Study The Expression of DYRK1B Gene And Its Association With Metabolic Syndrome Among The Egyptians

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Abstract

Background: A cluster of many risk factors for type 2 diabetes and cardiovascular disease is used to describe the metabolic syndrome (MetS). Moreover, genetic differences associated with metabolic syndrome play a key role in its prevalence and side effects. This study aims to investigate the expression of DYRK1B and its association with metabolic syndrome in a small cohort of Egyptian.

Materials and methods: A total of 100 adult Egyptians (50 with MetS and 50 healthy control subjects) were included to this study. Clinical, biochemical and anthropometric analysis were assessed. Relative gene expressions of DYRK1B were compared between two groups of subjects using real time PCR.

Results: We observed marked overexpression in DYRK1B ($p<0.05$) in MetS subjects when compared with the healthy control subjects.

Conclusion: This is the first study to provide evidence that DYRK1B is highly expressed among the MetS subjects.

Introduction

The metabolic syndrome (MetS) is an agglomeration of several risk factors for cardiovascular disease (CVD) such as hypertension, dyslipidemia, obesity, insulin resistance and high fasting plasma glucose [1]. Parallel to the rise in overweight and obesity, the prevalence of MetS has increased worldwide [2]. This is a common condition affecting approximately one-quarter of the world's adult population; about 1 billion is affected by MetS [3]. In Egypt, about 60% of the adult population has MetS [4]. The development of metabolic risk factors is liable to implicate both genetic and environmental components [5]. Approximately fifty percent of serum lipid levels, including HDL and triglycerides are highly heritable [6]. Further confirmation of common genetic effects on multiple components of MetS is provided by the finding of a number of genome-wide linkage studies [7-9]. Moreover, the MetS has a significant genetic component that leads to changes in gene expression [10]. Previous study found that fifteen up-regulated and down-regulated genes for individuals with MetS versus healthy candidates [11].

DYRK1B (dual-specificity tyrosine(Y)-phosphorylation regulated kinase 1B) (also recognized as Mirk) belongs to the DYRK family of protein kinases, which comprise five conserved members, DYRK1A, DYRK1B, DYRK2, DYRK3, and DYRK4 [12]. DYRKs are dual function kinases family with the ability to autophosphorylate themselves on tyrosine during translation and subsequently phosphorylate other substrates on serine and threonine residues [13]. DYRK1B has been characterized as a regulator of cell differentiation such as myogenesis and undergoes differential splicing during adipogenesis[14,15]. In fact, DYRK1B can trigger cell cycle arrest through various mechanisms, including cyclin D1 degradation enhancement [16]. Evidence from a previous study indicated that mutations in DYRK1B are an inherited form of MetS associated with early-onset coronary artery disease, obesity, hypertension and diabetes [17]. However, the role of DYRK1B gene expression in MetS is not fully understood; hence, the objective of the

present study is to explore the involvement of DYRK1B gene expression in MetS inside a small cohort of adult Egyptian subjects.

Materials And Methods

2.1. Study design and subjects

A total of 100 Egyptians adult subjects was divided into 2 groups 50 with MetS (25 males and 25 females) and 50 healthy control subjects (12 males and 38 females). Samples were collected from local, public, and private hospitals after obtaining informed consent according to WHO instructions. The study was carried out at National Research Centre of Egypt. The study protocol was approved by the ethics committee board of the Ministry of Health and Population in Egypt (No: 23-2019/20). In the present study MetS was diagnosed by the presence of three or more of the following risk factors according to the International Diabetes Federation (IDF) [18]: waist circumference ≥94 cm in men and ≥80 cm in women, serum triglycerides (TG) ≥150 mg/dL; high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL in men and ≤50 mg/dL in women, blood pressure (BP) ≥130≥85 mmHg; or fasting plasma glucose (FPG) ≥ 5.6 mmol/L.

2.2. Anthropometric parameters and Biochemical analysis

Anthropometric measurements were obtained according to standardized equipment and following the recommendations of the International Biological Program. Body weight, height, waist and hip circumferences were measured. All measurements were taken 3 times on the left side of the body, and the mean of the 3 values was used. Body weight was measured with the patients in light clothing and without shoes. Height was measured with the patients standing with their backs leaning against the stadiometer of the same scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters square (kg/m^2). Waist circumference (WC) and hip circumference (HC) were measured in cm using a plastic, non-stretchable tape. WC was measured with light clothing at a level midway between the lower rib margin and the iliac crest standing and breathing normally, Waist to hip ratio (WHR) was calculated. Blood pressure was measured by the auscultatory method after the subject had been sitting at rest for a minimum period of 5 min, and the cuff involved 80% of the right arm circumference. The arm rested on a support surface at the level of the precordium. Blood pressure was measured three times and was averaged for analysis.

Venous blood samples were collected by direct venipuncture after an overnight fast. Fasting plasma glucose and serum lipids (total cholesterol, high-density lipoprotein cholesterol (HDL-C) triglycerides (TG) were measured by enzymatic colorimetric methods using a Hitachi autoanalyzer 704 (Roche Diagnostics. Switzerland). Low density lipoprotein cholesterol (LDL-C) was calculated according to certain equation (LDL-C= Total cholesterol –Triglycerides/5+ HDL-C) [19].

2.3. RNA extraction and quantitative real-time PCR

RNA was extracted using RNeasy kit of Qiagen (Germany) according to the manufacturer's instructions. For RNA reverse transcription, RNA was reverse transcribed to cDNA using RNA Reverse Transcription Kit (Applied Biosystems) and random primer according to the manufacturer's instructions. Reverse transcription was performed under the following conditions: 2 hrs at 37°C, 20 min at 85°C, then the resulting cDNA was kept at -80°C until use. A real-time quantitative PCR (qRT-PCR) was carried out to quantify the expression levels in triplicate of RNA using Taqman® RNA Assay kit (Applied Biosystems) and Taqman® Universal Master Mix (Applied Biosystems) using step one real time PCR system (Applied Biosystems) according to the manufacturer's instructions. GAPDH (Applied Biosystems) was used as endogenous control to normalize the expression levels of DYRK1B gene. The qRT-PCR protocol was as follows: initial denaturation at 94℃ for 20s followed by annealing at 56°C for 20s and extension at 72°C for 30s for 45 cycles. Relative quantification (Rq) of DYRK1B expression was calculated using the $2^{-\Delta\Delta CT}$ threshold cycle method. ΔCt was determined by subtracting the Ct values for GAPDH from the Ct values for the DYRK1B gene.

2.4. Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using [20]. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing gender, Chi-square test was performed**.** Two-sided *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

Clinical, biochemical characteristics and anthropometric parameters of 50 MetS patients and 50 healthy control subjects are summarized in **Table 1**. Compared with the healthy control group, anthropometric results showed that all the MetS patients were obese with high BMI (33.9±6.023 kg/m^2) and high waist to hip ratio (0.97± 0.0453). In addition, blood pressure (systolic and diastolic BP), fasting plasma glucose (FPG), total cholesterol and triglycerides (TG) were all statistically significant (p<0.05) in MetS patients. However, results showed that values of HDL-C and LDL-C were not statistically significant in MetS patients compared to normal healthy control.

Table 1: Clinical, biochemical characteristics and anthropometric parameters in study groups

rs	MetS Patients (n=50)	Healthy Control Subjects (n=50)	*p* value
er			
(n, %)	25(50)	12(24)	**0.007**
le (n, %)	25(50)	38(76)	**0.007**
ic BP (mmHg)	129.2±14.3	110.5 ± 6.32	**0.0001**
olic BP (mmHg)	81.7±12.5	75 ± 11.24	**0.0001**
kg/m^2)	33.9±6.023	25.3±5.6	**3.9986417055536E-11**
	0.97± 0.0453	0.804± 0.052	**2.09294468585921E-30**
mmol/L)	8.5±2.123	5.22±0.444	**3.45426875037029E-30**
profile			
sterol(mg/dL)	197.44±44.99	175.36±45.3	**0.016**
C (mg/dL)	40.31± 9.45	40.44± 8.21	0.940
C(mg/dL)	120.538± 42.10	107.97± 41.25	0.135
ıg/dL)	191.6± 87.01	138.36± 54.33	**0.0004**

* Plus–minus values are means ±SD included in this analysis, BP: blood pressure, BMI: Body mass index, WHR: waist to hip ratio, FPG: fasting plasma glucose, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, TG: triglyceride, Bold values indicate statistically relevant differences.

Real time PCR was used to investigate the expression of DYRK1B gene in both MetS patients and healthy control subjects. **Table 2** shows the difference in fold change of DYRK1B in study groups. The results found that there is a significant increase (p <0.05) in fold change in MetS patients when compared to healthy control subjects (**Fig. 1**).

Table 2: Fold changes difference of DYRK1B gene between study groups

	MetS patients (n=50)	Control group (n=50)	*p* value
Fold change	9.95±5.6	0.77±0.42	**0.0004**

*Plus–minus values are means ±SD included in this analysis; Bold value indicate statistically relevant differences.

Discussion

The severity of MetS in Egypt is surprisingly high and the etiology of MetS is associated with many genetic and lifestyle variables [21]. Thus, over the long term, early diagnosis and management of the MetS will reduce health complications [3]. Therefore, we examined alterations in DYRK1B gene expression in 50 Egyptians adults with MetS to 50 healthy control group.

Because DYRK1B is a specific co-activator of the forkhead transcription factor FKHR, which transactivates the expression of the glucose-6-phosphatase enzyme, this discovery suggests that this protein kinase may play a role in regulating hepatic glucose synthesis [22]. Argaud et al. reported that glucose-6 phosphatase activity is responsible for the inappropriate elevated fasting glucose levels in patients with type 2 diabetes, where insulin is either low or absent or insulin insensitivity exist [23]. Our findings are consistent with those recent observations and showed a statistically significant increase in the expression of DYRK1B and fasting plasma glucose among MetS patients when compared to a healthy control group. Furthermore, DYRK1B has been shown to be a nutrient-sensing protein that is well-known for its role in glucose uptake and glycolysis regulation [24]. Likewise, a study found overexpression of DYRK1B in mice and drosophila contributes to an increase in food intake and body weight [25].

Our findings revealed that the DYRK1B gene is overexpressed in the majority of MetS Egyptian patients with high triglyceride levels. As there is a strong association between adipocyte triglyceride turnover and metabolic conditions [26]; this finding support prior research that suggested DYRK1B up-regulation during adipogenic differentiation [15]. Also, a study including three Iranian families postulated that DYRK1B promotes adipogenesis [17], since the gene inhibits sonic hedgehog (SHH) and Wnt signalling pathways [27, 28].

Hence, MetS has a clear connection to cancer [29]; DYRK1B is overexpressed and highly activated in several types of solid tumors, including pancreatic, lung, ovarian, colon cancer, rhabdomyosarcoma, osteosarcoma and breast cancer [30-36]. Moreover, a study confirmed the high expression of DYRK1B in liposarcoma [37]. Such researches have contributed to the belief that the inflammatory state plays a causal role in the growth of type 2 diabetes and metabolic syndrome [38]; so, a study related the up-regulation of DYRK1B expression might be involved in controlling the activation of astrocytes in neuroinflammation [39].

The key drawback of this study is the limited number of individuals and large population studies are necessary to validate these findings.

In conclusion, our study demonstrated for the first time the differentially expressed DYRK1B gene and its implementation in the pathogenesis of MetS in patients when compared with the healthy control group in

a small cohort of Egyptian.

Declarations

Conflict of interest

There is no conflict of interest.

Funding

No funding was received for this study

Data availability

There are no restrictions on availability of the presented materials data and associated protocols.

Authors' contributions:

Authors equally contributed to this manuscript.

Ethics approval

The study protocol was approved by the ethics committee board of the Ministry of Health and Population in Egypt (No: 23-2019/20).

Consent to participate

Written informed consent was provided by the participants, as per the guidelines of Helsinki declarations on human Experimentation.

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Figures

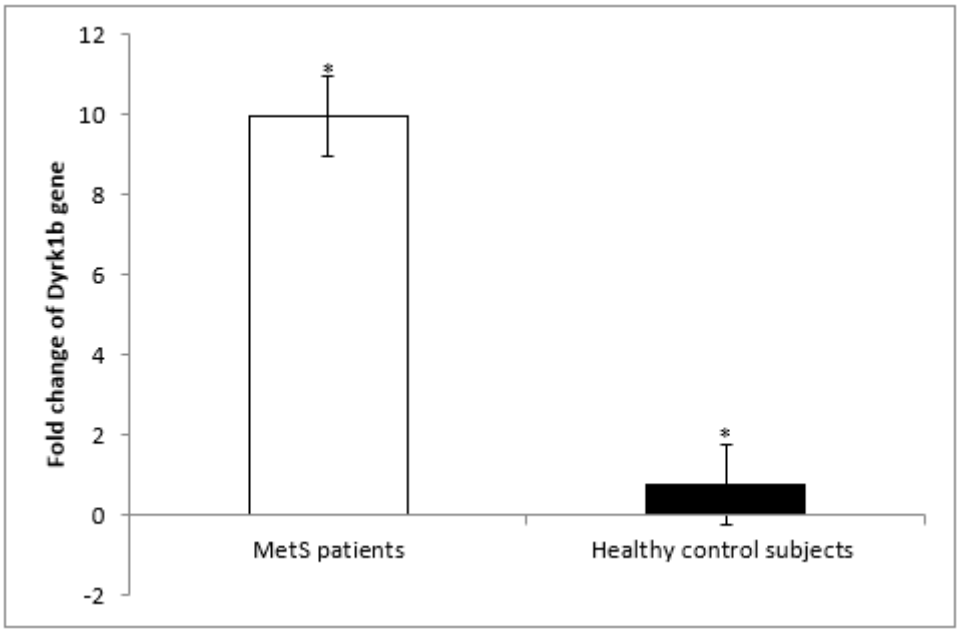

Figure 1

Fold change difference of DYRK1B gene in MetS patients (n=50, open bars) and healthy control subjects (n=50, solid bars). Values are given as mean ±SD, *p<0.05.