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Article: Complications

Impaired fasting glucose in combination with silent myocardial ischaemia is associated with poor prognosis in healthy individuals

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Abstract

Aim As both impaired fasting glucose and silent myocardial ischaemia are risk factors for cardiovascular disease and death, we hypothesized that these risk factors in combination would identify those subjects at the highest risk of adverse events.

Methods Healthy individuals without diabetes (n = 596, 55–75 years) were examined for silent myocardial infarction (≥ 1 mm ST-interval during ≥ 1 min) by ambulant 48-h continuous electrocardiogram monitoring and impaired fasting glucose (fasting plasma glucose 5.6–6.9 mmol/l).

Results After 6.3 years, 77 subjects met the endpoint of myocardial infarction and/or death. The prevalence of silent myocardial ischaemia at inclusion was 12.3% in subjects with impaired fasting glucose and 11.7% in subjects with normal fasting glucose, P = 0.69. Subjects with impaired fasting glucose/silent myocardial ischaemia more often met the endpoint (36%) than subjects with impaired fasting glucose/no silent myocardial ischaemia (15%), subjects with normal fasting glucose/silent myocardial ischaemia (12%), and subjects with normal fasting glucose/no silent myocardial ischaemia (10%), respectively, (P < 0.001). In a Cox model including these four study groups of interest, gender, age, smoking habits, blood pressure and total cholesterol, only subjects with impaired fasting glucose/silent myocardial ischaemia exhibited an increased risk of death or myocardial infarction (hazard ratio 2.5, P = 0.016).

Conclusion The combination of impaired fasting glucose and silent myocardial ischaemia was associated with the poorest prognosis in middle-aged and older subjects without previously known glucose metabolic aberration and heart disease.

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Keywords cardiovascular disease, diabetes mellitus, impaired fasting glucose, silent myocardial ischaemia

Introduction

Silent myocardial ischaemia was described in 1974 by Stern [1], who observed a prevalence of 46% of silent myocardial ischaemia in subjects with typical angina pectoris. Studying silent myocardial ischaemia is relevant because approximately one half of the first coronary heart events including sudden cardiac death occurs in asymptomatic individuals [2]. It has been demonstrated that the majority of new ischaemic episodes in patients with established coronary artery disease are not associated with angina [3,4] and that 10–15% of new myocardial infarctions are silent [5]. In subjects with known coronary artery disease, the presence of silent myocardial ischaemia is associated with a poor prognosis, displaying a 3.5-fold increased risk of an additional major cardiovascular event, compared with patients with coronary artery disease without silent myocardial ischaemia [6]. The prognostic significance of silent myocardial ischaemia, as detected by Holter monitoring in asymptomatic subjects without known coronary artery disease, is poorly evaluated [7,8]. According to these studies, the presence of silent myocardial ischaemia is associated with increased risk, implicating an increase in the cardiac event rate of 2- to 4-fold, especially in middle-aged and elderly subjects and subjects with conventional risk factors [7,8].

The prevalence of silent myocardial ischaemia is increased in patients with diabetes mellitus [9]. Raised plasma glucose concentration, as seen in diabetes mellitus, has been identified

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as an independent risk factor for cardiovascular disease and cardiovascular disease mortality [10,11].

Recent studies have indicated that elevated glucose levels in patients without diabetes with ischaemic heart disease are associated with increased mortality [12,13]. Whether the same association exists in individuals without known cardiovascular disease is unclear. The process of atherosclerosis is accelerated and silent cardiac events are frequent in patients with diabetes [14,15]. Some studies have reported a higher incidence of silent myocardial ischaemia in patients with diabetes and a poorer prognosis [16,17]. Prevalence and prognosis of subjects with both silent myocardial ischaemia and impaired fasting glucose has not been evaluated before, but may be of interest, as it may identify a subgroup with a high risk that may be subject for more intensive prevention and treatment.

In the present study, the association between silent myocardial ischaemia and the pre-diabetic state, defined as impaired fasting glucose, was investigated in healthy middle-aged and elderly subjects aged 55–75 years with no previous heart disease. Moreover, the prognostic significance of silent myocardial ischaemia and impaired fasting glucose in combination according to death and myocardial infarction was evaluated.

Subjects and methods

The study is based on data from the Copenhagen Holter study [8]. The study was performed from 1998 to 2000 and aimed to address the value of 48-h Holter recording in risk assessment of middle-aged and elderly men and women with no apparent heart disease. A representative epidemiological survey of subjects living within two well-defined postal regions in Copenhagen was performed. Each citizen in Denmark can be identified by a unique number in the 'central personal register', administered by the Ministry of the Interior. A total number of 2969 subjects, including every man aged exactly 55 years and all men and women aged exactly 60, 65, 70 and 75 years, received a questionnaire on cardiovascular risk factors, use of medication and history of health problems (Fig. 1), of whom 1743 answered and 1226 did not respond or refused. After excluding those with a history of myocardial infarction, cardiovascular disease, stroke, cancer and other significant or life-threatening conditions, 1395 individuals remained. Subjects with two or more risk factors were all invited to participate in the study (n = 576, of which 412 accepted), as were 60% (n = 490) of the subjects who exhibited one or no apparent risk factor, among whom 363 subjects accepted to participate. Ninety-seven individuals were excluded because of detection of either one or more exclusion criteria and/or technically unacceptable or incomplete Holter recordings among those who accepted. In the Copenhagen Holter study, 678 subjects participated and were interviewed by a physician, followed by physical examination, fasting biochemical test and 48-h continuous Holter monitoring. In the present study on individuals without diabetes, 596 subjects participated following exclusion of seven subjects as a result of missing blood glucose measurements and a further 75 because of fasting plasma glucose of ≥ 7.0 mmol/l. Impaired fasting glucose was set as fasting plasma glucose of 5.6–6.9 mmol/l defining a state of pre-diabetes.

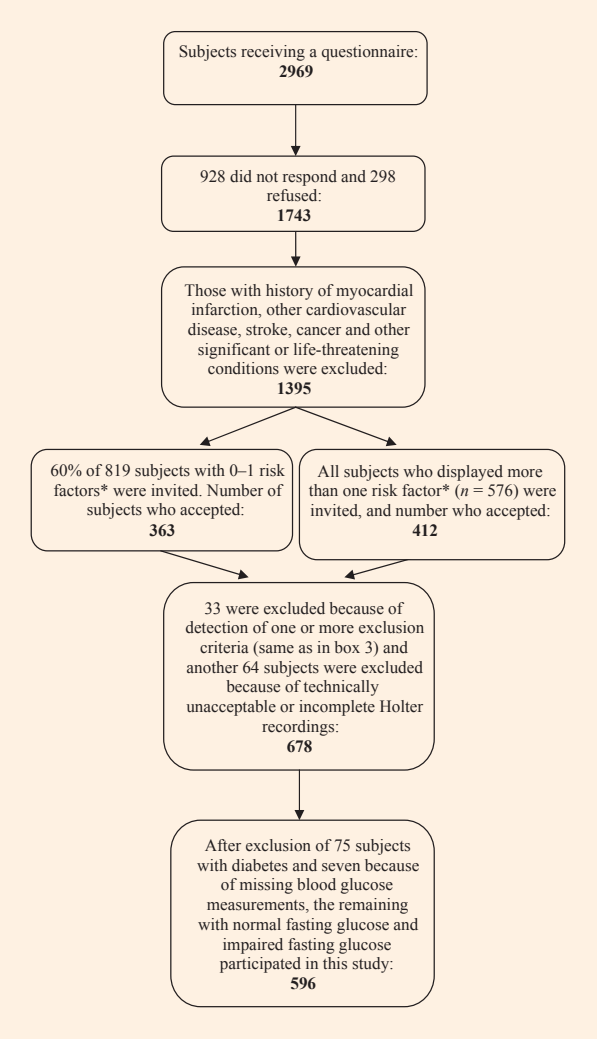

FIGURE 1 Flow diagram demonstrating the study population at different steps. *Self-reported risk factors: hypertension, diabetes mellitus, smoking habits, predisposition to cardiac disease, i.e. sudden death or acute myocardial infarction in a parent or sibling before the age of 60 years, obesity (BMI > 30 kg/m^2) and hypercholesterolemia.

Continuous 48-h Holter recording was made by two-channel SpaceLabs tape recorders (9025; Spacelabs Inc., Redwood, WA, USA). Lead II and V5 were selected in all participants. Analysis of ST-segment depression was performed semi-manually by trained personal at the Holter laboratory. An episode of ischaemia was defined by a downsloped or horizontal ST depression of at least 1 mm and duration of at least 1 min, separated from another episode by at least 1 min of no ST depression. The episodes of ischaemia were detected by the computer program and were evaluated by the technicians, who decided to accept or discard the episode, and additionally accepted or changed the

suggested level of ST depression by the computer program. Evaluation of the Holter recordings were completed before follow-up studies and performed by subjects blinded to and without any access to the files of the participants [8].

Endpoints

We defined the endpoint as a combination of all-cause death and/or a myocardial infarction during a median follow-up period of 6.33 (range 0.32–6.88) years.

The information was obtained from validated registries, including the Denmark National Board of Health, National Hospital Discharge Register and National Death Certificate Register; all of which use the International Classification of Diseases (ICD)-10 code and are available in electronic form.

All deaths, hospital admissions and discharges in Denmark are reported to the registries within 2 weeks. Hospital admissions and discharge letters for these patients were additionally studied, to insure that the diagnosis of myocardial infarction was consistent with our criteria, i.e. based on history, typical electrocardiograph (ECG) changes and cardiac enzyme elevation. The diagnosis of acute myocardial infarction (ICD-10: I21–I22) in the National Hospital Registry has been validated and has a sensitivity of 91% and predictive value of 93%. [18]

Ethics

All participants provided written informed consent. The Regional Ethical Committee of Copenhagen and Frederiksberg approved the study. The Helsinki Declaration II was complied with.

Statistical analyses

The SAS statistical software programme (SAS Institute, Cary, NC, USA; version 9.1) and Stata IC/10 (StataCorp, College Station, TX, USA.) were applied for statistical analyses. Univariate associations between impaired fasting glucose and other variables were evaluated by Kruskal–Wallis or χ^2-test as appropriate. Two-tailed tests of significance are reported and *P*-values less than 0.05 are considered statistically significant. Regression analyses (logistic or linear) were performed to evaluate the covariate-adjusted association of the variable of interest. Event-free survival in patients with normal fasting glucose or impaired fasting glucose and silent myocardial ischaemia or no-silent myocardial ischaemia was compared by the method of Kaplan–Meier, and statistical differences were evaluated by means of the log-rank test. Cox proportional hazard models were used to evaluate the risk factor-adjusted associations of impaired fasting glucose and silent myocardial ischaemia with death or acute myocardial infarction, and were presented as hazard ratios by exponentiating the regression coefficients.

The assumption of proportional hazards was assessed by visual judgement of the log-minus-log survival plots. The assumption of linearity for continuous variables in Cox models was assessed by entering the logarithmic or squared transformed variables in models with the variable concerned in continuous form. A significant change in the –2 log-likelihood for any model was considered as a sign of non-linearity, otherwise the linearity assumption was accepted. All variables met the linearity assumption, except cholesterol, that showed a J-form association with combined events but not with cardiac events. The introduction of cholesterol in dichotomized form (above or below the level 4 mmol/l) vs. continuous form in the Cox models did not changed any of the main results. We thus kept the cholesterol value as continuous in all models. High sensitivity C-reactive protein (hs-CRP) was dichotomized at 3 μg/ml according to current guidelines.

Results

The baseline characteristics of the 596 participants of this study are shown in Table 1. Two hundred and-twenty-nine subjects

Table 1 Baseline variables (normally and not normally distributed) between subjects with and without impaired fasting glucose

Baseline variables	Impaired fasting glucose (pre-diabetes) *n* = 229	Normal fasting glucose *n* = 367	*P*-value
Age (year)	64.5 (± 6.9)	64.3 (± 6.7)	0.771
Male, *n* (%)	143 (62.5%)	198 (54%)	0.042
Current smoker	111 (48.5%)	173 (47.1%)	0.75
Systolic blood pressure, mmHg	159.0 (± 25.0)	154.2 (± 24.0)	0.022
Diastolic blood pressure, mmHg	91.8 (± 11.4)	90.2 (± 11.1)	0.089
BMI, kg/m^2	27.3 (± 4.5)	26.1 (± 4.1)	0.0005
Cholesterol, mmol/l	6.1 (± 1.0)	6.0 (± 1.1)	0.58
HDL, mmol/l	1.4 (1.2–1.7)	1.5 (1.2–1.8)	0.0755
Triglycerides, mmol/l	1.3 (1.0–2.0)	1.1 (0.9–1.6)	0.004
High-sensitivity CRP, μg/ml	2.6 (1.5–4.8)	2.3 (1.0–4.2)	0.040
NT-proBNP, pmol/l	6.3 (3.5–11.0)	7.61 (4.0–14.7)	0.027
Silent myocardial ischaemia, yes/no	28 (12.2%)	41 (11.2%)	0.695

Variables are represented as mean (± SD), median (interquartile range) and number (%).
CRP, C-reactive protein; NT-proBNP, N-terminal prohormone brain natriuetic peptide.

(38.4%) had impaired fasting glucose and, as expected, these subjects exhibited higher levels of BMI, systolic blood pressure, plasma triglycerides and hs-CRP compared with those with normal fasting glucose. The prevalence of silent myocardial ischaemia was not greater in subjects with impaired fasting glucose compared with subjects who had normal fasting glucose (12.3 vs. 11.7%, $P = 0.69$).

Follow-up and events

During the follow-up period (median 76 months, interquartile range 74–78 months) 77 combined events were recorded (65 deaths and 12 myocardial infarctions). Subjects with impaired fasting glucose had a higher event rate (41/229) compared with subjects with normal fasting glucose (36/367): hazard ratio 1.89, 95% CI 1.21–2.95, $P = 0.006$ in univariate analysis and hazard ratio 1.68, 95% CI 1.06–2.66, $P = 0.026$ after adjustment for conventional risk factors (smoking, total cholesterol, systolic blood pressure, gender and age). In subjects with silent myocardial ischaemia the event rates were (15/69) compared with individuals without silent myocardial ischaemia (62/527); hazard ratio 1.99, 95% CI 1.13–3.50, $P = 0.017$ in univariate analysis, but when adjusting for risk factors (smoking, total cholesterol, systolic blood pressure, gender and age) the hazard ratio of 1.49 became non-significant (Table 2). Testing for interaction (impaired fasting glucose/silent myocardial ischaemia) showed a hazard ratio of 1.96, although non-significant ($P = 0.27$). Impaired fasting glucose remained as a significant predictor of primary endpoint (hazard ratio 1.77, 95% CI 1.12–2.79, $P = 0.015$), even after further adjustment for potent prognostic biomarkers such as N-terminal prohormone brain natriuetic peptide (NT-proBNP) and hs-CRP.

Combined events were seen in 31 of 326 subjects with normal fasting glucose and no silent myocardial ischaemia (9.5%), five of 41 subjects with normal fasting glucose and silent myocardial ischaemia (12.2%), 31 of 201 subjects with impaired fasting glucose and no silent myocardial ischaemia (15.4%) and 10 of 28 subjects with both impaired fasting glucose and silent myocardial ischaemia (35.7%), respectively, $P = 0.0003$ over strata.

In a Cox univariate regression analysis with no silent myocardial ischaemia and normal fasting glucose subjects as reference, only impaired fasting glucose in combination with silent myocardial ischaemia exhibited increased risk for the combined endpoint of acute myocardial infarction and/or death (hazard ratio 3.98, 95% CI 1.95–8.13, $P < 0.0001$), while subjects with silent myocardial ischaemia and normal fasting glucose, including subjects with impaired fasting glucose and no silent myocardial ischaemia, were not significantly associated with

Table 2 Cox proportional hazard models of impaired fasting glucose, silent myocardial ischaemia, combined impaired fasting glucose and silent myocardial ischaemia in relation to the endpoint acute myocardial infarction and/or death

Analysis of maximum likelihood estimates									
	Univariate			Multivariate (a)*			Multivariate (b)†		
Variable	Hazard ratio	95% hazard ratio confidence limits	*P*-value	Hazard ratio	95% hazard ratio confidence limits	*P*-value	Hazard ratio	95% hazard ratio confidence limits	*P*-value
Impaired fasting glucose‡ ($n = 229$)	1.89	1.21–2.95	0.0055	1.68	1.06–2.66	0.026	1.77	1.12–2.79	0.0153
Silent myocardial infarction ($n = 69$)	1.99	1.13–3.50	0.0168	1.49	0.83–2.68	0.179	—	—	—
Impaired fasting glucose with silent myocardial infarction ($n = 28$)	3.98	1.95–8.13	< 0.0001	2.5	1.20–5.20	0.016	3.15	1.49–6.65	0.0026
Impaired fasting glucose without silent myocardial infarction ($n = 201$)	1.56	0.94–2.57	0.083	1.42	0.85–2.36	0.181	—	—	—
Normal fasting glucose with silent myocardial infarction ($n = 41$)	1.32	0.51–3.40	0.562	1.10	0.42–2.85	0.852	—	—	—
Normal fasting glucose without silent myocardial infarction (reference group, $n = 326$)	1	1	1	1	1	1	1	1	1

*Adjusted for smoking, total cholesterol, systolic blood pressure, gender and age.
†Additional adjustment for NT-proBNP and high-sensitivity CRP, including the adjustment made in (a).
‡Impaired fasting glucose (fasting plasma glucose range 5.6–6.9 mmol/l).
CRP, C-reactive protein; NT-proBNP, N-terminal prohormone brain natriuetic peptide.

increased event rates (Table 2). In a multiple Cox regression analysis, which adjusted for gender, age, smoking habits, blood pressure and total cholesterol, respectively, the association of subjects with combined impaired fasting glucose and silent myocardial ischaemia to death and/or myocardial infarction remained strong (hazard ratio 2.5, 95% CI 1.2–5.2, $P = 0.016$). The corresponding hazard ratio was 3.15 ($P = 0.0026$) by including NT-proBNP and hs-CRP in the model (Table 2).

Kaplan–Meier event curves for the combined endpoint of death and/or myocardial infarction are presented in Fig. 2a and b for the study population with normal fasting glucose vs. impaired fasting glucose ($P = 0.006$) and silent myocardial ischaemia vs. no silent myocardial ischaemia ($P = 0.017$), respectively. Figure 3 presents event curves for the four study populations of interest, i.e. individuals with normal fasting glucose/impaired fasting glucose in combination with no silent myocardial ischaemia/silent myocardial ischaemia, respectively ($P < 0.0001$).

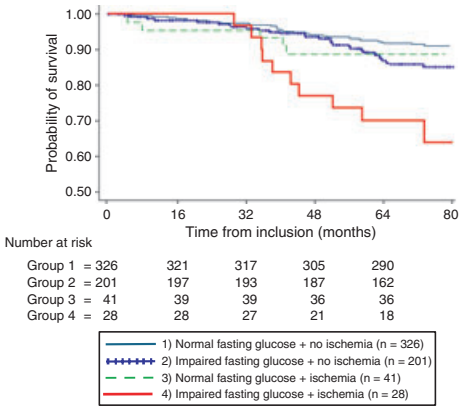

FIGURE 3 Kaplan–Meier survival curves showing survival free of myocardial infarction in the study population with or without impaired fasting glucose (impaired or normal fasting glucose) and with or without silent myocardial ischaemia ($P < 0.0001$).

Discussion

In middle-aged community-dwelling individuals without diabetes, who were apparently cardiovascular healthy and without any known malignancy, a combination of impaired fasting glucose and silent myocardial ischaemia as measured by 48-h Holter monitoring provided a 4-fold increased risk of death and/or myocardial infarction. After correction for covariates identified as the Framingham risk factors of myocardial infarction [19], there remained a residual risk for meeting the combined endpoint of 2.5-fold as compared with persons with a normal fasting glucose and no silent myocardial ischaemia. However, the prevalence of silent myocardial ischaemia was not significantly different between subjects with or without impaired fasting glucose. There is no obvious explanation for this, but it may be attributable to shorter duration of impaired fasting glucose in the population or exclusion of subjects with manifest coronary artery disease or cardiovascular death.

To our knowledge, this is the first study of prevalence and prognostic significance of silent myocardial ischaemia in apparently healthy community-dwelling subjects with pre-diabetes. The fact that impaired fasting glucose per se exhibited prognostic value is in accordance with the results of previous studies, including a meta-analysis of 20 prospective studies, which observed a significant graded relationship between increasing levels of fasting and postprandial glucose concentration and risk of cardiovascular events [20–23]. Further adjustment for hs-CRP and NT-proBNP did not change the results significantly, which indicates that the poor prognosis associated with impaired fasting glucose is beyond the effect of these covariates. It is well known that persons with overt diabetes exhibit an increased risk of cardiovascular morbidity and overall mortality compared with individuals free of diabetes [10].

Silent myocardial ischaemia documented as ST-depression on a Holter monitoring is often an early warning of coronary artery stenosis, and the accuracy of the Holter monitoring is more than 95% specific for myocardial ischaemia [24]. The prevalence of silent myocardial ischaemia is dependent of many factors, i.e. age, burden of the risk factors in the population

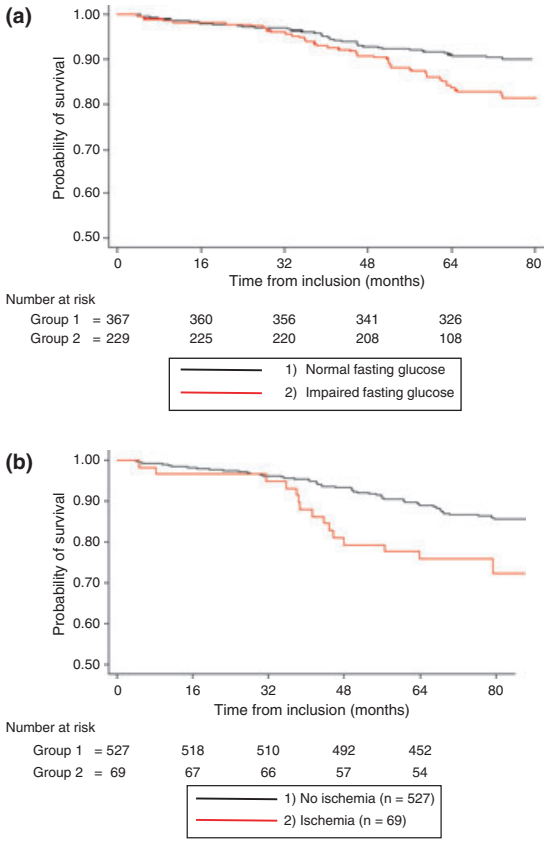

FIGURE 2 Kaplan–Meier survival curves showing survival free of myocardial infarction in the study population (a) with or without impaired fasting glucose ($P = 0.006$) and (b) with or without silent myocardial infarction ($P = 0.0147$). Normal fasting plasma glucose < 5.6 mmol/l; impaired fasting glucose 5.6–6.9 mmol/l.

studied, and inclusion or exclusion of the subjects with known coronary artery disease from the population studied. In an unselected population of 68-year-old men, Hedblad *et al.* [7] showed that asymptomatic ST-depression was a frequent finding, with a prevalence of 24%. In a subpopulation among these men, who were without any history of coronary heart disease, silent myocardial ischaemia was associated with a hazard ratio of 4.4 of a subsequent cardiac event. The Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects (DIAD) study [16] reported that more than one in five asymptomatic patients with Type 2 diabetes, aged 50–75 years, exhibited silent myocardial ischaemia. Cosson *et al.* [25] showed that, among subjects with diabetes with silent myocardial ischaemia, 48% had coronary stenosis (> 70%) on coronary angiography.

Among individuals without apparent heart disease, the predictive value of silent myocardial ischaemia as detected by Holter monitoring has not been studied properly. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study, which studied asymptomatic and mildly symptomatic individuals, showed that 61% of the subjects with significant heart disease had a positive Holter test and only 47% of these subjects had a positive stress myocardial perfusion test (SPECT). In addition, comparative studies demonstrated that silent myocardial ischaemia as detected by Holter monitoring was a significant predictor of an adverse outcome while ST-segment depression on exercise testing did not predict an adverse outcome [26,27]. Therefore, Holter testing may not be inferior to exercise testing when it comes to examining for ischaemia associated with an adverse outcome. Actually, some authors consider Holter recordings as a superior method for evaluating of ischaemia compared with exercise testing [28,29]. However, exercise testing is much better studied and current guidelines recommend exercise testing for detection of ischaemia. This study is not aimed to compare silent myocardial ischaemia detected by each test, but to focus on the pathophysiological phenomenon and the prospect of using it in clinical practice. Because of the relatively low prevalence of silent myocardial ischaemia in these subjects, screening is not recommended in unselected populations. Detecting a subpopulation with a higher prevalence of silent myocardial ischaemia may be a key issue if this should be implemented in screening protocols. Targeted screening for silent myocardial ischaemia in selected populations may be recommended after proper evaluation of its expected sensitivity and positive predictive value for relevant endpoints, which in the present study was shown to be low.

The present study used the classification of impaired fasting glucose suggested by The Expert Committee [30] and, even although we did not perform coronary angiography, our results support the hypothesis that the combination of impaired fasting glucose and silent myocardial ischaemia were associated with an increase in morbidity and mortality. In fact, the same association was observed when we used World Health Organization [31] classification and diagnostic criteria of pre-diabetes defining impaired fasting glucose as fasting plasma glucose 6.1–6.9 mmol/l (data not shown).

These present findings must be reproduced before a firm conclusion can be drawn on the clinical significance of an increased risk of adverse endpoints in those subjects with combined impaired fasting glucose and silent myocardial infarction. The study exhibits additional limitations, i.e. the numbers of events in the group of interest were rather few, which limit the statistical power on endpoints. The data on glucose tolerance were derived from fasting plasma glucose only, thus the lack of a standard oral glucose challenge may limit the interpretation of the association between glucose tolerance and silent myocardial ischaemia. As we used all-cause death as part of the endpoint, it is not possible to determine whether cardiovascular disease mortality is an important contributor. As not all eligible subjects were able to or willing to participate, and risk factors were self reported, selection bias to some extent cannot be excluded. Application of these data on other ethnic groups and subjects of younger age should be carried out with caution. This study is observational, and therefore conclusions on cause and effect cannot be drawn. Among the strengths of the study is the high precision of the diagnosis acute myocardial infarction in Denmark of more than 90% and almost all patients with this diagnosis are admitted to a hospital [10].

The study observed a 2.5-fold increased risk of myocardial infarction and/or death after adjustment for conventional risk factors of cardiovascular disease during 6.3 years of follow-up in middle-aged and elderly individuals, who displayed impaired fasting glucose and silent myocardial ischaemia with no apparent heart disease compared with a control group with normal fasting glucose and no silent myocardial ischaemia. The result may emphasize the need for further examination for silent ischaemia in the subjects without diabetes with elevated plasma glucose, which potentially could help to identify individuals at high risk

Competing interests

Nothing to declare.

Acknowledgement

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