RESEARCH
O&G Forum 2024; 34 – 3s: 1394-1398

EVALUATION OF MYOSIN BINDING PROTEIN- C3 (MyBP-C3) IN SERUM OF MEN HYPERTENSIVE PATIENTS

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Abstract
Introduction: Hypertension is often referred as a silent killer disease, because it is often patients for years without feeling any disturbance or symptoms. (Myosin binding protein-C slow) comprises a family of accessory proteins in skeletal muscles that bind both myosin and actin filaments. MyBP-C is a thick filament regulatory protein that is only present in the vertebrate striated muscle sarcomeres' C-zone of the A-band. The roles of the cardiac, slow skeletal, and fast skeletal MyBP-C (fMyBP-C) paralogs are distinct. Although the three paralogs' protein structures are similar, their expression and functions most likely differ significantly, which may be necessary to support the different physiologies of fast and slow muscle fibres..
Methods: The case-control study included (90) subjects divided into (60) male patients. Samples were collected for patients with high blood pressure. Height and weight were measured, and other information was also collected. The ELISA test was performed. control group study of 30 men was also conducted. All groups that appeared healthy were matched in age.
Results: a significant positive correlation between MyPBC-3 and cholesterol, TG and LDL-C while indicate a negative correlation with HDL. These results were documentation in currant study and no previous studies deals with the relation between MyPBC-3and lipid profile, also High biomarker level associated with ages especially at new diagnosis without treatment and with short duration of disease. The genetic, Smoking and Obesity play acrucial role in present study by high level of MyPBC3 in familial hypertensive patients.
Highlights
The exact Structure of arrangement Knowledge of the relationship between thick and thin filaments and cMyBP-C facilitates comprehension of the consequences of cMyBP-C phosphorylation, which is essential for regular cardiac function and seems to guard against ischemia harm., also (cMyBP-C) is a sarcomere thick filament-associated protein that may be used as a therapeutic target to treat heart failure's contractile dysfunction.
Present study concluded MyBC3 considered as a progress marker for prediction of hypertension. Significant positive correlation between MyPBC-3 and lipid profile also other factors such as genetic and age.
significant positive correlation between MyPBC-3 and cho, TG and LDL-C while indicate a negative correlation with HDL. These results were documentation in current study. The genetics, Smoking and Obesity play a crucial role in present study by high level of MyPBC3 in familial hypertensive patients.
Conclusions: present study concluded MyBC3 considered as a progrestc marker for prediction of hypertension.
Keywords: Myosin-binding protein-C3(MyBC3), Low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and cholesterol (Cho)

I. INTRODUCTION

Hypertension is often referred as a silent killer disease, because it is often hypertensive patients for years without feeling any disturbance or symptoms[1]. Blood pressure is the amount of pressure that is created inside the arteries as a result of the heart pumping blood against the artery walls. We treat this reading as high blood pressure (HBP) if it is higher than the ideal level. The number of HBP victims worldwide is increasing in the present era.[2].

High blood pressure Blood pressure ≥140/90 mm Hg, which can also be measured as 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic.[3].

About 1 billion individuals worldwide suffer from hypertension (HTN), and finding a single cause makes therapy more difficult. Although there is a significant genetic component, environmental factors can have an impact on blood pressure (BP) levels. Linkage analysis has revealed multiple genes implicated in Mendelian forms of hypertension, and the corresponding pathophysiological processes have been elucidated, paving the way for focused therapeutic interventions.

(cMyBP-C) is a sarcomere thick filament-associated protein that may be used as a therapeutic target to treat heart failure's contractile dysfunction.[4].

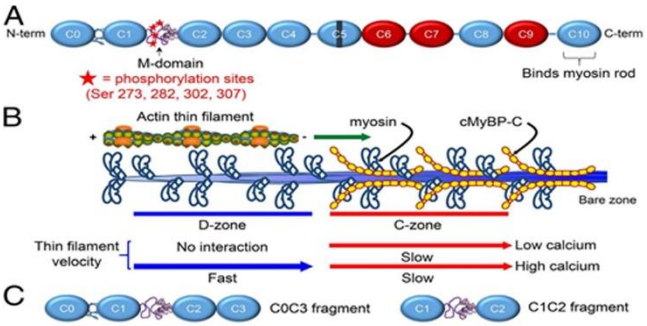

Figure 1: cMyBP-C's structure **[5]**

In previous study Accelerated cardiac contractility is caused by phosphorylation of cardiac myosin binding protein-C (cMyBP-

C). The theory that phosphorylation of releases myosin heads from the inhibited super-relaxed state (SRX), hence influencing the proportion of myosin available for contraction, is based on the methods by which cMyBP-C phosphorylation boosts contractile kinetics[6]**.**

The thick filament regulating protein known as myosin-binding protein-C, or MyBP-C, is only present in the C-zone of the A-band in the sarcomeres of vertebrate striated muscle. The roles of the cardiac, slow skeletal, and fast skeletal MyBP-C (fMyBP-C) paralogs are distinct. Although the three paralogs' protein structures are similar, their expression and functions most likely differ significantly, which may be necessary to support the different physiologies of fast and slow muscle fibres[7].

It was discovered through the characterization of "impurities" found alongside myosin in sodium dodecyl sulphate (SDS) polyacrylamide gel electrophoresis. The resulting bands were labelled alphabetically, with the third heaviest correctly identified at the band corresponding to a molecular weight of 140 kDa. Offer et al. originally referred to this protein as the C-protein in 1973. Provide et al **[8].**

The precise organisation and comprehension of the interaction between thick and thin filaments and cMyBP-C also contribute to a better understanding of the consequences of phosphorylation of cMyBP-C, which is required for normal cardiac function and appears to protect against ischemia injury[9].

The (cMyBP-C) amino terminus (N′)-region (C0-C2 domains, 358 amino acids) of the protein is phosphorylated, which modulates actomyosin interactions and controls heart contraction[7].

Function of cMyBP-C

The precise organisation and comprehension of the interaction between thick and thin filaments and cMyBP-C also contribute to a better understanding of the consequences of phosphorylation of cMyBP-C, which is required for normal cardiac function and appears to protect against ischemia injury. [8]. Myosin force-generating cross-bridges' rate of interaction with actin is regulated by cMyBP-C, or cardiac myosin-binding protein-C, a tunable regulator of heart function. Normal cardiac function and increased contractility in response to fight-or-flight stimuli, which phosphorylate cMyBP-C and accelerate cross-bridge dynamics, depend on cMyBP-C.[10]. By altering actomyosin interactions, phosphorylation of cardiac myosin binding protein-C (cMyBP-C) modulates heart contraction. This is achieved through the protein's amino terminal (N′)-region (C0-C2 domains, 358 amino acids) [6]. Because of its capacity to bind with thick (myosin S2, myosin RLC) and thin filament (actin and α-tropomyosin) proteins through its N′-terminal domain, cMyBP-C is regarded as a trans-filament protein.[11] . demonstrate that the regulatory N-terminal domains (C0C2) of cMyBP-C interact with the cardiac-specific m-motif and the myosin head (myosin S1) and tail domains (myosin S2) with micromolar affinity through interactions that are phosphorylation-dependent and -independent, respectively, of domain C1. Furthermore, the core domains of cMyBP-C, which bind myosin with submicromolar affinity, are home to the contact sites with the highest affinity between it and myosin S1[12].

Physiological role of cMyBP-C in the heart

The cardiac myosin binding protein-C (cMyBP-C) amino terminus (N′)-region (C0-C2 domains, 358 amino acids) of the protein is phosphorylated, which modulates actomyosin interactions and controls heart contraction[6]**.** The most common hereditary heart condition is hypertrophic cardiomyopathy (HCM), a condition marked by hypertrophy and hypercontractility of the cardiac muscle. The primary cause of HCM is variation in the genes that code for proteins found in the sarcomere, the fundamental contractile unit of cardiomyocytes[13].

Methods

Subject population

The present study was designed to investigate an important biomarker (MyBP-C3) as a prediction or prognostic biomarker in hypertensive patients and relation with lipid profile (cholesterol, triglyceride, HDL, and LDL)

The following criteria were dependent in a current study:

four biomarkers (MyBP-C3, Cholesterol, TG, and HDL) level in serum, Ages, Body mass index, hypertensive patients with and without treatment, Sex (only male), Duration of disease, Smoking or no, familial hypertensive or no.

Inclusion criteria

Criteria for inclusion of hypertensive patient in the current study, such as age, disease duration, smoker or not, body mass index, new patients diagnosed or treated, and hereditary hypertension or not.

Exclusion criteria

The current study excluded many criteria related to diabetic nephropathy, kidney disease, or any complications such as liver disease, heart disease, and anemia, also excluded.

Results

Comparison of psychological tests

Table 1 displays the physical and psychological scores for both hypertension patients and healthy controls (HC).

The findings are presented as the median and the mean ± standard deviation of normally distributed data.

Binomial data were expressed as ratios in hypertensive patients compared to control group in (Table 1) shows a significant increase (p value < 0.001) in hypertensive patients in both diastolic pressure and systolic pressure compared with the control group.

The results indicated a state of severe fatigue state in HTN patients extracted from the higher systolic pressure (p<0.001) in patients as compared with controls. Also, there is significantly higher diastolic pressure (p<0001) in HTN group in comparison with the control group

Table 1: psychological measures in hypertensive patients (HTN) and healthy controls (HC)

Variables	HC(n=30)	HTN (n=60)	Df	F	t	P
Systolic	12±0.001	16.23±1.226	88	60.421	-18.854	<0.001
Diastolic	8±0.00001	10.35±1.05	88	91.411	-12.214	<0.001

Effect of covariance and size effect of the MyBC3

In order to estimate the effect size of other founders on serum MyBC3 level, a multivariate Chi-Square analysis was performed using MyBC3 as the dependent variable to evaluate relationships between MyBC3 and diagnosis after controlling for confounding factors.

Effect of covariance and size effect of the MyBC3

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Table 2: results of multivariate Chi-Square analysis showing the associations between biomarkers and background variables

Dependent variable	Explanatory variable	Pearson's R	Spearman Correlation	P	Partial η^2
MyBC3	Age	-0.750	-0.919	<0.001	0.993
	BMI	0.847	0.909	<0.001	0.993
	Treatment	-0.793	-0.854091	<0.001	1.000
	smoking	-0.732	-0.854	<0.001	1.000
	Duration of disease	-0.751	-0.919	<0.001	0.994
	Family history	-0.765	-0.866206	<0.001	1.000

The results showed that the most influential factor on the level of MyBC3 serum is Treatment, smoking, and Family history (partial η2 = 1.000), meaning that the presence of patients with high blood pressure is the factor that causes an increase in the level of MyBC3 serum.

Correlation between the MyBC3and the demographic parameters

The correlation between the MyBC3 and In Table 3, the demographic parameters are displayed.

Table 3 shows the relationship between the demographic characteristics and the MyBC3.

variable	Age	Duration of disease	treatment	smoking	BMI	Familial hypertensive patients
MyBC3	-0.751**	-0.874**	-0.793**	-0.733**	0.847**	-0.765**

**Correlation is significant at the p<0.001 level (2-tailed).

From table (3) The results showed significant association between every parameter and serum level MyBC3 indicated the independence of the secretion of this protein on the mentioned parameters. To our best knowledge, we could not find any such correlations in the literature. However, more studies are required on a large sample size to obtain a whole picture of these correlations.

Correlation of MyBC3with the lipid profile parameters

The results of the correlation between the MyBC3 and Table 4 displays the parameters of the lipid profile.

Table 4: MyBC3 and cations and trace elements correlated

variable	TG	cho	HDL	VLDL	LDL	TG/HDL	LDL/HDL
MyBC3	0.690**	0.741**	-0.787**	0.138	0.809	- 0.876	-1.027

**Correlation is significant at the 0.01 level (2-tailed).

The findings revealed a strong negative link between MyBC3 and HDLc TG/HDL and LDL/HDL, but a significant positive relationship between MyBC3 and other lipid profile parameters. MyBC3 deficiency impacted the expression of various inflammatory and lipid metabolic genes in adipose tissue at the molecular level.

Discussion

table (1) allude to a noteworthy rise in MYBPC3 levels in hypertension individuals (p<0.001) when compared to the control group.

Some previous studies have been showed that (MYBPC3) is a major regulator of contractility of cardiac muscle expression mainly in cardiac tissue and regulate an availability of force generating myosin head by binding with S1, S2 and regulate light chain (RLC)so that control a force generation in myofilament c [14-17]. From truncating MYBPC3 variations, a convergent theory of allelic insufficiency has been seen in rat, human tissue, and induced pluripotent stem cell model systems[18].

Some researchers have been explained a role of (MYBPC3) by regulation of Ca^{+2} in myofilament sensitivity and interaction with actin to reduce flexibility and sliding speed with high tropomyosin Ca^{+2} concentration lead to high relaxation and sensitivity[19-24].

A recent studies have been indicated a role of MYBPC3 in hypertension patients (HTN) by incomplete relaxation and increase resting tension because of modifications in myofilament's processing of Ca+2 and slower retaliation linked [25-29].

table (2) showed some results in MYBPC3 serum that age (40-49) years has higher significant than other ages with no previous studies discuss these results therefore the same explanation of MYBPC3 in men depend on testosterone level with age and also these ages of patients checking into hospital early without treatment (new diagnosis).

The present results disagree with previous study in heart failure patients that showed a significant increase in MYBPC3 level with age which cause cardiomyopathy[26, 30-32].

From table (2), also in present study revealed a significant increase in MYBPC3 level in early duration one month -1 year also in new diagnosed patients in compare with treated. All hypertension patients at duration of disease one month -1year in current study has no administrated to any type of hypertension drugs also consider as new diagnosis whereas at high duration of disease patients taking different type of hypertensive drug therefore a level of MYBPC3 were less than a value of early duration of disease.

table (2) indicate a high significant increase in MYBPC3 level in smoker patients than non-smoker.

No previous studies deal with or study a relation between MYBPC3 and smoking therefore the explanation also may

depend on a present of harmful substancies in tobacco that may affect on across- bridge or forces of myosin -actin binding or Ca^{+2} in myofilament also dephosphorylation of PKA or serin 23 ,24.

table (2) in current results document that a higher level of MYBPC3 level in obese hypertensive patients than overweight and normal also, several studies has been suggested that obesity in mice associated with disturbed in calcium homeostasis and phosphorylation of MYBPC3 with significant transduction also cardiac contractile defect may be associated with hypertension and heart failure[13, 26, 33, 34].

table (2) Inflammation may be important role in oxidative stress with increase (ROS) with free radical all these may contribution in MYBPC3 high level.

table (2) in present results show a high level of MYBPC3 in familial hypertensive patients in compare with non-familial patients.

In a previous study a case of familial sarcomatoid cardiomyopathy caused by a pathogenic variant in the MyBPC3 gene was presented, which had a series of unique and universal aspects at the same time. The proband was first diagnosed with LVNC at the age of 64 years. The predominantly restrictive phenotype of cardiomyopathy is a result of the interaction between LVNC and sarcoidosis myocarditis. Younger family members have cardiomyopathy with an asymmetric non-obstructive HCM phenotype. The observed pattern suggests both initially different phenotypes within the same family or a gradual shift of the hypertrophic phenotype to LVNC. Myocarditis is an important epigenetic modifier of sarcomatous cardiomyopathy and one of the major drivers of fibrosis and arrhythmias in the range. This report supports the concept of a cascade of sarcomeric cardiomyopathies and reveals potential patterns of their clinical course and transformation over time.

In a previous studies has been revealed that MYBPC3 level was high in Hypertrophic Cardiomyopathy which associated with hypertension and observed that diastolic dysfunction, defect in cardiac relaxation also reduce filling with arterial stiffness in addition to hypertrophy and mitral valve abnormalities occur in familial hypertrophy cardiomyopathy (HCM)[18, 23, 26, 32].

table (4) revealed a substantial negative association between MyPBC3 and HDL and a positive correlation with cholesterol, TG, and LDL-C.

These results were documentation in currant study and no previous studies deals with the relation between MyPBC3and lipid profile.

Acknowledgment

We would like to thank College of Science, Department of Biology, Clinical sites, and the patients for their participation.

Conflict of interest

The authors declare no conflict of interest.

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