CLINICAL STUDY

IGF-I gene promoter polymorphism is a predictor of survival after myocardial infarction in patients with type 2 diabetes

Mojgan Yazdanpanah¹, Fakhredin A Sayed-Tabatabaei¹, Joop A M J L Janssen², Ingrid Rietveld^{1,2}, Albert Hofman¹, Theo Stijnen¹, Huibert A P Pols^{1,2}, Steven W J Lamberts², Jacqueline C M Witteman¹ and Cornelia M van Duijn¹

Departments of ¹Epidemiology and Biostatistics and ²Internal Medicine, Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands

(Correspondence should be addressed to C M van Duijn; Email: c.vanduijn@erasmusmc.nl)

Abstract

Objective: Previously we observed that non-carriers of the most common alleles of an IGF-I promoter polymorphism have low circulating IGF-I levels and an increased risk of developing myocardial infarction (MI), particularly in patients with type 2 diabetes.

Design: We investigated whether this IGF-I promoter polymorphism is associated with survival of type 2 diabetes in a Caucasian population aged 55 years and older.

Methods: The study was embedded in the Rotterdam Study, a prospective population-based cohort study. At baseline, 668 patients with type 2 diabetes were diagnosed, among which, 55 incident MI were ascertained during follow-up. For the present study, we used two genotype groups: non-variant carriers (homozygous for 192, 194, or 192/194 bp genotypes), and variant carriers.

Results: During a median follow-up of 8.8 years, 396 out of the 668 patients with type 2 diabetes (59.3%) died of various causes. The frequency of type 2 diabetes variant carrier and non-variant carriers was 28.7 and 71.3% respectively. The survival in patients with type 2 diabetes without an MI did not differ between the IGF-I genotype groups (hazard ratio (HR)=0.8, 95% confidence interval (CI): 0.7–1.1, $P=0.1$). In contrast, in those who developed an MI, variant carriers had a 2.4 times higher risk of mortality than non-variant carriers (95% CI: 1.2–4.8, $P=0.01$).

Conclusion: Our study suggests that genetically determined low IGF-I activity is an important determinant of survival in patients with type 2 diabetes who developed an MI. The IGF-I promoter polymorphism, therefore, may help to predict the future mortality risk in this group of patients.

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Introduction

Insulin-like growth factor-I (IGF-I) is a peptide that has an important role in the promotion and maintenance of insulin secretion and β -cell mass, and in regulation of myocardial structure (1). It is also an important determinant of glucose homeostasis and may play a role in the regulation of cardiovascular function and cardiac muscle survival (1–5). Low IGF-I levels have been associated with an increased risk of cardiovascular disease (CVD) (6–8). In patients with type 2 diabetes, low serum IGF-I levels are common (9) which may play a role in the development of vascular complications of type 2 diabetes (10, 11).

Since circulating IGF-I concentrations do not always directly reflect local production in tissues, identification of genetic polymorphisms could help to characterize long-term local and systemic exposure to IGF-I (8). Twin studies have shown that 40–60% of the individual variation in IGF-I levels is due to genetic variation (12, 13). We have previously studied a polymorphism in the IGF-I gene promoter region, which is associated with

circulating IGF-I levels (14). We observed an increased risk of myocardial infarction (MI) in non-carriers of the most common allele (192 bp) of this IGF-I gene promoter polymorphism, particularly among those with type 2 diabetes (14). In later studies, we found that variant carriers of this IGF-I gene promoter polymorphism had lower circulating IGF-I levels (15) and a higher risk of incident heart failure (16). Although patients with type 2 diabetes with an MI have an increased risk of CVD mortality and total mortality (17), the traditional risk factors, such as obesity, hypertension, and smoking partly explained the excess of mortality (18, 19). The previously found association between the IGF-I gene promoter polymorphism and the development of MI in type 2 diabetes suggests that this polymorphism might also modify mortality in patients with type 2 diabetes. The aim of this study was to investigate whether this IGF-I gene promoter polymorphism is indeed associated with survival of patients with type 2 diabetes. We investigated this association in patients with and without MI within the Rotterdam Study.

Materials and methods

Study population

This study was embedded in the Rotterdam Study, a population-based cohort study in which all residents of the Rotterdam suburb Ommoord aged 55 years or older were invited to take part. The Medical Ethics Committee of Erasmus University, Rotterdam approved the study. Written informed consent was obtained from all participants. The design of the study has been described elsewhere (20). The baseline data collection was conducted between March 1990 and July 1993. A total of 7983 subjects participated (response rate 78%) in the study. Figure 1 presents a flow chart outlining the participation of the present study population.

Information concerning cardiovascular risk factors was obtained by interview and physical examination at baseline. Anthropometric measurements were obtained at the research center. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Blood pressure was measured twice on the right arm using a random-zero sphygmomanometer. The average of the two blood pressure values was used in the analyses. Information on smoking habits was obtained during the interview, and participants were categorized into current smokers, never smokers, and former smokers.

Blood sampling and storage have been described previously (20). Serum was separated by centrifugation and quickly frozen in liquid nitrogen. Laboratory measurements were performed on non-fasting blood samples. Total serum cholesterol and high-density

lipoprotein (HDL) cholesterol levels were determined using an automated enzymatic procedure (21). A diagnosis of type 2 diabetes was made if subjects were treated for diabetes and/or a random non-fasting glucose level of 11.1 mmol/l or above (22). We have reported previously that the post-load glucose and insulin levels are similar to the fasting post-load levels (23). Type 2 diabetes was diagnosed in 748 patients at baseline.

Follow-up procedures

For the diagnosis of an MI, the modular ECG analysis system (MEANS) was used. An MI detected without the evidence of symptoms (silent MI) was verified by an experienced cardiologist (24). Data on the incident MI were verified by the research physicians, who collected information from the patients' medical records. The information also included the copies of discharge letters for hospital admissions. The present analyses on mortality are based on follow-up data collected from baseline (1990–1993) until 1 January 2004. Information on the vital status of the participants was obtained at regular intervals from the municipal population registry. After notification, cause and circumstances of death were established by information from general practitioners (GPs). Letters and, in case of hospitalization, discharge reports from medical specialists were obtained. Subsequently, two research physicians (of whom one was a cardiologist) independently coded all causes of death according to the International Classification of Diseases-10 (25). In case

Figure 1 Flow chart outlining the participation of the study population. MI, myocardial infarction.

Table 1 General characteristics of patients with type 2 diabetes stratified by insulin-like growth factor (IGF)-I genotype. Data are presented as mean $\pm$ s.d.

	Variant carriers (n=192)	Non-variant carriers (n=476)	P
Male gender (%)	40.6	38.7	0.6
Age (years)	73.7 $\pm$ 9.5	73.4 $\pm$ 8.9	0.7
Body mass index (kg/m ²)	26.2 $\pm$ 3.9	27.0 $\pm$ 4.2	0.04
Total cholesterol (mmol/l)	6.5 $\pm$ 1.3	6.6 $\pm$ 1.3	0.3
HDL cholesterol (mmol/l)	1.3 $\pm$ 0.4	1.3 $\pm$ 0.4	0.9
Hypertension (%)	49.7	54.2	0.3
Systolic blood pressure (mmHg)	145.2 $\pm$ 25.0	149.0 $\pm$ 23.4	0.06
Diastolic blood pressure (mmHg)	72.3 $\pm$ 11.2	73.4 $\pm$ 13.0	0.4
Anti-hypertension medication (%)	47.9	49.8	0.7
Current smoking (%)	22.5	22.3	0.9

HDL, high-density lipoprotein.

of disagreement, consensus was reached. We defined CVD mortality as death from MI or other ischemic heart disease (ICD-10: I20–I25), sudden cardiac death (I46), sudden death undefined (R96), death from ventricular fibrillation or tachycardia (I49), congestive heart failure (I50), or stroke (I60–I64).

Genotyping

PCR was performed using oligonucleotide primers designed to amplify the polymorphic cytosine–adenosine repeat, 1 kb upstream of the promoter of the *IGF-I* gene, as described previously (26). We used a previously described approach, which distinguishes two genotype groups: non-variant carriers and variant carriers (15). As non-variant carriers, we included all subjects homozygous for 192, 194, or having the 192/194 bp genotype (15). As variant carriers, we included subjects heterozygous for 192, 194 bp, or non-carriers of these two alleles.

Statistical analysis

Hardy–Weinberg equilibrium of the *IGF-I* gene promoter polymorphism genotypes was tested with the χ^2 test. We used the χ^2 test to compare categorical variables and the two-sample *t*-test to compare

continuous variables. Survival curves for the *IGF-I* gene promoter polymorphisms were estimated by the Kaplan–Meier method and were compared using the two-sample log rank test. Cox's proportional hazards analysis was used to evaluate the contribution of the *IGF-I* gene promoter polymorphism to all mortality in patients with type 2 diabetes, and subsequently in type 2 diabetes patients with and without an MI. Survival time was calculated as the number of years from entry into the study until the first event or until the end of follow-up. In the subgroup 'without an MI', a subject is censored at the time he/she develops an MI. In patients with type 2 diabetes who developed an MI, survival time after MI was calculated. We examined interaction between *IGF-I* gene promoter polymorphism and incident MI in predicting survival using Cox's proportional hazards model by including the interaction term in the model. For Cox's proportional hazards analysis, all analyses were adjusted for gender and age, and additionally for known cardiovascular risk factors. Data were analyzed using SPSS for windows version 11.0. All *P* values were based on two-sided tests and a *P* value <0.05 was considered statistically significant. We applied Bonferroni correction for multiple comparisons and a *P* value <0.03 was considered significant.

Results

In 668 (89.3%) patients with type 2 diabetes, the *IGF-I* gene promoter polymorphism was successfully genotyped. Genotype distributions were in Hardy–Weinberg equilibrium ($P=0.6$). General characteristics of the study sample stratified by IGF-I genotypes are presented in Table 1. The frequency of this *IGF-I* gene promoter polymorphism in variant carriers was 28.7% and in non-variant carriers was 71.3%. No significant difference was observed between the genotype groups for gender, age, cholesterol levels (total and HDL), lipid-lowering drugs, hypertension, systolic and diastolic blood pressures, anti-hypertension medication, and smoking. Variant carriers had a significantly lower BMI ($P=0.04$) and tended to have a lower systolic blood pressure ($P=0.06$; Table 1).

Table 2 Relative risk of mortality in type 2 diabetes stratified by IGF-I genotype and incidence of MI during a mean follow-up of 9.6 years.

	All diabetic patients			Diabetic patients without an MI			Diabetic patients with an MI		
	Total subjects	Total death	HR (95% CI)	Total subjects	Total death	HR (95% CI)	Total subjects	Total death	HR (95% CI)
Variant carriers	192	115		175	98		17	17	
Model 1			0.9 (0.7–1.1)			0.8 (0.7–1.1)			2.4 (1.2–4.8)*
Model 2			0.8 (0.6–1.0)			0.8 (0.6–1.0)			2.7 (1.1–6.2)*
Non-variant carriers	476	281	1.0 (reference)	438	251	1.0 (reference)	38	30	1.0 (reference)

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; model 1, adjusted for gender and age; model 2, adjusted for gender, age, BMI, serum cholesterol levels (total and HDL), blood pressure (systolic and diastolic), baseline history of cardiovascular disease, and smoking. *Significant *P* value ($P<0.03$ after adjusting for multiple comparisons).

Figure 2 Kaplan–Meier survival curve of all patients with type 2 diabetes stratified by IGF-I genotypes.

The median (s.d.) follow-up time for all patients was 8.8 (4.0) years. During this follow-up, 396 out of the 668 patients with type 2 diabetes (59.3%) died of various causes. Mortality due to CVD occurred in 44.5% of these 396 subjects and was 77.1% in subjects who developed an MI during follow-up. Table 2 shows the relative risk of mortality in variant carriers and non-variant carriers of this *IGF-I* gene promoter polymorphism stratified by incident MI. In the whole study sample, the *IGF-I* gene promoter polymorphism was not significantly associated with risk of mortality (hazard ratio (HR)=0.9, 95% confidence interval (CI): 0.7–1.1, $P=0.2$, after adjustment for gender and age; Table 2 and Fig. 2).

During the follow-up, 55 patients with type 2 diabetes developed an incident MI, including 18 patients with a history of a prior MI. The median (s.d.) follow-up time after an incident MI was 2.3 (3.5) years. There was no significant interaction between the *IGF-I* gene promoter polymorphism and incident MI in predicting survival ($P=0.19$). No significant association was observed between this *IGF-I* gene promoter polymorphism and risk of mortality in patients without an MI (HR=0.8, 95% CI: 0.7–1.1, $P=0.1$) (Table 2 and Fig. 3A). However, variant carriers with diabetes and MI had a

2.4 times higher risk for mortality than non-variant carriers (95% CI: 1.2–4.8, $P=0.01$; Table 2 and Fig. 3B). This risk increased to 2.7 after further adjustment for cardiovascular risk factors including baseline history of CVD (95% CI: 1.1–6.2, $P=0.02$; Table 2). These results remained significant after using Bonferroni correction (P value <0.03). When we confined our analysis only to those subjects who died due to CVD, these results did not change (HR=2.1, 95% CI: 0.8–5.3, $P=0.1$). In addition, after excluding patients with a prior MI at baseline, variant carriers with an MI had a 2.3 times higher risk for mortality than non-variant carriers (95% CI: 1.0–5.7, $P=0.06$).

Discussion

In this population-based study, we observed an increased risk of mortality in variant carriers of the *IGF-I* gene promoter polymorphism among subjects with type 2 diabetes who developed an MI during follow-up. This higher risk of mortality remained significant after further adjustment for clinically relevant cardiovascular risk factors. In patients with type 2 diabetes without an MI, there was no difference in survival between the genotype groups of the *IGF-I* gene promoter polymorphism.

Our findings suggest that this *IGF-I* gene polymorphism is particularly important in the survival of patients with type 2 diabetes who have developed an MI. Although we did not measure IGF-I levels in the present study, we previously demonstrated that variant carriers of this *IGF-I* polymorphism have lower circulating IGF-I levels (15) and a higher risk of incident heart failure (16). In our previous study in non-diabetic subjects (16), we observed that both the short alleles (the two alleles <192 bp) and the long alleles (the two alleles >194 bp) were associated with significantly lower serum total IGF-I levels (mean (s.e.)=15.6 (1.4) nmol/l and 12.0 (1.2) nmol/l) when compared with the 192 and the 194 bp alleles. The highest IGF-I levels were observed for homozygous carriers of the 192 bp allele (18.7 (0.6) nmol/l) and homozygous carriers of the 194 bp allele (17.7 (1.4) nmol/l). It has been found that in the early phase of an MI, serum IGF-I levels are often

Figure 3 Kaplan–Meier survival curves stratified by IGF-I genotype: in (A) patients with type 2 diabetes without an incident MI and (B) patients with type 2 diabetes and an incident MI. * $P=0.02$.

markedly reduced and it has been suggested that this contributes to the adverse outcome (27, 28). Another study showed that patients who died after an acute MI during 2 years of follow-up had significantly lowered IGF-I levels at admission compared with survivors (29). Since IGF-I can coordinate a set of actions promoting the survival of myocardial cells (30–32), reduced IGF-I levels may impair the recovery of metabolic cell function after acute MI. Thus, reduced IGF-I may represent a negative prognostic factor, as supported by the study by Friberg *et al.* (29). Furthermore, it has been reported that low IGF-I levels are related to poor outcome, especially death, in patients with stroke (33). The results of the present study suggest that in patients with type 2 diabetes after an MI, variant carriers of this *IGF-I* gene promoter polymorphism have a lower survival rate than non-variant carriers. Our results are in accordance with previous studies suggesting that relatively low circulating IGF-I levels are not only associated with an increased risk of developing CVD but also influence survival after an MI (6, 7). IGF-I may be a determinant of survival after MI, since it has been demonstrated that it promotes the survival of cardiomyocytes affected by ischemia (1, 27). One of the most important actions of IGF-I is an anti-apoptotic effect (30). In various animal models of myocardial ischemia, administration of IGF-I is able to decrease the size of an MI (30). In addition, it has also been suggested that IGF-I reduces angiotensin levels in the heart and interferes with the development of diabetic cardiomyopathy (34). Circulating IGF-I levels may stimulate nitric oxide synthesis and release, and favor glucose metabolism (35, 36). Finally, IGF-I may increase cardiac output and myocardial contractility (27, 37), and improve the response to ischemia (31, 32). All these IGF-I-mediated effects may influence survival after an MI.

In the present study, since the number of diabetic patients who developed an MI (both in variant carriers and non-variant carriers) was small, the observed increase in the risk of mortality in variant carriers showed a wide confidence interval; and true results may be smaller or larger than the observed results here. We could not find an effect in diabetic patients without an MI; however, we cannot conclude that we would find an effect in a larger population. Because these findings are only observed in subgroups, the results are explorative and need to be confirmed by replication in another population.

In conclusion, our study shows that patients with type 2 diabetes who are variant carriers of an *IGF-I* gene promoter polymorphism have a lower life expectancy after an MI than non-variant carriers. This *IGF-I* gene promoter polymorphism, therefore, may help to predict the future mortality risk for patients with type 2 diabetes after an MI. Clinical trials are necessary to investigate how the overall cardiovascular risk in diabetic variant carriers can be improved by IGF-I increasing therapies.

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