Results of studying the association between the rs11212617 polymorphism in the ATM gene and response to metformin therapy in patients with type 2 diabetes mellitus

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Rationale. The genetic aspects influencing the effectiveness of metformin (MF) therapy in patients with type 2 diabetes mellitus (DMT2) have recently been intensively studied.

Objective — to study the association between the rs11212617 polymorphism in the ATM gene and response to metformin therapy in DMT2 patients in the Novosibirsk region and to conduct a metaanalysis of the previously reported data.

Material and methods. 460 DMT2 patients (97 males and 363 females) who received MF, both as a part of monotherapy and in combination with sulfonylurea (SU) drugs, were subjected to cross-sectional examination. Depending on HbA1c level, patients were divided into the following groups: patients who have attained the target HbA1c on the background of MF, and those who did not attain the target HbA1c level although receiving the maximum dose of MF (n=251). Alleles and genotypes were determined by real-time PCR using TaqMan probes at the Institute of Chemical Biology and Fundamental Medicine (SB RAS).

Results. Frequency of the rare C allele of the rs11212617 polymorphism in the ATM gene in the examined patients was 0.41 and statistically did not differ between the subgroups who received MF monotherapy and combination therapy. Statistically significant association between the genotype of the rs11212617 polymorphism in the ATM gene and the type of response was revealed neither in the total group of patients (OR=0.94, 95% CI 0.73—1.23; p=0.67) nor in the MF monotherapy (OR=0.94, 95% CI 0.73—1.23; p=0.67) or combination therapy subgroups (OR=1.02, 95% CI 0.72—1.43; p=0.92). However, the metaanalysis results verify that the C allele is associated with attainment of the target HbA1c level (summed OR=1.27; 95% CI 1.10—1.46; p=0.0008).

Conclusions. The rs11212617 polymorphism in the ATM gene can influence the effectiveness of MF therapy in DMT2 patients.

Keywords: type 2 diabetes mellitus, metformin, ATM (rs11212617).

BACKGROUND

Currently, metformin (MF) is the first-line medication in the treatment of type 2 diabetes mellitus (T2DM) [1, 2]. It is known that the effectiveness of MF therapy may vary among T2DM patients. This variability may be due to psychological and social factors, malabsorption of the drug from the gastrointestinal tract, changes in metabolism, distribution and excretion, which in turn de-
pend on renal function, enzyme systems activity, and
drug interactions, leading to alteration of MF pharma-
cinetics and pharmacodynamics. MF is used in clinical
medicine for more than 50 years. However, the mecha-
nisms underlying its therapeutic effects are not fully un-
derstood. After entering the cell, MF is accumulated in
the mitochondrial matrix. Mitochondrial respiratory
chain complex I is a key target of MF, whose inhibition
results is decreased production of ATP and increased lev-
els of AMP and ADP. This change in cellular energy me-
tabolism is detected by AMP-activated protein kinase
(AMPK), the main cellular energy sensor. MF enhances
phosphorylation processes, which leads to increased cel-
lar level of AMPK followed by with inhibition of mTOR
(mammalian target of rapamycin) protein kinase, which
affects metabolism and growth factor signaling, different-
tiation, aging, apoptosis, and autophagic processes [3, 4].
Activation of AMPK reduces activity of cell cycle en-
zymes, gluconeogenesis, and glycogenolysis; stimulates
anaerobic glycolysis, fatty acid oxidation in liver, and ke-
togenesis; inhibits lipogenesis, synthesis of cholesterol
and triglycerides, inhibits lipolysis and lipogenesis in adi-
pcocytes; stimulates fatty acid oxidation and glucose up-
take in skeletal muscles through enhanced biosynthesis of
GLUT-1 and GLUT-4 glucose transporters; modulates
insulin secretion by beta cells [5]. It is assumed that de-
creased expression and activity of AMPK is associated
with obesity, metabolic syndrome, disturbance of carbo-
hydrate metabolism, cancer, and myocardial ischemia
[2, 5]. In recent years, genetic aspects affecting the effi-
cacy of MF therapy are being extensively studied. The
study of the effect of MF on AMPK, the product of atax-
ia-telangiectasia (ATM) gene expression, is of greatest
interest [6]. According to the literature, the minor C al-
lele at the polymorphic locus rs11212617 in the ATM gene
is associated with good response to MF [7].

AIM

The study was aimed at assessing association of the polymorphic locus rs11212617 in the ATM gene with the response to MF therapy in T2DM patients in the Novo-
sibirsk region and conducting metaanalysis of previously published data.

METHODS

Study Design

A single-step cross-sectional survey of 2000 T2DM
patients (450 males and 1550 females) was carried out on
the basis of the mobile diabetes center (Diamobil) in the
Novosibirsk region.

Inclusion criteria

A total of 2000 patients were examined and 460 of
them were included in the study (97 males and 363 fe-
males), who received MF either as monotherapy or in
combination with sulfonylurea (SU) medications. Exclu-
sion criteria were as follows: type 1 diabetes mellitus
(T1DM), other types of diabetes, T2DM with insulin
therapy, cancer, NYHA III—IV heart failure, hepatic in-
sufficiency (more than 7 points on the Child-Pugh scale),
decreased glomerular filtration rate (GFR) of less than 45
mL/min × 1.73 m², treatment with corticosteroids or es-
trogens, alcoholism, drug addiction, dementia, or severe
mental disorders.

Study conditions

The study included only patients, who provided written
informed consent.

Duration of the study

From 2012 to 2015.

Description of medical intervention

All 460 patients underwent complete clinical exami-
nation; the level of glycated hemoglobin (HbA1c) was as-
sumed using immuno-turbidimetric method on BIO-
RAD D10 analyzer (US). DNA isolation and genotyping
of rs11212617 polymorphic locus of the ATM gene was
carried out in the laboratory of Pharmacogenomics at the
Institute of Chemical Biology and Fundamental Medi-
cine, Siberian Branch of the Russian Academy of Sci-
ences (SB RAS) using TaqMan real-time PCR. PCR was
performed in a final volume of 25 μl, containing 65 mM
Tris–HCl (pH 8.9), 24 mM ammonium sulfate; 3.5 mM
MgCl2, 0.05% Tween-20; 300 nM of each primer; 100
nM of each Taq Man-probe conjugated to FAM or R6G;
200 μM of dNTP, 20—100 ng of DNA, and 1 activity unit
of Taq-DNA polymerase. Amplification was carried out
using CFX384 amplifier (Bio-Rad, USA) under the fol-
lowing conditions: initial 3’ denaturation at 96 °C fol-
dowed by 50 cycles, including denaturation at 96 °C dur-
ing 8 sec, primer annealing and subsequent elongation at
T_m = 60 °C for 40 seconds (each step was followed by
registration of the fluorescence signal in the range corre-
sponding to fluorescence intervals of FAM and R6G flu-
ophores). Genotype of the polymorphic locus
rs11212617 was determined using the following oligonu-
cleotides: forward primer 5’-GATCTACATATACCAT-
TACAAAAGG-3’, reverse primer 5’-GGATAA-
CATATGGGCTCTTTG-3’, probe for A allele
5’-FAM-CAGAGATGTCAAGCGG-BHQ-3’,
probe for C allele 5’-R6G-CAGAGACTGTCAGAGC-
GG-BHQ-3’.

The main result of the study

Association of the polymorphic locus rs11212617 in the
ATM gene with the response to MF therapy in T2DM
patients in the Novosibirsk region was evaluated based on
HbA1c level. Patients who have attained target HbA1c val-
ues in accordance with the algorithms of specialized
medical care for diabetic patients (2015) were included in
the group with good response to MF. Patients who have not attained target HbA1c values were included in the group with poor response to MF.

**Subgroup analysis**

Depending on the level of HbA1c, patients were divided into groups: patients with target HbA1c level during MF therapy (the group with good response to MF administered both as monotherapy and in combination with SU medications) and the group of patients who have not attained the target HbA1c level, while receiving the maximum dose of MF.

**Ethical review**

Research protocol was approved by the ethics committee of the Novosibirsk State Medical University (Protocol No 52 of 19.03.13). All patients signed an informed consent before entering the study.

**Statistical analysis**

We used standard descriptive and comparative analysis. In the case of normal distribution, the data were represented as a mean value (M) and standard deviation (SD), in the case of asymmetric distribution, the data were represented as a median (Me) with 25 and 75 percentiles (25; 75). Pearson’s χ² test was used to compare the frequency of alleles between the groups. Depending on the type of data distribution, analysis of variance (ANOVA) or Kruskal—Wallis test was used to evaluate the differences between the groups. The critical significance level was set at 0.05. Compliance with Hardy—Weinberg equilibrium was assessed using Fisher’s exact test. Statistical analysis was performed using Genetics statistical package as implemented in R-project software (www.r-project.org) and Statistica 6.0 program.

Metaanalysis, evaluation of the «archival box» effect (publication bias), and construction of «forest plots» and «funnel plots» were carried out using meta and rmeta packages as implemented in R-project software (www.r-project.org). PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) was searched for articles published up to and including May 12, 2016 using various combinations of «rs11212617», «T2DM», and «diabetes mellitus» keywords. Inclusion criteria were as follows: 1) the design of the study «case-control», 2) evaluation of the association of rs11212617 with attainment of target HbA1c level of <7%, 3) presentation of the results in English, 4) availability of all information required to calculate OR. Metaanalysis included the results of two studies, Zhou [8, 11] and van Leeuwen [9], along with our results. We did not include the findings of Zhou (2014, RS11212617 is associated with metformin treatment response in type 2 diabetes in Shanghai local Chinese population) obtained for Chinese population, since the article is not available and the summary does not contain the required information. A total of 5494 T2DM patients, who received MF, were included in metaanalysis.

**RESULTS**

**Objects (participants) of the study**

The average age of the examined patients was 58.8±8.6 years, duration of T2DM — 6.2±5.7 years, HbA1c level — 8.4±1.9%, BMI — 34.8±6.7 kg/m². The patients were divided into groups depending on HbA1c level: the group with target HbA1c level during MF therapy (the group with good response to MF (n=209), of whom 110 patients received MF monotherapy and 99 patients received a combination of the MF with SU; and the group of patients, who have not attained target HbA1c level, while receiving the maximum dose of MF (n=251), of whom 58 patients received MF monotherapy and 193 patients received a combination of the MF with SU).

**Table 1. Clinical and laboratory characteristics of the examined patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group with good response to MF, n=209</th>
<th>Group with poor response to MF, n=251</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>29/128</td>
<td>17/68</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>60.4±8.9</td>
<td>57.5±8.1*</td>
<td>0.0002</td>
</tr>
<tr>
<td>DM duration, years</td>
<td>5.1±5.1</td>
<td>7.2±6.0*</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age of DM onset, years</td>
<td>55.4±9.6</td>
<td>50.2±8.6*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>35.2±6.2</td>
<td>34.2±7.1</td>
<td>0.21</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.7±0.4</td>
<td>9.8±1.6*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.4±2.2</td>
<td>3.5±2.7</td>
<td>0.93</td>
</tr>
<tr>
<td>GFR, ml/min × 1,73 m²</td>
<td>73.8±11.4</td>
<td>75.4±14.7</td>
<td>0.37</td>
</tr>
<tr>
<td>ALT, units/l</td>
<td>27.8±22.7</td>
<td>29.8±20.8</td>
<td>0.52</td>
</tr>
<tr>
<td>AST, units/l</td>
<td>26.7±12.9</td>
<td>26.5±11.5</td>
<td>0.90</td>
</tr>
</tbody>
</table>

**Table 1. Clinical and laboratory characteristics of the examined patients**
**Key findings**

The distribution of genotypes of polymorphic locus rs11212617 in the *ATM* gene demonstrated no statistical deviations from Hardy-Weinberg equilibrium (p=0.21). In the examined patients, the frequency of the minor C allele at the polymorphic locus rs11212617 in the *ATM* gene was 0.41; in the subgroup of patients with poor response to MF monotherapy, it reached 0.46, and in the subgroup with good response it was 0.39 (p>0.05); in the overall group of patients with poor response to MF in combination with SU, the frequency of C allele was the same, 0.4 and 0.41, respectively and did not differ significantly from that in the group with good response (Figure 1).

Logistic regression analysis of the relationship between the attainment of target HbA1c level of <7% during MF treatment and genotypes of the polymorphic locus rs11212617 in the *ATM* gene demonstrated no statistically significant association of rs11212617 genotype with the type of response both in the overall group of patients (OR=0.94, 95% CI 0.73—1.23; p=0.67) and in subgroups of patients, who received MF monotherapy (OR=0.90, 95% CI 0.65—1.25; p=0.54) and combination therapy (OR=1.02, 95% CI 0.72—1.43; p = 0.92) (Table 2).

**Additional findings**

We carried out meta-analysis of the results of our investigation and previously published studies. This meta-analysis included a total of 5494 T2DM patients, who received MF (Table 3).

According to the results of meta-analysis, minor C allele is a factor associated with good response to MF therapy (overall OR=1.27, 95% CI 1.10—1.46; p=0.0008, the level of heterogeneity p=0.02, the random effects model). We found no bias in the results published by other researchers, as shown by the correlation analysis (Begg’s correlation analysis; z = –0.45; p=0.65) and regression test (Egger’s test: t=-0.470; p=0.66). In addition, we carried out metaanalysis in both of the MF monotherapy and combination therapy subgroups. However, while the results in the MF monotherapy subgroup were similar (overall OR = 1.26, 95% CI 1.12—1.42; p=0.0001, the level of heterogeneity p=0.15, fixed-effects model, Begg’s correlation analysis (z=1.32 and p=0.19), Egger’s test (t=0.79; p=0.48), no impact of the polymorphic locus on the attainment of target HbA1c level was observed in the group with combination therapy: overall OR=1.13, 95% CI 0.98—1.29; p=0.09, the level of heterogeneity p=0.75, fixed-effects model, Begg’s correlation analysis (z=–0.56 and p=0.57), Egger’s test 0.73). The results of metaanalysis and bias analysis of publications are plotted in Figure 2.

**Adverse events**

No adverse events were registered during this study.

**DISCUSSION**

The first pharmacogenetic genome-wide associative study of MF was carried out in Scotland in 1024 T2DM patients involved in the GoDARTS (Genetics of Diabetes Audit and Research Tayside) study [8]. Efficacy of MF therapy was assessed based on HbA1c levels during the first 18 months from the start of therapy. The target HbA1c level was <7%, which was considered as evidence of the effectiveness of hypoglycemic therapy. The statistical analysis considered the initial level of HbA1c, its dynamics during MF therapy, and creatinine clearance. Researchers have identified 14 polymorphisms in the region, comprising *ATM* gene. It was found that the carriers of minor C allele at the polymorphic locus rs11212617 in the *ATM* gene attained target HbA1c level more frequently (OR= 1.64, 95% CI 1.37—1.99; p=1.9

<table>
<thead>
<tr>
<th>rs11212617 genotype in the ATM gene</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>168 (0.37)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>209 (0.45)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>83 (0.18)</td>
<td></td>
</tr>
<tr>
<td>Patients with poor response to MF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>87 (0.35)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>121 (0.48)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>43 (0.17)</td>
<td></td>
</tr>
<tr>
<td>Patients with good response to MF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>81 (0.39)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>88 (0.42)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>40 (0.19)</td>
<td></td>
</tr>
<tr>
<td>MF monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>45 (0.41)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>44 (0.40)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>21 (0.19)</td>
<td></td>
</tr>
<tr>
<td>MF combination therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>36 (0.36)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>44 (0.44)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>19 (0.19)</td>
<td></td>
</tr>
</tbody>
</table>

Additive inheritance model was used to calculate OR for C allele in each cohort. The following parameters were added to the regression: patient sex, age at the time of the survey, daily dose of MF, and the creatinine level.
The authors genotyped the polymorphic locus in two independent groups consisting of 1783 Scottish T2DM patients (the other part of the GoDARTS study) and 1113 patients involved in the UKPDS study (UK Prospective Diabetes Study) in order to replicate the original results of the genome-wide study. Significant association with response to MF therapy was found in both populations. The cumulative effect in attaining the objectives of hypoglycemic MF therapy was statistically significant at the genome-wide level (OR=1.35, 95% CI 1.12—1.60; p=2.9 × 10^{-7}). Later on, the same group of researchers have determined the genotypes of the polymorphic locus rs11212617 in three more cohorts: DCS, Rotterdam Study, and CARDS [8, 9]. Subsequent metaanalysis in five cohorts under study (the first one was excluded in order to avoid biased results) included 4443 T2DM patients and it also confirmed the relationship between the minor C allele and attainment of target HbA1c level (OR=1.25, 95% CI 1.13—1.38; p=7.8 × 10^{-6}). It is noteworthy that, when dividing the group into MF monotherapy and combination therapy subgroups, association of C allele was preserved only in the monotherapy subgroup. Van Leeuwen et al. hypothesized that some effects of MF therapy (particularly, AMPK-mediated ones, may partially be neutralized due to SU medications intake [10]). Possibly, this gene portion controls the cell cycle, and its changes can lead to decrease in phosphorylation and activation of AMPK, and therefore to different hypoglycemic effect of MF [10].

**Table 3. Metaanalysis of the studies of the relationship between the attainment of target HbA1c level of <7% during MF therapy and the genotype of polymorphic locus rs11212617 in the ATM gene**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GoDARTS (Discovery) [11]</td>
<td>1024</td>
<td>1.64 (1.37—1.99)</td>
<td>1.9×10^{-7}</td>
</tr>
<tr>
<td>GoDARTS (Replication) [11]</td>
<td>1783</td>
<td>1.21 (1.05—1.38)</td>
<td>0.007</td>
</tr>
<tr>
<td>UKPDS [11]</td>
<td>1113</td>
<td>1.37 (1.1—1.72)</td>
<td>0.006</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Discovery)+GoDARTS (Replication)+UKPDS] [11]</td>
<td>3920</td>
<td>1.35 (1.22—1.49)</td>
<td>2.9×10^{-7}</td>
</tr>
<tr>
<td>DCS [15]</td>
<td>929</td>
<td>1.27 (1.03—1.58)</td>
<td>0.028</td>
</tr>
<tr>
<td>Rotterdam Study [15]</td>
<td>182</td>
<td>1.44 (0.87—2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>CARDS [15]</td>
<td>254</td>
<td>1.03 (0.68—1.57)</td>
<td>0.86</td>
</tr>
<tr>
<td>Metaanalysis (DCS + Rotterdam Study + CARDS) [15]</td>
<td>1365</td>
<td>1.24 (1.04—1.49)</td>
<td>0.016</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Replication)+ UKPDS+DCS+RotterdamStudy+CARDS] [15]</td>
<td>4443</td>
<td>1.25 (1.13—1.38)</td>
<td>7.8×10^{-6}</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Discovery) + GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS]+ Russia (our own data)</td>
<td>5494</td>
<td>1.27 (1.10—1.46)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Metaanalysis (DCS + Rotterdam Study + CARDS) [10]</td>
<td>693</td>
<td>1.38 (1.07—1.80)</td>
<td>0.015</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS] [10]</td>
<td>2437</td>
<td>1.33 (1.16—1.50)</td>
<td>1.4×10^{-2}</td>
</tr>
<tr>
<td>Russia (our own data)</td>
<td>110</td>
<td>0.90 (0.65—1.25)</td>
<td>0.54</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS]+ Russia</td>
<td>2547</td>
<td>1.26 (1.12—1.42)</td>
<td>0.0011</td>
</tr>
<tr>
<td>MF monotherapy</td>
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<td></td>
<td></td>
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<tr>
<td>GoDARTS (Replication) [8]</td>
<td>1460</td>
<td>1.25 (1.07—1.46)</td>
<td>0.005</td>
</tr>
<tr>
<td>UKPDS [8]</td>
<td>284</td>
<td>1.82 (1.20—2.78)</td>
<td>0.005</td>
</tr>
<tr>
<td>DCS [9]</td>
<td>547</td>
<td>1.32 (0.99—1.78)</td>
<td>0.062</td>
</tr>
<tr>
<td>Rotterdam Study [9]</td>
<td>65</td>
<td>1.97 (0.72—5.42)</td>
<td>0.19</td>
</tr>
<tr>
<td>CARDS [10]</td>
<td>81</td>
<td>1.50 (0.76—2.95)</td>
<td>0.23</td>
</tr>
<tr>
<td>Metaanalysis (DCS + Rotterdam Study + CARDS) [10]</td>
<td>672</td>
<td>1.15 (0.89—1.48)</td>
<td>0.29</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS] [10]</td>
<td>2006</td>
<td>1.15 (0.99—1.34)</td>
<td>0.067</td>
</tr>
<tr>
<td>Russia (our own data)</td>
<td>99</td>
<td>1.02 (0.72—1.43)</td>
<td>0.92</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + RotterdamStudy + CARDS]+ Russia (our own data)</td>
<td>2105</td>
<td>1.13 (0.98—1.29)</td>
<td>0.09</td>
</tr>
<tr>
<td>Combination therapy (MF + SU)</td>
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</tr>
<tr>
<td>GoDARTS (Replication) [8]</td>
<td>505</td>
<td>1.08 (0.84—1.40)</td>
<td>0.54</td>
</tr>
<tr>
<td>UKPDS [8]</td>
<td>829</td>
<td>1.23 (0.94—1.62)</td>
<td>0.13</td>
</tr>
<tr>
<td>DCS [9]</td>
<td>382</td>
<td>1.20 (0.87—1.66)</td>
<td>0.26</td>
</tr>
<tr>
<td>Rotterdam Study [9]</td>
<td>117</td>
<td>1.40 (0.77—2.57)</td>
<td>0.27</td>
</tr>
<tr>
<td>CARDS [10]</td>
<td>173</td>
<td>0.82 (0.46—1.46)</td>
<td>0.51</td>
</tr>
<tr>
<td>Metaanalysis (DCS + Rotterdam Study + CARDS) [10]</td>
<td>672</td>
<td>1.15 (0.89—1.48)</td>
<td>0.29</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + Rotterdam Study + CARDS] [10]</td>
<td>2006</td>
<td>1.15 (0.99—1.34)</td>
<td>0.067</td>
</tr>
<tr>
<td>Russia (our own data)</td>
<td>99</td>
<td>1.02 (0.72—1.43)</td>
<td>0.92</td>
</tr>
<tr>
<td>Metaanalysis [GoDARTS (Replication) + UKPDS + DCS + RotterdamStudy + CARDS]+ Russia (our own data)</td>
<td>2105</td>
<td>1.13 (0.98—1.29)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Figure 2. Graphical representation of the results of meta-analysis and bias analysis in publications.

A — «forest plot» for rs11212617 association with attainment of target HbA\(_1c\) level of <7% in the overall group; B — «forest plot» for rs11212617 association with attainment of target HbA\(_1c\) level of <7% in the group with metformin monotherapy; C — «forest plot» for rs11212617 association with attainment of target HbA\(_1c\) level of <7% in the group with combination therapy; D — «funnel plot» for rs11212617 association with attainment of target HbA\(_1c\) level of <7% in the overall group; E — «funnel plot» for rs11212617 association with attainment of target HbA\(_1c\) level of <7% in the group with metformin monotherapy; F — «funnel plot» for rs11212617 association with attainment of target HbA\(_1c\) level of <7% in the group with combination therapy.
Other researchers, who studied the effect of the polymorphic locus rs11212617 in the *ATM* gene on the likelihood of developing T2DM in patients with obesity and impaired glucose tolerance (IGT) involved in the Diabetes Prevention Program, DPP, including representatives of five American ethnic groups (n=988), suggested that the time of IGT conversion to T2DM in patients, who receive MF and have different genotypes of the polymorphic locus rs11212617, may differ. However, no significant difference was found. Florez et al. suggested that the effect of the polymorphic locus during MF treatment is noticeable only in the case of high HbA1c, which is possible only in patients who were already diagnosed with T2DM. In the patients involved in their study, T2DM developed later and HbA1c levels were low [11].

Recently, Vilvanathan et al. evaluated association of polymorphic locus rs11212617 with the development of T2DM in the residents of South India (118 T2DM patients and 112 healthy controls). However, this polymorphic locus had no effect on predisposition to T2DM: OR=1.09, 95% CI 0.75—1.60 [12].

**CONCLUSION**

Our study showed no association of polymorphic locus rs11212617 in the *ATM* gene with response to MF therapy in T2DM patients in the Novosibirsk region. However, meta-analysis of our own data with previously published reports confirms the association of C allele with attainment of target HbA1c level (overall OR=1.27, 95% CI 1.10—1.46; p=0.0008). Thus, polymorphic locus rs11212617 in the *ATM* gene may influence the effectiveness of MF therapy in T2DM patients.

**ADDITIONAL INFORMATION**

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