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Silent myocardial infarction in women with impaired glucose tolerance: The Northern Sweden MONICA study

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Abstract

Background: Patients with impaired glucose tolerance (IGT) have an increased risk of cardiovascular disease (CVD) that is independent of traditional risk factors. Hence, slightly elevated glucose levels, even in the non-diabetic range, might be associated with increased macrovascular disease.

Methods: Within the Northern Sweden MONICA project a population survey was performed in 1986. Electrocardiograms (ECG's) were recorded for half of the survey (n = 790) and oral glucose test was carried out in 78 % of those. The association between subjects with ECG's indicating previously unknown myocardial infarction (ukMI), IGT and conventional risk factors were analyzed by logistic regression for men and women separately, adjusting for age, smoking, hypercholesterolemia and hypertension.

Results: Impaired glucose tolerance was significantly more common among women with ukMI, but not in men, compared to the group with normal ECG. In men, no variable was significantly associated with ukMI although the odds ratio (OR) for hypercholesterolemia was of borderline significance, 3.2 (95% confidence interval (CI) 0.9 to 11). The OR of having ukMI was 4.1 (CI 1.1 to 15) in women with IGT compared to women with normal glucose tolerance after multiple adjustment. The OR for hypertension was of borderline significance; 3.3 (CI 0.97 to 11).

Conclusion: We found that IGT was associated with ECG findings indicating silent myocardial infarction in women in a middle-aged general population in northern Sweden. The results persisted even after adjusting for known risk factors.

Background

Diabetes contributes strongly to the risk of CVD with a risk that is increased four to six times, both for stroke and myocardial infarction [1]. The increase in risk for myocardial infarction seem to be more pronounced in women than in men [2].

The prevalence of IGT in the general population is 2–3 times higher than that of previously unknown diabetes, which, in turn, is as common as known diabetes [3]. Patients with impaired glucose tolerance have an increased risk of CVD that is independent of traditional risk factors such as hypertension, smoking and hypercholesterolemia [4] and it has been suggested that slightly elevated glucose levels, even in the non-diabetic range, might

be associated with increased macrovascular disease. Thus, the risk of CVD is already present in the prediabetic state [5]. Several publications have focused on the relationship between IGT and coronary heart disease (CHD). The results have indicated that ethnicity, sex and age might be factors that modify the strength of the risk of CHD with impaired glucose tolerance [6–11].

The aim of the present investigation was to further evaluate the possible relation between IGT and CHD. Therefore, we examined ECG's to identify signs of clinically undiagnosed myocardial infarction together with cardiovascular risk factors in a randomly selected population of men and women from northern Sweden, a region with an ethnically homogenous population and a high incidence of cardiovascular disease [12].

Methods

This study was performed within the framework of the Northern Sweden MONICA project which, in turn, is a part of the WHO MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease) [13]. During January to April 1986, a population was screened for cardiovascular risk factors. A total of 2000 individuals in the 25 to 64 year range were invited. Within each age group (25–34, 35–44, 45–54, 55–64 years) 250 men and 250 women were randomly selected from continuously updated population registers in Norrbotten and Västerbotten, the two northernmost provinces of Sweden. They were invited by letter to an examination. If they did not attend, a reminder with a new appointment was sent. People who still did not come, were contacted by telephone to ascertain reasons for reluctance to attend and to get basic information on social background and risk factors. The participants were asked to complete a questionnaire with items on, *inter alia*, social background, smoking habits, medical history and intake of drugs. The questionnaire was returned on the site of the survey, which was performed by two mobile teams in local health centres (or corresponding) throughout the MONICA area. ECG's were recorded for the Västerbotten part of the population.

Seven hundred ninety subjects from Västerbotten participated in the study (79 % of all invited). Six hundred seventeen subjects, without known diabetes, underwent a 75 g oral glucose tolerance test (OGTT) with measurement of plasma glucose [3]. The results were classified according to WHO criteria from 1999 [14]. Anthropometric measurements and biochemical analyses were as previously described [15]. Clinically diagnosed myocardial infarction, or known MI (kMI), was defined by a positive answer to the question "Have you ever had a myocardial infarction?". Clinically diagnosed, or known diabetes, was defined by a positive answer to the question "Do you have diabetes?". A validation study of 70 incident diabetes

cases in this cohort using clinical case records show these answers to be highly accurate (unpublished data). Hypertension was defined as systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 95 mm Hg or a positive answer to the question "Are you being treated with pharmaceutical drugs for high blood pressure". Hypercholesterolemia was defined as total cholesterol values more than 6,5 mmol/l. Subjects smoking more than 1 cigarette per day were defined as regular smokers.

The Northern Sweden Monica Study has been approved by the Research Ethics Committee of Umeå University and the data handling procedures by the National Computer Data Inspection Board.

Electrocardiography

All electrocardiograms (ECG's) were recorded with a Cardiovit CS-6 microprocessor-based electrocardiograph (Schiller AG, Basel, Switzerland). Twelve leads were recorded for 10 seconds and used for interpretation by the CS-6 recorder. Original readings were printed on paper (paper speed 50 mm/s) together with an averaged ECG and a diagnostic statement made by the computer. ECG's were assessed according to the Minnesota Code by two trained observers and Q/QS-wave; codes 1.1–1.3 were designated as myocardial infarction. ECG's from two subjects were coded differently by the observers and were therefore excluded from the MI group.

Statistical analysis

Continuous data are presented as means and SD. Students t-test and χ^2 were used to test for differences between subjects with normal ECG and subjects with ukMI. In a stepwise logistic regression with ukMI as dependent variable, traditional risk factors (hypertension, smoking, hypercholesterolemia) and the occurrence of IGT were entered as dichotomous independent variables and age as a continuous variable. Results are given as odds ratios with 95 % confidence intervals. All statistical analysis were carried out with the SPSS programme, version 10.1.

Results

Table 1 shows baseline characteristics of 790 subjects, 25 to 64 years of age. Both sexes were evenly represented. Previously known MI (kMI) was present in 2.7 %, hypertension in 18,5 %, hypercholesterolemia in 36.3 % and diabetes in 2.8 %. Nearly one quarter was smokers and more than 10 % used smokeless tobacco. Half of the population was overweight and with increased waist circumference. Mean serum cholesterol was high, 6.2 mmol/l.

A gender-specific analysis are shown in table 2. Clinically diagnosed myocardial infarction and diabetes were more prevalent in men. Cigarette smoking were more common

Table 1: Characteristics of the total study population, 25 to 64 years of age in the Northern Sweden MONICA population survey in 1986. Mean (SD) or proportions (%).

Subjects (n)	790
Age (years)	45.2 (11.3)
Sex	
Men	409 (51.8 %)
Women	381 (48.2 %)
Previous disorders	
Clinically diagnosed myocardial infarction (kMI)	21 (2.7 %)
Hypertension	146 (18.5 %)
Hypercholesterolemia	287 (36.3 %)
Diabetes	22 (2.8 %)
Tobacco use	
Current cigarette smoker	179 (22.8 %)
Current smokeless tobacco user	80 (10.6 %)
Anthropometric variables	
Height (cm)	170.3 (9.2)
Weight (kg)	72.8 (13.3)
BMI (kg/m ²)	25 (3.8)
Hip circumference (cm)	99.2 (7.4)
Waist circumference (cm)	88.1 (11.6)
Waist-hip ratio	0.9 (0.1)
Biochemical markers (mmol/l)	
Total cholesterol	6.2 (1.3)
HDL cholesterol	1.2 (0.3)
Triglycerides (n = 495)	1.3 (0.9)
Fasting plasma glucose (n = 774)	5.1 (1.4)
2 hour postload plasma glucose (n = 629)	5.5 (2.0)
Glucose tolerance (n = 617)	
Normal	550 (89.1 %)
Impaired glucose tolerance	53 (8.6 %)
Diabetes	14 (2.3 %)
ECG	
Normal	741 (93.8 %)
MI	49 (6.2 %)

BMI = body mass index. HDL = high-density lipoprotein. MI = myocardial infarction (Q/QS wave; Minnesota code 1.1–1.3). kMI = known myocardial infarction.

in women but the use of smokeless tobacco was rare compared to men. The number of subjects with IGT was much higher in women.

An OGTT was carried out in 617 subjects, showing IGT in 8.6 % and unknown diabetes in 2.3 %. A gender-specific analysis of this population did not differ significantly regarding age, anthropometric variables or biochemical markers compared to the total study population shown in table 1 and 2 (table 3).

All ECG's not interpreted as MI were considered normal (93.8 %). Interestingly, there were twice as many subjects with ECG indicating MI (ukMI) that had not been clinically diagnosed than with known infarctions (kMI). The majority of kMI's were not detected on ECG (Table 4). The 21 subjects with kMI were excluded from further analysis.

Table 2: Characteristics of the study population, men and women, 25 to 64 years of age in the Northern Sweden MONICA population survey in 1986. Mean (SD) or proportions (%).

	Men	Women
Age (years)	45.7 (11.4)	44.8 (11.2)
Previous disorders		
Clinically diagnosed myocardial infarction (kMI)	18 (4.5 %)	3 (0.8 %)
Hypertension	81 (19.8 %)	65 (17.1 %)
Hypercholesterolemia	148 (36.2 %)	139 (36.5 %)
Diabetes	16 (4.0 %)	6 (1.6 %)
Tobacco use		
Current cigarette smoker	80 (19.7 %)	99 (26.2 %)
Current smokeless tobacco user	76 (19.6 %)	4 (1.1 %)
Anthropometric variables		
Height (cm)	176.6 (6.8)	163.5 (6.0)
Weight (kg)	79 (11.0)	66 (12.1)
BMI (kg/m ²)	25.3 (3.2)	24.7 (4.4)
Hip circumference (cm)	99.1 (5.6)	99.2 (9.0)
Waist circumference (cm)	92.5 (9.1)	83.2 (12.1)
Waist-hip ratio	0.9 (0.1)	0.8 (0.1)
Biochemical markers (mmol/l)		
Total cholesterol	6.2 (1.2)	6.2 (1.3)
HDL cholesterol	1.1 (0.3)	1.4 (0.4)
Triglycerides (n = 495)	1.5 (1.1)	1.1 (0.7)
Fasting plasma glucose (n = 774)	5.3 (1.8)	4.8 (0.7)
2 hour postload plasma glucose (n = 629)	5.3 (2.2)	5.8 (1.9)
Glucose tolerance (n = 617)		
Normal	290 (91.8 %)	260 (86.4 %)
Impaired glucose tolerance	19 (6.0 %)	34 (11.3 %)
Diabetes	7 (2.2 %)	7 (2.3 %)
ECG		
Normal	381 (93.2 %)	360 (94.5 %)
MI	28 (6.8 %)	21 (5.5 %)

BMI = body mass index. HDL = high-density lipoprotein. MI = myocardial infarction (Q/QS wave; Minnesota code 1.1–1.3). kMI = known myocardial infarction.

A gender-specific analysis comparing subjects with normal ECG to ukMI subjects are shown in Table 5. Subjects of both sexes with ukMI were older and had a greater burden of previous CVD than did subjects with normal ECG's. Diabetes and hypercholesterolemia were more prevalent in men with ukMI than in women. Body mass index and waist-hip ratio were higher in subjects with ukMI, more so in women than in men. There was a tendency to higher lipid levels in the ukMI group, at least in women. The number of subjects with IGT was significantly higher in the ukMI group in women, but not in men compared to the group with normal ECG.

The association between ukMI and sex, age, smoking, hypercholesterolemia, hypertension and IGT was analyzed in a multiple logistic regression model. 617 subjects with complete data sets were included. None of the varia-

Table 3: Characteristics of the glucose tolerance tested subjects, men and women, 25 to 64 years of age in the Northern Sweden MONICA population survey in 1986. Mean (SD) or proportions (%).

	Men	Women
Age (years)	44.9 (11.3)	44.8 (11.2)
Previous disorders		
Clinically diagnosed myocardial infarction (kMI)	10 (3.2 %)	2 (0.7 %)
Hypertension	60 (19.0 %)	52 (17.3 %)
Hypercholesterolemia	117 (37.0 %)	110 (36.5 %)
Tobacco use		
Current cigarette smoker	57 (18.2 %)	73 (24.3 %)
Current smokeless tobacco user	56 (18.8 %)	2 (0.7 %)
Anthropometric variables		
Height (cm)	176.5 (7.0)	163.7 (5.9)
Weight (kg)	79 (11.0)	66.4 (12.5)
BMI (kg/m ²)	25.4 (3.3)	24.8 (4.5)
Hip circumference (cm)	99.1 (5.8)	99.5 (9.0)
Waist circumference (cm)	92.3 (9.1)	83.2 (12.6)
Waist-hip ratio	0.9 (0.1)	0.8 (0.1)
Biochemical markers (mmol/l)		
Total cholesterol	6.2 (1.3)	6.2 (1.3)
HDL cholesterol	1.2 (0.3)	1.4 (0.4)
Triglycerides (n = 495)	1.3 (0.8)	1.1 (0.7)
Fasting plasma glucose (n = 774)	5.1 (1.1)	4.8 (0.5)
2 hour postload plasma glucose (n = 629)	5.3 (2.0)	5.8 (2.0)
ECG		
Normal	299 (94.6 %)	286 (95.0 %)
MI	17 (5.4 %)	15 (5.0 %)

BMI = body mass index. HDL = high-density lipoprotein. MI = myocardial infarction (Q/QS wave; Minnesota code 1.1-1.3). kMI = known myocardial infarction.

Table 4: Comparison of clinically diagnosed myocardial infarctions and ECG indicating myocardial infarction (n = 771).

MI on ECG	Known MI (kMI)	
	Yes	No
Yes	7	37
No	14	713

ECG = electrocardiogram. MI = Myocardial infarction

bles, except for age, showed significant association with ukMI (table 6).

Men and women were analyzed separately and the results are shown in Table 7. In men, no variable was significantly associated with ukMI although the odds ratio for hypercholesterolemia was of borderline significance; 3.22 (CI 0.92 ; 11.22). In women, IGT was significantly associated with ukMI and hypertension had a tendency towards

association. The odds ratio of having ukMI was 4.14 (CI 1.13; 15.14) in women with IGT compared to women with normal glucose tolerance. The odds ratio for hypertension was of borderline significance; 3.33 (CI 0.97; 11.43). The results were similar if subjects with ST/T changes and left ventricular hypertrophy were excluded from the "normal ECG" group. If, on the other hand, ST/T changes are included in the MI group no significant association between any variable was seen (data not shown).

Discussion

Our findings indicate that previously unknown Q-wave infarction is considerably more common in women 25-64 years of age with impaired glucose tolerance than in women with normal glucose tolerance, even after adjustment for traditional risk factors. No such relationship was noted in men. The total number of participants was rather small which is a limitation of the study but the attendance rate of 80 % is in accordance with other major population surveys. The variables measured are strictly validated according to WHO criteria [3].

Cross-sectional studies concerning resting ECG abnormalities indicating IHD in subjects with IGT have reported varying results. In younger south Asian men (40-54 years) settled overseas, major Q-waves were strongly associated with glucose intolerance and hyperinsulinemia [7]. This association was less strong for European men in the same study. In a Chinese population, IGT was associated with ECG abnormalities in both men and women, but the ECG criteria used also included T-wave abnormalities and complete left bundle branch block, which differs from the stricter Q-wave criteria used in our study [8]. Data from the Rancho Bernardo Study, an older population of white subjects, showed that ECG abnormalities were more common in subjects with non-insulin dependent diabetes (NIDDM) but not in those with IGT. Also in this study, ECG criteria were wider than our criteria [9]. In the San Luis Valley Diabetes Study, 20-74-year-old Hispanics and non-Hispanic whites of both sexes were studied. An association between NIDDM, but not IGT, with mainly Q/QS waves was seen [10]. A study of North American white males, aged 40-59 years, could not show any association between blood glucose and major ECG abnormalities indicating MI [11].

Hence, no consistent data concerning association between IGT and silent myocardial infarctions have been shown and only few studies have included women. To our knowledge no European data have been published. In most studies, MI's were somewhat more common in subjects with IGT, although not reaching conventional levels of significance. This indicates a problem of statistical power and perhaps differing impact of blood glucose

Table 5: Cardiovascular risk factors in subjects with normal ECG and in subjects with ukMI. Mean (SD) or proportions (%). Test for differences between groups with χ^2 or t-test.

A. Men	Normal ECG	ukMI	p
ECG classification (n)	364 (94.8 %)	20 (5.2 %)	
Age (years)	44.4 (11.1)	52.2 (11)	0.002
Previous disorders			
Hypertension	65 (17.9 %)	8 (40 %)	0.02
Hypercholesterolemia	122 (33.5 %)	12 (60 %)	0.02
Diabetes	9 (2.5 %)	3 (15 %)	0.002
Tobacco use			
Current smoker	75 (20.8 %)	1 (5 %)	0.17
Current snuff user	71 (20.7 %)	3 (15.8 %)	0.61
Anthropometric variables			
Height (cm)	176.9 (6.8)	176.3 (6.1)	0.68
Weight (kg)	78.9 (10.9)	81.5 (11.9)	0.30
BMI (kg/ m ²)	25.2 (3.2)	26.2 (3.3)	0.19
Hip circumference (cm)	99 (5.7)	100.8 (5.1)	0.18
Waist circumference (cm)	92.2 (9.1)	95.3 (7.8)	0.14
Waist-hip ratio	0.93 (0.1)	0.95 (0.1)	0.19
Biochemical markers (mmol/l)			
Total cholesterol	6.1 (1.3)	6.6 (0.8)	0.08
HDL	1.1 (0.3)	1.2 (0.2)	0.77
Triglycerides (n = 231)	1.4 (1.1)	1.9 (1.3)	0.12
Fasting plasma glucose	5.2 (1.6)	5.7 (2.5)	0.22
2 hour postload plasma glucose	5.3 (2.2)	5.1 (1.5)	0.71
Glucose tolerance (n = 304)			
Impaired glucose tolerance	17 (5.9 %)	1 (7.1 %)	0.83
Diabetes	7 (2.4 %)	0	
B. Women	Normal ECG	ukMI	p
ECG classification (n)	349 (95.4 %)	17 (4.6 %)	
Age (years)	44 (11)	53.8 (7.1)	<0.001
Previous disorders			
Hypertension	54 (15.5 %)	8 (47.1 %)	0.003
Hypercholesterolemia	123 (35.2 %)	8 (47.1 %)	0.32
Diabetes	3 (0.9 %)	0 (0 %)	
Tobacco use			
Current smoker	92 (26.6 %)	3 (17.6 %)	0.41
Current snuff user	4 (1.2 %)	0	
Anthropometric variables			
Height (cm)	163.7 (6)	162.1 (5.0)	0.30
Weight (kg)	65.6 (11.8)	75.4 (15.9)	0.001
BMI (kg/m ²)	24.4 (4.1)	28.7 (6.5)	<0.001
Hip circumference (cm)	98.6 (8.3)	106.6 (12)	<0.001
Waist circumference (cm)	82.6 (11.3)	92 (18.7)	0.001
Waist-hip ratio	0.84 (0.1)	0.86 (0.1)	0.2
Biochemical markers (mmol/l)			
Total cholesterol	6.1 (1.3)	6.6 (1.4)	0.17
HDL	1.4 (0.4)	1.2 (0.3)	0.16
Triglycerides (n = 240)	1 (0.6)	1.4 (1)	0.04
Fasting plasma glucose	4.8 (0.7)	5 (0.4)	0.26
2 hour postload plasma glucose	5.7 (1.9)	6.9 (2.2)	0.02
Glucose tolerance (n = 293)			
Impaired glucose tolerance	28 (10.1 %)	5 (38.5 %)	0.006
Diabetes	7 (2 %)	0	

ECG = electrocardiogram. HDL = high-density lipoprotein. ukMI = unknown myocardial infarction. BMI = body mass index

Table 6: Predictors of ukMI in a multiple logistic stepwise regression analysis

Risk factor	OR	95 % CI
Male sex ?	0.88	0.39; 1.96
Age (years)	1.07	1.02; 1.13
Smoking	0.54	0.16; 1.88
Hypercholesterolemia	1.38	0.58; 3.30
Hypertension	2.00	0.85; 4.70
IGT	2.40	0.87; 6.68

ukMI = unknown myocardial infarction. OR (= odds ratio) calculated with all variables entered simultaneously, with age as a continuous variable. CI = confidence interval. IGT = impaired glucose tolerance. Risk factor definitions were as described in Methods.

abnormalities in different ethnic groups. Some of these studies found that increases in risk were attenuated by adjustment for other known risk factors. The wide definition of CHD based on ECG findings may also dilute effect sizes. Our population-based study is thus the first to show that in middle-aged European women, there is a strong and independent relationship between IGT and previously unknown MI, defined by strict criteria.

The correlation between ECG findings indicating MI and known infarctions is not strong. Major Q-waves were shown to occur in only 43 % of subjects in whom old myocardial infarcts were detected at autopsy, and Q/QS abnormalities were found to be rather common in non Q-wave infarctions as well [16]. Twenty to thirty percent of major Q/QS infarctions are known to be silent [17]. Moreover, Q/QS abnormalities often disappear during recovery from an acute myocardial infarction [16]. This was also evident in our study where only a minority of reported previous MI were classified as MI on ECG. Q/QS abnormalities are also seen in other diseases affecting the heart [18]. Interestingly, it was recently shown that left ventricular hypertrophy (LVH) mass and wall thickness increased with worsening glucose intolerance, an effect that was more striking in women compared with men [19]. Hence, since LVH can mimic MI this might lead to misclassification bias in the ECG interpretation.

In the present investigation there are more than twice as many subjects with ukMI as with kMI. This supports previously results in a population over 65 years of age [20]. Many kMI's were seen in the group with normal ECG, a not surprising observation considering the findings mentioned. Specificity for Q/QS-infarctions was high but sensitivity was low when ECG was compared to autopsy-verified infarctions. Less than 60 % of all verified infarctions were diagnosed in this material [16]. Thus, some infarctions might be undetected in our material which could lead to misclassification bias and a dilution of effect.

Table 7: Predictors of ukMI in a multiple logistic stepwise regression analysis

A. Men	OR for ukMI	95 % CI
Age (years)	1.07	1.01; 1.14
Smoking	0.28	0.04; 2.29
Hypercholesterolemia	3.22	0.92; 11.22
Hypertension	1.13	0.31; 4.07
IGT	0.68	0.08; 5.90
B. Women	OR for ukMI	95 % CI
Age (years)	1.09	1.01; 1.18
Smoking	0.97	0.19; 4.95
Hypercholesterolemia	0.60	0.16; 2.27
Hypertension	3.33	0.97; 11.43
IGT	4.14	1.13; 15.14

Conditions and abbreviations were as in table 4

An increased IHD mortality has been described in subjects with IGT, particularly in women [21]. In the DECODE study, which included MONICA data from our survey, IGT predicted mortality from all causes, CVD and CHD [4]. Previous studies indicate that the risk of CVD is increased at the time of diabetes diagnosis. The risk seem to be independent of the duration of diabetes suggesting that factors operating before the development of overt diabetes contribute to the risk of CVD [5]. This was recently shown in women where the risk for MI or stroke was substantially increased before diagnosis of type 2 diabetes [22].

Hyperglycemia has also been suggested to be a direct cause of some of the changes associated with atherosclerosis [23,24], but several other factors could act as casual links in this association such as impaired fibrinolysis and high fibrinogen levels [25], high levels of leptin [26] as well as others which have not been assessed in population studies. These factors could link IGT to atherosclerosis and thereby to the Q/QS abnormalities found in the present investigation although the diverging results in men and women are difficult to explain.

In conclusion, we found that IGT was associated with ECG findings indicating silent myocardial infarction in women in a middle-aged general population in northern Sweden. The results persist even after adjusting for known risk factors. As encouraging results have recently been published on the effect of life-style modification to prevent high risk individuals from developing diabetes [27], our study underlines that such efforts may also lead to decreased cardiovascular risks. Also, more research is needed to

improve our understanding of the pathogenesis of coronary artery disease in subjects with early glucose dysregulation.

Competing interests

None declared.

Authors' contributions

DL participated in the design of the study, performed the statistical analyses and drafted the manuscript. ME participated in the design of the study and in the final preparation of the manuscript.

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