ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 10, Issue, 03(E), pp. 31523-31527, March, 2019

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

A REVIEW OF AORTIC STIFFNESS IN TYPE 2 DM PATIENTS AND ITS CORRELATION WITH MICROVASCULAR COMPLICATIONS

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DOI: http://dx.doi.org/10.24327/ijrsr.2019.1003.3277

ARTICLE INFO

Article History:
Received 4th December, 2018
Received in revised form 25th January, 2019
Accepted 18th February, 2019
Published online 28th March, 2019

Key Words:

type 2 diabetes mellitus.aortic stiffness. 2d echo cardiography. Neuropathy. Retinopathy. Nephropathy.

ABSTRACT

Background: Arterial stiffness is found to be significant in pathogenesis of cardiovascular diseases Aortic stiffness depends on the structural and geometric properties of the arterial wall and on the distending pressure, and ageing and blood pressure (BP) are its main determinants .Furthermore, aortic stiffness has been demonstrated to predict cardiovascular morbidity and mortality above and beyond other traditional cardiovascular risk factors .Type 2 diabetic patients have increased aortic stiffness and are at particularly augmented risk for cardiovascular morbidity and mortality. Therefore, we planned to investigate the multivariate correlates of increased aortic stiffness, assessed 2D echo in a patients with type 2 diabetes, with particular attention to the relationships between increased stiffness and the presence of micro vascular complications. To assess aortic stiffness in patients with type 2 diabetes mellitus patients and to correlate aortic stiffness with micro vascular complications of diabetes mellitus

INTRODUCTION

Diabetes mellitus is a chronic disease, which occurs due to ineffective utilization of insulin by the body or insufficient production of insulin from pancreas. Because of this phenomenon there is hyperglycaemia (increased concentration of glucose in the blood). Adults with diabetes mellitus are 2-3 fold increased risk of developing ischemic heart disease and stroke.(1) In addition, diabetic neuropathy increases the chance of foot ulcers eventually leading to amputation of the affected limb.Arterial stiffness is considered to be an age-related progressive and continuous process whichis a shared consequence of various different diseases inclusive of diabetes mellitus (DM), hypertension, the metabolic syndrome and chronic kidney disease (CKD). Recent evidences and the available research material on the same suggests that arterial stiffness is a key component in the pathogenesis of diabetes mellitus, and endothelial dysfunction may even occur with early insulin resistance and impaired fasting glucose, before the development of overt diabetes mellitus. Both angiotensin converting enzymes and endothelial nitrous oxide dysregulation play avital role in the pathogenesis of arterial stiffness. Both in cases of diabetic population and in the population as a whole arterial stiffness is an independent predictor of mortality, and appears to be linked to the development and progression of target organ dysfunction in diabetics.

METHODS

In this article, we reviewed various observational studies, clinical and experimental studies and from electronic databases PUBMED and AHA JOURNALS for potentially relevant articles comparing various studies.KEYWORDS: Type 2 Diabetes Mellitus. Aortic Stiffness. 2d Echo Cardiograph. Neuropathy. Retinopathy. Nephropathy.

Arterial Stiffness

Pathophysiology

Arterial stiffness is considered to be ana complex phenomenon characterized by reduced complacency (distensibility) especially in large arteries. This phenomenon of distensibility of the large arteries occurs with aging process(2) and also in the presence of certain cardiovascular system associated

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diseases viz; diabetes, (3) (4) and chronic kidney disease.(4)Clinically, raised pulse pressure (PP) and isolated systolic hypertension are the prime manifestation of raised arterial stiffness.(5)Aortic stiffness also leads to raised systolic blood pressure (SBP) and reduced levels of diastolic blood pressure (DBP). Further, increased post-load of the left ventricle and decrease in mean coronary perfusion pressure which is associated with arterial stiffness, this phenomenon is noted to occur mainly during the diastole. Hypertrophy of the left ventricle is the resultant change,(6)which further worsens the coronary ischemia.(7)Also the raised stress in the vascular wall, further facilitates the rupture of atherosclerotic plaques in vessels. There is a complex interaction between involving cellular elements and the extracellular matrix of the vascular wall in arterial stiffness. Such changes are influenced by hemodynamic forces14 and extrinsic factors, such as hormones(8) and inflammatory mediators, (9) which are found to be related to balance of glucose and sodium.(10) A balance between formation and degradation of collagen and elastin is found to mediate the arterial rigidity. Increase in arterial wall stiffness is defined by the disorganization of elastin and further its replacement by collagen. Collagen overproduction or reduction in elastin may be results of imbalance in this system, which may further be a consequence of pro-inflammatory substances, changes in the activation or inhibition of metalloproteinase enzymes and pressure overload, hence resulting in a reduction in distensibility of vessels.(11)

Evaluation of Arterial Stiffness and Cardio Metabolic Phenotypes

Various invasive and non-invasive methods are applied in the evaluation of arterial stiffness. In routine clinical practise, non-invasive methods are highly applicable and three difference techniques are commonly applied: measurement of distensibility (derived by measurement of intravascular volume and pressure simultaneously), (12) arterial pulse waveform analysis (arterial tonometry), (13) and measurement of pulse wave velocity (PWV). The latter is considered the gold standard method for evaluation of arterial stiffness, according to consensus of researchers.(14)

Various research work subtilize these non-invasive techniques to identify the association of this phenotype with various different disease conditions. Blacher *et a l*(15)studied patients with atherosclerosis, and demonstrated that PWV is associated with the presence of atherosclerosis and also with the extension of the atherosclerosis. Yet another research work, Furthermore, several epidemiological research works have reported the vital role of arterial stiffness in predicting morbidity and mortality, independent of other cardiovascular risk factors. In a met analysis of 17 research works by Vlachopoulos *et al* (16) it was reported that raised PWV (≥ 12 m / s) predicted a 102% increase in the risk of mortality from cardiovascular factors. Also, it was also showed in their research work that the 1 m/s increase in PWV corresponded to an increase in cardiovascular risk by 15%. These research works has led to carotid-femoral PWV being included as part of the evaluation of cardiovascular risk among all high risk individuals. The contracting heart which generates the pulse wave travels at a higher pace in stiff arteries, and also this pulse wave velocity can be assessed noninvasively. Measurement of aortic stiffness from, the measurement of the pulse wave velocity from the carotid to the femoral artery (c-f PWV), is considered to be the gold standard. (16,17) However, Pulse wave velocity can also be evaluated between various other arteries in different location, like the brachial and tibial artery also (brachial-ankle, b-a PWV). Though, caution to be exercised on the fact that peripheral (muscular) arteries are not found to go through the same stiffening process with age like that of the central arteries. Hence c-f PWV and b-a PWV cannot be implied interchangeable. (16) Also, C-f PWV has been found to significantly contribute to additional value beyond time lapsed Cardio vascular risk factors in prediction of cardio vascular events and mortality.(16,18)Furthermore, various research works also have stated that patients at intermediate Cardio vascular risk shall be reclassified into categories of lower or higher risk, based on c-f PWV.(16,18) Hence, the pulse pressure can also be considered as a marker of arterial stiffness. Though, pulse pressure is also found to be mediated by certain other factors, like the pulse rate, the peripheral vascular resistance, and stroke volume. (19) Echo-tracking is an ultrasound technique used for measuring the arterial stiffness locally.(20)

Determinants of Arterial Stiffness

Progression of age is considered to be one of the vital biological factor associated with raised arterial stiffness. (2) Hypertension, (21) diabetes, (3) dyslipidaemia (22) and obesity (23) are some of the other potential factors augmenting the increase in arterial stiffness. Certain research works have stated that that African ancestry would be associated with higher incidence of arterial stiffness.

Heritability of Arterial Stiffness

Many research works have demonstrated the vital role of genetic factors in the modulation of phenotypes relating to arterial stiffness. (24) In addition, various valuations with families have demonstrated moderate heritability (21-66%) for arterial stiffness associated traits. (24). Aortic stiffness has been evaluated with advanced echocardiography techniques such as tissue Doppler and strain imaging. Furthermore, assessment by transthoracic and transesophageal echocardiography has a high degree of accuracy when compared with invasive measurements. On transthoracic echocardiography, M mode measurements are obtained at 3 cm above the aortic valve on parasternal long-axis view. On transesophageal echocardiography, measurements are done at the level of pulmonary artery bifurcation (2 to 3 cm above the aortic valve) and in the descending thoracic aorta just distal to the branching site of the left subclavian artery

Micro Vascular Complication of Diabetes

Complications of Diabetes Mellitus are Divided into

- Microvascular (due to damage to small blood vessels) and
- Macrovascular (due to damage to larger blood vessels).

Microvascular complications are those which includes damage to eyes (retinopathy) leading to blindness, to kidneys (nephropathy) leading to renal failure and to nerves (neuropathy) leading to diabetic foot disorders (which include severe infections leading to amputation).
Diabetic Nephropathy:

Diabetic kidney disease is a glomerulopathy defined by characteristic structural and functional changes. Some of the predominant structural changes are mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis. The important clinical manifestations of diabetic nephropathy are as follows;

- Albuminuria,
- Less often haematuria,
- Progressive chronic kidney disease, which can be slowed or prevented with optimal therapy.

In Caucasians, the rate of prevalence of progressive renal disease commonly was found to be lower in type 2 diabetes than in type 1 disease.(25)Though, this finding may be a function of the commonly later-onset disease and shorter-duration "exposure" in type 2 than type 1 diabetes, and shall not apply to all groups with type 2 diabetes, some of whom have had a more obvious renal prognosis. In a 1990s research work, nephropathy developed in up to half of diabetic Pima Indians at twenty years, with fifteen percent having progressed to end stage renal disease by this time. As previously described, though, the utilization of modern therapies lowers the incidence of end stage renal disease, even in groups at extremely high risk like, the Pima Indians. In a subsequent research work, the incidence of diabetic end stage renal disease was observed to have reduced significantly from the period 1991-1994 to the period 1999-2002 (32 to 15 cases per 1000 patient-years, respectively)(26).Diabetes mellitus is a well-known cause of chronic kidney disease, and along with hypertension, is presently one of the most common causes of progression to end stage renal disease. The development of albuminuria is considered to be a poor prognostic sign in populations with and without Diabetes mellitus, and is also an independent predictor of all-cause and cardiovascular mortality The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy The magnitude of the health problem from diabetic neuropathies remains inadequately estimated due to the lack of prospective population-based studies employing standardized and validated assessments of the type and stage of neuropathy as compared with background frequency. All Rochester, Minnesota, residents with diabetes mellitus on January 1, 1986, were invited to participate in a cross-sectional and longitudinal study of diabetic neuropathies (and also of other microvascular and macrovascular complications). Of 64,573 inhabitants on January 1, 1986 in Rochester, 870 (1.3%) had clinically recognized diabetes mellitus (National Diabetes Data Group criteria), of whom 380 were enrolled in the Rochester Diabetic Neuropathy Study. Of these, 102 (26.8%) had insulin-dependent diabetes mellitus (IDDM), and 278 (73.2%) had non-insulin-dependent diabetes mellitus (NIDDM). Approximately 10% of diabetic patients had neurologic deficits attributable to nondiabetic causes. Sixty-six percent of IDDM patients had some form of neuropathy; the frequencies of individual types were as follows: polyneuropathy, 54%; carpal tunnel syndrome, asymptomatic, 22%, and symptomatic, 11%; visceral autonomic neuropathy, 7%, and other varieties, 3%. Among NIDDM patients, 59% had various neuropathies; the individual percentages were 45%, 29%, 6%, 5%, and 3%. Symptomatic degrees of polyneuropathy occurred in only 15% of IDDM and 13% of NIDDM patients. The more severe stage of polyneuropathy, to the point that patients were unable to walk on their heels and also had distal sensory and autonomic deficits (stage 2b) occurred even less frequently--6% of IDDM and 1% of NIDDM patients. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based Neuropathy is the most common and debilitating complication of diabetes and results in pain, decreased motility, and amputation. Diabetic neuropathy encompasses a variety of forms whose impact ranges from discomfort to death. Hyperglycemia induces oxidative stress in diabetic neurons and results in activation of multiple biochemical pathways. These activated pathways are a major source of damage and are potential therapeutic targets in diabetic neuropathy. Though therapies are available to alleviate the symptoms of diabetic neuropathy, few options are available to eliminate the root causes. The immense physical, psychological, and economic cost of diabetic neuropathy underscore the need for causally targeted therapies. This review covers the pathology, epidemiology, biochemical pathways, and prevention of diabetic neuropathy, as well as discusses current symptomatic and causal therapies and novel approaches to identify therapeutic (28,29) (27) Severalre search works have evaluated the association between arterial stiffness and diabetic nephropathy.

Diabetic Neuropathy

Involvement of the peripheral and autonomic nervous systems is probably the most common complication of diabetes. Clinical diabetic neuropathy is categorized into distinct syndromes according to the neurologic distribution, although many overlap syndromes occur. In both type 1 and type 2 diabetes, variation is noted in prevalence with both the severity and duration of hyperglycaemia. Diabetic polyneuropathy is the found to be the most common neuropathy especially in the Western world.(27) Clinical and subclinical neuropathy has been found to occur in a wide range starting from ten percent to all of the diabetic patients, depending upon the diagnostic criteria and patient populations evaluated. Prevalence is a function of disease duration, and a reasonable figure, based upon several large research works, is that approximately half of the patients with diabetes will eventually develop neuropathy. (27)5(28)Neural dysfunction is another common manifestation of Diabetes Mellitus, its prevalence raises with duration of Diabetes Mellitus, with rates as raised as seventy percent in subjects with long term Diabetes Mellitus. Neural involvement can manifest either as autonomic (central) or peripheral neuropathy. Autonomic dysfunction, like other micro vascular complications of Diabetes Mellitus, is also an independent predictor of cardiovascular mortality.(29,30) Meyer *et al* assessed autonomic dysfunction in forty five type 2 Diabetes Mellitus and healthy controls. They identified that central PWV correlated with autonomic dysfunction, and hypothesized that autonomic dysfunction leads to blunting of the circadian variation of Blood Pressure, causing to overall raise in 24-h Blood Pressure load. They also postulated that a loss of nocturnal dip in heart rate as occurs in autonomic neuropathy, might lead to accelerated fatigue of elastic stretch fibers and thus raised arterial stiffness, by either increasing the number of stretch cycles or by not allowing sufficient relaxation time for large arteries between ventricular contractions.(31).

Diabetic Retinopathy

Diabetic retinopathy (DR) is one of the most vital causes of visual loss worldwide, and is the principal cause of impaired vision in patients between 25 and 74 years of age. Visual loss from diabetic retinopathy may be secondary to macular edema (retinal thickening and edema involving the macula), hemorrhage from new vessels, retinal detachment, or neovascular glaucoma. The vast majority of patients who develop diabetic retinopathy have no symptoms until the very late stages (by which time it may be too late for effective treatment). Because the rate of progression may be fast, and therapy can be beneficial for both symptom amelioration and de(32)crease in the rate of disease progression, it is vital to screen patients with diabetes at regular time intervals for the development of retinal disease. Most of the patients who develop diabetic retinopathy have nil symptoms until the very late stages (by which time it may be too late for effective treatment). Considering the fact that the rate of progression is rapid, and therapy can be much beneficial for both symptom amelioration and reducing the rate of progression of disease, hence it becomesvital to screen patients with diabetes regularly for the development of retinal disease. The presence of Diabetic Retinopathyseems to be a marker of excess morbidity and mortality risk (primarily cardiovascular).(32).Arterial stiffness has been demonstrated to be associated with the development of diabetic retinopathy, an independent predictor of mortality in the populations with Diabetes Mellitus. (32,33)

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How to cite this article:

Suresh kumar S, Arun Prasath P and jayasingh k., 2019,A Review of Aortic Stiffness in Type 2 Dm Patients And its Correlation with Microvascular Complications. *Int J Recent Sci Res.* 10(03), pp. 31523-31527.
DOI: http://dx.doi.org/10.24327/ijrsr.2019.1003.3277

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