Homocysteine and Thyroid Hormones in Patients with Familial Dilated Cardiomyopathy

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ABSTRACT:

BACKGROUND:

Familial linkage of primary dilated cardiomyopathy (DCM) occurs more commonly than often is appreciated. In 10-20 percent of patients, a first degree relative also shows evidence of primary DCM suggesting that familial transmission is relatively frequent.

METHODS:

this study included 7 patients aged 40-70 years (2 females and 5 males) with familial dilated cardiomyopathy (FDCM) and 17 healthy subjects aged 29-60 years (6 females and 11 males). Plasma fasting total homocysteine tHCY, serum folic acid (FA), vitamin B6, total triiodothyronine (T3), and total thyroxine (T4) were measured in these two groups.

RESULTS:

The mean value of plasma tHCY was significantly higher in patients with FDCM than in control ($P<0.001$). The mean (±SD) values of serum folic acid and vitamin B6 were significantly decreased in FDCM patients when compared with those of control group ($P<0.05$, $P<0.01$, respectively).

A significant inverse relationship between plasma tHCY concentration and the values of serum FA was shown in the FDCM patients ($r=-0.78$, $P<0.05$). The mean values of serum T3 and T4 were insignificantly decreased in patients with FDCM than in controls.

CONCLUSION:

The level of plasma tHCY is significantly higher in FDCM patients than in healthy control. This severe hyperhomocyteinemia of FDCM patients may be related to evolution and development of myopathic state in such patients.

KEY WORDS: Familial dilated cardiomyopathy; Homocysteine, thyroid hormones.

INTRODUCTION:

Dilated cardiomyopathy (DCM) is a heart muscle disorder characterized by the occurrence of a dilated and dysfunctioning left ventricle (LV or both ventricles) in the absence of abnormal loading conditions (hypertension, valve disease) or ischemic heart disease sufficient to cause global systolic impairment [1]. It has been observed that DCM has, as peculiar feature, the involvement of cardiac muscle itself [2]. Familial linkage of DCM occurs more commonly than often is appreciated. Some asymptomatic and/or dysfunction may progress to symptomatic DCM [3]. Iraqi families with more than one affected member have been shown by Al-Kubaisy and Al-Safar, 1996 [4]. Echocardiogram of those patients revealed dilated left sided heart chamber with severe impairment of LV function, normal valves and pericardium. Cardiac angiography of those patients observed global hypokinesia with poor LV function, normal valves, and normal coronary arteries [4]. All forms of mendelian inheritance have been demonstrated in familial dilated cardiomyopathy (FDCM) including autosomal dominant and recessive inheritance, X-linked transmission, and polygenic and mitochondrial inheritance [3, 5, 6].

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Homocysteine (HCY) is a sulfur containing amino acid that is not used for the synthesis of protein. The intracellular HCY concentration is precisely regulated and any excess is transported to plasma [7]. Among fasting individuals, normal total homocysteine (tHCY) in plasma is commonly ranges from 5 – 15 □mol/L (mean, 10 □mol/L) [8] and higher fasting values are classified arbitrarily as moderate (16-30), intermediate (31-100), and severe (>100 □mol/L) hyperhomocysteinemia [9]. Homocysteine metabolic defects can have nutritional background, i.e. an inadequate intake of folate or vitamin B6 or B12 that serve as substrate or cofactors to the enzymes involved in HCY metabolism [10]. Walker et al, 2004 [11] have suggested from their experimental study that relatively short term exposure to elevation of plasma tHCY results in alteration in LV structure without evidence for direct effect on myocardial contractile function. It has been observed that HCY significantly decreased endothelium-dependent relaxation and endothelial nitric-oxide (NO) immunoreactivity as well as induced endothelial injury in both porcine and carotid arteries [12]. Recently, it has been demonstrated that HCY elicits an acute negative inotropic effect on experimental ventricular myocardium which is

mediated via a coronary endothelium [3]. The thyroid gland secrets, principally two hormones, thyroxine (T4) and triiodothyronine (T3). The heart is a muscle which contains receptors for thyroid hormone; hence heart muscle growth and cardiac function may be influenced by too much or too little thyroid hormone [14].

SUBJECTS AND METHODS:

Seven patients with familial dilated cardiomyopathy (FDCM) aged 40-70 years (2 females and 5 males) are encountered during 10 months of conduction of this study at more than one center of cardiologic unit of Teaching Medical Hospital,and Ibn-Albitar Hospital in Baghdad city.

The diagnosis of FDCM was based on similar criteria for that of primary DCM diagnosis [15]. The diagnosis criteria was made when the echocardiogram showed a left ventricular ejection fraction (LVEF) less than 50% in the absence of angiographic coronary artery disease and other known causes of DCM, such as primary valvular disease and severe hypertension. Moreover, patients were considered to have had FDCM only when at least two members of the same family have disease with the primary DCM. 17 healthy persons aged 29 to 60 years (6 females and 11 males) were taken as control group. To be a control subject, he or she should have no history of heart disease, diabetes mellitus or hypertension. Ten milliliters of an overnight fasting blood sample was aspirated from peripheral vein of each patient and healthy control. The separated plasma and serum were used for the following biochemical investigations: 1. plasma t HCY concentration was determined by high performance liquid chromatography (HPLC) with ultraviolet-visible spectrophotometric detection according to the Dong and Gant assay, 1985 [16], 2. Serum folic acid (FA) and serum vitamin B6 were separated and Quantitatively determined using a HPLC system according to the methods of Augustin et al, 1985 [17], 3. Total serum triiodothyronine (T3) and total serum thyroxine (T4) were assayed quantitatively using the enzyme immunoassay (EIA) technique. The methods of Wisdom, 1976 [18] was used for serum T3 estimation. The method of Schuurs and Weeman, 1977 [19] was used for serum T4 determination. **Statistical analysis:** SPSS version 6 for Windows was used for all statistical analysis. Statistical significance was assayed by ANOVA, and student t-tests. P-value of less than (0.05) was considered significant.

RESULTS:

The study included 7 patients (2 females and 5 males) with FDCM and 17 healthy controls (6 females and 11 males). The mean (± SD) values of age and weight of patients with FDCM (50.57 ± 10.92 years, 81.57 ± 18.62 kg, respectively) are comparable to those of controls (44.24 ± 8.44 years, 75.41± 6.24 kg, respectively). Table 1 shows the results of biochemical parameters including plasma tHCY, serum folic acid (FA), vitamin B6, total T3 and total T4 in FDCM and control groups. The mean (± SD) value of the plasma tHCY was significantly higher in FDCM patients than in control group (79.52 ± 73.81 □mol/L, 6.41 ± 1.76 □mol/L; P<0.001, respectively). The mean value (± SD) of serum FA and vitamin B6 concentration were significantly (P<0.05, P<0.01, respectively) lower in patients with FDCM (37.45 ± 24.24 nmol/L, 3.86 ± 1.69 nmol/L, respectively) than in control group (62.01 ± 33.25 nmol/L, 17.01 ± 10.72 nmol/L, respectively). The mean ± SD of serum T3 and T4 levels did not differ significantly in patients with FDCM when compared to those of healthy controls (Table 1). In FDCM group, a significant negative relationship between plasma tHCY and serum FA (r=-0.78, P<0.05) was shown (Table 2).

Table 1: Mean (± sd) plasma values of homcysteine, serum folic acid, vitamin b6, total triiodothyronine (t3) and total thyroxine in fdcm patients and controls

	FDCM Patients n = 7		Controls
Homocysteine "HCY"; □mol/L	79.52 ± 73.81	a	6.41 ± 1.76
Folic acid FA; nmol/L	37.45 ± 24.24	b	62.01 ± 33.25
Vitamin B6; nmol/L	3.86 ± 1.69	c	17.01±10.72
T3; ng/ml	1.30 ± 0.62	d	1.51 ± 0.68
T4;ug/dl	10.50 ± 2.11	a	10.63 ± 2.73

FDCM: Familial Dilated CardioMyopathy *a ANOVA test between FDCM group and controls: P<0.001 *b ANOVA test between FDCM group and controls: P<0.05 *c ANOVA test between FDCM group and controls: P<0.01 *d ANOVA test: no significant difference between the two groups (FDCM and control)

Table 2: Simple Correlation (r) analysis of biochemical parameters for FDCM patient group n = 7.

Correlation (r)	HCY	FA	Vitamin B6	T3	T4
HCY	1.0	-0.78*	-0.717	0.23	-0.32
FA		1.0	0.27	-0.24	0.27
Vitamin B6			1.0	-0.53	-0.19
T3				1.0	0.63
T4					1.0

All results reperesent the correlation factor (r) *Significant correlation: P<0.05

DISCUSSION:

The low or limited number of FDCM patients of the present study when compared to that of another study [20] that conducted on Iraqi patients with IDC (50 patients), both during the same study's period, may emphasizes the reported range of incidence of familial form of primary DCM (10-20%) [21].

The results of current study showed that the mean (± SD) value of plasma tCHY levels of patients with FDCM (79.52 ± 73.81 □mol/L) was significantly higher than that in normal controls (6.41 ± 1.76 □mol/L, P<0.001). This result is similar to that reported by Schofield et al, 2003 [22] who observed that hyperhomocysteinemia (HHCY) is common in patients with severe heart failure.

It has been suggested that HCY exerts a direct contractile effect on the myocardium, while also acting to impair endocardial endothelial (EE) function via decreasing the bioavailability of NO[23]. Ungvari et al, 2002 [24] observed that flow induced dilation of isolated small intramural coronary arteries is substantially impaired in HHCY. This impairment is due to an enhanced production of (O_2-), which decreases the bioavailability of NO to mediate the dilation through the formation of peroxynitrate ONOO-. Such alteration in endothelial regulation of coronary circulation in HHCY could promote the development of heart diseases [24]. More recently, Saleh , 2005 [20] observed the severe elevated of plasma tHCY in Iraqi patients with IDC. He hypothesized that HHCY may play an important role in the pathogenesis and development of IDC, in particular, via the impairment of the coronary endothelial cells (coronary blood flow). The direct oxidative effect of HHCY, through auto-oxidation and thiolactone formation, may be responsible for the production of reactive oxygen species ROS (O_2-, H_2O_2 and OH^-) and a consequent increase in lipid peroxidation with resultant endothelial toxicity [25]. Elevated levels of lipid peroxides lead to an increase in peroxyl radicals that can inactivate NO through the formation of lipid peroxynitrites. Peroxynitrite may further react with cellular tyrosine residues to form nitrosated end products, or with thiols to form S-nitrosothiols leading to cellular damage [26]. The significant inverse relationship (r=-0.78, P<0.05) between plasma tHCY levels and serum FA concentration that was observed in the FDCM patients of the present study is in agreement with that shown by Genser et al, 2002 [27] and Ganji and Kafai, 2003 [28] who found a negative correlation between plasma tHCY and serum FA levels in their patients. Folate and vitamin B6 are required for the conversion of HCY to methionine, and a strong Inverse relationship exists between folate consumption and plasma tHCY levels among patients with and without HHCY [29].

Approximately two thirds of the cases of elevated tHCY levels have been estimated to be due to low or moderate concentration of the vitamins [30], or which folate is considered the most important [31]. In the present study, the mean (± SD) value of serum T3 and serum T4 levels (Table 1) in patients with FDCM was lower than that I control, but still beyond the significant level. These observations are similar to that reported by Saleh, 2005 [20].

However, the authors of the latter study [20] concluded that specific impairment of cardiac action of thyroid hormones may be a contributing causative factor in the progression of heart failure. A study conducted by Auer et al, 2003 [32] in patients referred for coronary angiography revealed that even variation of thyroid function was within the statistical normal range, but may influence the presence and severity of heart disease.

CONCLUSION:

The levels of plasma tHCY are significantly high in patients with FDCM than in healthy controls. These severe HHCY of FDCM patients may be related to evolution and development of myopathic state in such patients, but this hypothesis may need to be proved by further studies.

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