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Atrial Fibrillation and Its Association with Endocrine Disorders

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Abstract

Atrial Fibrillation (AF) is the most common arrhythmia affecting millions of people and the number is rising, it is therefore important to understand the risk factors causing AF. Risk factors such as hypertension, heart failure, coronary heart disease, and type 2 diabetes mellitus increase the risk of AF, however, the underlying etiology in a majority of patients remains elusive. Many of the endocrine disorders have been implicated in causing AF and an in depth knowledge of these disorders helps in early diagnosis and treatment. Due to the high prevalence of AF and its complications, it is therefore important to recognize these risk factors and have a low threshold for suspicion while other common causes are being excluded. In this review we summarize the issues related to AF and endocrine disorders. A better understanding of the relationship may lead to the development of the primary preventive strategies, fostering a more preventive and predictive approach that may result in decreased incidence of AF and its associated complications and provide personalized treatment options. For this review we carried out a search of Pubmed, the words or combination of words we used for our search include Endocrine disorders, metabolic disorders, Dyslipidemia, Diabetes mellitus type 2, Vitamin D, Hyperthyroidism, Primary aldosteronism, Pheochromocytoma, Obesity, Hypercalcemia, Hypogonadism, Medications, and Atrial fibrillation. We also retrieved articles from the references of retrieved articles.

Introduction

Atrial fibrillation (AF), is the most common arrhythmia in the United States with an estimated prevalence of 2.7 to 6.1 million in 2010 and it is expected to rise to 5.6 and 12 million in 2050.[1,3] It has significant effect on morbidity and mortality: it is estimated that AF increases the risk of stroke by fivefold and about 15% of all patients who have stroke have AF too.[1,3] The percentage of strokes attributable to AF increases from 1.5% at 50-59 years of age to 23.5% at 80-89 years of age.[1] AF most commonly occurs secondary to cardiovascular pathologies as well as systemic disorders. This relationship was first demonstrated in the Framingham Heart Study.[2,3] Ischemic heart disease, heart failure, valvular heart disease, hypertension (HTN), diabetes, and hyperthyroidism have long been shown to increase the risk for AF. Despite this understanding, the etiology of AF in majority of patients is still unknown. Understanding the underlying cause may lead to effective treatment and thus can improve prognosis, reducing the disability and deaths associated with this complicated medical problem. Proper treatment of the underlying causes can control AF and the associated root cause thus reducing the risk of serious complications; and with the introduction of new therapeutic approaches the treatment paradigms are rapidly evolving. In this review, we will discuss the various endocrine causes that have been implicated in the development of AF and the possible mechanisms.

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None

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Pituitary

Thyroid stimulating hormone (TSH) secreting pituitary adenoma is a rare cause of hyperthyroidism. While the relationship between primary hyperthyroidism and AF is well established, it is also important to recognize that central hyperthyroidism also can also lead to AF, this is a rare but important cause of AF.[4] For this it is important to perform thyroid function test to provide appropriate treatment as inadvertent ablation of thyroid can increase the size of the tumor.[4] Elevated free T4 and/or T3 with normal or non-suppressed TSH should prompt investigating pituitary cause of AF and treating TSH secreting adenomas appropriately with surgery. A combination of Surgery, Medical therapy (Somatostatin analogues) and Radiotherapy may be required for long-term management of these patients.

Thyroid Disease

Subclinical Hyperthyroidism

Defined as low thyroid stimulating hormone (TSH) with normal thyroid hormone levels has also been recognized as a cause of AF.[5] Causes of subclinical hyperthyroidism could be either exogenous or endogenous. Most common exogenous cause being excessive thyroxine replacement in hypothyroid patients or may be because

of iatrogenic suppression in thyroid cancer patients.[6,7] Endogenous causes are those of overt hyperthyroidism, due to autonomous thyroid function: Graves', Toxic multinodular goiter and toxic adenoma.[6,7] Untreated for a long time, subclinical hyperthyroidism can lead to increased left ventricular mass, impaired diastolic filling and impaired exercise tolerance due to increased work load and adrenergic over activity.[8] Subclinical hyperthyroidism was associated with 2-3 fold-increased risk of AF in elderly patients with low or undetectable serum TSH.[9,10] A large Danish population based cohort study [11]that analyzed the relationship between the whole spectrum of thyroid diseases and AF has found a linear relation between the levels of thyroid dysfunction and AF risk. Subclinical hyperthyroid patients and patients with high normal thyroid function are more at risk than normal and hypothyroid individuals, this finding was also supported by the Rotterdam study.[12,13]

Diagnosis of subclinical hyperthyroidism can be established with persistently low or undetectable TSH by repeating the serum TSH at 3 or 6 months. Transient causes of hyperthyroidism (Thyroiditis, drugs, pregnancy, non-thyroidal illnesses) have to be excluded. Task force recommends treating patients with persistently low TSH <0.1 mU/L, age >65, patients with cardiac risk factors, heart disease and symptomatic individuals. When TSH >0.1 mU/L treatment should be initiated if the patient is >65 years of age, heart disease or symptomatic individuals.[5] Treatment of Subclinical hyperthyroidism depends on the cause, and is similar to the treatment of overt hyperthyroidism. Treatment options include medical therapy (antithyroid drugs, Beta-adrenergic blockers) or Ablative therapy (radioactive iodine or surgery); methimazole is considered first line treatment, whereas radioactive iodine is considered appropriate if the cause is a multinodular goiter.[8]

Hyperthyroidism

The estimated prevalence of hyperthyroidism is 1.2% (0.5% overt and 0.7% subclinical).[5] AF is the most common cardiac complication of hyperthyroidism, 10-25% of patients with overt hyperthyroidism have AF.[14] Additional risk factors include advancing age, male sex, ischemic heart disease, valvular heart disease and congestive heart failure.[15] Thyroid hormones act on the thyroid nuclear receptors, or by their sympathoadrenergic action alter the peripheral vascular resistance, increase the heart rate, systolic hypertension, increase ventricular contractility and cardiac hypertrophy,[10] Once thyroid function tests confirm thyrotoxicosis, Electrocardiogram findings may help in identifying hyperthyroid patients at risk of developing AF. These changes include P wave duration and P-wave dispersion, which are both high in these patients.[16]

Main goal of treatment is to restore euthyroid status so that the rhythm is reverted to Sinus and to control the ventricular rate with β adrenergic blockers. Beta blockers may be initiated as soon as the diagnosis of hyperthyroidism is made and among the various β adrenergic blockers available Propranolol (Nonselective beta-adrenergic receptor blockade) at high doses (above 160mg/day) is believed to have an advantage of blocking the conversion of T4 to T3 in peripheral tissues but for that matter cardioselective long acting β blockers (Atenolol, Metoprolol, {Esmolol IV in ICU setting of severe thyrotoxicosis or storm}) are equally effective. Calcium channel blockers, both verapamil and Diltiazem given orally are also effective for rate control if patients cannot tolerate Beta-adrenergic blockers.[5] Beta blockers are used in the first few weeks of treating hyperthyroidism while awaiting the effect of antithyroid medications and can be tapered after 4-8 weeks of achieving a stable dose of antithyroid drugs. If the patient is unable to take anti-thyroid drugs, patient should be adequately treated with beta-blockers in pre-operative period.[5] Excess thyroid hormone can cause coagulation abnormalities including shortened aPTT, increased fibrinogen levels, increased Factor VIII and X activity amounting to 1.44-times greater risk of having a stroke in thyrotoxic patients.[17] Risk of stroke in hyperthyroidism-induced AF is still a matter of debate. It is not considered a risk factor for stoke by the international guidelines, while many observational studies reported a higher incidence of systemic embolism. A lot of available clinical evidence in regards to systemic embolism in these patients recommends anticoagulation,[18,19,20,21]in patients without any specific contraindications, until euthyroid state is restored,[22] while some subsequent studies concluded that age was an important predictor of increased risk of stroke. However one observational study noticed the clustering of ischemic stroke in the early phase of uncontrolled hyperthyroidism so early initiation of anticoagulation therapy should be considered mainly if AF is persistent along with presence of validated stroke risk factors.[23]

Table 1: Endocrine causes that can cause AF

1	Pituitary • TSHoma
2	Thyroid Disease • Subclinical • Overt
3	Iatrogenic Cushing's
4	Primary Aldosteronism
5	Pheochromocytoma
6	Osteoporosis & Bisphosphonates
7	Metabolic Syndrome
8	Diabetes Mellitus
9	Vitamin D
10	Androgen Deficiency
11	Estrogen Deficiency

Adrenal Disorder (Iatrogenic Cushing's)

Corticosteroids are used widely in clinical practice for a number of conditions. Corticosteroids, primarily methylprednisolone was found to increase the risk of AF in many studies.[24,25,26,27] One of these studies showed that the risk was two times high among oral corticosteroid users compared to nonusers.[27] This association was mainly observed in patients on high doses, defined as ≥7.5 mg prednisone equivalent. Hypothesis to explain the arrhythmogenic effect include sodium and fluid retention[25] and an increase in potassium efflux.[28] This effect of corticosteroids also causes hypertension, Left atrial enlargement and congestive heart failure that are all risk factors for AF.[26] No research studies have been done to provide information on how to manage these patients but based on the mechanisms that have been proposed it is prudent to monitor these patients before and after treatment with EKGs, correct electrolytes and assess the patient risk factors of developing atrial fibrillation. In most of the studies that reported high dose steroids causing atrial fibrillation, the arrhythmia reversed spontaneously however using prophylactic propafenone,[29] replacing high dose steroids with fluocortolone have been proposed in high risk patients.[30]

Primary Aldosteronism

Excess aldosterone exerts deleterious effects on the heart.[31] In

a recent case-control study patients with primary aldosteronism (PA) were found to have a 12 fold-increased risk of AF along with increased risk of stroke and Myocardial infarction.[32] The study concluded that because of increased risk of cardiovascular events, primary aldosteronism should be more carefully detected to prevent such complications. High aldosterone levels are thought to induce AF by causing potassium loss. Other hypotheses that have been proposed include an increase in left atrial volume, an excess Left ventricular mass due to excess aldosterone and hypertension, myocardial fibrosis, magnesium losses and catecholamine potentiation, reduced baroreceptor sensitivity.[33] Treatment with aldosterone antagonists has shown to be effective in patients with refractory paroxysmal and persistent AF and suppress atrial and ventricular remodeling in chronic AF patients.[34] In a Meta-analysis of Randomized control trials to assess the effectiveness of Blockade of RAAS for primary prevention of atrial fibrillation, aldosterone antagonists did not appear to prevent onset of AF unlike ACEi and ARBs.[35] However Eplerenone significantly improved maintenance of sinus rhythm after catheter ablation in patients with long standing persistent AF.[36] These results along with findings from a recent review of aldosterone antagonists impact on AF substrate,[37] suggest aldosterone antagonists may be more helpful in preventing the progression of AF rather than preventing new onset AF. A multicenter prospective study (PAPPHY) is ongoing which will study the prevalence of PA in hypertensive patients presenting with Atrial flutter or fibrillation, it will also provide evidence for the outcome of specific treatment for PA on risk of incident and recurrent atrial fibrillation or flutter.[38]

Pheochromocytoma

High levels of catecholamines due to Pheochromocytoma lead to stimulation of β-adrenoreceptors, thus causing arrhythmias. Sinus tachycardia is most frequently associated with pheochromocytoma; however, AF has also been reported in a few studies.[39,40] Presence of paroxysmal arrhythmia with accompanied symptoms like hypertension, sweating, anxiety, pallor and nervousness should prompt physician to look for a diagnosis of pheochromocytoma.[40] In one study, complete resolution of these arrhythmias occurred with α1-adrenoceptor blockers followed by short acting cardioselective beta-blockers.[40]

Osteoporosis and Bisphosphonates

Bisphosphonates are widely prescribed antiresorptive agents in osteoporosis and have shown to decrease fracture risk at spine, hip and other nonvertebral skeletal sites. A large number of studies have shown a possible association of bisphosphonates and AF.[41,42] First and foremost study indicating this association was the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) Pivotal fracture trial[41] which was a large multicenter, randomized, double blind, placebo controlled study of 7765 post-menopausal women with osteoporosis who received zoledronic acid 5mg intravenously once a year. Another big one was the Fracture Intervention Trial (FIT)[42] with 6459 patients who were randomized to receive 5mg once daily alendronate or placebo. Both studies reported increased risk of serious AF. However, there are numerous cohort or case controlled studies[43,44,45] that showed bisphosphonates were not associated with increased risk of AF. Because the evidence is conflicting and equivocal National osteoporosis foundation (NOF;[46]) believes the benefit of taking bisphosphonates far outweighs the risk of serious side effects and that bisphosphonates are not to be withheld when needed. However there should be a high risk of suspicion, and at risk patients need to be monitored frequently for symptoms of new onset AF.

Metabolic Syndrome

Diagnosed as per the guidelines provided by Adult Treatment Panel III[47] when at least 3 of the following criteria are met: 1) Abdominal obesity; waist circumference >102 cm in men and >88 cm in women, 2) Elevated triglycerides (>150 mg/dl), 3) Low HDL (<40 mg/dl in men, <50 mg/dl in women), 4) Elevated Blood pressure (≥130 mm Hg Systolic, ≥85mm Hg Diastolic), 5) Impaired glucose tolerance (≥110 mg/dl). Hypertension,[48,49] elevated blood glucose,[50,51,52] Dyslipidemia,[53,54] abdominal adiposity[55] have been individually identified as risk factors for AF. Presence of multiple comorbidities in the same individual may increase the risk even further. This association was studied from the data collected for large population based national study of US adults (REGARDS).[56] It was found that higher the number of metabolic syndrome components, the more the prevalent AF.[56,57,58] Inflammation and oxidative stress have been implicated as common etiological factors in the pathogenesis of AF in these patients. Together they facilitate atherosclerosis that can cause structural and electrical remodeling.[59,60] Because of the increasing prevalence of metabolic syndrome in the general population, it is important for the treating physician to be aware of the risk of AF in these patients and aggressively treat individual components to prevent the development of serious complication thereof. Important treatment strategy involves lifestyle modification, exercise, and aggressive treatment of hypertension and other risk factors.

Diabetes Mellitus

Evidence supporting diabetes, as a risk factor in causing AF is equivocal. Few studies have shown the impact of insulin resistance on new onset AF.[50,51] Alternatively, some studies have concluded that there is no significant association between diabetes and AF.[61, 62] More recently, a study concluded that diabetes was an independent determinant of AF only among women.[50] There are several hypotheses, which have been proposed to explain this association. Firstly, oxidative stress and inflammation have been implicated in the pathophysiology of AF associated with diabetes mellitus[59,60] and elevated CRP levels were found in these patients. The second possibility being hypoglycemia in both diabetics and non-diabetics, which increases the susceptibility to AF.[63] Neural remodeling as a possibility of increased vulnerability of AF was proposed as another mechanism in these patients, which involves parasympathetic denervation and heterogeneous sympathetic denervation.[64] The European Society of Cardiology guidelines recommend the use of CHA_2DS_2-VASc for the Management of Atrial Fibrillation with oral anticoagulants after assessing the risk of major bleeding. Thiazolidinedione, agonists of PPAR-γ, may be a novel upstream therapy for AF in DM patients because of their anti-inflammatory and anti-oxidant effects other than their hypoglycemic effect.[65] Because of these properties, a study on DM patients with paroxysmal AF showed that Pioglitazone significantly increased the success rate of catheter ablation and the rate of maintenance of sinus rhythm was higher in the proportion of patients treated with pioglitazone.[66]

Vitamin D

Vitamin D deficiency has been linked to cardiovascular morbidity and mortality in recent times.[67,68,69] There are a few studies that reflect

that vitamin D deficiency can predispose to AF.[70] It is known that vitamin D suppresses proinflammatory cytokines causing increase in IL-10, which has anti-inflammatory function. Deficiency also increases the vulnerability to AF through its TGFB1 expression, thus causing atrial fibrosis and conduction heterogeneity.[70] Vitamin D inhibits RAAS and PTH and through its negative regulatory role for renin, it was hypothesized that vitamin D deficiency may increase the risk of AF. Low levels of vitamin D may also increase the risk of HTN and left ventricular hypertrophy through its activation of RAAS and relative hyperparathyroidism.[70,71] On the other hand, a large study showed that high levels of vitamin D could increase the risk of AF.[72] In a community-based sample of 2930 participants in Framingham heart study [73,74] vitamin D status was not related to the development of AF. All these studies have raised concerns about a possible U-shaped relationship, but before any conclusions can be drawn more trials on vitamin D role in AF and the safety margins for vitamin D supplementation are needed. In the study that concluded that excessive Vitamin D is associated with 2.5-fold increased incidence of AF had a Vitamin D level of >100ng/dl[64] which is a difficult level for a person to reach without multivitamin, Supplements and dairy products, it is prudent to ask each patient pertinent questions and making sure baseline vitamin D level is not too low (<20 ng/dl) nor too high (>100 ng/dl) to decrease the risk of AF.

Androgen Deficiency

Prevalence of AF increases with age. This finding seems to coincide with the well-known predisposing factors for the development of AF like Coronary artery disease, HTN, Congestive heart failure which are also linked to increasing age. Age related decline in testosterone levels in males[75,76,77] is thought to be the main risk factor in these patients. The proposed mechanism for AF includes elevated proinflammatory cytokines like TNF and IL-1 in men with hypogonadism. Testosterone treatment in these patients increases the levels of anti-inflammatory cytokine IL-10 to induce vasodilatation and improve vascular reactivity.[78] There is also an inverse relationship between the level of CRP and testosterone.[79] This finding adds to support the evidence that implicates inflammation and oxidative stress in AF. However the benefits of testosterone supplementation to prevent AF in hypogonadism are unknown since there are studies to prove that anabolic steroids may increase the risk of AF in athletes and body-builders.[80] This is due to the cardiovascular adverse effects of anabolic action of testosterone and the supraphysiological doses that athletes use to improve physical performance. The underlying etiology of AF in anabolic steroid use may be due to Left Ventricular hypertrophy and autonomic dysfunction.[81]

Estrogen Deficiency

Female sex hormones are believed to have a protective effect since the prevalence of AF is very low in premenopausal women.[82] The prevalence increases from 0.1% in women<55 yrs. to 9.1% in women ≥85 yrs. of age.[83] Estrogen was believed to restore pathologically shortened atrial refractoriness by inhibiting intracellular calcium overload or the delayed outward potassium current thus inhibiting atrial tachyarrhythmias.[82] Metabolites of estradiol, the active form of estrogen may induce many estrogen-receptor independent actions that protect the heart and blood vessels mediated by improvement in vascular endothelial cell function.[76] AF in women increases the risk for complication like stroke, congestive heart failure and heart attacks. However, Women's Health Initiative reported a modest but significant increased risk of AF in women who were assigned to post-menopausal hormones particularly in women with prior hysterectomy who were assigned to estrogen alone (baseline characteristics showed higher cardiovascular risk profile in these patients). Estradiol however may play less important role in male AF.[76]

Conclusions:

Endocrine disorders and other metabolic abnormalities should be considered in patients presenting with atrial fibrillation. Although thyroid hormones and primary aldosteronism have been clearly implicated, careful assessment of other endocrine functions should be undertaken to properly address and treat the underlying cause. The subclinical state of disease should be kept in mind as the natural history and long-term outcomes of treatment are largely unknown. Further studies are needed to properly assess the role of Diabetes mellitus, Vitamin D status, sex hormones and benefit of their supplementation. More studies are needed to further understand the bidirectional interaction between atrial fibrillation and the medications that have been implicated in causing atrial fibrillation like bisphosphonates and Corticosteroids. The knowledge of the association of endocrine causes and atrial fibrillation is ever more important as the population tends to be aged with many comorbidities while patients are on numerous medications.

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