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Research Article

Expression of atherosclerosis-associated genes in peripheral blood of drug-naïve hypertensive subjects with newly-diagnosed type 2 diabetes mellitus

Nikolay Stoynev[1,2], Ivanka Dimova[3], Blaga Rukova[3], Savina Hadjidekova[3], Dragomira Nikolova[3], Tsvetalina Tankova[2]

1 *Department of Physiology and Pathophysiology, Medical University Sofia, Sofia, Bulgaria*
2 *Department of Endocrinology, Medical University Sofia, Sofia, Bulgaria*
3 *Department of Medical Genetics, Medical University Sofia, Sofia, Bulgaria*

Corresponding author: Nikolay Stoynev (nstoynev@medfac.mu-sofia.bg)

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Abstract

Aim: To evaluate the expression of atherosclerosis-associated genes in peripheral blood of drug-naïve hypertensive subjects with newly-diagnosed type 2 diabetes mellitus.

Materials and methods: Eighteen subjects (15 males, 3 females), mean age 46.27 ± 12.07 years, divided into two groups: studied group - subjects with newly-diagnosed hypertension and newly-diagnosed type 2 diabetes (n = 9), control group – normotensive individuals with newly-diagnosed type 2 diabetes (n = 9) Gene expression analysis was performed with Human Atherosclerosis RT2 Profiler PCR Array.

Results: In gene expression analysis, 5 genes with increased expression in the studied group were found – CD44, ITGA5, ITGB2, PPARA and RXRA. No genes with decreased expression matching the criteria were found.

Conclusion: The presence of arterial hypertension in subjects with newly diagnosed type 2 diabetes tends to increase the expression of CD44, ITGA5, ITGB2, PPARA and RXRA in the peripheral blood.

Keywords

diabetes mellitus, gene expression, hypertension

Introduction

Arterial hypertension affects between 30 and 50% of the population in the developed countries (Lovic et al. 2013). The disease is influenced by the interaction of multiple factors. It is not linked to a single gene but rather to a group of genes, sometimes differing in the different subjects (Hingorani and Brown 1996). Many genes have already been reported as related to arterial hypertension (e.g. genes encoding angiotensin-I converting

enzyme, angiotensinogen, NOS3 etc.) (Hingorani and Brown 1996), but the identification of more hypertension-associated genes is always a field of further investigation because of the potential finding of new targets in the management of hypertension.

The identification of various genes linked with specific disorders has resulted in the development of sets for studying the expression of many related genes. The use of these sets could be helpful to identify genes with altered expression associated with other diseases. This method could attract attention to genes that have never been directly related to the disease studied.

Arterial hypertension is often associated with atherosclerosis and type 2 diabetes mellitus. Some authors have already reported gene expression alterations that link atherosclerosis and type 2 diabetes mellitus (Zhang et al. 2005).

The aim of this study was to evaluate the expression in the peripheral blood of a set of genes associated with atherosclerosis in hypertensive and normotensive subjects with newly-diagnosed type 2 diabetes mellitus, trying to identify genes associated with hypertension.

Materials and methods

Eighteen subjects (15 males, 3 females), of mean age 46.27 ± 12.07 years, were included in the study. We have recruited the participants after evaluation of both arterial blood pressure and glucose tolerance. All participants were without previously diagnosed hypertension and had never received any antihypertensive drug. All subjects signed an informed consent.

According to the results of ambulatory blood pressure monitoring and glucose tolerance tests the participants were divided into 2 age-matched groups: Group 1: subjects with newly- diagnosed arterial hypertension and newly- diagnosed type 2 diabetes (n = 9); Group 2: normotensive subjects with newly- diagnosed type 2 diabetes (n = 9), which serve as a control group.

Standard anthropometric parameters – weight, height and waist circumference – were measured in all subjects.

Glucose tolerance was evaluated according to 2006 WHO criteria (World Health Organization 2006).

Blood pressure was measured by ambulatory blood pressure monitoring (Oscar 2, SunTech Medical Instruments, USA). Evaluation of blood pressure was made according to ESH Guidelines (Williams et al. 2018).

RNA isolation and first complementary DNA synthesis

Total RNA was extracted from 3 ml of blood in K_3EDTA vacutainers. RNA was isolated with the QIAamp RNA Blood MiniKit according to manufacturer's instructions (Qiagen, Germany). RNA isolates were then analyzed using Nanodrop1000. Absorption ratio was determined at wavelength 260/280 nm. Only samples pure enough (absorption ratio > 2) were used as templates for complementary DNA synthesis. All samples were electrophoretically tested to exclude RNA degradation before reverse transcription was performed.

First strand complementary DNA was synthesized from total RNA (2 μg) with a commercially available kit High Capacity Reverse Transcription Kit - 2x Reverse Transcription Master Mix (N #4368814, Applied Biosystems). RNA concentration per reaction: 100 ng/μl. The reverse transcription reaction was performed at 37 °C for 2 h.

Gene expression profiling

Real-time PCR was performed on the 7500 Real Time PCR System (Applied Biosystems). Gene expression analysis was done on 96-well plates - human atherosclerosis RT^2 Profiler PCR Array (N # PAHS-038, SuperArray Bioscience Corporation). Each plate contained 84 genes, involved in atherosclerosis, four housekeeping genes for normalization of PCR data, two replicates for positive PCR controls, two replicates for the control of RT reaction and one well for genomic DNA contamination control. The list of genes included is presented on Table 1.

RT^2 Real-Time SYBR Green/ROX PCR Mix (SuperArray Bioscience Corporation) was applied as described in the User Manual – RT^2 Profiler PCR Array System - (N #1022A, Version 3.3, SuperArray Bioscience Corporation). Each well contained 25 μl Master Mix. Melting curve analysis was run at the following program: 95 °C – for 1 min; 65 °C – for 2 min; 65 °C to 95 °C for 15 min.

The quality control (dissociation curve analysis, genomic DNA contamination, reverse transcription and PCR control) was done as described in the User Manual – RT^2 Profiler PCR Array System - (N #1022A, Version 3.3, SuperArray Bioscience Corporation).

The study design was approved by the Ethics Committee of the Medical University, Sofia.

Data analysis

A Student T-test was used to determine whether any significant differences in anthropometric parameters between the three groups were present. We applied the same method to compare the gene expression levels between the two sexes in each of the studied groups. The accepted level of statistical significance is $p < 0.05$.

For the gene expression, the ΔΔCt method was used for data analysis. For each gene fold-changes were calculated as the difference in the gene expression between the studied and the control group. The positive values indicate genes' up-regulation while the negative ones - genes' down-regulation. According to the manufacturer's standart, significant up-/down-regulation is present when at least 3-fold change in gene expression as compared to the control group is observed. To be accepted any difference in gene expression as significant, it should be present in the individual expression profiles of > 50% of the patient samples in the group studied (in our study – in at least 5 individuals).

Table 1. Genes studied with human atherosclerosis PCR array.

Response to Stress:
Inflammatory Response: CCL2, CCL5, CCR1, CCR2, IL1R1, IL1R2, ITGB2, NFKB1, NOS3, SELE, SPP1, TNF.
Response to Oxidative Stress: APOE, CCL5, SOD1.
Response to Pests, Pathogens or Parasites: CCL2, CCR2, CSF2, FN1, IL4, ITGB2, TNF.
Response to Virus: CCL5, IFNAR2, TNF.
Response to Wounding: CCR1, CCR2, CTGF, FN1, PDGFB, TNF, VWF.
Other Genes Related to Stress Response: IFNG, PPARG, VEGFA.
Apoptosis:
Anti-apoptosis: BCL2, BCL2A1, BCL2L1, BIRC3, CCL2, CFLAR, FAS (TNFRSF6), IL1A, IL2, NFKB1, SERPINB2, SPP1, TGFB1, TNF, TNFAIP3.
Induction of Apoptosis: APOE, BAX, BID, CFLAR, FAS (TNFRSF6).
Other Genes Related to Apoptosis: IL5, ITGB2.
Blood Coagulation and Circulation:
Blood Coagulation: FGA, ITGA2, LPA, SERPINE1.
Circulation: APOA1, APOB, APOE, COL3A1, ELN, ENG, LPA, LPL, NPY.
Platelet Activation: PDGFA, PDGFB, PDGFRB, VWF.
Regulation of Blood Pressure: ACE, FGA.
Adhesion Molecules:
Cell-cell Adhesion: CD44, CDH5, ICAM1, ITGB2, SELE, SELL, TNF, VCAM1, VEGFA.
Cell-matrix Adhesion: CD44, ITGA2, ITGA5, ITGAX, ITGB2, SPP1.
Other Genes Involved in Adhesion: CCL2, CCL5, CCR1, CTGF, ELN, ENG, FN1, LAMA1, SELPLG, THBS4, TNC, VWF.
Extracellular Molecules:
ECM Protease Inhibitors: LPA, SERPINB2, SERPINE1.
ECM Proteases: ACE, MMP1, MMP3.
Extracellular Matrix (ECM) Structural Constituents: COL3A1, ELN, FN1.
Other Extracellular Molecules: ADFP, APOA1, APOB, APOE, CCL2, CCL5, CSF2, CTGF, FGA, FGF2, HBEGF (DTR), IFNAR2, IFNG, IL1A, IL2, IL3, IL4, IL5, LAMA1, LIF, LPL, NPY, PDGFA, PDGFB, SPP1, THBS4, TNC, VEGFA, VWF.
Lipid Transport and Metabolism:
Cholesterol Metabolism: ABCA1, APOA1, APOB, APOE, IL4, LDLR.
Fatty Acid Metabolism: FABP3, LPL, PPARA, PTGS1.
Lipid Transport: ABCA1, APOA1, APOB, APOE, FABP3, LDLR, LPA, LPL, MSR1.
Lipoprotein Metabolism: APOA1, APOE, LDLR, LPL.
Steroid Metabolism: NR1H3, PPARA, PPARD, PPARG, RXRA.
Other Genes Related to Lipid Metabolism: ADFP, APOE, LPA.
Cell Growth and Proliferation:
Growth Factors and Receptors: CSF2, KDR, PDGFRB, SPP1.
Negative Regulation of Cell Proliferation: BCL2, FABP3, IL1A.
Positive Regulation of Cell Proliferation: CSF1, FGA, FGF2, HBEGF (DTR), IL2, IL3, IL5, IL6, IL7, LIF, VEGFA.
Regulation of the Cell Cycle: FGF2, IL1A, PDGFA, PDGFB, TGFB1, TGFB2, VEGFA.
Other Genes Involved in Cell Growth and Proliferation: CTGF, ELN, IFNG, IL4, NPY.
Transcription Regulators:
Nuclear Receptors: NR1H3, PPARA, PPARD, PPARG, RXRA.
Other Transcription Regulators: EGR1, KLF2, NFKB1, TNF, TNFAIP3.

Results

We did not observe any differences in the anthropometric parameters between the two studied groups. (Table 2).

Table 2. Anthropometric parameters in the studied groups. Group 1 – newly-diagnosed arterial hypertension and newly-diagnosed type 2 diabetes mellitus; Group 2 (control group) – normotensive subjects with newly-diagnosed type 2 diabetes mellitus.

	Age (years)	BMI (kg/m^2)	Waist circumference (cm)
Group 1	47.55 ± 12.83	32.61 ± 6.91	112.22 ± 15.27
Group 2	45.00 ± 11.87	32.15 ± 6.53	108.67 ± 17.76

The blood expression levels of all genes were evaluated in both patient groups and we compared their expression in Group 1 to the expression in Group 2 (the control group).

In gene expression analysis, according to the applied criteria, 5 genes with increased expression were found – *CD44*, *ITGA5*, *ITGB2*, *PPARA* and *RXRA*. (Table 3, Fig. 1).

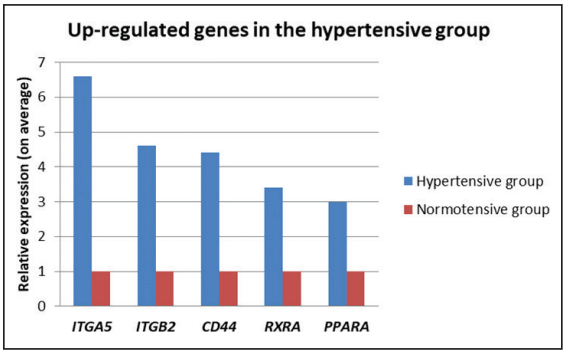

Figure 1. Average increase in the expression levels of the significantly up-regulated genes in the group of hypertensive patients compared to normotensive ones with newly-diagnosed type 2 diabetes mellitus.

Table 3. Average RQ (relative expression) of significantly up-regulated genes. The highest increase in expression was detected for *ITGA5* (6.6 times on average), followed by *ITGB2* (4.6 times on average), *CD44* (4.4 times), *RXRA* (3.4 times) and *PPARA* (3 times). No genes with decreased expression matching the criteria were found.

Gene	Fold regulation (comparing to control group)	Gene function
ITGA5	6.6	cell-surface mediated signaling (form a fibronectin receptor)
ITGB2	4.6	cellular adhesion and cell surface signaling
CD44	4.4	lymphocyte activation, recirculation and homing
RXRA	3.4	nuclear receptor – retinoic acid-mediated gene activation
PPARA	3	nuclear receptor - transcription factor and a major regulator of lipid metabolism in the liver

Discussion

We have identified 5 genes with increased expression matching our criteria – *ITGA5*, *ITGB2*, *CD44*, *RXRA* and *PPARA*.

The *ITGA5* gene encodes the integrin alpha 5 chain. The expression of *ITGA5* is reported to have an association with obesity (Chen et al. 2013). Our previous study revealed increased expression of *ITGA5* both in hypertensive subjects with normal glucose tolerance and normotensive subjects with type 2 diabetes (Stoynev et al. 2014). No other data about *ITGA5* levels in hypertension have been reported.

The product of the *ITGB2* gene is integrin subunit beta 2 (CD18). Increased expression of all three types of integrin involving this subunit is present in women with preeclampsia (Haller et al. 1997). In another study, higher levels of beta 2 integrin are present in the early stages of pregnancy in the women who eventually developed hypertensive complications compared with the women who did not (Bar et al. 2003). However, some authors did not observe any alteration in neutrophil CD11b and CD18 expression in preeclampsia (Barden et al. 2001). Overexpression of beta 2 integrin was found in subjects with hypertension (Hopps et al. 2009). Other authors have observed increased expression of beta 2 integrin in patients with systolic blood pressure values > 120 mmHg and diastolic blood pressure values > 80 mmHg (Rea et al. 2013). Some recent data suggest that upregulation of Itgam (CD11b) and Itgb2 (CD18) tends to play an important role in hypertensive cardiac remodeling (Zhang et al. 2024).

In a previous study we found increased expression of *ITGB2* both in hypertensive subjects with normal glucose tolerance and normotensive subjects with type 2 diabetes (Stoynev et al. 2014). The increased expression levels of *ITGA5* and *ITGB2* in this study might be related to an additive effect of type 2 diabetes and arterial hypertension.

The *CD44* gene encodes a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration. Some results suggest that increased local CD44 levels in the blood vessels in hypertension might result from angiotensin II signaling through the AT1-receptor (Bai et al. 2016). Increased levels of CD44 and osteopontin are reported in pulmonary hypertension (Anwar et al. 2012, Ohta-Ogo et al. 2012). Increased expression of CD44 and osteopontin mRNA has been observed in genetic low nephron hypertension model in rats (Freese et al. 2013). In humans, increased local tissue levels of CD44 in glomeruli from biopsy specimens are present in patients with collapsing focal segmental glomerulosclerosis (Merchant et al. 2020). Increased CD44/FKBPL(FK506-binding protein like) ratio in the plasma and the placenta has been reported to correlate with increased risk of preeclampsia (Todd et al. 2021). No data for increased expression of this gene in peripheral blood of subjects with hypertension have been reported yet.

The *RXRA* gene encodes retinoid X receptor alpha (also known as NR2B1). Single nucleotide polymorphisms (SNPs) in this gene have been hypothesized to have an influence on the variations of blood pressure but a large-scale comprehensive genetic association study including the genome-wide data of 92,689 people did not confirm that suggestion (Wang et al. 2014). Increased local overexpression of *RXRA* (in cardiomyocytes) was found in subjects with dilated cardiomyopathy (Subbarayan et al. 2000) while other authors observed lower local mRNA levels of *RXRA* in hypertrophic cardiomyopathy than in healthy controls (Pei et al. 2021). Low local expression of *RXRA* in atherosclerotic plaques is associated with more pronounced disease progression in patients with advanced carotid atherosclerotic lesions (Giaginis et al. 2011). The value of the increased expression of this gene in peripheral blood still has to be elucidated.

The *PPARA* gene encodes peroxisome proliferator activated receptor alpha. PPARα signaling has inhibitory effects on the development of left ventricular hypertrophy in patients with hypertension (Kieć-Wilk et al. 2005). A decreased level of PPARα protein was observed in the cytoplasm and nucleus of cardiomyocytes in patients with pressure overload-induced cardiac hypertrophy (Barger et al. 2000). The exact role of PPARα in atherosclerosis is controversial (Kieć-Wilk et al. 2005). However, a polymorphism in this gene has been reported to improve the cardiovascular benefit of fenofibrate in type 2 diabetes mellitus (Morieri et al. 2020). Some results indicate that PPARα activation attenuates hypertensive vascular remodeling by protecting vascular smooth muscle cells from angiotensin II-induced reactive oxygen species production (Liu et al. 2022). Our previous study demonstrated increased *PPARA* expression in peripheral blood both in hypertensive subjects with normal glucose tolerance and normotensive subjects with type 2 diabetes (Stoynev et al. 2014). The increased expression levels of *PPARA* in this study might be a result of an additive effect of type 2 diabetes and arterial hypertension.

Conclusion

The presence of arterial hypertension in subjects with newly diagnosed type 2 diabetes tends to increase the expression of *CD44*, *ITGA5*, *ITGB2*, *PPARA* and *RXRA* in

the peripheral blood. The increased expression of *ITGA5*, *ITGB2* and *PPARA* might be due to an additive effect of the presence of both diseases.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: The declarations of informed consent are stored in the Department of Physiology and Pathophysiology, Medical University Sofia and are on disposition of the first (corresponding) author - Nikolay Stoynev.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

N Stoynev and T Tankova created the study design. The study design has been approved by all authors. N Stoynev and T Tankova were responsible for the recruitment of the patients and for the verification of their blood pressure status and glycemic control. I Dimova, B Rukova, S Hadjidekova and D Nikolova obtained the blood samples and performed the genetic expression tests. I Dimova and N Stoynev performed the statistical analysis. N Stoynev has prepared the manuscript. All authors have read and approved the final text.

Data availability

All of the data that support the findings of this study are available in the main text.

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