, empagliflozin 25 mg—3.6%) of genital infections as compared with patients on placebo therapy (0.7%).

Genital infection usually appeared within the first 24–26 weeks of SGLT-2 inhibitors treatment (Table 2).

Patient education about perineal hygiene, which includes washing of genital organs followed by urination or defecation, routine hygienic wipes

TABLE 1: Genital infections commonly seen clinically.

	Common symptoms
Men: balanitis	Inflammation, soreness, redness, and skin cuts at the glans
Balanoposthitis	Thick curdy discharge under the foreskin
Urethritis	Itching and burning sensation
Epididymo-orchitis	Pain in the scrotal area
Genital warts	Lesions in the genital area
Women: Vulva infection	Itching, burning, and red skin of the vulva
Vaginal infection	Vaginal curdy and foul-smelling discharge
Pelvic inflammatory disease	Pelvis pain
Genital warts	Lesions in the genital area



(SGLT-2: sodium-glucose cotransporter-2)

FIG. 1: Overview of steps to prevent genital infections.

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TABLE 2: Treatment for vulvovaginal candidiasis.

Genital infection	Treatment recommendations	Strength of recommendation
Uncomplicated *Candida* vulvovaginitis	Topical antifungal agents, with no one agent superior to another, OR	Strong recommendation; high-quality evidence
	A single 150 mg oral dose of fluconazole	Strong recommendation; high-quality evidence
Severe acute *Candida* vulvovaginitis	Oral fluconazole, 150 mg, given every 72 h for a total of 2 or 3 doses	Strong recommendation; high-quality evidence
Candida glabrata vulvovaginitis that is unresponsive to oral azoles	Topical intravaginal boric acid, administered in a gelatin capsule, 600 mg daily, for 14 days OR	Strong recommendation; low-quality evidence
	Nystatin intravaginal suppositories, 100,000 units daily for 14 days OR	Strong recommendation; low-quality evidence
	Topical 17% flucytosine cream alone or in combination with 3% AmB cream administered daily for 14 days	Weak recommendation; low-quality evidence
Recurring vulvovaginal candidiasis	10–14 days of therapy with a topical agent, followed by fluconazole, 150 mg weekly for 6 months	Strong recommendation; high-quality evidence

(AmB: Amphotericin B)

Note: Oral fluconazole single dose 150 mg is as effective as intravaginal clotrimazole for 7 days.

Source: Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50.

TABLE 3: Topical antifungal agents for vaginal candidiasis.

Medicine	Preparation
Clotrimazole cream 1%	5 g single application at bedtime for 7–14 days
Clotrimazole vaginal suppository 100 mg	1 suppository at bedtime for 7 days
Clotrimazole vaginal suppository 200 mg	1 suppository at bedtime for 3 days
Miconazole cream 2%	5 g single application at bedtime for 7 days
Miconazole vaginal suppository 100 mg	1 suppository at bedtime for 7 days
Miconazole vaginal suppository 200 mg	1 suppository at bedtime for 3 days

or sprays, women should be advised to wash from front-to-back, uncircumcised males should retract the prepuce before wash, use clean water for washing or mild soap, if required, alcohol-based disinfectant should not be used for washing is necessary.

Safety and efficacy studies with SGLT-2 inhibitors have shown that genital infections reported in the study population are often mild-to-moderate in severity and respond well to conventional therapy. As per the Infectious Diseases Society of America, 2016, clinical practice guidelines for the management of candidiasis for the treatment of uncomplicated *Candida vulvovaginitis*, topical antifungal agents are recommended (Table 3). Whereas, for patients who have a recurrent infection, oral fluconazole 150 mg weekly for 6 months is recommended.[2,3]

Key Message

- ***Genital infections in such patients are mild-to-moderate in nature and respond well to standard treatment, and do not require discontinuation of SGLT-2 therapy.***

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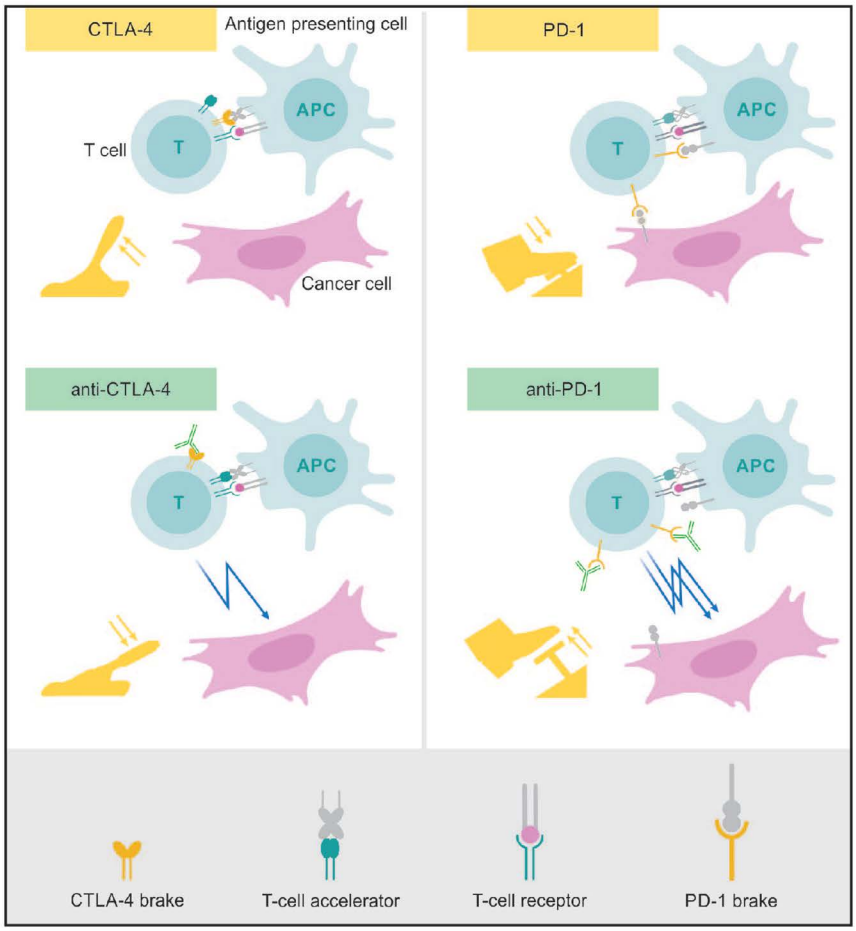
The Nobel Prize in Physiology or Medicine 2018

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to **James P Allison**, *Texas, USA* and **Tasuku Honjo**, *Kyoto, Japan*, "for their discovery of cancer therapy by inhibition of negative immune regulation."



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