The Level of Ferritin in Diabetic and Non Diabetic Patients with Non Ischaemic Cardiomyopathy

Thesis

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BY

Salah Zakarya Ahmed

M.B.B.CH

Under Supervision Of

Prof. Dr. Mohamed Gamal Abdul Bar

Professor of Cardiology

Faculty of medicine

Ain-shams University

Dr. Sherif Mansour Soliman

Lecturer of Cardiology

Faculty of Medicine

Ain-Shams University

Faculty of Medicine

Ain-Shams University

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مستوى مادة الفريتين بالدم لمرضى اعتلال عضلة القلب الغير مصاحب بقصور الشرايين التاجية للمصابين بمرض السكرى والغير مصابين به

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صلاح زكريا أحمد

بكالوريوس الطب والجراحة

تحت اشراف

الأستاذ الدكتور/ محمد جمال عبد البر

أستاذ القلب والأوعية الدموية

كلية الطب – جامعة عين شمس

دكتور/ شريف منصور سليمان

مدرس القلب والأوعية الدموية

كلية الطب – جامعة عين شمس

كلية الطب

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Introduction

Ferritin is a protein found inside cells that stores iron, the amount of ferritin in blood (serum ferritin level) is directly related to the amount of iron stored in the body **(Hoffman R, et al., 2005).**

Most of the ferritin is found in the liver cells, spleen and bone marrow. It is also found in the heart, pancreas and kidney. Human serum contains a small but significant quantity of ferritin **(Meral MERT et al., 2005)**

Serum ferritin levels are affected by age and sex. In normal individuals, ferritin levels are slightly higher at birth and decrease during childhood until puberty **(Kameneva MV et al., 1999).**

The relationship between high iron intake and high body iron stores outside the setting of genetic iron overload and type 2 diabetes is well recognized **(Ford ES** and **Cogswell ME, 1999)**.

Similarly, high body iron stores have been linked to insulin resistance (**Tuomainen TP et al.,1997**), metabolic syndrome (**Bozzini C et al., 2005**), and gestational diabetes (**Chen X et al., 2006**).

Jehn et al., argue that the modest elevations in ferritin levels observed in diabetes may be a consequence or marker rather than the cause of impending insulin resistance and that elevated ferritin may not reflect elevated body iron stores or an intracellular labile iron pool that participates in oxidant injury (**Jehn ML et al., 2007**).

The role of iron in endothelial and vascular disease:-

Epidemiologic studies in overt iron overload states such as transfusional iron overload and hemochromatosis have shown that the incidence of cardiac disease is increased (**Schafer AI et al., 1981**) and that treatment with iron chelation improves cardiovascular outcome (**Fabio G et al., 2007**).

Similarly, several studies have demonstrated a direct association between increased iron intake, body iron stores, and cardiovascular risk in the general population. Increased intake of heme iron is associated with increased cardiovascular events (**Ramakrishnan U et al., 2002**).

Varieties of cardiovascular risk factors are associated with iron overload and commonly cluster in the metabolic syndrome (**Tuomainen T-P et al., 1998**).

Ramakrishnan et al. have demonstrated this close relationship between iron stores and cardiovascular risk factors in women of reproductive age in the U.S (**Ramakrishnan U et al., 2002**).

In human studies of end-stage renal disease patients, intravenous iron therapy has been shown increase vascular and systemic oxidative stress (**Agarwal R et al., 2004**), promote atherosclerosis(**Drueke T et al., 2002**), and increase the risk of arterial thrombosis (**Day SM et al., 2003**).

Further, intravenous iron has been shown to cause impaired flow-mediated dilatation in the brachial artery, a surrogate for endothelial

dysfunction (**Zheng H et al., 2006**). Conversely, improvement in vascular reactivity after phlebotomy in patients with high-ferritin type 2 diabetes further supports these observations (**Fernandez-Real JM et al., 2002**).

Additionally, several recent studies on cardiovascular evaluation and outcome in high frequency blood donors demonstrate improvement in surrogate markers of vascular health such as decreased oxidative stress and enhanced vascular reactivity when compared with low-frequency donors (**Zheng H et al., 2006**).

Iron is essential for a variety of metabolic processes but may also cause potentially deleterious effects. It plays a key pathophysiological role in cardiac diseases as seen in iron-overload cardiomyopathy (**Oudit GY et al., 2004**), myocardial ischemia-reperfusion injury (**Turoczi T et al., 2003**), and atherosclerosis (**Ramakrishna G et al., 2003**).

Myocardial ischemia results in an enhanced ferritin content in relation to the degree of ischemia (**Voogd A et al., 1992**). However, the mechanism(s) by which myocardial iron content is regulated is unclear.

Iron overload is associated with progressive iron deposition in a variety of tissues, including the heart and endocrine organs, leading to cardiomyopathy and various endocrinopathies (**Muhlestein JB**, **2000**) Iron-overload cardiomyopathy is characterized by marked diastolic dysfunction, increased propensity for arrhythmias, and an end-stage dilated cardiomyopathy (**Liu P and Olivieri N**, **1994**).

Aim of the work

- The aim of this study is to determine if there is any significant difference in serum ferritin level in diabetic non ischaemic cardiomyopathy versus non diabetic non ischaemic cardiomyopathy patients.
- Also, we will investigate if there is any significant correlation between serum ferritin level and the degree of systolic dysfunction in diabetic non ischaemic cardiomyopathy.

DILATED CARDIOMYOPATHY

(I)-Definition:

Dilatation and impaired contraction of the left or both ventricles. Caused by familial/genetic, viral and/or immune, alcoholic/toxic, or unknown factors, or is associated with recognized cardiovascular disease.

Diagnosis of DCM requires evidence of dilatation and impaired contraction of the left ventricle or both ventricles (eg, left ventricular ejection fraction <40 percent or fractional shortening less than 25 percent). The disease is considered idiopathic if there is active exclusion of ≥50 percent obstruction of one or more coronary arteries and of active myocarditis or a primary or secondary form of heart muscle disease as determined by angiography, echocardiography, and, although not performed in many cases, endomyocardial biopsy (***Richardson et al., 1996).***

(II)-Incidence:

The incidence of DCM is reported to be 5 to 8 cases per 100,000 population per year and appears to be increasing, although the true figure likely is higher as a consequence of underreporting of mild or asymptomatic cases ***(Dec and Fuster, 1994).***

It occurs almost three times more frequently in blacks and males as in whites and females, and this difference does not appear to be related solely to differing degrees of hypertension, cigarette smoking, or alcohol use ***(Adams and Zannad, 1998).***

Survival in blacks and males appears to be worse than in whites and females **(*Dries et al., 1999) & (Thomas et al., 2005).***

(III)- Natural History:

The natural history of DCM is not well established. Many patients have minimal or no symptoms, and the progression of the disease in these patients is unclear, although there is some evidence that the long-term prognosis is not good ***(Redfield et al., 1994).***

About a fourth of patients with recent-onset DCM improve spontaneously, even some sick enough initially to be considered for cardiac transplantation. In some patients clinical and functional improvement may occur years after initial presentation ***(Semigran et al., 1994).***

(IV)-Prognosis:

A variety of clinical predictors of patients at enhanced risk of dying of DCM have been identified, including the presence of a (S3) gallop, ventricular arrhythmias, advanced age, and specific endo-myocardial biopsy features ***(Fruhwald et al., 1994).***

However, the predictive reliability of any single feature is not high, and it may be difficult to predict with any accuracy the clinical course and outcome in an individual patient. Nevertheless, greater ventricular enlargement and worse dysfunction tend to correlate with poorer prognosis, particularly if the right ventricle is dilated and dysfunctional as well ***(Sun et al., 1997).***

It has been suggested that specific endo-myocardial biopsy morphological findings (such as loss of intracellular myofilaments) may offer some predictive information regarding prognosis ***(Brown and O'Connell, 1995).***

(V) Etiology:

It is likely that idiopathic DCM represents a common expression of myocardial damage that has been produced by a variety of as yet un-established myocardial insults. Although the causes remain unclear, interest has centered on possible basic mechanisms of damage:

(1) Familial and genetic factors:

Familial linkage of DCM occurs more commonly than often is appreciated. In twenty percent or more of patients, a first-degree relative also shows evidence of DCM, suggesting that familial transmission is relatively frequent. Some asymptomatic relatives of patients with DCM have sub-clinical left ventricular enlargement and/or dysfunction that may progress to overt symptomatic DCM **(*Baig et al., 1998).***

Most familial cases demonstrate autosomal dominant transmission; six chromosomal loci have been identified, and more are likely to be found. However, the disease is genetically quite heterogeneous and autosomal recessive and X-linked inheritance have been found **(*Anan et al., 1995) & (Garcia et al., 1996).***

(2) Viral myocarditis:

Wide speculation exists that an episode of subclinical viral myocarditis initiates an autoimmune reaction that leads to the development of full-blown DCM (***Luppi et al., 1998).***

Although this hypothesis is inviting, it remains largely unsupported ***(Michelle and Michael, 2006).***

Other evidence favoring the concept that DCM is a post-viral disorder includes the presence of high antibody viral titers, viral-specific RNA sequences, and apparent viral particles in patients with "idiopathic" DCM ***(Why et al., 1994).***

On the other hand, the more rigorous technique of polymerase chain reaction generally has not confirmed the presence of viral remnants in the myocardium of most cardiomyopathy patients, although data are conflicting ***(Pauschinger et al., 1999).***

(**3) Immunological abnormalities:**

Abnormalities of both humoral and cellular immunity have been found in patients with DCM, although the findings have not been completely reproducible ***(Limas, 1997).***

There is speculation that antibodies might be the result of myocardial damage, rather than the cause ***(Pohlner et al., 1997).***

There appears to be an association with specific HLA Class II antigens (particularly DR4), suggesting that abnormalities of immunoregulation may play a role in DCM (***Limas et al., 1994).***

Additional evidence for the significance of circulating antimyocardial antibodies comes from the demonstration of short-term clinical improvement in the manifestations of heart failure in a small number of patients treated with immunoadsorption and elimination of anti-beta1-adrenergic receptor antibodies ***(Felix et al., 2000) & (Schimke et al., 2001).***

These immunological abnormalities may be the consequence of prior viral myocarditis, It has been postulated that viral components may be incorporated into the cardiac sarcolemma, only to serve as an antigenic source that directs the immune response to attack the myocardium ***(Caforio, 1994).***

(4) Pro-inflammatory Cytokines:

A variety of pro-inflammatory cytokines such as tumor necrosis factor-alpha (and the related tumor necrosis factor-alpha converting enzyme) are expressed in DCM and may play a role in producing contractile dysfunction; whether viral infection, autoimmune abnormalities, or other factors induce their expression is unknown (***Satoh et al., 1999).***

Similarly, the vasoconstrictor peptide endothelin is increased in decompensated DCM and has been implicated as a cause of the heightened vascular tone that accompanies congestive heart failure ***(Bristow, 1998).***

(5) Other Causes:

a) Endocrine abnormalities as well as the effects of chemicals or toxins have been suggested as possible etiological factors. It has been suggested that microvascular hyperreactivity (spasm) may lead to myocellular necrosis and scarring, with resultant heart failure, although this remains speculative ***(Siu and Sole, 1994).***

b) Apoptosis, or programmed cell death, has been demonstrated in the hearts of patients with DCM and arrhythmogenic right ventricular

cardiomyopathy, although there is some controversy regarding the veracity of these findings in DCM ***(Kanoh et al., 1999).***

c) From a clinical standpoint, the more important causes of nonidiopathic DCM include alcohol and cocaine abuse, human immunodeficiency virus (HIV) infection, metabolic abnormalities, and the cardiotoxicity of anticancer drugs (especially doxorubicin) ***(Herskowitz et al., 1993).***

(VI) Clinical Manifestations:

(1)- History:

Symptoms usually develop gradually in patients with DCM. Some patients are asymptomatic and yet have left ventricular dilatation for months or even years. This dilatation may be recognized clinically only later when symptoms develop or when routine chest roentgenography demonstrates cardiomegaly ***(Dec and Fuster, 1994).***

The most striking symptoms of DCM are those of left ventricular failure. Fatigue and weakness due to diminished cardiac output are common. Right-sided heart failure is a late and ominous sign and is associated with a particularly poor prognosis. Chest pain occurs in about one third of patients and may suggest concomitant ischemic heart disease ***(Dec and Fuster, 1994).***

(2) Physical Examination:

Examination usually reveals variable degrees of cardiac enlargement and findings of congestive heart failure. The systolic blood pressure is usually normal or low, and the pulse pressure is narrow,

reflecting a diminished stroke volume. Pulsus alternans is common when severe left ventricular failure is present ***(Dec and Fuster, 1994).***

Cheyne-Stokes breathing may be present and is associated with a poor prognosis ***(Lanfranchi et al., 1999).***

The jugular veins are distended when right-sided heart failure appears, but on initial presentation most patients do not have evidence of this. Prominent "a" and "v" waves may be visible. Grossly pulsatile jugular veins with prominent regurgitant waves indicate the presence of tricuspid valvular regurgitation; this is usually a late and often ominous finding. The liver may be engorged and pulsatile. Peripheral edema and ascites are present when right-sided heart failure is advanced ***(Dec and Fuster, 1994).***

The precordium usually reveals left and, occasionally, right ventricular impulses, but the heaves are not sustained as they are in patients with ventricular hypertrophy. The apical impulse is usually displaced laterally, reflecting left ventricular dilatation. A presystolic "a" wave may be palpable on occasion and is generated in a similar manner as a presystolic (S4) gallop heard on auscultation. The second heart sound (S2) is usually normally split, although paradoxical splitting may be detected in the presence of left bundle branch block, an electrocardiographic (ECG) finding that is not unusual in DCM. If pulmonary hypertension is present, the pulmonary component of S2 may be accentuated and the splitting may be narrow. Presystolic gallop sounds (S4) are almost universally present and often precede the development of overt congestive heart failure. Ventricular gallops (S3) are the rule once cardiac decompensation occurs, and a summation gallop is heard when there is concomitant tachycardia ***(Dec and Fuster, 1994).***

Systolic murmurs are common and are usually due to mitral or, less commonly, tricuspid valvular regurgitation. Mitral regurgitation results from enlargement and abnormal motion of the mitral annulus; ventricular dilatation with resultant distortion of the geometry of the subvalvular apparatus ("papillary muscle dysfunction") plays a lesser role. Gallop sounds and regurgitant murmurs can often be elicited or intensified by isometric handgrip exercise with its attendant enhancement of systemic vascular resistance and impedance to left ventricular outflow. Systemic emboli resulting from dislodgement of intracardiac thrombi from the left atrium and ventricle and pulmonary emboli that originate in the venous system of the legs are common late complications ***(Dec and Fuster, 1994).***

(VII) Investigations:

(1) Laboratory Examinations:

To identify potentially reversible causes of DCM, several basic screening biochemical tests are indicated, including determination of levels of serum phosphorus (hypophosphatemia), serum calcium (hypocalcaemia), and serum creatinine and urea nitrogen (uremia), thyroid function studies (hypothyroidism and hyperthyroidism), and iron studies (hemochromatosis). It is prudent to test for HIV as well, because this infection is an important and often unrecognized cause of congestive heart failure ***(Herskowitz et al., 1993).***

(2) The chest X-Ray:

The chest X-Ray usually reveals generalized cardiomegaly and pulmonary vascular redistribution; interstitial and alveolar edema are less common on initial presentation. Pleural effusions may be present, and the

azygos vein and superior vena cava may be dilated when right-sided heart failure supervenes ***(Dec and Fuster, 1994).***

(3) Electrocardiography:

The ECG often shows sinus tachycardia when heart failure is present. The entire spectrum of atrial and ventricular tachyarrhythmias may be seen. Poor "R" wave progression and intraventricular conduction abnormalities, especially left bundle branch block, are common. Anterior "Q" waves may be present when there is extensive left ventricular fibrosis, even without a discrete myocardial scar or evidence of coronary artery disease. "ST" segment and "T" wave abnormalities are common, as are "P" wave changes, especially left atrial abnormality. Ambulatory monitoring demonstrates the ubiquity of ventricular arrhythmias, with about half of monitored patients with DCM exhibiting non-sustained ventricular tachycardia ***(Singh et al., 1998).***

(4) Echocardiography:

Two-dimensional and Doppler forms of echocardiography are useful in assessing the degree of impairment of left ventricular function and for excluding concomitant valvular or pericardial disease***(Manolio et al., 1992).***

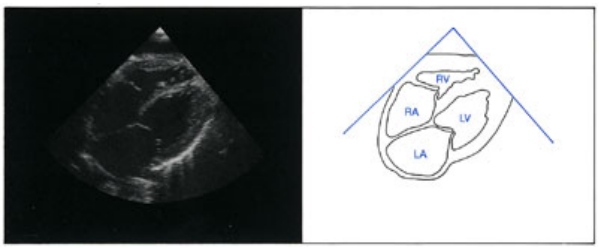

Fig. (1) 2-D subcostal four-chamber view showing right ventricular hypertrophy.

(JOSEPH A. KISSLO, DAVID B. S and GRAHAM J. LEECH 2002)
Duke Center for Echo, Educational Media Services. Echo in Context Teleconferences.