

CLINICAL STUDY

Type II deiodinase polymorphism: A potential risk factor of type 2 diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) remains one of the most challenging global epidemics of the twenty-first century. It is estimated that more than 350 million people worldwide are affected by this metabolic disorder. It has many risk factors. Several studies presume that type II iodothyronine deiodinase polymorphism Thr92Ala (DII-Thr92-Ala, rs225014) is yet another risk factor. The aim of the study was to assess the impact of this polymorphism on parameters of glycid metabolism. Our group consisted of 200 subjects (74 males and 126 females) at average age of 63.85 ± 18.98 without prediabetes, diabetes mellitus or any thyropathy. Blood tests were performed to evaluate glucose metabolism parameters as well as DII-Thr92Ala polymorphism. Our study confirmed the relationship between Ala homozygotes and glycosylated haemoglobin (HbA_{1c}) serum levels (Tab. 2, Ref. 14). Text in PDF www.elis.sk.

KEY WORDS: diabetes mellitus 2, deiodinase II, polymorphism Thr92Ala.

Introduction

DII is produced in myocardial cells, skeletal muscle cells, central nervous system, brown adipose tissue, thyroid gland and hypophysis. Type 2 deiodinase gene (*DIO2*) is located on the long arm of the 14th human chromosome in 14q24.3. It is an intracellular enzyme which catalyses the conversion of thyroxine to its active form triiodothyronine (T_3). Therefore, *Dio2* is a very important regulator for tissue-specific metabolic activity (1).

A single nucleotide polymorphism in the *Dio2* gene (A/G) results in a threonine change into alanine (Thr92Ala) at codon 92 (1). Many studies have shown that Thr92Ala polymorphism is related to T2DM, insulin resistance, and body mass index (BMI) (2–6). However, the relationship between Thr92Ala polymorphism and glycemic control in T2DM patients is still unclear. Subjects with Ala92Ala genotype have lower DII activity in comparison with other genotypes (7), hence, the course of potential hypothyreosis is more complicated (3, 8), supplementation therapy must be more potent (9) and on the contrary, the course of potential hyperthyreosis is mild (10).

Glucose metabolism is regulated also by thyroid hormones which regulate type 4 insulin-dependent glucose transporters (GLUT4) expression in skeletal muscles (11). Skeletal muscles

produce DII predominantly, therefore, the research on possible connections focuses on this type of deiodinase and its polymorphisms.

DII activity in tissues in individuals with Ala92Ala genotype is lower than that in individuals with other genotypes (1). Accordingly, they have lower T_3 serum and intracellular levels (10). Lower intracellular T_3 might create a state of relative intracellular hypothyroidism and decreased expression of genes involved in energy use, such as GLUT4. This state results in increased insulin resistance and possible prediabetes or T2DM (2–6).

According to these findings, it is plausible to postulate that individuals with Ala92Ala genotype are at the highest risk for developing T2DM.

Patients and methods*Patients*

In this cross-sectional study a total of 400 subjects (148 males and 252 females) at average age of 63.85 ± 18.98 in range of 20–92 years, without prediabetes, diabetes mellitus or any thyreopathy constituted the study population, while 62 (31 %) of them were obese or overweight and 22 (11 %) had metabolic syndrome.

All subjects were consecutively recruited from the 1st Department of Internal Medicine of the Louis Pasteur University Hospital in Košice, Slovak Republic from January 2014 to December 2017.

The study was approved by the ethical committee of the Louis Pasteur University Hospital in Košice, Slovak Republic. Written informed consent for the study was obtained from all patients.

Methods

All subjects underwent laboratory evaluation. The following variables were assessed: age, gender and BMI.

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Acknowledgement: This work was supported by the Scientific Agency of the Slovak Republic VEGA (grant number 1/0048/11).

Fasting blood samples were collected from the subjects to assess fasting glycaemia, C-peptide, insulin, HbA_{1c} and DII-Thr92Ala-polymorphism.

The examination of glycaemia was performed using photometric colorimetry while C-peptide, insulin and HbA_{1c} were performed using electrochemiluminescent immunochemistry. The DNA isolation was performed using the Wizard Genomic DNA Purification Kit. The Thr92Ala polymorphism was analysed by melting curve of the short amplicon.

HbA_{1c} was assessed by using DCCT and IFFC standards (% , mmol/mol, respectively). BMI was calculated as weight (kg) divided by the square of height (m²). HOMA index was used to assess insulin sensitivity (glycaemia x insulinaemia / 22.5) with values < 2.4 considered for normal insulin sensitivity.

Statistical analysis

Continuous variables are presented as mean ± standard error of mean (SEM), categorical variables are expressed as numbers or percentage of patients. Statistical significance of comparison of categorical variable was conducted using ANOVA test. Deviation from Hardy–Weinberg equilibrium was analyzed using Chi-square (*chi*²) test. The software program of MS Excel 2003 and SPSS for Windows ver. 15.0 was used for statistical purpose. p value < 0.05 was considered statistically significant.

Tab. 1. Mean values of glycid parameters.

n = 400	CC	CT	TT	p
age (years)	68.64±16.78	63.26±19.65	62.92±19.22	NS
fasting glycaemia (mmol/l)	5.16±0.78	5.04±0.94	4.96±0.67	NS
C-peptide (µg/l)	3.75±2.02	3.58±2.21	3.83±2.3	NS
insulin (mIU/l)	9.26±6.16	11.95±12.76	11.80±7.33	NS
HOMA index	2.22±1.75	3.06±3.86	2.57±1.7	NS
HbA _{1c} (% (mmol/mol))	5.8 (40)±1.4 (13)	5.2 (33)±0.8 (7)	5.2 (34)±0.8 (7)	> 0.05
BMI (kg/m ²)	27.0±6.76	25.1±3.87	24.4±4.21	NS

Tab. 2. Studies investigating the relationship between type II deiodinase Thr92Ala polymorphism and type 2 diabetes mellitus.

Authors	Publication year	State (race or nation)	Results
Mentuccia et al	2002	USA (Americans -Caucasians)	higher risk of T2DM was confirmed in Ala-homozygotes in comparison with Thr-homozygotes and heterozygotes non-diabetic Ala-homozygotes have higher HOMA index in comparison with non-diabetic Thr-homozygotes and heterozygotes
Canani et al	2005	Brasil (Brazilians)	non-diabetic Ala-homozygotes have higher HOMA index in comparison with non-diabetic Thr-homozygotes and heterozygotes
Mentuccia et al	2005	USA (Amishes)	higher risk of T2DM was not confirmed in any group
Grarup et al	2007	Denmark (Danes)	higher risk of T2DM was not confirmed in any group non-diabetic Ala-homozygotes have higher fasting glycaemia levels in comparison with non-diabetic Thr-homozygotes and heterozygotes
Maia et al	2007	USA (Americans)	higher risk of T2DM was not confirmed in any group
Dora et al	2010	Brazil (Brazilians)	higher risk of T2DM was confirmed in Ala-homozygotes in comparison with Thr-homozygotes and heterozygotes Ala-homozygotes with T2DM have higher HbA _{1c} in comparison with Thr-homozygotes and heterozygotes with T2DM
Estivalet et al	2011	Brazil (Brazilians)	Ala-homozygotes with T2DM have higher insulin resistance in comparison with Thr-homozygotes and heterozygotes with T2DM
Nair et al	2012	USA (Pima Indians)	higher risk of T2DM was confirmed in Ala-homozygotes in comparison with Thr-homozygotes and heterozygotes

References 2–6, 12–14

Results

C-allele (92Ala) frequency was 0.32.

Genotype frequencies of D2 Thr92Ala polymorphism (TT=196 (49 %), CT=152 (38 %), and CC=52 (13 %)) did not deviate from Hardy–Weinberg equilibrium proportions (p = 0.42; expected frequencies: TT = 184 (46.24 %), CT = 174 (43.52 %) and CC = 40 (10.24 %)).

Ala-homozygotes had significantly higher serum HbA_{1c} levels (5.8 (40) ± 1.4 (13) vs. 5.2 (33) ± 0.8 (7) vs 5.2 (34) ± 0.8 (7) % (mmol/mol), respectively, p = 0.014) than Thr-homozygotes and heterozygotes. However, no significant difference between groups was found either in fasting serum glycaemia, C-peptide and insulin levels, or in HOMA and BMI indexes (Tab. 1).

Discussion

Eight large studies aimed at DII-Thr92Ala-polymorphism and glucose metabolism were published between years 2002 and 2012. Four of them were from USA, three from Brazil and one from Denmark. Every study included a few thousand subjects. Subjects in every study were divided into three genetic groups: Ala-and Thr-homozygotes and heterozygotes. These groups were compared to each other. Results are controversial (Tab. 2).

Some studies demonstrated that the group most at risk for the development of DM2 are Ala-92 homozygotes. Mentuccia et al (2002), Dora et al (2010) and Nair et al (2012) observed higher risk of development of insulin resistance and later T2DM in Ala homozygotes in comparison with Thr homozygotes and heterozygotes (2, 4, 6).

On the other hand, Mentuccia et al (2005), Grarup et al (2007), and Maia et al (2007) did not confirm higher prevalence of glycid metabolism disorders in any genotype group as compared with other two groups (12–14).

However, Grarup et al (2007) found higher fasting glycaemia levels in Ala homozygotes when compared to heterozygotes and Thr homozygotes in non-diabetic persons (5.6 ± 1.1 vs 5.5 ± 0.7 vs 5.5 ± 0.8 mmol/l, respectively, $p < 0.05$) (13).

Our findings are in conflict with those of Grarup et al (2007). We did not confirm significantly higher glycaemia serum levels in non-diabetic patients (5.16 ± 0.78 vs 5.04 ± 0.94 vs 4.96 ± 0.67 mmol/l, respectively, $p = 0.24$).

Dora et al (2010) in their study with 1,057 patients confirmed higher prevalence of Ala92Ala in non-diabetic persons ($p < 0.05$) (4) in contrast to our and Grarup's study.

Moreover, Dora et al (2010) also demonstrated higher fasting insulin levels in Ala92Ala subjects (16.8 ± 4.17 vs 11.3 ± 3.52 mIU/l, respectively, $p < 0.01$) (4).

We did not confirm the latter findings. Our patients with Ala92Ala genotype (52 (13 %)) had lower mean fasting plasma insulin level as compared to the rest of our group (348 (87 %)), while the difference was not significant (9.26 ± 6.16 vs 11.87 ± 7.21 mIU/l, respectively, $p = 0.53$).

In our study, insulin resistance evaluated by HOMA index was lower in Ala homozygotes when compared to the rest of our group. However, in contrast to Dora's study, the difference was statistically nonsignificant (2.22 ± 1.75 vs 2.78 ± 1.88 , $p = 0.54$). Dora et al (2010) found significantly higher values of HOMA index in Ala92Ala when compared to Thr92Thr and Thr92Ala (8.5 ± 3.11 vs 4.5 ± 2.3 , respectively, $p < 0.01$) (4).

In our study, we demonstrated that HbA_{1c} levels in Ala92 homozygotes were significantly higher than in other two groups (5.8 (40) ± 1.4 (13) vs 5.2 (33) ± 0.8 (7) vs 5.2 (34) ± 0.8 (7) % (mmol/mol), respectively, $p = 0.014$) (Tab.1). Also, Canani et al (2005) detected higher HbA_{1c} levels in non-diabetic Ala homozygotes, albeit with nonsignificant results (7.1 (54) ± 2.33 (23) vs 6.14 (44) ± 1.95 (19) vs 6.49 (47) ± 2.08 (20.4) % (mmol/mol), respectively, $p = 0.102$) (3). Not even Maia et al (2007) found difference between serum HbA_{1c} levels (5.7 (39) ± 1.0 (8.6) vs 5.7 (39) ± 0.9 (7) vs 5.7 (39) ± 1.1 (10) % (mmol/mol), respectively, $p = 0.6$) (14).

Conclusion

Some studies claim that Ala-92 homozygotes of DII-Thr-92-Ala polymorphism have higher risk of DM2 or higher mean values of glucose metabolism. Many factors induce development of DM2. Genetic influence has an important role, but external risk factors resulting from unhealthy lifestyle are dominant in the Slovak population. Our patients are older, obese (often as a component of metabolic syndrome) and polymorbid.

In summary, we can suppose that the genetic influence of DII-Thr92Ala polymorphism is possible, but in our subjects, this influence was overlapped by several other factors.

Further studies of larger populations are needed.

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Received June 9, 2018.

Accepted September 29, 2018.