ENDOCRINOLOGICAL ASPECTS OF CARDIOVASCULAR DISORDERS

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ABSTRACT
Normal endocrine function is essential for cardiovascular health. Disorders of the endocrine system, consisting of hormone hyperfunction and hypofunction, have multiple effects on the cardiovascular system. The syndromes of insulin resistance actually make up a broad clinical spectrum, which includes obesity, glucose intolerance, diabetes and the metabolic syndrome, as well as an extreme insulin-resistant state. Many of these disorders are associated with various endocrine, metabolic and genetic conditions. These syndromes may also be associated with immunological diseases and may exhibit distinct phenotypic characteristics. The metabolic syndrome, a state of insulin-resistance that is also known as either syndrome X or the dysmetabolic syndrome has drawn the greatest attention because of its public health importance. In clinical practice, no single laboratory test is used to diagnose insulin resistance syndrome. Diagnosis is based on clinical findings corroborated with laboratory tests. Individual patients are screened based on the presence of comorbid conditions. Treatment involves pharmacologic therapy to reduce insulin resistance, along with surgical management of underlying causes if appropriate. Comorbid conditions should be evaluated and addressed; this is generally feasible on an outpatient basis, though some patients will require admission. The metabolic syndrome requires aggressive control of cardiovascular and metabolic risk factors. In this study, the author investigates the impact of endocrine dysfunction on insulin resistance; cardiovascular system and the conditions to be evaluated and discussed.

KEYWORDS: Insulin resistance (IR), Metabolic syndrome, Impaired glucose tolerance (IGT), Pancreas, Insulin like growth factor (IGF).
INTRODUCTION
Diabetes mellitus is one of the major threats to human health in the twenty-first century. The total number of people with diabetes worldwide was estimated up to 171 million in 2000 (Whiting et al., 2011) which increased to 221 million in 2010 and is projected to reach 366 million by 2030 (Kashweer & Cornwell, 2014). Needless to say, the increase in the number of people with diabetes will be accompanied by an increase in the number of those with diabetic complications such as nephropathy, retinopathy, neuropathy and atherosclerosis. In 2014 the global prevalence of diabetes was estimated to be 9% among adults aged 18+ years (WHO, 2012). In 2012, an estimated 1.5 million deaths were directly caused by diabetes (WHO, 2014). More than 80% of diabetes deaths occur in low- and middle-income countries (WHO, 2014). WHO projects that diabetes will be the 7th leading cause of death in 2030 (Mathers & Loncar, 2006). Given that type 2 diabetes accounts for more than 90% of cases of diabetes worldwide, it is important that we understand the pathogenesis of this condition and develop new approaches to its prevention and treatment.

Type 1 and type 2 diabetes directly relate to problems with insulin and therefore involve the pancreas. Glucagon and insulin are the two primary hormones – both produced by the pancreas – that stimulate or depress the level of glucose in the blood. In type 1 diabetes, the pancreas completely loses the ability to produce insulin. In type 2 diabetes, insulin resistance, the cells of the body partially or fully lose their ability to use insulin. Human type 2 diabetes is characterized by a decrease in non oxidative muscle glycogen synthesis and by the deposition of amyloid in the islets of Langerhans (Marzban et al., 2003). Amylin is a 37 aminoacid peptide which is a major component of islet amyloid and has structural similarity to human calcitonin gene related peptide 2 (CGRP2). CGRP2 is a neuropeptide which may be involved in motor activity in skeletal muscle. Either way, the level of blood sugar increases and if untreated, will cause serious damage to the body and is fatal in some situations. There are other forms of diabetes mellitus, some due to genetic factors, and others to pregnancy, cystic fibrosis and steroid use (Marzban et al., 2003). All forms are detectable through blood tests for glucose levels and all are treatable. Both type 1 and type 2 diabetes are chronic, incurable diseases although regular insulin injection is effective in controlling type 1 and lifestyle changes combined with medication are effective in controlling type 2.

According to National Diabetes Statistics Report 2014, (released June 10, 2014) by American Diabetes Association, National Health Institute, USA, insulin resistance affects 90% of persons with diabetes, 30% of the population aged 40-74 and 60% of persons with confirmed
CVD without known diabetes. At least half of persons with hypertension have insulin resistance. Heart disease causes 55% of the deaths among persons with diabetes and stroke causes an additional 10%. Women may suffer disproportionately from diabetes, with diabetes in women particularly increasing the likelihood of heart failure and peripheral vascular disease. Diabetes and other insulin-resistant states are associated with endothelial dysfunction and oxidative stress is a potential underlying mechanism. Normal endocrine function is essential for cardiovascular health (Marzban et al., 2003). Disorders of the endocrine system, consisting of hormone hyperfunction and hypofunction, have multiple effects on the cardiovascular system. The main problems with all types of diabetes are the long-term effects. Cardiovascular disease has long been associated with diabetes, as has other chronic conditions like kidney failure and damage to the eyes (diabetic retinopathy). High levels of blood sugar are notorious for damaging blood vessels, which can affect the cardiovascular system in many and sometimes subtle ways. Long-term effects of diabetes can be more serious than the original diabetes.

The Endocrine system, Insulin Resistance and related disorders

Diabetes disturbs the body’s mechanism to regulate blood glucose levels. Insulin helps to reduce levels of blood glucose whereas glucagon works the reverse way. In people without diabetes, insulin and glucagon work together to keep blood glucose levels balanced. In diabetes, the body either doesn't produce enough insulin or doesn't respond properly to insulin causing an imbalance between the effects of insulin and glucagon.

Defective function of the pancreatic β-cells is now accepted to be a hallmark of type 1 and type 2 diabetes. The importance of the β-cells in type 1 diabetes has long been accepted. On the contrary, the necessity of a pancreatic defect in type 2 diabetes has been widely appreciated (Marzban et al., 2003; Anderson et al., 2003). For many years, it was considered that insulin resistance alone could engender hyperglycemia in those without immune etiology of disease. Results based on modelling indicating that β-cells upregulation would compensate for even severe insulin resistance and not result in fasting hyperglycemia were supported by the laboratory of C.R. Kahn and colleagues, who demonstrated that knockout of the muscle insulin receptor using Cre-loxP methodology did not result in a diabetic phenotype (Kasuga, 2006). Compensatory hyperinsulinemia was sufficient to allow for regulation of the blood glucose in the normal range. On the contrary, modeling studies predicted that a β-cells defect in the face of insulin resistance would engender a diabetes phenotype.[8] This result was
likewise confirmed by knockout of the insulin receptor as well as IRS-1, which led to insulin resistance, β-cells defect and diabetes (Anderson et al., 2003; Kasuga, 2006). Thus, type 2 diabetes is most often a “2-hit” phenomenon, in which insulin resistance is accompanied by a β-cells defect preventing compensatory upregulation of insulin secretion.

The various endocrine glands lead to insulin resistance and cardiovascular disorders in one way or the other as discussed below.

**The Pituitary Gland**

**Growth Hormone Deficiency, insulin resistance and Cardiovascular Disease**

Pituitary plays a key role in secretion and regulation of growth hormone, the deficiency of which is associated with atherosclerosis and cardiovascular disorders in turn. Growth hormone deficiency (GHD) is associated with increased body fat and central adiposity, dyslipidemia (low high density lipoprotein cholesterol [HDLc], high total cholesterol and high low density lipoprotein cholesterol [LDLc]), endothelial dysfunction and insulin resistance (Attanasio et al., 2010). Increased carotid arterial intima-media thickness (IMT), a marker of early atherosclerotic development, has also been described in GHD. GH replacement therapy can result in increased lean body mass and decreased visceral adipose tissue and may decrease total and LDLc levels, although effects on HDLc have been inconsistent. Endothelial dysfunction improves with growth hormone (GH) replacement therapy, with increased flow-mediated dilatation and reduced arterial stiffness due to improved nitric oxide (NO) availability.

Echocardiography in patients with childhood- or adolescent-onset GHD has revealed significant reductions in left ventricular (LV) posterior wall thickness and interventricular septal thickness, with resultant decreases in LV mass index and LV internal diameter. Most adult patients with GHD have impaired LV performance at peak exercise and report exercise intolerance. Studies have also shown that GH replacement therapy reduces intima-media thickness, improves cardiac performance, increases LV mass, LV end diastolic volume (LVEDV) and stroke volume (Calao et al., 2006; Soo & Elizabeth, 2011).

**Adrenocorticotropic Hormone, insulin resistance and Cardiovascular Disease**

Adrenocorticotropic hormone palys a key role in production and release of cortisol by the cortex of adrenal gland. Excessive production of cortisol (hypercortisolism) is associated with
hypertension, central obesity, insulin resistance, dyslipidemia and alterations in clotting and platelet function. Hypertension is present in about 80% of adult patients with endogenous Cushing’s syndrome and results from changes in regulation of plasma volume, systemic vascular resistance, and vasodilatation (Soo & Elizabeth, 2011). Treatment of Cushing’s syndrome usually results in improvement or resolution of hypertension, although hypertension may persist in patients with long-standing hypercortisolism and/or co-existing essential hypertension (Magiakou et al., 2006). Abnormal glucose metabolism in Cushing’s syndrome results from stimulation of hepatic gluconeogenesis and glycogenolysis. Patients with hypercortisolism may have impaired fasting glucose, impaired glucose tolerance, hyperinsulinemia, insulin resistance and/or diabetes mellitus. Cushing’s syndrome has been associated with increased lipoprotein (a), decreased HDLc and increased triglycerides (Soo & Elizabeth, 2011). The duration of cortisol excess correlates with the degree of dyslipidemia seen. Cortisol also increases the synthesis of several coagulation factors, stimulating endothelial production of von Willebrand factor and concomitantly increasing factor VIII. Hypercortisolism may also enhance platelet aggregation and reduce plasma fibrinolytic capacity (Pereria et al., 2010).

Cushing’s syndrome has been associated with left ventricular hypertrophy (LVH), concentric remodeling, diastolic dysfunction and subclinical LV systolic dysfunction. Echocardiography has revealed increased interventricular septum thickness and posterior wall thickness, increased LV mass index and increased relative wall thickness in Cushing’s patients (Soo & Elizabeth, 2011). Diastolic dysfunction has been demonstrated, with impaired early LV relaxation, longer isovolumetric relaxation times and evidence of global myocardial relaxation impairment. The abnormalities of LV structure and function may be reversible with normalization of hypercortisolism. However, patients may continue to exhibit exercise intolerance due to steroid-induced myopathy and resultant muscle weakness (Pereria et al., 2010).

The Thyroid and Parathyroid Glands

Hypothyroidism, insulin resistance and Cardiovascular Disease
Thyroid hormones play an important role in regulation of cholesterol level in body, which in turn have a great significance in cardiovascular diseases. Lipid metabolism is altered in hypothyroidism and approximately 90% of patients with overt hypothyroidism have elevated total cholesterol and LDLc levels (Biondi & Cooper, 2008). Serum total and LDLc levels are increased by approximately 30% in hypothyroidism, with greater increases in LDL levels seen in patients with insulin resistance and in smokers. These increased low-density lipids (LDL) levels are primarily because of decreased fractional clearance of LDL that results from a reduced number of hepatic LDL receptors. Apolipoprotein B and the atherogenic LDL variant, lipoprotein (a), are also increased in hypothyroidism. Triglyceride and very low density lipoprotein levels are normal to increased, whereas changes in high-density lipids (HDL) are variable (Osman et al., 2007). These lipid abnormalities are generally reversible with restoration of euthyroidism. Subclinical hypothyroidism has been associated with increased LDL and total cholesterol levels in several cross-sectional studies, but the effects of treatment in small trials have been inconsistent (Biondi & Cooper, 2008).

Hyperparathyroidism, insulin resistance and Cardiovascular Disease

Parathyroid hormone (PTH) plays a critical role in maintaining an adequate calcium–phosphorus homeostasis. PTH affects three principal target organs to maintain calcium balance: bone, intestinal mucosa and kidney. The incidence of primary hyperparathyroidism (PHPT) is approximately 21.6 per 100,000 annually, with a higher incidence in females and in older adults, reaching a peak of 63.2 per 100,000 annually at ages 65-74 (Golden et al., 2009). The cardiovascular risk associated with PHPT is attributable in large part to an increased prevalence of hypertension, obesity, glucose intolerance and insulin resistance. Proposed mechanisms of hypertension in patients with PHPT include increased calcium deposition leading to arterial stiffness in long standing and/or severe disease, direct PTH-mediated stimulation of the renin-aldosterone system and PTH-mediated endothelial dysfunction and increased sympathetic activity. Surgical correction of hyperparathyroidism has not consistently demonstrated improvement in hypertension (Heylinger et al., 2009). Treatment of PHPT with surgery has been shown to improve insulin sensitivity in patients with more severe disease (Silverberg et al., 2009). Carotid IMT has been shown to be higher in patients with PHPT and measures of carotid stiffness are associated with the degree of PTH elevation. This suggests that vessel stiffness may be related to the severity of hyperparathyroidism (Walker et al., 2009).
LVH has also been associated with hyperthyroidism. The hemodynamic changes in hyperthyroidism result in increased cardiac work and compensatory cardiac hypertrophy over time. In the short term, hyperthyroidism may be associated with improved diastolic function but in the long term, chronic thyrotoxicosis may induce LVH and diastolic dysfunction.

LVH has been observed in PHPT in many studies, particularly in patients with moderate to severe hyperparathyroidism, independent of the effects of hypertension. Data from animal studies suggest that PTH has trophic effects on cardiomyocytes that results in hypertrophy. Surgical correction of hyperparathyroidism has resulted in regression of LVH in some studies (Soo & Elizabeth, 2011). Calcifications of the aortic valve, mitral valve and myocardium have been demonstrated in PHPT patients with significant hypercalcemia (Silverberg et al., 2009).

The Pancreas

Pancreatic β-cell failure

Pancreatic β cells initially compensate for the insulin resistance associated with obesity by upregulating the secretion of insulin. The β cell failure and diabetes that follow this period of β cell compensation may result from inadequate expansion of β cell mass or failure of the existing β cell mass to respond to glucose. Each of these 2 possible scenarios might result from a defect in insulin and IGF1 signaling in pancreatic β cells. As mentioned earlier, mice that lack insulin receptors in β cells have a defect in glucose sensing and a reduced β cell mass. In contrast, mice lacking IGF1 receptors in β cells manifest only a defect in glucose sensing (Ueki et al., 2006). Mice deficient in both insulin receptors and IGF1 receptors, however, develop early onset diabetes as a result of reduced β cell mass (Ueki et al., 2006). We also recently showed that mice with β cells deficient in PDK1, a common downstream mediator of both insulin and IGF1 signaling, develop a similar diabetic phenotype (Hashimoto et al., 2006). These data suggest 2 interesting notions: (a) The phenotype associated with a disturbance in insulin and IGF1 signaling in β cells may depend on the severity of the disturbance, with a virtually complete elimination of such signaling resulting in a substantial decrease in β cell mass and a less severe impairment resulting in a decrease in the insulin secretory response to glucose. (b) Both of the prominent features of type 2 diabetes — insulin resistance in peripheral tissues and β cell failure — may result from a defect in insulin signaling. Interestingly, another such unifying hypothesis was recently proposed: that mitochondrial dysfunction may cause both insulin resistance in peripheral
tissues and impairment of glucose induced insulin secretion in β cells (Lowell & Shulman, 2005). Pancreatic β cells are exposed during β cell compensation to metabolic changes associated with obesity, so factors commonly associated with obesity — such as insulin resistance (including that in β cells), adipokines, FFAs, reactive oxygen species and endoplasmic reticulum–associated stress should therefore be examined as candidates for inducers of β cell failure.

Insulin resistance caused by the faulty functioning of various endocrine glands leads to severe disorders. The normal metabolic functions of insulin are affected because of the disturbed downstream signalling resulting into upregulation of eNOS genes and associated factors that ultimately lead to cardiovascular disorders (fig. 1).

Fig 1. Insulin stimulates production of nitric oxide (NO) and secretion of endothelin-1 (ET-1) from endothelial cells. Regulation of endothelial function by insulin results in production and release of mediators with opposite hemodynamic activities on vascular tone, vascular permeability and hemostatic processes. Activation of endothelial NO synthase (eNOS) increases production of NO. NO reduces expression of adhesion molecules in endothelium, promotes vasorelaxation and inhibits proliferation in vascular smooth muscle cells (VSMC) and adhesion, activation, secretion and aggregation in platelets. Insulin-stimulated release of ET-1 increases expression of adhesion molecules, favors platelet aggregation and promotes VSMC contraction, migration and proliferation. ECE, endothelin-converting enzyme.

(Source: Potenza et al., 2009).[29]
Insulin resistance in specific tissues

An understanding of insulin resistance, which is an impairment of insulin action, requires knowledge of the mechanisms of insulin action in cells. Studies with cultured cells have revealed that a signaling pathway that includes the insulin receptor, insulin receptor substrate (IRS), PI3K (class IA), phosphoinositide dependent kinase 1 (PDK1) and the protein kinase Akt plays a central role in the metabolic actions of insulin in many cell types (Soo & Elizabeth, 2011). Whether or not this insulin signaling pathway contributes to energy homeostasis in the whole body has been investigated with mouse models that harbor tissue specific mutations in genes that encode the various pathways. Mice that lack insulin receptors specifically in the liver exhibit insulin resistance, glucose intolerance and a failure of insulin to suppress hepatic glucose production and regulation hepatic gene expression. A similar phenotype was demonstrated for mice in which PI3K activity was inhibited specifically in the liver as a result of the expression of a dominant negative mutant of this enzyme (Soo & Elizabeth, 2011). These observations suggest that insulin resistance in the liver contributes to the pathogenesis of type 2 diabetes, consistent with results obtained with cultured cells. In contrast, mice lacking insulin receptors in muscle exhibit hyperlipidemia but normal glucose tolerance (Soo & Elizabeth, 2011). However, given that transgenic mice that express a dominant negative mutant of the IGF1 receptor specifically in muscle develop insulin resistance and early onset diabetes (Fernandez et al., 2001), loss of insulin signaling via insulin receptors in muscle may be compensated for by IGF1 receptor signaling. Mice that lack insulin receptors in adipocytes are lean and are protected against obesity related glucose intolerance (Fernandez et al., 2001), suggesting that insulin signaling in adipocytes per se may not contribute to the systemic insulin resistance associated with obesity. Surprisingly, studies of mouse models with targeted mutations in genes that encode mediators of insulin signalling have suggested that such signaling in non classical insulin target tissues, such as the brain and pancreatic β cells, plays an important role in the regulation of energy metabolism.

The importance of insulin signaling in the central nervous system for the regulation of energy metabolism as well as for reproduction was directly demonstrated by the generation of mice that lack insulin receptors in the brain. Transgenic rescue of insulin receptor–deficient mice also suggested that insulin action in the brain plays a dominant role in maintenance of energy homeostasis (Okamoto et al., 2004). One of the actions of insulin in the brain is the
suppression of hepatic glucose production. It was shown that mice that lack STAT-3 specifically in the liver manifest insulin resistance associated with an increase in hepatic glucose production (Inoue et al., 2004). It was identified that signaling by IL6 and STAT-3 in the liver as being responsible in part for the inhibition of hepatic glucose production induced by intra cerebro ventricular injection of insulin (Inoue et al., 2006). These data thus suggest that insulin resistance in the brain may also contribute to the pathogenesis of type 2 diabetes by increasing hepatic glucose production and caloric intake.

The hyperbolic sensitivity-secretion relationship

It is of interest to consider why several decades passed between the demonstration of severe insulin resistance and the recognition of the absolute necessity for a β-cell defect for the pathogenesis of type 2 diabetes. To understand the role of the β-cell, it has been useful to elucidate the quantitative relationship between insulin sensitivity and insulin action as it exists in normal (i.e., not prediabetic) individuals. Some years ago, we postulated that, if β-cells are normal, the sensitivity-secretion relationship could most efficiently be expressed as a rectangular hyperbola (Buchana et al., 2000). The product of insulin sensitivity and insulin secretory response would equal a constant, which we named the “disposition index”. Based on a limited data set obtained in human volunteers, it was postulated that shifts in insulin sensitivity would be accompanied by compensatory alterations in β-cell sensitivity to glucose (Mittelman et al., 2000). Thus, reduction in insulin action (1 insulin resistance) should upregulate β-cell sensitivity, whereas enhancement of insulin action (2 insulin resistance) would down regulate β-cell sensitivity (fig. 2).

Fig 2. The importance of expressing β-cell responsivity in relation to insulin sensitivity is illustrated by using the disposition index metric; i.e., the product of β-cell responsivity and insulin sensitivity is assumed to be a constant. A normal subject reacts to impaired insulin sensitivity by increasing β-cell responsivity (state II), whereas a subject with impaired tolerance does not (state 2). In state II, β-cell responsivity is increased but the
disposition index β-cell metric is normal, whereas in state 2, β-cell responsivity is normal but the disposition index is impaired.

(Source: Saisho, 2015)\[^{30}\]

CONCLUSIONS
Endocrine dysfunction may have a significant impact on the cardiovascular system. Restoration of normal endocrine function often results in reversal of adverse cardiovascular changes. Hormone-mediated cardiac changes should be considered when evaluating endocrine and cardiac patients. This assessment of the mechanisms that may lead to HF in patients with endocrine dysfunction confirms the link between various hormone and cardiovascular function. This, in turn, reinforces the importance of early detection and effective treatment of cardiac abnormalities in patients affected by endocrine disorders leading to insulin resistance. Close cooperation between endocrinologists and cardiologists to identify the best treatment options is essential if we are to improve the prognosis of severe cardiac involvement in patients with overt and subclinical endocrinological dysfunction.

REFERENCES


