

Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors

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Summary

Background Individuals with diabetes are at higher risk of myocardial infarction than non-diabetics. However, much less is known about the incidence of, and risk factors for, development of diabetes and impaired fasting glucose in patients who have had a myocardial infarction. We set out to estimate this incidence and investigate whether lifestyle factors such as dietary habits might alter this risk.

Methods We used prospectively obtained data for 8291 Italian patients with a myocardial infarction within the previous 3 months, who were free of diabetes (determined by medication use, a physician-reported diagnosis, or fasting glucose ≥ 7 mmol/L) at baseline. Incidence of new-onset diabetes (new diabetes medication or fasting glucose ≥ 7 mmol/L) and impaired fasting glucose (fasting glucose ≥ 6.1 mmol/L and < 7 mmol/L) were assessed at follow-up at 0.5, 1.0, 1.5, 2.5, and 3.5 years. Baseline data for body-mass index (BMI), other risk factors, dietary habits, and medications were updated during follow-up. A Mediterranean diet score was assigned according to consumption of cooked and raw vegetables, fruit, fish, and olive oil. Associations of demographic, clinical, and lifestyle risk-factors with incidence of diabetes and impaired fasting glucose were assessed with multivariable Cox proportional hazards.

Findings During 26 795 person-years (mean follow-up 3.2 years [SD 0.9]), 998 individuals (12%) developed new-onset diabetes (incidence 37 cases per 1000 person-years). Of the 7533 without impaired fasting glucose at baseline, 2514 (33%) developed new-onset impaired fasting glucose or diabetes (incidence 123 cases per 1000 person-years), rising to 3859 (62%) of 6229 with the lower cutoff for impaired fasting glucose of 5.6 mmol/L (incidence 321 cases per 1000 person-years). Independent risk factors for new-onset diabetes or impaired fasting glucose included older age, hypertension, use of beta-blockers, lipid-lowering medications (protective), and diuretic use. Independent lifestyle risk-factors included higher BMI, greater BMI gain during follow-up, current smoking, a lower Mediterranean dietary score, and wine consumption of more than 1 L/day. Data for physical activity were unavailable, but inability to perform exercise testing was associated with higher incidence of diabetes and impaired fasting glucose.

Interpretation Compared with population-based cohorts, patients with a recent myocardial infarction had a higher annual incidence rate of impaired fasting glucose (1.8 vs 27.5% in our study) and diabetes (0.8–1.6% compared with 3.7%) in this study. Thus, our results indicate that myocardial infarction could be a prediabetes risk equivalent. Smoking cessation, prevention of weight gain, and consumption of typical Mediterranean foods might lower this risk, which emphasises the need for guidance on diet and other lifestyle factors for patients who have had a myocardial infarction.

Introduction

Individuals with diabetes mellitus and no known coronary heart disease have rates of acute myocardial infarction and mortality similar to those for non-diabetic individuals with established coronary heart disease.^{1–5} However, individuals with both coronary heart disease and diabetes are at far higher risk of myocardial infarction and death than those with either condition.^{1–5} Although the incidence of, and risk factors for, the development of myocardial infarction in diabetic individuals have been given great attention,⁶ much less is known about the converse relationship: development of diabetes in patients with myocardial infarction.

It is plausible that a confluence of predisposing risk factors would increase the incidence of diabetes or impaired fasting glucose (IFG), a prediabetic condition, in patients with myocardial infarction. However, although

the cross-sectional prevalence of impaired glucose tolerance is known to be high in patients who recently had a myocardial infarction,^{7,8} the incidence of new-onset impaired glucose homeostasis in post-MI patients has not been established.

We aimed to investigate the incidence of diabetes and IFG in a large cohort of patients who had had a myocardial infarction within the previous 3 months^{9,10} and to assess the independent demographic, clinical, and lifestyle risk factors related to an increased risk. We were particularly interested in modifiable lifestyle behaviours that might affect the incidence of diabetes and IFG after a myocardial infarction, including components of a traditional Mediterranean dietary pattern that in short-term randomised experimental trials improves insulin sensitivity and other vascular-metabolic risk factors.^{11–25}

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Methods

Patients

We used information from the GISSI-Prevenzione study,^{9,10} a randomised trial of fish oil and vitamin E in patients who had had a myocardial infarction. The study design and primary results have been described.^{9,10} 11 323 men and women with recent (≤ 3 months) myocardial infarction were enrolled from 172 centers in Italy between October, 1993 and September, 1995. Ethics approval was obtained, and all patients provided written informed consent. For this study, we excluded 3032 individuals: 2139 with prevalent diabetes at enrolment (defined by physician diagnosis, use of diabetic medication, or fasting glucose ≥ 7 mmol/L) and 893 with missing information about diet or weight at baseline, or about glucose at baseline or during follow-up, leaving 8291 participants for analysis.

Procedures

At baseline, information was obtained for demographics, cardiovascular risk factors, medications, dietary habits, and results of cardiac echocardiography, exercise testing, and coronary angiography. We measured height, weight, heart rate, and blood pressure. Fasting blood samples were drawn for assessment of glucose, lipids, fibrinogen, and complete blood count. The baseline assessment was done on average 3.5 weeks (mean 25 days [SD 21]; < 5 days in 14 people) after myocardial infarction, which would reduce to a minimum the effects of the peri-myocardial infarction period on glucose levels.

At enrolment, patients were advised to consume low-fat dairy products, poultry, fish, lean meat, fruits, vegetables, legumes, whole grains, and olive oil instead of butter or other oils. Because this was not a dietary intervention trial, the advice was not systematically reinforced; thus, the dietary habits of participants during the study were probably their usual habits and were unlikely to have been greatly altered because of this general advice. Participants were followed-up at regular clinic visits at 0.5, 1.0, 1.5, 2.5, and 3.5 years. At each visit, they were weighed, had fasting blood drawn for laboratory evaluation; up-to-date information was obtained on smoking habits, medications, and interim events. Dietary habits were assessed at baseline, 0.5 years, and 1.5 years.

In view of the benefits of a traditional Mediterranean dietary pattern on markers of insulin sensitivity and other vascular-metabolic risk factors,^{11–25} we assessed the combined effect of consumption of several typical components of a traditional Mediterranean diet. The GISSI-Prevenzione study was designed as a pragmatic trial to assess patients in the real-world setting who were enrolled and followed-up by their own cardiologists. Thus, full-scale diet questionnaires were not administered at numerous follow-up visits by cardiologists in the busy clinic setting.

Patients	
Age (years)	59 (11)
Sex (female)	1075 (13%)
Body mass index (kg/m ²)	26.3 (3.4)
Obese (body mass index ≥ 30 kg/m ²)	1076 (13%)
Physician-diagnosed hypertension	3702 (45%)
Previous acute myocardial infarction	907 (11%)
Intermittent claudication	287 (3%)
Current smoker	3699 (45%)
Former smoker	2922 (35%)
Systolic blood pressure (mm Hg)	123 (15)
Diastolic blood pressure (mm Hg)	77 (9)
Heart rate (beats per minute)	68 (10)
Ejection fraction	53 (10)
Heart Failure	
None	2924 (35%)
NYHA Class 1	4647 (56)
NYHA Class 2 to 3	708 (9%)
Angina	
None	5006 (60%)
CCS 1	2656 (32%)
CCS 2 to 4	482 (6%)
Exercise stress test	
Negative	4137 (50%)
Positive	1632 (20%)
Not done	2522 (30%)
Exercise cycleergometer test (Watts)	101 (33)
Exercise treadmill test (mins)	8.1 (3.2)
Laboratory	
Fasting glucose (mg/dl)	92 (12) [5.1 (0.7) mmol/L]
LDL cholesterol (mg/dl)	139 (38)
HDL cholesterol (mg/dl)	42 (12)
Triglycerides (mg/dl)	159 (80)
Fibrinogen (mg/dl)	389 (137)
Leukocyte count ($\times 10^9$ L)	7.7 (2.2)
Medications	
Fish oil assignment	4166 (50%)
Antiplatelet medication	7652 (92%)
ACE inhibitors	3698 (45%)
Beta-blockers	3897 (47%)
Diuretics	694 (8%)
Cholesterol-lowering medication*	399 (5%)

Data are mean (SD) or number (%). ACE=angiotensin-converting-enzyme. CCS=Canadian Cardiovascular Society. NYHA=New York Heart Association. *Use of lipid-lowering medications increased during follow-up (coincident with a statin subrandomisation²³ and publication of several statin trials) to 31% at 6 months, 42% at 1.5 years, and 45% at 3.5 years. Time-varying covariates were used to account for all changes in medication use.

Table 1: Baseline characteristics of non-diabetic patients with recent myocardial infarction

Therefore, we administered a brief questionnaire about specific food items that would give a good indication of the dietary variation in Italian adults.²⁶ Widely consumed foods such as pasta, pasta sauces, or bread did not feature

on the questionnaire; instead, we included questions on the usual consumption of cooked and raw vegetables, fruit, fish, olive oil and other oils, butter, cheese, wine, and coffee. The questionnaire did not assess other components of a Mediterranean-type diet, such as grains, nuts, or legumes. Each item was scored on a scale from 0 to 3 on the basis of frequency of consumption,²⁶ and scores were summed to obtain a Mediterranean diet score (range 0–15) that was evaluated according to prespecified categories. We also evaluated the benefits of each food component separately. Dietary habits were updated over time (baseline, 0·5 years, and 1·5 years) using cumulative updating.²⁷

At each clinic visit, cases of type II diabetes mellitus were recorded by either new use of diabetes medications (insulin or oral hypoglycemic agents) or a fasting glucose of 7 mmol/L or higher.²⁸ IFG was defined as fasting glucose 6·1 mmol/L or higher but lower than 7 mmol/L, in the absence of diabetic medication; we also evaluated IFG using the lower cutpoint (5·6 mmol/L) (in November, 2003 the American Diabetes Association expert committee on the diagnosis and classification of diabetes mellitus suggested a revision of the diagnostic criteria for IFG, lowering the diagnostic threshold from 6·1 to 5·6 mmol/L).²⁸ Risk of IFG ($\geq 6\cdot1$ mmol/L) was assessed in the 7533 individuals with fasting glucose $<6\cdot1$ mmol/L at baseline, and risk of IFG ($\geq 5\cdot6$ mmol/L) was assessed in the 6229 individuals with fasting glucose $<5\cdot6$ mmol/L at baseline.

Statistical analysis

We used Kaplan-Meier analysis to evaluate time to development of new-onset diabetes or IFG, and the Cox proportional hazards model to evaluate the independent associations of demographic, clinical, and lifestyle risk factors, with time-at-risk until first event, death, or last follow-up visit. The proportional hazards assumption was confirmed with the use of Schoenfeld residuals. Multivariable models were adjusted for age, sex, smoking, and other potential risk factors on the basis of biological plausibility and associations with exposures or outcomes in this population.

We also assessed factors that might mediate higher risk of diabetes, including a rise in body-mass index (BMI) during follow-up, serum lipid levels, systemic inflammation assessed by fibrinogen and leukocyte count, and dietary intake of butter or other oils. Time-varying analyses were used to update covariate information on diet, BMI, smoking, medications, lipids, and other laboratory measures. Indicator variables were used for missing data on baseline covariates or on smoking; values were otherwise carried forward for missing time-varying covariates. For parsimony in model construction, we excluded from the final models several covariates (eg, blood pressure, intermittent claudication, use of antiplatelet medication) that were neither independently associated with diabetes risk nor materially

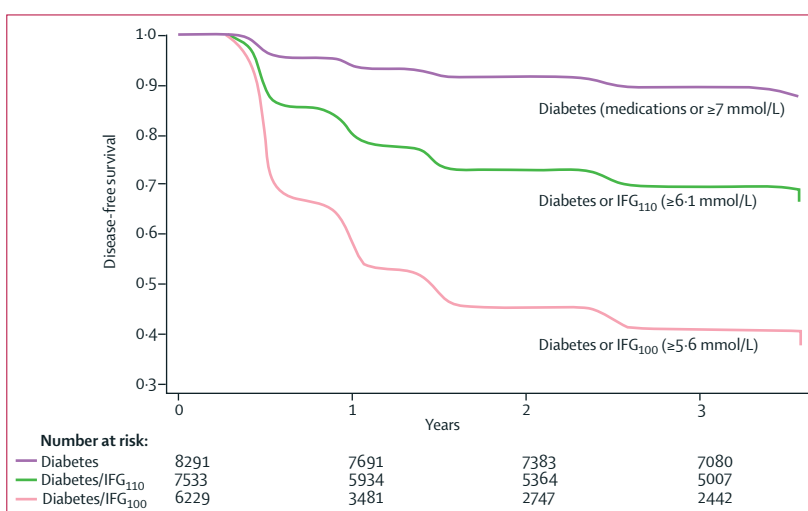


Figure 1: Time to development of new-onset diabetes or impaired fasting glucose

Risk Factors	Multivariable-adjusted* Hazard ratio (95% CI)	p
Age (per 5-year increase)	1.07 (1.03–1.11)	<0.001
Female sex (compared with male)	0.82 (0.66–1.02)	
Body mass index (each increasing unit, kg/m ²)	1.09 (1.07–1.11)	<0.001
Physician-diagnosed hypertension	1.22 (1.07–1.39)	0.003
Previous acute myocardial infarction	1.04 (0.85–1.27)	
Current smoker (compared to never)	1.60 (1.34–1.90)	<0.001
Former smoker (compared to never)	1.06 (0.90–1.24)	
Days from acutemyocardial infarction to enrollment (each day)	1.00 (0.99–1.01)	
NYHA Class 1 (compared with 0)	1.11 (0.96–1.29)	
NYHA Class 2–3 (compared with 0)	1.10 (0.85–1.43)	
Angina CCS 1 (compared with 0)	0.95 (0.81–1.10)	
Angina CCS 2–4 (compared with 0)	0.96 (0.72–1.28)	
Positive exercise stress test	1.07 (0.91–1.26)	
Exercise capacity (comparing high with low quintiles)	0.84 (0.64–1.10)	
Inability to undergo exercise testing	1.52 (0.48–4.75)	
Medications		
Fish oil	0.98 (0.86–1.11)	
Vitamin E	1.04 (0.92–1.18)	
ACE inhibitor	1.11 (0.97–1.26)	
Beta-blocker	1.27 (1.12–1.45)	<0.001
Diuretic	1.08 (0.87–1.34)	
Lipid-lowering medication	0.78 (0.67–0.90)	0.001
Dietary habits		
Mediterranean diet score (11–15 vs 0–5)	0.65 (0.49–0.85)	0.002
Cheese consumption (regularly vs never)	1.05 (0.73–1.52)	
Wine consumption (≥ 1 L/day vs never or rarely)	1.08 (0.64–1.83)	
Coffee consumption (≥ 5 cups/day vs never or rarely)	1.19 (0.88–1.61)	

*Includes each of the variables listed in this table.

Table 2: Risk factors for incident diabetes patients with recent myocardial infarction

altered the relation between the Mediterranean diet score and incidence of diabetes. We calculated the tests for trend by determining the median value of each category

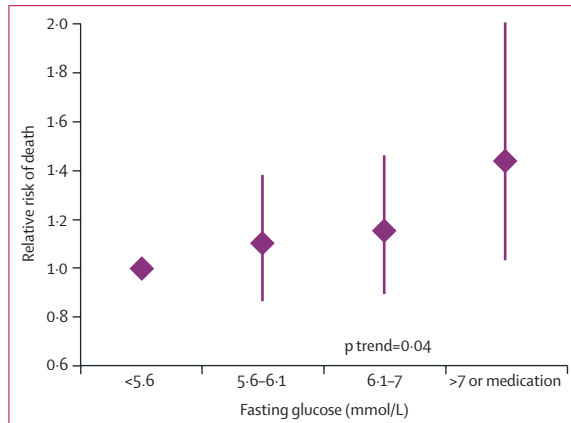


Figure 2: Multivariable-adjusted relative risk of death associated with development of diabetes or IFG

and evaluating this as a continuous variable. Analyses were done with Stata (version 8.2).

Role of the funding source

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Results

Table 1 shows baseline characteristics of participants. The average age was 59 years (range 20–90), and 13% of participants were women. Patients were, on average, overweight (mean BMI 26.3 kg/m²), and 1078 (13%) were obese. Substantial proportions of patients had hypertension, were current smokers, or had heart failure or angina symptoms. Nearly all patients were taking antiplatelet medications, and about half were taking ACE-inhibitors, beta-blockers, or (by the end of follow-up) lipid-lowering medications.

Of the 8291 patients without diabetes at baseline followed-up for 26 795 person-years (mean 3.2 years [SD 0.9]), 998 (12%) developed diabetes—an incidence of 37 cases per 1000 person-years (figure 1). Four (0.05%) of the 8291 participants were lost to follow-up. Among the 7533 patients with fasting glucose lower than 6.1 mmol/L at baseline, 2514 (33%) either developed diabetes (n=769) or IFG (n=1745) during follow-up—an incidence of IFG alone of 85 cases per 1000 person-years and of diabetes and IFG of 123 cases per 1000 person-years. With the lower cutpoint for IFG (5.6 mmol/L) and evaluating the 6229 patients with fasting glucose lower than 5.6 mmol/L at baseline, 3856 (62%) either developed diabetes (n=548) or developed IFG (n=3308) during follow-up—an incidence of IFG₁₀₀ alone of 275 cases per 1000 person-years and of diabetes and IFG of 321 cases per 1000 person-years.

Independent clinical risk factors for diabetes included older age, higher BMI, hypertension, and current smoking (table 2). Each unit of higher BMI was associated with 9% greater risk (95% CI 7–11). Hypertension was associated with a 22% higher risk (7–39), and current smoking was associated with a 60% higher risk (34–90). Female sex and greater exercise capacity were associated with trends toward lower risk, although these were not significant. β-blocker use was associated with 27% (12–45%) higher risk and lipid-lowering medications were associated with a 22% (10–33%) lower risk of incident diabetes. A higher Mediterranean diet score was associated with 35% (15–51%) lower risk of diabetes, consumption of cheese, wine, and coffee were not associated with diabetes incidence.

	Baseline dietary score					p for trend†
	4.1 (0–5)* (n=1104)	6.6 (6–7)* (n=2030)	8 (n=1439)	9.4 (9–10)* (n=2504)	11.7 (11–15)* (n=1214)	
Risk factors						
Age (years)	56 (11)	58 (11)	59 (11)	60 (10)	59 (10)	<0.001
Sex (female)	115 (10%)	221 (11%)	199 (14%)	346 (14%)	194 (16%)	<0.001
Body-mass index (kg/m ²)	26.0(3.4)	26.3(3.4)	26.5(3.4)	26.3(3.4)	26.4 (3.4)	0.002
Obese (body mass index ≥30 kg/m ²)	133 (12%)	256 (13%)	191 (13%)	329 (13%)	167 (14%)	
Physician-diagnosed hypertension	458 (41%)	873 (43%)	639 (44%)	1156 (46%)	576 (47%)	
Previous acute myocardial infarction	98 (9%)	208 (10%)	150 (10%)	297 (12%)	154 (13%)	0.01
Intermittent claudication	49 (4%)	66 (3%)	47 (3%)	78 (3%)	47 (4%)	
Current smoker	663 (60%)	1045 (51%)	612 (43%)	983 (39%)	396 (33%)	<0.001
Former smoker	297 (27%)	666 (33%)	503 (35%)	963 (38%)	493 (41%)	<0.001
Systolic blood pressure (mm Hg)	123 (15)	123 (15)	123 (15)	123 (15)	123 (15)	
Diastolic blood pressure (mm Hg)	77 (9)	76 (9)	77 (9)	77 (8)	77 (8)	
Heart rate (beats per minute)	68 (10)	68 (10)	68 (11)	68 (10)	68 (10)	
Ejection fraction percentage	53 (10)	53 (10)	53 (10)	53 (10)	53 (11)	
Heart failure						
None	432 (39%)	700 (35%)	481 (33%)	826 (33%)	485 (40%)	
NYHA Class 1	595 (54%)	1149 (57%)	809 (56%)	1449 (58%)	645 (53%)	
NYHA Class 2–3	75 (7%)	179 (9%)	147 (10%)	226 (9%)	81 (7%)	
Angina						
None	689 (62%)	1199 (59%)	831 (58%)	1487 (59%)	800 (66%)	
CCS 1	329 (30%)	690 (34%)	511 (36%)	811 (32%)	315 (26%)	
CCS 2–4	72 (7%)	110 (5%)	77 (5%)	159 (6%)	64 (5%)	
Exercise stress test						
Negative	561 (51%)	1009 (50%)	691 (48%)	1252 (50%)	624 (51%)	
Positive	229 (21%)	390 (19%)	262 (18%)	489 (20%)	262 (22%)	
Not completed	314 (28%)	631 (31%)	486 (34%)	763 (30%)	328 (27%)	
Exercise cycloergometer test (Watts)	103 (33)	100 (31)	101 (35)	100 (34)	101 (31)	
Exercise treadmill test (mins)	8.3(3.6)	8.2(3.2)	8.0(3.0)	8.2(3.2)	8.0 (2.9)	

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Findings for each of these risk factors were generally similar for incidence of diabetes and IFG (data not shown), except significantly higher risk was seen for inability to perform exercise testing (HR 2.43 [95% CI 1.21–4.91]), use of diuretics (1.15 [1.00–1.33]), and wine consumption of more than 1 litre a day (1.45 [1.09–1.91]). Treatment assignment (fish oil or vitamin E) did not reduce incidence of diabetes or IFG (data not shown).

Adjusting for other risk factors (as in table 1), significant independent potential mediators of diabetes incidence included greater BMI gain (for each unit increase, HR 1.17 [95% CI 1.11–1.22], $p < 0.001$), higher triglycerides (interquintile HR 1.61 [95% CI 1.30–2.00], $p < 0.001$), lower high-density lipoprotein (HDL) cholesterol (1.46 [1.17–1.81], $p = 0.001$), higher leucocyte count (1.23 [1.00–1.53], $p = 0.05$), and higher consumption of butter or other oils (1.26 [1.02–1.56], $p = 0.03$). Fibrinogen levels were not associated with risk (0.98 [0.80–1.21], $p = 0.87$).

We assessed whether the incidence of new-onset diabetes or IFG was associated with risk of adverse clinical outcomes. During 28885 person-years of follow-up, 475 people died. Compared with individuals with normal fasting glucose (< 5.6 mmol/L), there was a trend toward 10% higher risk of death after development of IFG between 5.6–6.05 mmol/L, a trend toward 15% higher risk of death after development of IFG between 6.1–7 mmol/L, and 44% higher risk of death after development of diabetes (p for trend < 0.05) (figure 2). Findings were similar for risk of death or recurrent myocardial infarction (data not shown).

To determine the potential effects of a Mediterranean-type diet, we investigated this association in more detail. A higher score, indicating greater intake of traditional Mediterranean dietary components, was associated with older age, being female, slightly greater BMI, hypertension, previous acute myocardial infarction, and former rather than current smoking (table 3). There were no major differences between the different scores in terms of blood pressure, heart rate, ejection fraction, heart failure severity, anginal symptoms, or medications. Higher Mediterranean diet scores were associated with slightly higher HDL, and lower triglycerides and leucocyte count. Moderate intake of coffee (< 2 cups a day) and wine (≤ 0.5 L/day) was more common, in people with higher Mediterranean diet scores. Consumption of butter and oils other than olive oil was less common with higher Mediterranean diet scores.

After adjustment for age, sex, and smoking, greater intake of traditional Mediterranean dietary components was associated with lower incidence of diabetes (p for trend = 0.001). Those with the highest score had a 37% lower risk of developing diabetes than did those with the lowest scores (table 4). Findings were similar after additional adjustment for other risk factors (table 4). Evaluating individual components of the score, several were associated with trends toward lower risk, but only the association for cooked vegetables was significant: comparing high to low quartiles of intake, the

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Laboratory tests

Fasting glucose (mmol/L)	5.1 (0.7)	5.1 (0.7)	5.1 (0.7)	5.1 (0.7)	5.1 (0.7)	
LDL cholesterol (mmol/L)	3.6 (1.0)	3.6 (1.0)	3.6 (1.0)	3.6 (1.0)	3.6 (1.0)	
HDL cholesterol (mmol/L)	1.06 (0.3)	1.07 (0.3)	1.07 (0.3)	1.09 (0.3)	1.10 (0.3)	0.03
Triglycerides (mmol/L)	1.9 (1.0)	1.8 (1.0)	1.8 (1.0)	1.7 (1.0)	1.7 (1.0)	0.003
Fibrinogen (mg/L)	3.9 (1.4)	3.9 (1.4)	3.8 (1.3)	3.9 (1.4)	3.9 (1.4)	
Leucocyte count ($\times 10^9$ L)	7.9 (2.2)	7.8 (2.3)	7.7 (2.3)	7.6 (2.2)	7.5 (2.1)	< 0.001

Medications

Fish oil assignment	563 (51%)	1016 (50%)	734 (51%)	1241 (50%)	612 (50%)	
Antiplatelet medication	1035 (94%)	1874 (92%)	1328 (92%)	2303 (92%)	1112 (92%)	
ACE inhibitors	471 (43%)	913 (45%)	641 (45%)	1155 (46%)	518 (43%)	
Beta-blockers	545 (49%)	961 (47%)	679 (47%)	1155 (46%)	564 (46%)	
Diuretics	60 (5%)	164 (8%)	125 (9%)	239 (10%)	106 (9%)	0.03
Cholesterol-lowering medication†	73 (7%)	92 (5%)	55 (4%)	114 (5%)	65 (5%)	

Other dietary habits

Other oil consumption						< 0.001
Almost never	304 (28%)	675 (33%)	554 (39%)	1031 (41%)	601 (50%)	
Sometimes	412 (37%)	965 (48%)	679 (47%)	1144 (46%)	486 (40%)	
Often	188 (17%)	223 (11%)	139 (9%)	218 (9%)	80 (7%)	
Regularly	200 (18%)	167 (8%)	67 (5%)	111 (4%)	47 (4%)	
Butter consumption						< 0.001
Almost never	377 (34%)	855 (42%)	632 (44%)	1213 (48%)	684 (56%)	
Sometimes	416 (38%)	899 (44%)	666 (46%)	1069 (43%)	448 (37%)	
Often	187 (17%)	192 (10%)	104 (7%)	157 (6%)	61 (5%)	
Regularly	124 (11%)	84 (4%)	37 (3%)	65 (3%)	21 (2%)	
Cheese consumption						< 0.001
Almost never	57 (5%)	101 (5%)	48 (3%)	109 (4%)	60 (5%)	
Sometimes	337 (31%)	591 (29%)	467 (33%)	809 (32%)	422 (35%)	
Often	384 (35%)	855 (42%)	628 (44%)	993 (40%)	428 (35%)	
Regularly	326 (30%)	483 (24%)	296 (21%)	593 (24%)	304 (25%)	
Wine consumption						< 0.001
Almost never	378 (34%)	647 (32%)	468 (33%)	874 (35%)	489 (40%)	
≤ 0.5 L/day	459 (42%)	1004 (50%)	714 (50%)	1301 (52%)	616 (51%)	
0.5–1.0 L/day	206 (19%)	302 (15%)	223 (16%)	279 (11%)	95 (8%)	
> 1 L/day	61 (6%)	77 (4%)	34 (2%)	50 (2%)	14 (1%)	
Coffee consumption						< 0.001
Almost never	121 (11%)	242 (12%)	210 (15%)	392 (16%)	252 (21%)	
< 2 cups per day	261 (24%)	637 (31%)	493 (34%)	905 (36%)	439 (36%)	
2–4 cups per day	470 (43%)	768 (38%)	539 (38%)	882 (35%)	393 (32%)	
> 4 cups per day	252 (23%)	383 (19%)	197 (14%)	325 (13%)	130 (11%)	

Values are mean (SD) or n (%). ACE=angiotensin-converting-enzyme. CCS=Canadian Cardiovascular Society. NYHA=New York Heart Association. *Mean (range). †Age-adjusted for differences across categories of the Mediterranean dietary score. ‡Use of lipid-lowering medications increased during follow-up (coincident with a statin subrandomisation³⁰ and publication of several statin trials) to 31% at 6 months, 42% at 1.5 years, and 45% at 3.5 years. Time-varying covariates were used to account for all changes in medication use.

Table 3: Patients' characteristics categorised by baseline consumption of a Mediterranean-type diet in patients with recent myocardial infarction

multivariable-adjusted HR for cooked vegetables was 0.65 (95% CI 0.43–0.99); for raw vegetables 1.03 (0.77–1.38); for fruit 0.82 (0.60–1.11); for fish 0.81 (0.63–1.05); for olive oil 0.78 (0.51–1.21).

	Dietary score					p
	0-5	6-7	8	9-10	11-15	
Diabetes						
Person-years	1423	4530	4289	10264	6289	
Number of cases	83	197	161	378	179	
Incidence rate per 1000 person-years	58	43	38	37	28	
HR (95% CI)						
Adjusted for age, sex, and smoking	10	0.81 (0.63-1.05)	0.74 (0.57-0.97)	0.76 (0.60-0.97)	0.63 (0.48-0.82)	0.001
Multivariable*	10	0.81 (0.63-1.05)	0.74 (0.57-0.97)	0.77 (0.60-0.98)	0.65 (0.49-0.85)	0.004
Diabetes and IFG						
Person-years	1150	3552	3288	7640	4852	
Number of cases	222	490	438	905	459	
Incidence rate per 1000 person-years	193	138	133	118	95	
HR (95% CI)						
Adjusted for age, sex, and smoking	10	0.77 (0.66-0.91)	0.79 (0.67-0.93)	0.74 (0.64-0.86)	0.64 (0.54-0.75)	<0.001
Multivariable*	10	0.78 (0.67-0.92)	0.80 (0.68-0.94)	0.75 (0.65-0.88)	0.66 (0.56-0.78)	<0.001

*Adjusted for age, sex, smoking (current, former, never), time from myocardial infarction to enrolment, treatment assignment (four categories), BMI (kg/m²), maximum exercise tolerance during stress testing (quintiles), ischaemia during stress testing (present, absent, not done), New York Heart Association heart failure symptoms (none, class 1, class 2-3), Canadian Cardiovascular Society angina symptoms (none, class 1, class 2-4), history of hypertension (yes/no), prior myocardial infarction previous to index myocardial infarction (yes/no), angiotensin-converting-enzyme inhibitor use (yes/no), β -blocker use (yes/no), diuretic use (yes/no), lipid-lowering medication use (yes/no), and consumption of cheese, wine, and coffee (each in four categories).

Table 4: Risk of diabetes or diabetes and IFG according to consumption of a Mediterranean-type diet in patients with recent myocardial infarction

Comparing multivariable models with and without adjustment for potential mediators (BMI gain, serum lipid levels, fibrinogen and leucocyte count, intake of butter or oils other than olive oil), the risk associated with the Mediterranean-type diet was about one-fifth lower including these factors (28% risk reduction) than not including them (35% risk reduction; table 4), suggesting that these factors might mediate about one-fifth of the observed potential effect. Based on the changes in the risk estimates, the most important potential mediators seemed to be better HDL and triglyceride levels and lower consumption of butter or oils other than olive oil.

Consumption of traditional Mediterranean dietary components was also associated with lower incidence of diabetes and IFG (p for trend <0.001) (table 4). The magnitude (34%) of the lower incidence was similar to the lower risk (35%) seen for incidence of diabetes alone. Investigating potential mediators, differences in weight gain, serum lipid levels, inflammatory markers, and intake of butter or oils other than olive oil seemed to mediate about 25% of the association. Based on changes in the risk estimates, the most important factor in preventing the development of diabetes and IFG seemed to be lower consumption of butter or oils other than olive oil. Findings were similar using the lower IFG cutpoint (5.6 mmol/L). A Mediterranean-type diet was associated with lower incidence of diabetes and IFG₁₀₀ (p<0.001), with 28% lower risk comparing the highest to the lowest Mediterranean dietary scores (multivariable HR 0.72 [95% CI 0.63-0.82], table 4). Comparing absolute rates, individuals with the highest Mediterranean-type diet scores (11-15) developed far fewer cases of diabetes or

IFG (incidence 247 cases per 1000 person-years) than did individuals with the lowest scores (0-5) (incidence 458 cases per 1000 person-years).

Discussion

These results show that the incidence of prediabetes (IFG) and diabetes is high in patients with recent acute myocardial infarction free of glucose abnormalities in the peri-myocardial infarction period. One-third of patients developed new diabetes or IFG (≥ 6.1 mmol/L) during 3.5 years' follow-up, a proportion that rose to nearly two-thirds when the lower IFG cutpoint (5.6 mmol/L) was used. This finding was not due to undiagnosed prevalent disease at the time of myocardial infarction, since we measured baseline fasting glucose to exclude prevalent cases. These findings indicate that, just as diabetes can be considered a coronary heart disease risk-equivalent,³¹ acute myocardial infarction should potentially be considered a prediabetes risk-equivalent.

Two previous studies investigated the cross-sectional prevalence of impaired glucose tolerance in patients with acute coronary syndromes or recent myocardial infarction,^{7,8} but these represented the burden of undiagnosed (predisposing) disease at the time of myocardial infarction, not the development of new cases in ensuing years. Of 2499 patients with stable angina or remote (>6 months previously) myocardial infarction,³² 22% developed new-onset diabetes or IFG (≥ 6.1 mmol/L) during 6 years' follow-up, an incidence rate of about 4.1% per year.

In comparison, in our study, 33% developed diabetes or IFG during 3.5 years' follow-up, an incidence rate of

12.3% per year. This higher incidence suggests that, compared with patients with stable angina or remote myocardial infarction, patients with recent myocardial infarction have a stronger propensity towards prediabetes or diabetes. Compared to the more general population, the contrast is even greater. In population-based cohorts of middle-aged white adults followed-up in roughly the same years as our study, annual incidence rates of diabetes ranged from 0.8–1.6%^{33–35} (vs 3.7% in our study) and the annual incidence rate of IFG alone (5.6–7 mmol/L) was 1.8%³⁴ (vs 27.5% in our study). The high risk of incident IFG and diabetes in patients who had a myocardial infarction has clinical implications, indicating the importance of both surveillance and prevention of prediabetes and diabetes in these individuals. Regular screening might be appropriate for all such patients, using fasting glucose measurements, possibly along with other screening tests such as oral glucose tolerance testing.

These results also highlight the need for investigation of mechanisms and pathways that might account for this risk. It seems less likely that acute myocardial infarction itself would increase the risk of subsequent diabetes. We postulate that high rates of diabetes and IFG in the years after myocardial infarction are at least partly due to shared pathways between risk factors for acute plaque rupture and a propensity toward metabolic dysfunction. In our analysis, independent risk factors for diabetes included BMI, hypertension, current smoking, and in analyses of potential mediators, greater BMI gain, higher triglycerides, lower HDL cholesterol, and higher leucocyte count. Each of these could be markers of or risk factors for both plaque instability and metabolic dysfunction.

Medications commonly used to treat myocardial infarction patients (such as β blockers, lipid-lowering drugs, and diuretics) were also independently associated with diabetes incidence. These findings were consistent with earlier reports that specific drugs might affect insulin sensitivity and diabetes risk.^{36–39} The inverse association with lipid-lowering agents could also reflect selections of patients prescribed such medications, generally those with high LDL (and lower risk of IFG or diabetes), compared with those with low HDL or high triglycerides (at higher risk of IFG or diabetes). ACE-inhibitor use was not associated with diabetes risk in this analysis, which could be due to confounding by indication—ie, prescription of ACE-inhibitors to higher-risk patients. Additional attention to the possible effects of these medications on risk of IFG, as well as diabetes, is needed.

Patients with both coronary heart disease and diabetes have significantly worse outcomes than people with only one of these conditions.^{1–5} In this study, patients who have had a myocardial infarction and then developed diabetes had a higher risk of adverse events than those who maintained normal fasting glucose, even though the follow-up period was relatively short and measured only

the initial impact of new onset—and largely subclinical—IFG and diabetes. Given these adverse outcomes, identification of modifiable risk factors to prevent development of IFG and diabetes in patients who have had a myocardial infarction is imperative.

Addressing lifestyle behaviours can be particularly important in preventing disease. The high risks we noted from both high baseline BMI and BMI gain are warnings that the growing obesity pandemic will continue to offset gains in treatment of cardiac patients.³⁹ The 60% higher risk associated with current smoking also provides another powerful motivation for providers to emphasise smoking cessation and for patients to heed their advice. Although we did not have information on physical activity, inability to perform exercise testing was associated with more than two-fold higher incidence of diabetes and IFG, and it is clear that greater physical activity, combined with modest weight loss, lowers incidence of diabetes.³⁹ Coffee intake was not linked with risk of diabetes or IFG, possibly due to misclassification on the limited diet questionnaire. In additional exploratory analyses, compared with never or rare consumption, any coffee intake was associated with a trend towards lower incidence of diabetes and IFG₁₀₀ (multivariable HR=0.92, 95% CI 0.83–1.02).

The lower risk associated with a Mediterranean-type diet suggests that diet could help reduce incidence of prediabetes and diabetes after a myocardial infarction. Many,^{11–24} though not all,²⁵ trials have indicated that a Mediterranean-type diet lowers risk factors linked to insulin resistance and diabetes, including serum triglycerides, HDL cholesterol, systemic inflammation, endothelial function, and insulin sensitivity. These physiological effects in short-term randomised trials provide biological plausibility for the inverse association between consumption of a Mediterranean-type diet and incidence of IFG and diabetes in this study.

Also consistent with these trials, the lower incidence of diabetes and IFG seemed partly related to differences in serum triglycerides, HDL cholesterol, and inflammatory marker levels. Typical components of a Mediterranean-type diet—eg, olive oil, fruits, vegetables, whole grains, legumes, nuts, and fish, have each been linked to reductions in risk factors, but it is unclear whether one specific food, or a combination of foods, is most important. The results of one study suggest that different combinations of these foods may be similarly beneficial.²⁴ Our findings indicate that a combination of such foods could more strongly affect risk or better identify individuals consuming a Mediterranean-type diet than any single food. Assignment to fish oil treatment did not reduce IFG or diabetes risk, suggesting that findings were not related to n-3 fatty acids in fish (but other factors, such as protein and selenium, are present in fish but not fish oil). The beneficial effects of a Mediterranean-type diet could also be related to what is

not consumed: fewer processed meats, other processed foods, refined grains, and trans fats. Consistent with this, the lower incidence of diabetes and IFG seemed partly related to lower consumption of butter or oils other than olive oil. Notably, however, modern diets in Mediterranean regions are increasingly inconsistent with traditional Mediterranean-type diets.⁴⁰

Our analysis had several strengths. Participants were enrolled and followed-up by general cardiology practitioners, representing a real-world cross-section of patients who have had a myocardial infarction. Fasting glucose levels were measured at baseline and at multiple times during follow-up, enabling accurate diagnosis of prevalent diabetes or IFG at baseline and development of diabetes or IFG during follow-up. Data for exposures, risk factors, and events were obtained prospectively, which kept selection or recall bias to a minimum. Also, few patients were lost to follow-up, thus minimising bias from differential censoring. Data on risk factors, dietary habits, and potential mediators were obtained prospectively at multiple time points during follow-up, allowing time-varying multivariable adjustment. The large numbers of new cases of diabetes and IFG provided substantial statistical power.

There were also several potential limitations. The use of oral glucose tolerance tests would probably have captured additional new cases of diabetes or IFG; thus, the true incidence of abnormal insulin-glucose homeostasis was probably underestimated. Detailed information on medications, such as type of diuretics, was not available. Misclassification of both clinical and lifestyle exposures could have occurred due to measurement error or biological variation; because data were collected prospectively, such errors would probably be random with respect to the outcomes and cause underestimation of the observed associations.

Lifestyle habits could have been partially driven by changes in response to chronic disease development and physician guidance (eg, individuals consuming a Mediterranean-type diet were more likely to have a history of hypertension and higher BMI at baseline); because such individuals might be more likely to develop diabetes or IFG, this would also drive the observed beneficial associations toward the null. We did not have information on physical activity, although we adjusted for exercise tolerance during stress testing, which is a well-validated measure of underlying physical fitness. The serum lipid and inflammatory measures might not have perfectly captured the activity of these physiological pathways, underestimating the degree to which such pathways mediated risk. Although we adjusted for a variety of risk factors, residual confounding by unmeasured or incompletely measured factors cannot be excluded. The results were seen in Italian patients with recent myocardial infarction and might not be generalisable to other populations. For example, the range of dietary differences in an Italian population may be less than in other

populations, which would cause an underestimation of the magnitude of benefit of a Mediterranean-type diet compared with other Western diets.

Our findings indicate that incidence of IFG and diabetes is high in the years after myocardial infarction, suggesting that acute myocardial infarction could be a prediabetes risk-equivalent. The results highlight the need to screen such patients and investigate potential pathways (eg, shared risk factors, medication use, lifestyle behaviours) that might mediate this relation. Our findings also suggest that smoking cessation, prevention of weight gain, and consumption of typical Mediterranean foods could substantially lower this risk, which has important implications for counselling patients soon after they have a myocardial infarction—an opportune time to institute lifestyle changes in patients motivated by a life-changing event.

Contributors

DM participated in the conception and design, statistical analysis and data interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, and approval of the final manuscript for submission. R Marfisi and R Marchioli participated in the conception and design, data collection, statistical analysis and data interpretation, critical revision of the manuscript for important intellectual content, and approval of the final manuscript for submission. GL, MS, LT, GT, and FV participated in the data collection, critical revision of the manuscript for important intellectual content, and (except for FV) approval of the final manuscript for submission.

Conflict of interest statement

We declare that we have no conflict of interest.

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