Women, diabetes and coronary heart disease

Annika Dotevall

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ABSTRACT

Aims: The aim of the present study was to explore the reason why women with diabetes lose the female protection against MI, by investigating cardiovascular risk factors, markers of inflammation, early predictors for future development of diabetes and clinical manifestations in diabetes and coronary heart disease.

Subjects and methods: Women with (n=29), and without diabetes (DM) (n=64), hospitalised with a smyocardial infarction (MI) 1994-96, were compared with DM-women without MI (n=46) and healthy controls (n=125). They were invited to a screening examination with questionnaires, physical examination and blood sampling *(Paper I)*. Furthermore, titers of antibodies to malondialdehyde-treated LDL (oxLDL), and CRP levels, as a measure of the immune response and inflammation, were assessed. *(Paper II)*. In addition, 1351 women, aged 39-65 years, without prior DM or CVD, took part in a screening investigation in 1979-81 with questionnaires, physical examination and blood sampling. Development of DM up to 1998 was identified at a second screening 1997-98 (P*aper III*). Finally, we investigated the influence of DM on clinical presentation, in-hospital course, and short-term prognosis in 6488 men (21.2 % DM) and 2809 women (28.7% DM) $\leq$ 80 years old who were prospectively enrolled in the Euro Heart Survey of Acute Coronary Syndromes (ACS) *(Paper IV)*.

Results: Women with prior MI had, compared with DM women without MI, significantly higher waist/hip ratio, and very high s-triglycerides (TG) and low HDL-cholesterol levels. They also had higher p-fibrinogen, were smokers and lived a sedentary life to a higher degree than the other women. The women with DM and/or MI had higher IgG and lower IgM titers of antibodies against oxLDL and higher CRP levels than the healthy controls. S-TG, overweight, high blood pressure (BP) and low physical activity significantly increased the risk of future diabetes. Even slightly elevated s-TG resulted in a considerably enhanced risk of DM, which was independent of the other factors. Women with DM and ACS were more likely to present with ST-elevation ACS, to develop Q-wave MI, and had higher mortality than non-DM women, whereas the differences were smaller in men. The interaction between sex and DM was significant.

Conclusions: Women with DM who have manifested a MI carry a very substantial CVD risk factor burden. A pronounced inflammation and differentiated immune response against modified LDL might result in a more aggressive atherosclerotic process in women with DM and/or MI. Even slightly elevated TG levels and moderately increased BP and overweigt have a strong influence on DM risk, independent of other factors. Women with ACS are more likely to with ST-elevation ACS, develop Q-wave MI, and have worse prognosis than non-DM women, whereas the differences in men are less pronounced. The results underscore the importance of implementing evidence based primary and secondary preventive measures. They also suggest a differential effect of diabetes on the pathophysiology of ACS based on the patient's sex and emphasize the importance of analyzing men and women with DM separately.

Key words: diabetes mellitus, women, myocardial infarction, risk factors, autoantibodies, oxidized LDL, triglycerides, WHR, BMI, HDL-cholesterol, ACS

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Conclusions: Women with DM who have manifested a MI carry a very substantial CVD risk factor burden. A pronounced inflammation and differentiated immune response against modified LDL might result in a more aggressive atherosclerotic process in women with DM and/or MI. Even slightly elevated TG levels and moderately increased BP and overweigt have a strong influence on DM risk, independent of other factors. Women with ACS are more likely to with ST-elevation ACS, develop Q-wave MI, and have worse prognosis than non-DM women, whereas the differences in men are less pronounced. The results underscore the importance of implementing evidence based primary and secondary preventive measures. They also suggest a differential effect of diabetes on the pathophysiology of ACS based on the patient's sex and emphasize the importance of analyzing men and women with DM separately.

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CONTENTS

ABBREVIATIONS

ACS	acute coronary syndrome
ADA	American Diabetes Association
ASA	acetylic salicylic acid (aspirin)
AGE	advanced glycosylation end products
AMI	acute myocardial infarction
APO-B100	apolipoprotein B 100
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DM	diabetes mellitus
DBP	diastolic blood pressure
ECG	electrocardiogram
EHS	Euro Heart Survey
ELISA	enzymelinked immunoadsorbent assay
GLM	General Linear Model
HbA_{1c}	glycosylated haemoglobin A_{1c}
HDL-cholesterol	high-density lipoprotein cholesterol
HR	hazards ratio
ICD	The International Statistical Classification of Diseases and Related Health Problems
Ig	immunoglobulin
IGT	impaired glucose tolerance
LDL-cholesterol	low-density lipoprotein cholesterol
LPL	lipoprotein lipase
LVEF	left ventricular ejection fraction
MDA-LDL	malondialdehyde-LDL
MI	myocardial infarction
MONICA	MONItoring trends and determinants in CArdiovascular disease
OGTT	oral glucose tolerance test
OR	odds ratio
OxLDL	oxidized LDL-cholesterol
PCI	percutaneous coronary intervention
SBP	systolic blood pressure
SD	standard deviation
TG	triglycerides
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World health organization
WHR	waist/hip ratio

INTRODUCTION

Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from a defect insulin secretion, impaired insulin action or both. Cardiovascular disease (CVD) is the greatest single cause of morbidity and mortality associated with DM (Joron 1986, Panzram 1987, Haffner 1998, Turner 1998, Laing 2003).

Diabetes is classified into two major types with different pathophysiology. Type 1 diabetes is usually caused by autoimmune destruction of the insulin-producing beta cells of the pancreas in genetically susceptible persons. The process eventually results in absolute insulin deficiency and need for exogenous insulin for survival. Type 2 diabetes is a multifactorial disease resulting from a combination of insulin resistance and relative insulin deficiency. It is frequently a part of the metabolic syndrome, which also includes central obesity, hypertension, and hyperlipidemia (Table 1) (Alberti 1998). The typical clinical manifestations of diabetes are similar in both types, with pronounced thirst, excessive drinking, large urine volumes and fatigue. However, it is not unusual for type 2 DM to develop slowly, with few symptoms, so that a patient may have been diabetic several years before the diagnosis is established.

Table 1. The metabolic syndrome defined by the US National Cholesterol Education Program Expert Panel 2001.

In clinical practice, the diagnosis of the metabolic syndrome is made when three or more of the following features are present:

Waist circumference	>102 cm in men >88 cm in women
s-triglycerides	≥1.7 mmol/l
HDL-cholesterol	<1.0 mmol/l in men <1.3 mmol/l in women
Blood pressure	≥130/80 mmHg
Plasma glucose	≥6.1 mmol/l

Although type 1 DM is most common in children, adolescents, and younger adults, there is no upper age limit. Type 2 DM is usually diagnosed in adults, but may appear also in younger subjects. In addition, genetic defects in insulin production may result in a syndrome similar to type 2 DM that occurs in young people. Definition and classification of diabetes have been extensively described in reports from the World Health Organization, WHO (Alberti 1998) and American Diabetes Association ADA (Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997).

The prevalence of diabetes worldwide was estimated to be 2.8-4.2 % in 2000, with an expected increase to 4.4-5.4 % in 2030 (King 1998, Wild 2004). However, prevalence figures vary widely between different parts of the world, ranging between 1 and 18% (King 1998, Wild 2004). In the Nordic countries the estimated prevalence of diabetes is reported to be 2-6 % (Andersson 1991, Tuomilehto1991, Larsson 1995, Vilbergsson 1997, Lidfeldt 2001, Eliasson 2002). Whereas type 1 diabetes only constitutes 5 to 10%, type 2 diabetes comprises the great majority of the diabetic population. With increasing rates of obesity and concomitant type 2 diabetes, the total number of diabetic subjects worldwide is estimated to be more than 350 million in the year 2030 (Wild 2004).

Acute coronary syndromes

Coronary thrombi develop on ruptured atherosclerotic plaques built up by a lipid-rich core with a thin fibrous cap. However, not all plaques are lipid-rich, and thrombi may also develop on non-ruptured plaques (Naghavi 2003). Acute manifestations of coronary heart disease, or acute coronary syndromes (ACS), comprise a range of clinical conditions, from milder forms, such as unstable angina, to myocardial infarction (MI) without ST-elevation and MI with ST-segment elevation. Pathophysiologically, patients with ST-elevation who progress to Q-wave MI are characterized by occlusive thrombi in the vast majority of cases (deWood 1983), whereas total occlusion is infrequently observed in the early hours of non-Q-wave MI (deWood 1986). Among patients with acute MI, those who present with ST elevation develop larger infarctions, have more in-hospital complications, and have higher short-term mortality than patients without ST elevation (Yusuf 1984).

In studies of patients with acute MI or sudden coronary death, the lipid rich plaques prone to rupture were more common in men, whereas women more often seemed to develop thrombi on superficial erosions on plaques rich in smooth muscle cells and proteoglycans (Farb 1996, Arbustini 1999). In

women plaque ruptures seemed to be associated with age (Burke 2001) and serum cholesterol (Burke 1998), whereas eroded plaques with thrombi were associated with smoking (Burke 1998). In a Norwegian population study of 6000 men and women, the prevalence of large, lipid-rich plaques was higher in men than in women (Joakimsen 1999). Moreover, the presence of diabetes increased the likelihood of developing lipid rich atherosclerotic lesions (Moreno 2000).

Furthermore, angiographic studies revealed a more severe and diffuse coronary atherosclerosis in patients with diabetes, especially in women, that was not explained by established CVD risk factors (Natali 2000, Pajunen 2000). This suggests that plaque morphology might differ in women compared with men, and in diabetic compared with non-diabetic subjects, and that different pathophysiologal processes may be involved in ACS (Arbustini 1999).

In contrast to men, women with ACS are older (Kudenchuk 1996, Hochman 1997, Maynard 1997, Hochman 1999, Hanratty 2000), have more hypertension (Kudenchuk 1996, Hochman 1997, Maynard 1997, Hochman 1999, Chua 2000, Hanratty 2000) and congestive heart failure (Kudenchuk 1996, Maynard 1997, Hochman 1999), but are less often smokers than men (Hochman 1999, Hochman 1997, Chua 2000, Hanratty 2000). Previous studies have shown that the electrocardiographic changes characteristic of MI are less pronounced in women than in men (Hochman 1999, Lundberg 2002). Furthermore, women less often present with ST elevation (Lundberg 1997, Hochman 1999, Vaccarino 1999), but more often with unstable angina (UAP) compared to men (Hochman 1999).

Prognosis after an MI has been described to be worse in women than in men (Greenland 1991, Kudenchuk 1996, Maynard 1997, Hochman 1999, Hanratty 2000, Rosengren 2001), mostly because women are older and have more co-morbidity. In addition, this difference seems to be present only in younger patients (Johansson 1984, Vaccarino 1999, Rosengren 2001) and is partly due to the fact that men with MI tend to die early outside hospital (Rosengren 2001, Macintyre 2001). According to Framingham data, women are more likely to manifest coronary heart disease as unstable angina, whereas men develop manifest MI to a higher degree than women (Lerner 1986).

Diabetes mellitus and acute coronary syndromes

In many studies diabetes mellitus (DM) emerges as an important risk factor influencing clinical presentation, course and prognosis of ACS. While the

prevalence of diabetes is 3 to 6% in the general Swedish population (Andersson 1991, Larsson 1995, Lidfeldt 2001, Eliasson 2002), 20 to 25% of patients with myocardial infarction have known diabetes (Abbud 1995, Lundberg 1997, Löwel 2000, Malmberg 2000, Tenerz 2001). An even greater proportion of the MI patients have previously undiagnosed diabetes or impaired glucose tolerance when arriving in the coronary care unit (Norhammar 2002). Indeed, recent studies have shown that only about a third of the patients with acute MI have normal glucose tolerance (Norhammar 2002).

Diabetes is associated with markedly increased risk of myocardial infarction (MI) and cardiovascular mortality in diabetic compared with non-diabetic subjects (Lapidus 1985, Ulvenstam 1985, Krolewski 1987, Abbott 1988, Barrett-Connor 1991, Manson 1991, Lehto 1994, Abbud 1995, Hanefeld 1996, Herlitz 1996, Chun 1997, Mukamal 1997, Adlerberth 1998, Haffner 1998, Miettinen 1998, Vilbergsson 1998, Lee, 2000, Hu 2002, Kanaya 2002, Löwel 2000, Malmberg 2000, Yusuf 2004). In addition, women with diabetes seem to be more vulnerable than men with diabetes (Abbott 1988, Barrett-Connor 1991, Lehto 1994, Chun 1997, Benderly 1997, Mukamal 1997, Miettinen 1998, Lee, 2000, Malmberg 2000, Yusuf 2004) although findings have not been entirely consistent (Abbud 1995, Krolewski 1987, Vilbergsson 1998, Löwel 2000). However, a recent meta-analysis demonstrated this to be due to more risk factors in diabetic women (Kanaya 2002).

Whereas mortality from coronary heart disease has declined in the general Western population during the last decades, the pattern has not been consistent in the diabetic population. Among diabetic men a smaller reduction (Gu 1999), or no decrease at all (Chun 1997), was reported, while in women with diabetes coronary mortality was unchanged (Chun 1997) or even increased (Gu 1999). Accordingly, the difference in coronary heart disease (CHD) morbidity and mortality between diabetic and non-diabetic individuals seems to have increased more in women than in men.

Patients with diabetes are often characterized by a worse cardiovascular risk factor pattern, including obesity, high blood pressure (BP) and disturbed lipid levels. However, few studies have compared risk factors in men and women with diabetes or investigated to what extent the major CHD risk factors contribute to the risk of MI in women with diabetes (Barrett-Connor 1991).

Acute CHD do not always manifest with typical symptoms. Diabetic patients often present with less chest pain at admission to hospital (Culic

1992, Gustafsson 2000, Vaccarino 2000), and similar or lower rates of ST-elevation (Gustafsson 2000, Vaccarino 2000, McGuire 2000), compared with non-DM patients. In addition the proportion of patients hospitalised with unstable angina has increased and now form an important subset of patients with ACS (McGovern 2001). Studies of women, diabetes and CHD have, so far, mostly focused on acute MI. Few studies have analyzed men and women with diabetes across the whole range of ACS.

The immune system, atherosclerosis and inflammation

It is well known that patients with diabetes have more atherosclerosis than non-diabetic subjects. Atherosclerosis is a process in which inflammation plays an important role (Libby 2002). Because lipids are insoluble in water, they can only circulate if they are bound in lipoprotein complexes. These consist of a central core of non-polar lipids, primarily triglycerides and cholesteryl esters, and a surface built up of a phospholipid monolayer including free cholesterol and apoprotein molecules. Low-density-lipoprotein- (LDL) cholesterol is the main cholesterol-bearing lipoprotein, with apoprotein B-100 as the characteristic feature at the surface (Howard 1993). Circulating LDL-cholesterol can enter the vessel wall, where it may become oxidized. Oxidized LDL (oxLDL) has been suggested to be a key antigen in the development of atherosclerosis by stimulating monocytes to infiltrate into the vessel intima; these then differentiate into macrophages, which produce cytokines, oxygen radicals and heat shock proteins, and form foam cells (Hansson 1997).

Oxidation of LDL-cholesterol involves oxidation of polyunsaturated fatty acids in the lipoprotein core, with formation of highly reactive breakdown products such as malondialdehyde, MDA (Esterbauer 1990). MDA may form covalent adducts with lysine and histidine residues in apo-B100, making them highly immunogenic (Palinski 2000). Similarly immunogenic so-called neoepitopes may result from oxidation by other agents, such as cupper ions, which, besides MDA, are widely used in laboratory situations. Immunogenic epitopes may also result from non-enzymatic glycation of LDL (Palinski 2000).

Hyperglycemia increases non-enzymatic glycosylation, whereby glucose molecules bind to amino groups on different structures, forming advanced glycosylation end products (AGE). Also, hyperglycemia enhances free radical formation by autooxidation. Furthermore, glucosylation of vascular structural proteins may alter the characteristics of the vessel wall itself and influence its interaction with circulating plasma constituents. (Lyons 1993).

Modified lipoproteins, especially oxLDL, have been the focus of much research in the last decade (Hulthe 2004). Several studies support the hypothesis that oxLDL is involved in the development of atherosclerosis in humans. However, it is not well established whether the immune response is predominantly pro- or atherogenic in man. Immunization of animals with oxLDL seems to protect against atherosclerosis (Hulthe 2004). Even so, unspecific antibodies have been shown to reduce atherosclerosis in animal models, making the interpretation of these results difficult.

Antibodies against oxLDL have been demonstrated in human and rabbit atherosclerotic lesions (Ylä-Herttuala 1994). Immunization of apoE knock-out mice with homologous plaque homogenates or MDA-modified LDL resulted in reduced development of atherosclerotic lesions (Zhou 2001). Furthermore, increased levels of antibodies against oxLDL were predictive of MI (Puurunen 1994) and progression of carotid atherosclerosis (Salonen 1992) in men. However, in other studies no association with cardiovascular events (Uusitupa 1996), carotid intima-media thickness (Uusitupa 1996, Hulthe 1998) or the extent of coronary atherosclerosis (van de Vijver 1996) was found.

The demonstration of antibodies against oxLDL indicates that lipid peroxidation may occur in vivo. Lipid peroxidation may be increased in diabetes, as hyperglycaemia influences the production of free radicals by auto-oxidation of glucose and the formation of advanced glycation end-products and superoxide radicals (Oranje 1999). Previous studies have reported elevated levels of antibodies against modified LDL in diabetic compared with non-diabetic subjects (Bellomo 1995, Festa 1998, Leinonen 1998, Mäkimattila 1999), but studies have not been consistent (Uusitupa 1996, Lopes-Virella 1999). Antibodies against modified LDL were recently reported to be elevated in diabetic subjects with macrovascular disease, but not in diabetic subjects without macrovascular disease or in healthy controls (Hsu 2002).

C-reactive protein (CRP) is considered to be a sensitive marker for systemic inflammation. Its concentration is mainly determined by the liver in response to cellular cytokines (Pepys 1995). CRP is associated with several CVD risk factors (Mendall 1996, Rohde 1999) and is also an independent risk factor for diabetes (Pradhan 2001, Freeman 2002, Hu 2004), stroke (Rost 2001), and cardiovascular disease in both men and women (Ridker 1997, Ridker 1998). Furthermore, Ridker reported CRP to be a stronger risk factor than LDL-cholesterol for first cardiovascular events in women (Ridker 2002).

Risk factors for the development of diabetes

With increasing incidence and prevalence of type 2 diabetes throughout the world (King 1998, Wild 2004), finding strategies to prevent diabetes and its complications has developed into a major issue, and perhaps even more in women than in men, because they seem more vulnerable to the devastating effects of diabetes (Barrett-Connor 1991, Miettinen 1998, Gu 1999, Malmberg 2000). Previous prospective studies of different populations have reported several factors to be important for the subsequent development of diabetes, such as increased body mass index (BMI) (Medalie 1975, Balkau 1985, Ohlson 1988, Lundgren 1989, McPhillips 1990, Charles 1991, Mykkänen 1993, Perry 1995, Haffner 1997, Carey 1997), high waist/hip ratio (WHR) (Ohlson 1988, Lundgren 1989, Mykkänen 1993), high blood pressure (Ohlson 1988, McPhillips 1990, Mykkänen 1993, Haffner 1997), an unhealthy lifestyle (Hu 2001), dyslipidemia (Balkau 1985, McPhillips 1990, Mykkänen 1993, Perry 1995, Haffner 1997), insulin resistance (Lillioja 1993, Haffner 1997), and high glucose- and insulin levels in the fasting state and/or after an oral glucose tolerance test (Balkau 1985, Ohlson 1988, Lillioja 1993, McPhillips 1990, Charles 1991, Mykkänen 1993).

More than half of these studies did not give further details on, or did not even include, women. Studies which did assess women were a study of middle-aged Mexican-Americans and non-Hispanic whites from Texas (Haffner 1997), two studies of elderly subjects in California (McPhillips 1990) and Finland (Mykkänen 1993), one earlier study from Sweden (Lundgren 1989) and the American Nurses Health Study (Carey 1997, Hu 2001). However, the 18-year follow-up of the present study of risk factors for incident diabetes is the longest described so far.

GENERAL AIM

To explore the reason why women with diabetes lose the female protection against MI, by investigating cardiovascular risk factors, markers of inflammation, early predictors for future development of diabetes and clinical manifestations in diabetes and coronary heart disease.

SPECIFIC AIMS

- To estimate the cardiovascular risk factor burden in women with diabetes, MI or both compared with healthy women, and to investigate to what extent the differences in risk factors might explain the increased risk of MI and complication rate in women with diabetes. *(Paper I)*

- To explore the association between the immune response, as measured by antibody titers to malondialdehyde-treated LDL, CRP, a marker of inflammation, and diabetes mellitus and MI in women. *(Paper II)*

- To investigate risk factors for the development of diabetes mellitus in middle-aged women. *(Paper III)*

- To investigate the influence of diabetes mellitus on clinical presentation, in-hospital complications and outcome in women and men with acute coronary syndromes (ACS). *(Paper IV)*

SUBJECTS AND METHODS

The Göteborg myocardial infarction register

The Göteborg MI Register started in 1968 with the aim to register all events of MI and deaths from CHD in subjects below 65 years of age in the city (Elmfeldt 1975). Specially trained personnel scrutinized patient and diagnosis lists of the emergency department, and the medical wards, several times every week. Patients with suspected or obvious MI were recorded and followed up until a definite diagnosis was verified or refuted. An MI was considered to have occurred when at least two of the three criteria chest pain, enzyme leakage and typical ECG changes were fulfilled. For the years 1988-1998 enzyme changes defining MI were serial serum aspartate-aminotransferase (ASAT) >0.7 μkat/l, serial creatine kinase (CK) >3.3 μkat/l or serial creatine-kinase MB subunit mass (CKMB) >15 μg/l. The methods of registration and diagnosis of MI are described in detail elsewhere (Wilhelmsen 1997a). A validation of the register showed that less than 10% of the surviving patients with a clinical MI were missed by the registration procedure (Elmfeldt 1975). The register continued to run until 1996.

Study I

MI-women with and without diabetes

All surviving women below the age of 65 years, who had been hospitalised with an MI according to the Göteborg MI Register in any of the two Göteborg hospitals in 1994 to 1996, were invited to participate in the study. The prevalence of diabetes was not known before examination. As there turned out to be only 19 eligible women with both diabetes and MI in the original cohort, diabetic women hospitalised due to MI in 1993 and diabetic women hospitalised with MI at the two neighbouring hospitals during the same time interval were also invited. Table 2 shows numbers of invited and participating women. In all, 29 women with diabetes and MI and 64 non-diabetic women with MI participated in the study. The time interval between the MI and examination varied between 2 and 42 months.

Control women with and without diabetes

In 1985, 1990 and 1995 random samples of the Göteborg population were examined within the framework of the WHO-MONICA project, a multinational study initiated to register risk factors and trends in the incidence of cardiovascular disease in the general population (Wilhelmsen 1997b). In each of these screenings 375 (75%), 432 (72%), and 470 (67%), respectively, of the originally invited women, 45 - 64 years of age were

examined. Women with diabetes participating in any of the three MONICA-screenings (n=28) were included in the study. Together with diabetic women non-consecutively enrolled from the hospital register of outpatients (n=16), and from a neighbouring general practitioner (n=2), they constituted the diabetic controls (n=46). A random fourth of the women invited to the 1995 MONICA-screening were selected to constitute the group of healthy controls (n=193), of whom 125 (64.8%) accepted to participate. None of the control women had a history of previous MI or clinical signs of ischaemic heart disease, and all had a normal resting ECG.

The participants arrived to the examination after an overnight fast. Present and past health status, smoking habits and medication were recorded by way of questionnaires. Height, weight and circumference of the waist and hip were measured with the subject standing, in light clothing, to allow calculation of body mass index and waist to hip ratio. Blood pressure was measured in the sitting position twice, after at least 5 minutes rest, to the nearest 2 mmHg. Venous blood samples were drawn for analyses of haemoglobin (HbA_{1c}), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG); all analyses were performed the same day. Further blood samples were collected and serum was kept frozen in -70°C. Glycated haemoglobin (HbA_{1c}) was analysed with a HPLC method, normal range 3.6 to 5.3%. Fibrinogen was analysed according to the Clauss method (Clauss -57).

Table 2. Numbers of participating women with diabetes and MI (DM+MI), MI but not diabetes (MI not DM), diabetes but not MI (DM not MI) and healthy controls. (*Paper I*)

	DM+MI	DM not MI	MI not DM	controls	total
Eligible, n	19	7	97	193	376
Died before screening, n(%)	3(15.8)		14(14.4)		17
Refused, n	2	21	19	68	110
Non-consecutively identified, n	15				15
Included, n	29	46	64	125	264
Questionnaire only, n	6	2	10	5	23
Examined, n(%)	23(59.0)	44(65.7)	54(55.7)	120(62.2)	241(60.9)

Study II

The participants of Study II constitute a subsample of the cohort in Study I, because blood samples were not available in all. Altogether, 18 women with diabetes and MI, 46 non-diabetic women with MI, 35 diabetic women without MI and 70 healthy controls were included in Study II. IgM and IgG antibodies against MDA-LDL were analysed with a solid phase ELISA technique (Hulthe 1998). CRP was determined with a highly sensitive immunometric assay (Oy Medix Biochemia AB, Kauniainen, Finland), modified at the Wallenberg laboratory, Sahlgrenska University Hospital in Göteborg.

Study III

A random population sample of 1351 women, aged 39-64 years, without previous CVD or diabetes, participated 1979-81 in a screening investigation with questionnaires, a physical examination and blood sampling. The questionnaires included questions about present and past health status, smoking habits, physical activity, education, alcohol intake and menopausal state. The participants were examined in the morning after an overnight fast. Weight and height were measured and BMI was calculated. Blood pressure was measured after 5 minutes rest with the subject seated. Serum cholesterol concentrations were measured according to Cramér (Cramér 1959) and concentrations of serum triglycerides according to Carlsson (Carlsson 1959). There were no data on blood-glucose, HDL- or LDL-cholesterol from the first screening.

Follow-up procedures

By 31 December, 1997, 150 of the initially participating women had died. Among the 1201 surviving women, 875 (73%) returned for a second examination between 1997 and 1998, 18 years after the first screening. The procedures for the second screening were similar to those of the first examination.

Of the women returning for a second examination, 41 had been diagnosed with diabetes during the intervening period. Five more women were diagnosed at the examination, presenting with a fasting plasma glucose level of $\geq$ 8.0 mmol/l, and confirmed at clinical follow-up. In addition, the Swedish national register on deaths due to specific causes from 1980 to 1998 and the Swedish hospital discharge register were matched against a computer file of the women in the study to identify diabetes among those who did not participate in the second examination. In this manner we identified diabetes in another 27 women with a principal or secondary diagnosis of diabetes during follow-up. Twenty of these women were still

alive but did not take part in the second screening, and seven women had died. Altogether, among the 1351 women participating in the initial screening, 73 women (5.4%) were diagnosed with diabetes during the follow-up period up to 1999 (Fig. 1).

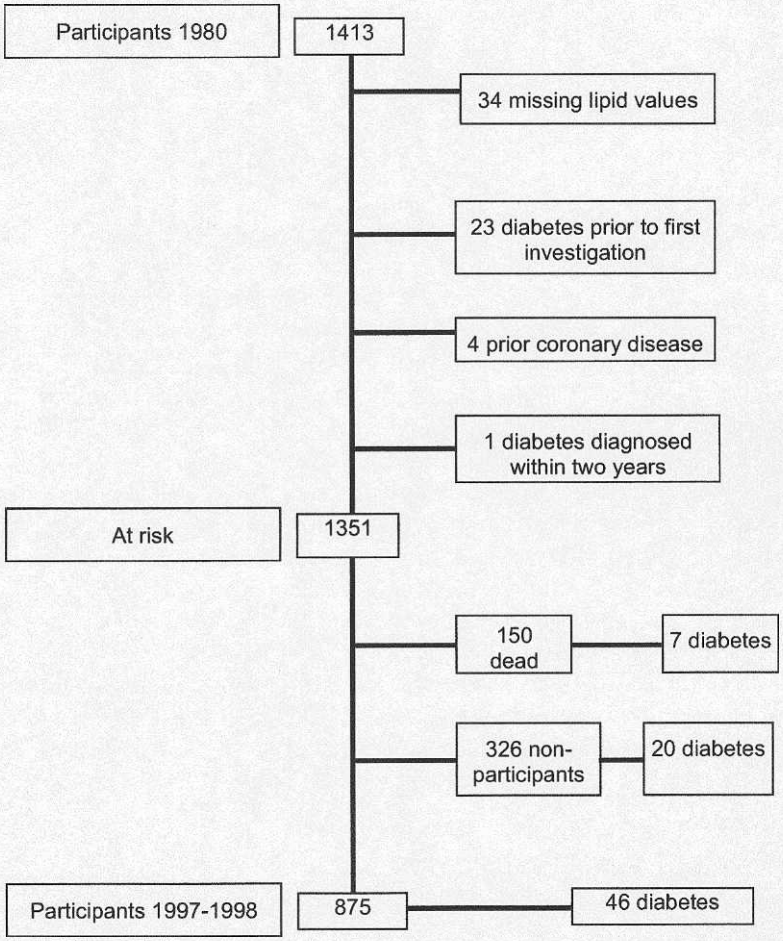

Figure 1. Participants in the study of risk factors for incident diabetes in middle aged women. (*Paper III*)

Study IV

Onehundred-three hospitals in 25 countries in Europe and the Mediterranean basin participated in this study of consecutive patients presenting with symptoms compatible with ACS. All patients were categorised according to the primary diagnosis by the attending physician, based on the initial electrocardiographic pattern, i.e. ACS with ST-elevation, ACS without ST-elevation or ACS with an undetermined electrocardiographic pattern. When the definite diagnosis of unstable angina or MI was confirmed, the patient was included in the study and a full case report form was filled out.

The case report form comprised data on demographics, previous history and cardiovascular risk factors, presenting symptoms, electrocardiographic findings, medical therapy, coronary angiography, evaluation of left ventricular function, reperfusion and intervention therapy, in-hospital complications, discharge status and 30-day follow-up status. The attending physician classified the discharge diagnosis as Q-wave MI, non- Q-wave MI, or unstable angina pectoris. The enrolment period ran between 4 September, 2000 and 31 May, 2001.

In all, 10484 patients were included. For the purpose of the present study, patients aged more than 80 years (n=1187) were excluded, as elderly patients often have concomitant disease not detailed in the register, leaving 9297 patients who form the study population of this analysis. Diabetes was present in 2182 (23.5 %) subjects, of whom 806 (36.9 %) were women. The prevalence of diabetes was 21.1 % in men and 28.7 % in women (Fig 2).

Definition of diabetes

Study I and II

Diabetes was defined as an affirmative response to the question "Did a doctor tell you that you have diabetes?" and/or antidiabetic treatment with diet, oral agents and/or insulin. No systematic testing for previously unknown diabetes was performed. Age <35 years at diagnosis or starting continuous insulin treatment within one year of diagnosis was defined as type 1 diabetes, all other were defined as type 2. However, due to the small number of women with diabetes and MI, type 1 and type 2 diabetes were not separated in the analyses.

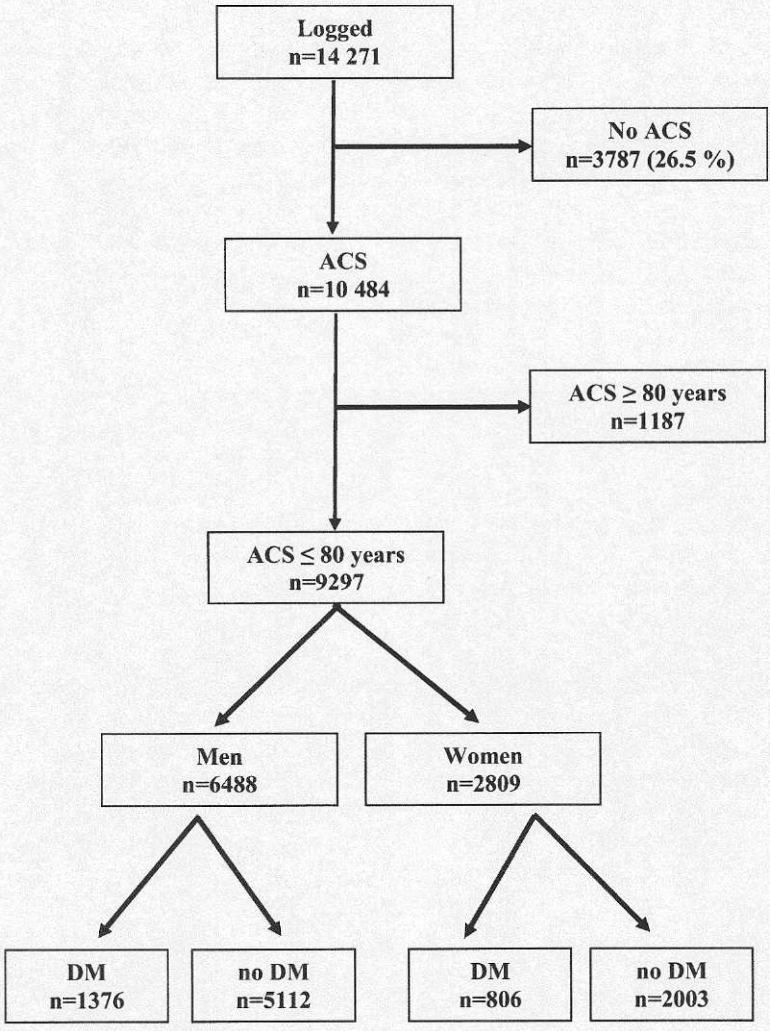

Figure 2. Participants of the Euro heart Survey ACS. *(Paper IV)*

Study III

Women were defined as diabetic if they had been diagnosed by a doctor during follow-up, or if they presented with a fasting plasma glucose level of $\geq$ 8.0 mmol/l at the second examination, with diabetes confirmed at a clinical follow-up. In non-participants of the second screening, those were defined as diabetic who were registered with a principal or secondary diagnosis of diabetes [ICD-8 and ICD-9 code of 250 and ICD-10 code E11 (from 1997)] in the Swedish hospital discharge register, or the Swedish national register on deaths due to specific causes from 1980 to 1998.

Only diabetes diagnosed more than two years after the first screening was defined as new onset diabetes. Since the women who developed diabetes were middle-aged at diagnosis, they were assumed to have type 2 diabetes.

Study IV

A participant was defined as having diabetes if he or she reported previously diagnosed diabetes, or if diabetes was stated in previous or present medical charts and documents. Furthermore, patients who were not reporting diabetes at admission, but were discharged with oral hypoglycaemic agents or insulin, were presumed to have had diabetes also before the index event. Biochemical confirmation of diabetes status or any systematic testing for previously undiagnosed diabetes was not performed in the study.

STATISTICAL PROCEDURES

All analyses were performed with SAS statistical software, version, 6.12 in Study II and version 8e in the other studies. Means and proportions were calculated with standard methods.

Study I

The differences between groups with respect to continuous variables were tested for statistical significance using the general linear model procedure (GLM). In the analyses of anthropometric data, lipids and hormones, only comparisons between non-diabetic women with MI and the healthy controls were age adjusted, because the mean age was similar in diabetic women with and without MI. Multiple logistic regression models were used to assess the independent association of risk factors, with MI as the dependent variable, in women with and without diabetes separately. Only diabetic women with MI who were examined (=23) were included in the multivariate analysis. Furthermore, smokers and ex-smokers were combined into one category in these models because many of the ex-smokers stopped smoking after MI. A p value less than 0.05 was considered significant.

Study II

Age-adjusted means were determined by analysis of covariance with age as covariate and presented as means $\pm$ 95% confidence intervals (CI). As CRP levels were not normally distributed, non-parametric Spearman´s correlation test was used to test correlations between CRP, LDL-antibodies and CVD risk factors. Multiple regression was used to test the association between diabetes and MI on the one hand and antibody titers and CRP on the other with respect to background variables such as BMI, WHR, SBP, TG, HDL-cholesterol, medication and menopause.

Study III

In the cross-sectional analysis of base line variables age-adjusted means (SD) or proportions were compared using the general linear model procedure (GLM). In the prospective part of the study age-adjusted proportional hazards regression analyses were used to calculate hazard ratios (HR). As the date of diagnosis of diabetes was unknown in women identified by the hospital discharge register only, the date for the first hospitalisation was used instead. However, because the date of diagnosis is, in itself, an approximation, with an unknown period of time of either asymptomatic or undiagnosed diabetes, the proportional hazards model may not be appropriate. Accordingly, we also repeated all analyses using

multiple logistic regression models instead, with diabetes as the dependent variable. Results were virtually identical whether logistic regression or proportional hazards models were used, and the proportional hazard models were kept throughout.

In the multiple regression analyses baseline smoking was entered as never, former, or current smoking of <15 cigarettes/day or ≥15 cigarettes/day. Menopause was coded as 1 for yes and 0 for no. BMI, SBP, serum cholesterol and TG were entered as continuous variables in the regression analysis of baseline variables. In the prospective study these variables were categorised with the aim of forming clinically meaningful cut-off limits. When BMI, SBP and serum TG were introduced into the models as potential confounders they were, however, entered as continuous variables. Results were essentially identical whether serum TG were log-transformed or not, and accordingly only non-transformed values were used throughout. Leisure time physical activity was entered as sedentary (level 1) versus non-sedentary (levels 2-3). With respect to education two dummy variables were created (secondary and college/university) with compulsory education as reference.

Study IV

Means (SD) and proportions were calculated with standard methods. The associations between diabetes and presentation, complications and outcome, were tested with Mantel-Haenszel Chi-square tests for men and women separately. Age adjusted odds ratios, OR, with 95 % confidence intervals (CI), for differences in proportions between diabetic and non-diabetic subjects were calculated by logistic regression for men and women separately. To determine whether differences in clinical presentation, complication and outcome between subjects with and without diabetes were due to differences in baseline characteristics, we adjusted for these by multiple logistic regression models in men and women separately. Variables that were included in the models were age, smoking, body mass index, hypertension, prior congestive heart failure (CHF), renal failure, previous drug use (ASA, beta-blockers and statins), previous angina pectoris, prior MI, and prior revascularisation. Possible interactions between sex and diabetes were tested with the interaction term (sex*diabetes) introduced in the logistic regression model with the relevant presenting or discharge diagnosis as the dependent variable. To investigate the effect of sex, age, and diabetes, on mortality, patients were divided in three subgroups based on age <65, 65-74, and ≥ 75 years, and odds ratios were calculated with a logistic regression model in men and women separately.

RESULTS

Study I

Data on age, smoking habits, menopause, physical activity, diabetes duration and metabolic control as well as antihypertensive and lipid-lowering therapy in the participants of Study I are shown in Table 3. Mean age was lower among the healthy control women, because, in the MONICA study, equal proportions of women in the 10-year age groups 45 to 54 and 55 to 64 years were included. Among the patients who were included, 4 (13.8%) of the women with both diabetes and MI, 10 (15.6%) of the women with MI but no diabetes, and 6 (13.0%) of the diabetic women without MI, respectively, were younger than 50 years of age, compared to 30 (24.0%) among the control women.

Table 3. Age, smokinghabits, menopausal state, metabolic control and medication in participants of Study I. (mean, 95% CI, or %)

Base of variables	DM+MI n=23	DM not MI n=44	MI not DM n=54	controls n=120
Age, years	56.3 (54.0, 58.7)	55.9 (54.0, 57.8)	56.4 (54.5, 58.3)	54.4 (53.4, 55.3)
Smokers, %	39.3	23.9	28.6	31.5
Ex-smokers, %	46.4	26.1	54.0	27.4
Postmenopausal, %	95.7	84.1	87.3	71.6
Age at menopause, years	50.4 (47.8, 53.0)	49.2 (47.5, 50.9)	47.6 (46.1, 49.1)	49.3 (48.2, 50.5)
Sedentary lifestyle, %	39.3	14.0	20.6	25.7
Diabetes duration, years	16.3 (9.8, 22.8)	15.3 (11.3, 19.3)		
HbA_{1c}, %	7.83 (6.98, 8.68)	7.22 (6.61, 7.82)		
Treatment with lipid-lowering agents, % (n)	65.2 (15)	4.5 (2)	54.5 (30)	1.7 (2)
Treatment with anti-hypertensive therapy, % (n)	95.7 (22)	43.2 (19)	87.0 (47)	12.5 (15)

Table 4 shows anthropomethric data, systolic and diastolic blood pressure, lipid levels, plasma fibrinogen, s-estradiol and sex-hormone binding globulin (SHBG). Despite the fact that diabetic women with and without MI had similar body mass index, those with a past MI had significantly higher waist/hip ratio, markedly elevated serum triglycerides, and low HDL cholesterol, indicating pronounced metabolic disturbances. Women with MI but no diabetes had intermediate values for waist/hip ratio, triglycerides and HDL cholesterol.

Although 65% of the women with diabetes and prior MI were on lipid lowering therapy, the recommended levels of total cholesterol $\leq$ 5.0 mmol/l and triglycerides $\leq$ 2.0 mmol/l were not achieved by more than 22% and 27%, respectively (Table 4). Furthermore, a considerably lower proportion of the women with diabetes and prior MI had HDL-cholesterol $\geq$ 1.0mmol/l, and less than 20 % of the diabetic women with MI had both triglycerides < 2 mmol/l and HDL-cholesterol > 1.0 mmol/l.

To explore the association of the different risk factors with MI, a multiple regression analysis was done with age, waist/hip ratio, systolic blood pressure, triglycerides, HDL-cholesterol and smoking as independent variables in diabetic and non-diabetic women separately. Because serum triglycerides and HDL-cholesterol were strongly correlated ($r = -0.45$, $p < 0.001$), we first performed an analysis with age, wais/hip ratio, systolic blood pressure, triglycerides and smoking as independent variables (Table 5). Smoking (i.e. current and former smoking combined) was independently associated with MI, both in women with diabetes, and in non-diabetic women. In diabetic women triglycerides were independently associated with MI, while waist/hip ratio was independently associated with MI solely in women without diabetes. However, when HDL-cholesterol was entered into the models, the association of serum triglycerides with MI disappeared, and the OR for waist/hip ratio in non-diabetic women was slightly attenuated. The association of smoking with MI persisted in both groups (Table 5).

Table 4. Anthropometric data, systolic (SBP), and diastolic (DBP) blood pressure, lipid levels, p-fibrinogen, s-estradiol and s-SHBG levels in participants of Study I (mean ± 95% CI).

	DM + MI n = 22	DM not MI n = 44	p	MI not DM n = 52	controls n = 120	difference*	p
BMI, kg/m^2	28.0 (25.9, 30.1)	27.3 (25.6, 29.1)	0.55	26.3 (25.3, 27.2)	25.4 (24.7, 26.2)	0.74	0.27
WHR	0.89 (0.87, 0.92)	0.84 (0.81, 0.86)	0.001	0.85 (0.84, 0.86)	0.80 (0.79, 0.81)	0.05	< 0.001
SBP, mmHg	148 (138, 159)	143 (137, 148)	0.27	135 (129, 140)	130 (128, 133)	2.3	0.40
DBP, mmHg	84 (77, 90)	82 (78, 85)	0.36	83 (81, 86)	82 (81, 84)	1.0	0.46
S-cholesterol, mmol/l	5.84 (5.26, 6.43)	6.42 (6.07, 6.78)	0.06	5.96 (5.59, 6.33)	6.29 (6.07, 6.51)	- 0.38	0.07
S-cholesterol ≤ 5.0 mmol/l, % (n)	22.0 (5)	6.8 (3)		21.1 (11)	14.2 (17)		
S-HDL-cholesterol, mmol/l	1.09 (0.94, 1.24)	1.56 (1.41, 1.71)	< 0.001	1.27 (1.17, 1.37)	1.65 (1.57, 1.73)	- 0.38	< 0.001
HDL-cholesterol > 1.0 mmol/l, % (n)	50.0 (11)	88.6 (39)		76.9 (40)	93.3 (112)		
S-triglycerides, mmol/l	3.03 (2.23, 3.83)	1.69 (1.39, 1.99)	< 0.001	1.87 (1.68, 2.06)	1.50 (1.35, 1.65)	0.36	0.008
S-TG < 2.0 mmol/l, % (n)	27.3 (6)	72.7 (32)		63.5 (33)	84.1 (101)		
P-fibrinogen, g/l	3.64# (3.31, 3.97)	3.10 (2.90, 3.31)	0.014	3.25 (2.99, 3.52)	2.75 (2.65, 2.84)	0.46	< 0.001
S-oestradiol	0.07 (0.04, 0.09)	0.11 (0.05, 0.17)	0.77	0.11 (0.07, 0.15)	0.27 (0.16, 0.38)	- 0.12	0.09
S-SHBG	42.4 (19.3, 65.4)	64.3 (53.3, 75.4)	0.024	49.7 (40.5, 58.8)	61.2 (55.3, 67.1)	- 12.2	0.026

*age adjusted difference between (MI not DM) and controls, # n=8

Table 5. Multiple logistic regression analysis of risk factors associated with myocardial infarction (MI) in diabetic and non-diabetic women with and without inclusion of HDL-cholesterol in the analysis. OR=odds ratio. *(Paper I)*

		Diabetes n=66		No diabetes n=172	
	unit	OR (95%CI)	p	OR (95% CI)	p
HDL-cholesterol not included in the analysis:					
age	1.0	1.09 (0.96-1.23)	0.20	1.04 (0.98-1.10)	0.23
WHR	0.1	-		4.22 (2.19-8.13)	<0.001
Systolic BP, mmHg	5.0	1.18 (1.00-1.39)	0.053	-	
S-triglycerides, mmol/l	1.0	2.70 (1.40-5.20)	0.003	-	-
Smoking*	1.0	15.35 (2.46-95.66)	0.003	3.07 (1.32-7.16	0.009
HDL-cholesterol included in the analysis:					
age	1.0	1.10 (0.96-1.25)	0.17	1.06 (0.99-1.12)	0.08
WHR	0.1	-	>0.3	3.69 (1.75-7.76)	<0.001
Systolic BP, mmHg	5.0	1.19 (0.99-1.42)	0.066	-	<0.3
S-HDL-cholesterol, mmHg	0.5	0.30 (0.09-0.96)	0.043	0.25 (0.12-0.50)	<0.001
S-triglycerides, mmol/l	1.0	1.73 (0.86-3.47)	0.13	0.70 (0.41-1.20)	0.19
Smoking*	1.0	18.78 (2.59-136.17)	0.004	3.43 (1.38-8.5)	0.008

*smokers and ex-smoker combined

Table 6. IgM and IgG titers of antibodies against MDA-LDL, and CRP levels (age adjusted means, 95 % CI). (*Paper II*)

	DM + MI n = 18	DM not MI n = 35	MI not DM n = 46	controls n = 70
Ig M	1.41 (1.24, 1.58)	1.45 (1.32, 1.57)	1.42 (1.31, 1.53)	1.61 (1.51, 1.70)
Ig G	0.98 (0.89, 1.06)	1.02 (0.96, 1.08)	1.07 (1.02, 1.12)	0.95 (0.90, 0.99)
CRP, mg/ml	7.81 (5.39, 10.22)	5.30 (3.56, 7.03)	3.58 (2.05, 5.11)	1.91 (0.60, 3.21)

Study II

Antibody titers and CRP levels in the four groups of women are shown in Table 6. Diabetic women with MI tended to have lower IgM titres than the controls ($p=0.053$). Diabetic women without MI and MI-women without diabetes had significantly lower IgM titers to MDA-LDL compared with controls ($p<0.05$). No significant differences in IgG titers were seen between diabetic women with MI and controls. However, in MI-women without diabetes, IgG titers were significantly higher ($p<0.001$) and there was a trend of higher titers ($p=0.07$) also in diabetic women without MI than in controls (Table 6).

Table 7. IgM and IgG titers of antibodies against MDA-LDL, and CRP levels in cases (= women with diabetes and / or MI) and healthy controls (age adjusted means, 95% CI). (*Paper II*)

	cases n = 97	controls n = 70	p
Ig M	1.43 (1.35, 1.50)	1.61 (1.51, 1.70)	0.005
Ig G	1.03 (1.00, 1.07)	0.95 (0.90, 0.99)	0.005
CRP, mg/l	4.75 (3.55, 5.94)	2.16 (1.29, 3.03)	< 0.001

CRP levels were elevated in all three groups of patients compared with controls (Table 6). Furthermore, diabetic women with MI had significantly higher CRP levels than MI-women without diabetes ($p<0.01$). There were no significant differences between diabetic women without MI and the two groups of women with MI in either antibody titers or CRP levels. Accordingly, when the three patient groups were analysed together, defined as "cases", they had, overall, significantly higher CRP levels and IgG titers, and lower IgM titers, compared with controls (Table 7). Adjustment for menopausal state into the analyses of IgG and IgM did not change the results, nor did logarithmic transformation of CRP (not shown).

Table 8. Age adjusted base-line cardiovascular risk factors in women with and without diabetes during follow-up [mean (SD) or %]. (*Paper III*)

Characteristics at baseline	no diabetes n = 1278	diabetes n =73	p
Age, years (SD)	49.1 (7.3)	51.6 (7.3)	0.003
Menopausal, %	43.8	42.6	0.77
S-cholesterol, mol/l (SD)	6.15 (1.23)	6.23 (1.21)	0.54
S-triglycerides, mmol/l (SD)	1.07 (0.53)	1.55 (0.75)	< 0.001
BMI, kg/m^2 (SD)	24.3 (3.7)	28.0 (5.0)	< 0.001
SBP, mmHg (SD)	134 (21)	147 (25)	< 0.001
DBP, mmHg (SD)	84 (11)	90 (12)	< 0.001
Leisure time physical activity, % sedentary	22.7	35.4	0.005
Occupational activity, % sedentary	29.0	23.2	0.29
Smoking, %	35.5	35.4	0.99
Compulsory education only, %	62.8	70.0	0.21

Table 9. Hazards ratio (95% CI) of diabetes in women during 18-years follow-up. (*Paper III*)

	Number (n)	DM cases (n)	DM cases per 1000 observation years (n)	Hazard ratio adjusted for age	Hazard ratio multiple adjusted
S-cholesterol, mmol/l					
< 6.0	658	27	2.2	1.00	
6 -6.9	393	30	4.2	1.61 (0.94-2.75)	--
7.0-7.9	208	8	2.2	0.73 (0.31-1.67)	
≥ 8.0	90	8	5.2	1.64 (0.71-3.77)	
p for trend				0.41	--
S-triglycerides, mmol/l					
< 1.0	801	16	1.0	1.00	1.00
1.0-1.4	334	26	4.3	4.01 (2.13-7.57)	2.97 (1.57-5.65)
1.5-1.9	143	19	7.7	7.08 (3.58-14.0)	3.73 (1.82-7.65)
≥ 2.0	73	12	9.8	9.28 (4.27-20.19)	4.49 (2.01-10.03)
p for trend				< 0.001	< 0.001
BMI, kg/m^2					
< 22	366	6	0.88	1.00	1.00
22 - 24	338	7	1.09	1.18 (0.39-3.50)	1.03 (0.34-3.07)
24 - 27	348	19	2.98	3.21 (1.28-8.07)	2.41 (0.95-6.11)
≥ 27	298	41	7.82	8.27 (3.47-19.71)	4.53 (1.84-11.16)
p for trend				< 0.001	< 0.001
SBP, mmHg					
< 130	564	14	1.32	1.00	1.00
130 - 144	396	16	2.19	1.60 (0.78-3.32)	1.21 (0.58-2.52)
145 - 159	206	18	4.95	3.55 (1.70-7.43)	2.21 (1.03-7.74)
≥ 160	185	25	7.58	5.55 (2.71-11.37)	2.51 (1.15-5.50)
p for trend				0.004	0.010
physical activity					
not sedentary	1034	46	2.39	1.00	1.00
sedentary	317	27	4.80	2.08 (1.29-3.34)	1.56 (0.96-2.53)
p for trend				0.003	0.071

Study III

Table 8 shows age-adjusted cardiovascular risk factors at baseline among the participating women with and without diabetes at follow-up. Women who developed diabetes were older and had significantly higher age-adjusted BMI, serum triglycerides, and blood pressure at the first screening than women who remained free from diagnosed diabetes during follow-up. They also reported a more sedentary lifestyle, whereas smoking habits and educational level did not differ.

73 women (5.4%) were diagnosed with diabetes during the 18 years of follow-up. Table 9 shows that, as expected, increasing obesity and blood pressure resulted in an increasing age-adjusted risk of future diabetes, p for trend <0.001. Also, low physical activity significantly predicted diabetes. S-triglycerides (TG) carried a steeply increasing age adjusted risk. Smoking and total serum cholesterol were not associated with increased risk of diabetes. After adjustment for BMI, SBP and physical activity, increasing TG level remained a strong and significant risk factor for the development of diabetes.

Table 10 shows basal characteristics in non-participating compared with participating women in the second BEDA screening. Women who did not take part in the second screening were older, more obese, had higher BP and serum triglyceride levels, were smokers and lived a sedentary life to a higher degree than non-participants. The HR of diabetes with increasing TG level was higher in women with incident diabetes identified only through the registers than in women identified at the second screening (Table 11). However, the marked increase in risk at slightly elevated TG levels was seen in both categories.

Table 10. Basal characteristics in women participating and not-participating in the second BEDA-screening 1997-98. (*Paper III*)

	Participants n=875	Non-participants n=476
Age, years	48 (47, 48)	51 (51, 52)
Smokers, %	31	43
Body mass index, kg/m^2	24.2 (23.9, 24.4)	25.2 (24.8, 25.6)
Systolic blood pressure, mmHg	132 (131, 133)	141 (139, 143)
S-cholesterol, mmol/l	6.05 (5.97, 6.12)	6.34 (6.29, 6.46)
S-TG, mmol/l	1.02 (0.99, 1.05)	1.24 (1.18, 1.29)
Low physical activity, %	20	30
Compulsory education only, %	60	69

% or means ±. 95% CI

Table 11. Multiple adjusted hazards ratio of diabetes by triglyceride levels in women with diabetes diagnosed at second screening (n=44) and in women with diabetes diagnosed by the Swedish national register on deaths due to specific causes, or the Swedish hospital discharge register (n=29)*. Adjustments were made for age, BMI, and SBP. (*Paper III*)

	Diagnosis at 2nd screening HR (95% CI) n=44	Diagnosis by register only HR (95% CI) n=29
S-triglycerides, mmol/l		
<1.0	1.00	1.00
1.0-1.4	2.70(1.25-5.86)	4.29(1.31-14.01)
1.5-1.9	3.94(1.67-9.34)	5.30(1.46-19.26)
≥2.0	2.49(0.75-8.19)	10.47(2.93-37.39)

*Of the 29 women identified by the Swedish hospital discharge register, 2 particpated at the second screening.

Study IV

Basal characteristics

Baseline characteristics in men and women with and without diabetes are shown in Table 12. As expected, patients with diabetes were older, and women were older than men. More men than women were smokers, irrespective of diabetes. Hypertension, obesity, a history of prior stroke, heart failure, MI, angina pectoris and prior revascularisation were all more common in men and women with diabetes.

At admission 25% of men and 19% of women with diabetes were on diet treatment only, 48 and 46%, respectively, were treated with oral hypoglycaemic agents, 5%, a similar proportion of men and women, with oral hypoglycaemic agents in combination with insulin, and 22 and 29%, respectively, of men and women with diabetes were treated with insulin only.

Table 12. Baseline risk factors, prior disease and medical treatment at admission by sex and diabetes in the Euro Heart Survey ACS.

	Men		Women	
	DM n=1376	no DM n=5112	DM n=806	no DM n=2003
Age, years	63.7 (9.8)	60.5 (11.6)	68.0 (9.2)	66.1 (10.5)
Smoking, % (n)	29 (392)	41 (2108)	13 (105)	22 (432)
Hypertension, % (n)	66 (908)	49 (2523)	77 (619)	65 (1294)
BMI, kg/m^2 (SD)	28.4 (4.2)	26.9 (3.7)	28.9 (4.9)	27.2 (4.9)
BMI kg/m^2, % (n)				
< 25	21 (251)	32 (1444)	22 (150)	36 (614)
25 - 30	49 (598)	51 (2322)	41 (283)	40 (688)
> 30	30 (361)	18 (807)	37 (252)	24 (416)
Heart rate, (SD)	83 (21)	77 (19)	84 (21)	79 (19)
SBP, mmHg (SD)	142 (27)	140 (27)	150 (33)	145 (31)
DBP. MmHg (SD)	82 (16)	83 (16)	83 (17)	83 (17)
Prior stroke, % (n)	11 (149)	5 (275)	12 (94)	6 (118)
Prior heart failure, % (n)	13 (183)	8 (401)	16 (132)	10 (209)
Prior angina pectoris, % (n)	31 (423)	28 (1408)	35 (286)	33 656)
Prior MI, % (n)	39 (539)	29 (1469)	34 (271)	23 (471)
Prior revascularisation, % (n)	25 (338)	18 (927)	17 (137)	12 (250)
Prior MI + revasc,% (n)	46 (636)	35 (1776)	41 (329)	28 (569)
Treatment at admission				
Aspirin, % (n)	50 (683)	38 (1960)	48 (385)	39 (782)
Betablockers, % (n)	37 (509)	31 (1609)	37 (299)	33 (662)
Statins, % (n)	25 (350)	21 (1049)	24 (195)	20 (394)
ACE-inhibitors, % (n)	36 (490)	22 (1125)	40 (325)	26 (530)

BMI=body mass index, MI=myocardial infarction. The results are presented as means (SD) or proportions and numbers of pats with the percentage rounded up or down based on decimal values above or below 0.5, respectively.

Clinical presentation

Clinical presentation, symptoms at admission and complications during hospital stay are shown in Table 13. The absolute majority of patients presented with typical chest pain at admission. However, significantly fewer diabetic than non-diabetic women stated typical chest pain, whereas there was only a small and non-significant difference among men. Men with diabetes were less likely to present with ST-elevation than non-diabetic men, whereas there was no difference in women when age was taken into account. Non-ST-elevation ACS was slightly less frequent in diabetic women.

Complications in hospital

All forms of heart failure were more likely to occur in diabetic than non-diabetic patients, especially in women (Table 13). Except asystole during hospital stay, other arrhythmias or mechanic complications, as well as recurrent ischemia, bleeding complications, and stroke, did not differ by sex or by diabetes.

Investigations and treatment.

85% and 77% ($p<0.001$) of diabetic and non-diabetic women, and 78% and 73% respectively ($p<0.001$) of men, performed a stress test during hospital stay. Angiographic investigation and findings by sex and diabetes are shown in Table 14, and interventions are shown in Table 15.

Discharge diagnosis and mortality

The impact of diabetes on the final diagnosis differed in men and women (Table 16). More women with than without diabetes, but fewer diabetic than non-diabetic men, were discharged with a definite diagnosis of MI. Furthermore, more diabetic than non-diabetic women developed a Q-wave MI, whereas the reverse was found in men. Accordingly, unstable angina was a more common discharge diagnosis in diabetic compared with non-diabetic men, whereas the opposite was true for women.

In-hospital mortality was significantly higher in diabetic than non-diabetic women, (7.3% vs 3.8%, $p<0.001$) (Table 16), irrespective of age group (Fig 3), whereas the difference was smaller and not significant in men (4.0% vs 3.3%, $p=0.20$). Thirty-day mortality was increased in diabetic compared with non-diabetic patients irrespective of sex (8.4% vs 4.6%, $p<0.001$ in women and 6.0% vs 4.1% $p=0.002$ in men, respectively) (Fig 4).

Table 13. Clinical presentation and complications during hospital stay by sex and diabetes in the Euro Heart Survey ACS. (*Paper IV*)

	Men			Women		
	DM n=1376	no DM n=5112	OR age adjusted	DM n=806	no DM n=2003	OR age adjusted
Typical chest pain, % (n)	86 (1187)	89 (4535)	0.85 (0.71-1.01)	82 (664)	87 (1751)	0.69 (0.55-0.86)
Heart failure, % (n)	3 (48)	2 (77)	2.07 (1.43-2.99)	4 (36)	2 (40)	2.14 (1.35-3.40)
ST-elevation ACS, % (n)	41 (557)	47 (2399)	0.83 (0.74-0.94)	39 (315)	36 (730)	1.14 (0.96-1.35)
Non-ST-elevation ACS, % (n)	51 (707)	48 (2453)	1.10 (0.97-1.24)	53 (426)	58 (1166)	0.80 (0.68-0.95)
Undetermined ECG, % (n)	8 (112)	5 (260)	1.45 (1.15-1.83)	8 (65)	5 (107)	1.46 (1.06-2.01)
Normal ECG, % (n)	16 (218)	16 (833)	0.98 (0.83-1.15)	13 (107)	19 (373)	0.69 (0.54-0.87)
Mild-moderate CHF, % (n)	18 (254)	14 (720)	1.29 (1.10-1.51)	24 (190)	15 (301)	1.67 (1.36-2.01)
Pulmonary edema, % (n)	7 (103)	4 (203)	1.75 (1.37-2.24)	12 (98)	5 (105)	2.37 (1.78-3.17)
Shock, % (n)	5 (64)	4 (196)	1.12 (0.83-1.50)	7 (60)	5 (91)	1.66 (1.19-2.33)
Total CHF, % (n)	23 (322)	18 (895)	1.33 (1.15-1.54)	31 (252)	19 (388)	1.82 (1.51-2.19)
LVEF < 40%, % (n)	19 (260)	12 (638)	1.56 (1.33-1.83)	18 (147)	10 (203)	1.93 (1.52-2-43)
Asystole, % (n)	3 (41)	2 (116)	1.19 (0.83-1.71)	6 (49)	3 (51)	2.35 (1.57-3.51)
Reinfarction, % (n)	2 (26)	2 (92)	1.00 (0.64-1.55)	3 (25)	2 (37)	1.70 (1.01-2.85)
Renal failure, % (n)	3 (47)	2 (118)	1.31 (0.92-1.84)	5 (43)	2 (39)	2.68 (1.72-4.17)
Stroke, % (n)	1 (13)	1 (27)	1.60 (0.82-3.11)	1 (6)	1 (16)	0.89 (0.35-2.28)

CHF: congestive heart failure, LVEF: left ventricular ejection fraction. All figures are percentages (numbers)

Table 14. Angiographic findings by sex and diabetes in the Euro Heart Survey ACS. (*Paper IV*)

	Men			Women		
	DM n=807	no DM n=3081	OR age adjusted	DM n=379	no DM n=980	OR age adjusted
Normal angiography, % (n)	2 (18)	4 (136)	0.57 (0.35-0.95)	3 (12)	11 (109)	0.28 (0.15-0.51)
3-vessel disease, % (n)	42 (341)	31 (967)	1.46 (1.24-1.71)	42 (160)	27 (263)	1.90 (1.48-2.45)

All figures are percentages (numbers)

Table 15. Intervention by sex and diabetes in the Euro Heart Survey ACS. (*Paper IV*)

	Men			Women		
	DM n=1376	no DM n=5112	OR age adjusted	DM n=806	no DM n=2003	OR age adjusted
Thrombolysis, % (n)	16 (216)	20 (1014)	0.8(0.68-0.94)	14 (110)	14 (275)	1.05 (0.83-1.03)
Reperfusion PCI, % (n)	11 (152)	15 (766)	0.76 (0.63-0.91)	9 (75)	10 (198)	0.98 (0.74, 1.30)
PCI in hospital, % (n)	32 (439)	37 (1911)	0.8(0.75, 0.97)	26 (206)	27 (536)	1.00 (0.83, 1.20)
CABG in hospital, % (n)	7 (99)	5 (238)	1.53 (1.20-1.96)	5 (42)	3 (70)	1.51 (1.02-2.23)

All figures are percentages (numbers). Reperfusion PCI: acute PCI. PCI in hospital: other PCI during hospital stay.

Table 16. Discharge diagnosis and mortality by sex and diabetes in the Euro Heart Survey ACS (*Paper IV*)

	Men			Women		
	DM n=1376	no DM n=5112	OR age adjusted	DM n=806	no DM n=2003	OR age adjusted
Definite MI, % (n)	54 (744)	61 (3118)	0.79 (0.70-0.90)	55 (455)	50 (1009)	1.22 (1.03-1.44)
Q-wave MI, % (n)	31 (425)	37 (1873)	0.83 (0.73-0.95)	30 (245)	26 (527)	1.23 (1.03-1.47)
Unstable AP, % (n)	46 (632)	39 (1994)	1.26 (1.12-1.42)	45 (361)	50 (994)	0.82 (0.70-0.97)
Hospital mortality, % (n)	4 (57)	3 (166)	1.13 (0.83-1.55)	7 (60)	4 (73)	1.98 (1.39-2.82)
30 day mortality, % (n)	6 (83)	4 (210)	1.33 (1.02-1.73)	8(68)	5 (92)	1.77 (1.28-2.46)

All figures are percentage (numbers)

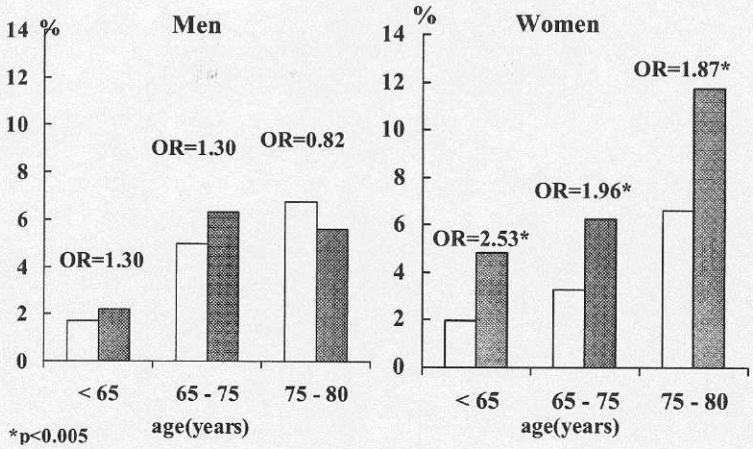

Figure 3. In-hospital mortality (%) by age group in men and women participating in the European Heart Survey ACS.
OR = odds ratios. Unfilled bars = patients without diabetes.
Filled bars=patients with DM. * p<0.05

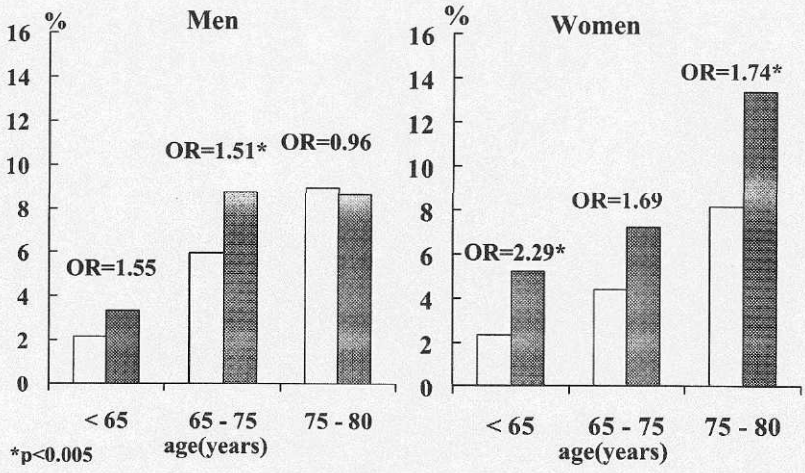

Figure 4. 30-day mortality (%) by age group in men and women participating in the European Heart Survey ACS.
OR=odds ratios. Unfilled bars=patients without diabetes.
Filled bars=patients with diabetes. * p<0.05

Multiple adjustments for differences in base-line variables

When differences in smoking, hypertension, BMI, heart failure, renal faiulure, prior medication, and prior disease were taken into account, women with diabetes significantly more often presented with ST-elevation ACS, developed Q-wave MI, and had higher in-hospital mortality than non-diabetic women, whereas the lower risk in diabetic men was no longer significant (Table 17). The interaction tests between sex, diabetes and ST-elevation at admission, development of Q-wave-MI and in-hospital mortality, respectively were significant (Table 17). Including ST-elevation or Q-wave MI in the multiple regression did not change the OR for mortality either in women or in men. Diabetes increased multiple adjusted OR for 30-d mortality in both men and women (Table 17).

Table 17. Odds ratios for ST-elevation-ACS, Q-wave MI, and in-hospital mortality in men and women with and without DM hospitalised due to ACS. (*Paper IV*)

	Men	Women	
	OR multiple adjusted	OR multiple adjusted	p for interaction DM and sex
ST-elevation ACS	0.99 (0.86 - 1.14)	1.46 (1.20 - 1.78)	<0.001
Q-wave MI	0.99 (0.85 - 1.15)	1.61 (1.30 - 1.99)	<0.001
Hospital mortality	1.13 (0.76 – 1.67)	2.13 (1.39 – 3.26)	0.021
30 d mortality, % (n)	1.44 (1.04 – 2.0)	1.95 (1.31 – 2.89)	0.13

OR were adjusted for age, smoking, BMI, heart failure, renal failure,hypertension, prior drug use and prior disease.

DISCUSSION

Diabetes prevalence

The proportion of subjects with diabetes is considerably higher among patients with MI/ACS than in the general population. Whereas the prevalence of diabetes in the Nordic countries is reported to be 2 to 6 % (Andersson 1991, Tuomilehto 1991, Larsson 1995, Vilbergsson 1997, Lidfeldt 2001, Eliasson 2002), 16.4% of the women with MI in Study I, and 21.2% of the men and 28.7% of the women in the study of ACS patients (Study IV) were diabetic. These figures are in accordance with previous studies concerning patients with MI (Abbott 1988, Abbud 1995, Lundberg 1997, Tenerz 2001, Norhammar 2003) and ACS (Malmberg 2000, McGuire 2000), and patients undergoing coronary angiography (Taubert 2003). Furthermore, a considerable proportion of patients with MI have previously undiagnosed diabetes and impaired glucose tolerance (Norhammar 2002, Rathmann 2002), leaving only a third of MI patients with normal glucose tolerance (Norhammar 2002). Moreover, previous studies have shown that the proportion of unrecognised diabetes was similar to that of known diabetes in patients undergoing coronary angiography (Taubert 2003) and in general population samples (Lidfeldt 2001, Eliasson 2002, Rathmann 2003).

Diabetes and coronary heart disease

Although the absolute hazard of MI in women is low until older age (Rosengren -01), a history of diabetes mellitus or previous MI greatly increases the risk. Women with diabetes are thereby more similar to men, with and without diabetes, than non-diabetic women (Barrett-Connor 1991).

In previous studies women with diabetes have been compared with non-diabetic women or diabetic men with respect to the prevalence of CVD risk factors (Koivisto -96, Vilbergsson -98), and to risk factors for CVD morbidity and mortality after MI (Löwel -00) and CABG (Sprecher -00). There are also several reports on CVD risk factors in diabetic compared with non-diabetic subjects, with data on men and women pooled together (Krolewski 1987, Hanefeld 1996, Turner 1998, Uusitupa 1993). However, there are few studies, if any, comparing CVD risk factors in diabetic and non-diabetic women with and without a prior MI.

Clinical characteristics of the women with MI in the present study were similar to those of women enrolled in previous Swedish investigations on women and MI (Johansson 1988, Engström 2000, Al-Khalili 2002). That

is, women who have sustained an MI are characterized by a high proportion of diabetes, obesity, hypertriglyceridemia and low HDL cholesterol levels, whereas total serum cholesterol is not markedly higher than in healthy controls.

ACS

In recent years, the focus with respect to acute coronary disease has shifted from only MI to the whole spectrum of acute coronary syndromes, including MI with and without ST elevation, as well as unstable angina. The different forms of ACS are all the same disease, but with different symptoms, clinical signs and implications. In addition, patients with unstable angina now form an important subset of the ACS population (McGovern 2001). The present study IV, based on a recently investigated large sample, adds information about the clinical manifestation and short-term prognosis in men and women across the whole range of ACS.

Most studies dealing with diabetes and ACS have investigated patients with MI only, and it is often reported that diabetic patients with ACS less frequently present with ST-elevation at admission (Gustafsson 2000, Vaccarino 2000, McGuire 2000). However, in prior studies the men and women were not analysed separately and, accordingly, the results might reflect the higher proportion of men among the patients (Gustafsson 2000, McGuire 2000), or rates that were not adjusted for other baseline variables (Vaccarino 2000). The GUSTO IIb study found diabetes to be associated with an increased likelihood of ST-elevation at admission, however, a possible interaction with sex was not reported (Hochman -99).

Atypical presentation, which is more common in diabetic women, might contribute to a misjudgement of the severity of disease in patients with diabetes and consequently result in less intensive treatment and worse prognosis. This dilemma is supported by previous studies showing that diabetic patients with MI receive less treatment with thrombolysis, beta-blockers and aspirin (Löwel 2000, Norhammar 2003, Gitt 2003), even though the benefit of those treatments are as well established in diabetic as in non-diabetic patients (Löwel 2000, Norhammar 2003, Gitt 2003).

Although patients with diabetes do not develop larger infarctions (Lehto 1994, Miettinen 1998, Melchior 1999), heart failure is more common in subjects with than without diabetes (Lehto 1994, Melchior 1999). Furthermore, diabetic women are more likely to develop heart failure than men with diabetes after MI (Vaccarino 2000, Crowley 2003). This finding is underscored by the present study, where decreased ventricular function (LVEF < 40%) was much more common among the patients with diabetes,

particularly in the women. A contributing factor might be the more severe and diffuse coronary atherosclerosis reported in diabetic women (Natali 2000, Pajunen 2000). Accordingly, three-vessel disease was diagnosed in 42 % of patients with and 30.3 % without diabetes ($p<0.001$) in the present study, which is similar to another recent Swedish study (Norhammar 2004).

We identified only one previous study that compared diabetic and non-diabetic men and women with Q-wave-MI, but this study did not analyse a potential interaction between sex and diabetes (Vaccarino 2000). However, the crude proportions did not differ between diabetic and non-diabetic subjects, irrespective of sex. In contrast, the diabetic women of the present study were significantly more likely to develop Q-wave-MI than non-diabetic women, whereas there was no difference in men. It might be that the patients of the present study constitute a more representative sample, as all consecutive patients with suspected ACS were screened, reducing the risk of missing subjects with less typical presentation but who finally developed MI.

Diabetes increases the risk for in-hospital mortality after MI (Malmberg 2000, Vacccarino 2000, Gitt 2003, McGuire 2000, Cooper 1991), especially in women (Donahue 1993, Crowley 2003, Greenland 1991). However, the influence of diabetes is attenuated after adjustment for baseline clinical and angiographic characteristics (Cooper 1991, Granger 1993), and some studies found a greater impact of diabetes on long-term than on short-term mortality (Melchior -99). In the present study, in-hospital mortality was significantly higher in women with than without diabetes, irrespective of age, smoking or other diseases, whereas the difference between diabetic and non-diabetic men was smaller and not significant. Inclusion of ST-elevation or Q-wave MI in the multiple regression analysis did not change the results, and accordingly, the type of MI did not seem to influence the diabetes related mortality. However, the relatively low absolute number of deaths might have contributed to a type 2 error, explaining why difference in mortality did not reach statistical significance in diabetic compared with non-diabetic men.

In accordance with previous studies, (Lehto 1994, Chun 1997, Miettinen 1998), the age-adjusted 30-day mortality was significantly increased in both men and women with diabetes, but slightly more so among the women. However, among the oldest men there was no discernible difference between diabetics and non-diabetics.

Lipid abnormalities in diabetes

Dyslipidemia is a strong risk factor for CVD, especially in subjects with diabetes (Hanefeld 1996, Adlerberth 1998, Turner 1998, Sprecher 2000, Koivisto 2001). Serum total and LDL cholesterol levels are usually similar in patients with type 2 diabetes and in non-diabetics, whereas serum triglycerides are higher and HDL cholesterol levels are lower (UKPDS 27). However, elevated cholesterol levels carry similar risk of coronary artery disease in subjects with and without diabetes, but the absolute risk is considerably higher in diabetics (Stamler 1993, Adlerberth 1998). Furthermore, the UKPDS study clearly showed that elevated LDL and decreased HDL cholesterol levels were significant risk factors for coronary artery disease in subjects with type 2 diabetes (Turner 1998).

In accordance with previous studies, women with prior MI in the present study had significantly higher triglycerides and lower HDL cholesterol levels than women without MI. The most adverse levels were found in women with both diabetes and MI. Similarly elevated TG- and decreased HDL levels are reported from other studies of subjects of both type 1 (Koivisto -01) and type 2 diabetes (Uusitupa 1993, Pyörälä 1997), but few studies reported women separately. However, it has been claimed that the adverse effect of diabetes on lipid levels seems to be more marked in women than men (Walden 1984). The difference in triglycerides and HDL cholesterol between diabetic women with and without MI of the present study was not explained by a poorer metabolic control, because HbA1c levels were similar in the two groups.

In uncomplicated type 1 diabetic patients with good metabolic control, plasma lipids are in general fairly normal. However, levels of lipoproteinlipase (LPL), an important enzyme in LDL-cholesterol metabolism, decrease in insulin deficiency, and, accordingly, less well-controlled type 1 diabetic patients may have higher levels of LDL (Reaven 1993). Intensive insulin treatment in patients with type 1 diabetes resulted in significantly reduced levels of total and LDL cholesterol and of triglycerides, while HDL levels increased (Rosenstock 1987).

Primary and secondary prevention of hyperlipidemia

Several secondary prevention studies have shown the advantage of lipid lowering therapy in patients with CVD (4S -94, Sacks -96, Sever 2003). Indeed, diabetic patients at increased risk of recurrent CVD events may experience greater risk reduction by lipid lowering than non-diabetic patients (Pyörälä 1997, Goldberg 1998).

Recently, lipid lowering has shown to be effective also in primary prevention of CHD in diabetic subjects (Elkeles 1998, Collins 2003, Colhoun 2004), although not all studies showed significant effects (Frick 1987, Downs 1998). As a consequence it is now recommended that all diabetic patients should be treated as aggressively as non-diabetic patients with established coronary heart disease (Expert Panel 2001, deBacker 2003).

Triglycerides

The role and relative importance of elevated serum triglycerides in atherogenesis have been debated. As control of triglycerides and HDL cholesterol is interlinked through lipoprotein lipase and hepatic lipase activity, it may not always be feasible to separate the contributions of triglycerides and HDL cholesterol to coronar artery disease (Turner 1998). It is well known from previous studies that triglyceride levels are associated with previous MI when univariate analyses are performed. However, as in our study, the relation is often attenuated when other factors, especially HDL cholesterol, are adjusted for. Nevertheless, a recent meta-analysis reported triglycerides to be an independent risk factor for CVD, even after adjustment for HDL cholesterol (Austin 1998). These results were confirmed by several subsequent studies (Vilbergsson 1998, Sprecher 2000, Sharrett 2001, Iso 2001, Lindqvist 2002), although not in all (Turner 1998).

The situation in women and in diabetic subjects might differ from that in mainly white male study populations. Several studies reported the association of triglyceride levels to CVD to be more pronounced in women than in men (Austin 1998, Vilbergsson 1998, Sprecher 2000, Iso 2001, Sharrett 2001). Hypertriglyceridemia is often associated with other CVD risk factors, and may, together with decreased HDL cholesterol, be a marker of a high-risk metabolic syndrome (Sprecher 2000). Furthermore, elevated triglycerides are a major determinant of small, dense LDL particles, which are considered to be highly atherogenic (Taskinen 1996). Haffner reported LDL size to be significantly smaller in diabetic compared with non-diabetic subjects of both sexes, but the association with hyperglycemia was stronger in women than in men (Haffner 1994).

The cutpoints for treatment of high triglyceride levels have decreased during the last decades. In the 1980's, the upper desirable triglyceride level was $\leq$2.8 mmol/l (NHLBI 1984). In the next decade, the level was lowered to $\leq$2.0 mmol/l (Läkemedelsverket 1999, Mosca 1999). However, as the risk of both subsequent diabetes, as shown in the present study, and the risk of future MI, as reported by Miller (Miller 1998), is increased at

considerably lower levels, the cutpoint for desirable TG should probably also be lower. Indeed, the American Heart Association (Mosca 2004) and also Swedish health authorities (Läkemedelsverket 2003) recently lowered the cutpoint from 2.0 to 1.7 mmol/l, above which treatment should be considered. However, these new guidelines were not published when the present study was done. In addition, optimal triglyceride levels should possibly be lower in women than in men (Mosca -99).

Smoking

Smoking is a well established risk factor for MI in both men and women (Wilhelmsson 1975, Nyboe 1991, Doll 2004, Hsia 2004), and, perhaps, even more so in women (Nyboe 1991, Njolstad 1996, Janzon 2004). Besides HDL-cholesterol, smoking was the only factor that was independently associated with MI in women with diabetes in the present study. This finding confirms the previously well-known connection of smoking and risk of MI in diabetes (Barrett-Connor 1091, Hanefeld 1996, Turner 1998). It might be that smoking constitutes a stronger risk for MI in women than men with diabetes (Chun 1997).

Blood pressure

Blood pressure regulation is very important in diabetic patients, with a strong effect on diabetes related complications and mortality (UKPDS 38). Vigorous control of blood pressure decreases the risk of CVD events even more in patients with than without diabetes (Hansson 1998, Tuomilehto 1999). Previous studies indicated that blood pressure reduction per se was important, whatever agents were used (Hansson 1998, Tuomilehto 1999). However, subsequent studies have indicated that inhibitors of the renin-angiotensin system might be better, because they influence CVD morbidity and mortality favourably, particularly in patients with diabetes (HOPE 2000, Lindholm 2002). Indeed, the beneficial effects of the renin-angiotensin inhibitors on diabetic late complications might be attributable to mechanisms beyond the blood pressure reduction (HOPE 2000). In the present study, blood pressure was not a significant risk factor for MI, irrespective of diabetes. An explanation might be the limited number of participants and high utilisation of antihypertensives (Table 5).

Oxidized LDL and inflammation

Several lines of evidence support that modified LDL may be a key antigen in atherogenesis. The general hypothesis was previously that high titers of antibodies to modified LDL were proatherogenic (Puurunen 1994, Salonen1992). However, subsequent reports indicated that the immune response might be anti-atherogenic rather than pro-atherogenic and that immunisation of experimental animals with modified LDL leads to

dramatically enhanced IgG levels and inhibition of the progression of atherosclerosis (Palinski 1995, Ameli 1996, Fredriksson 2003). Furthermore, T-cell clones responsive to oxLDL have been isolated from human atherosclerotic lesions (Stemme 1995). Shaw et al demonstrated that naturally occurring IgM antibodies, structurally and functionally identical to antibodies of B-cell origin, protecting against pneumococcal infections, block the macrophage uptake of oxLDL in apo-E deficient mice (Shaw 2000). A further study showed that immunization of LDL-receptor deficient mice with *Streptococcus pneumoniae*, resulted in a marked increase in titers of IgM antibodies to oxLDL, and a reduction of atherosclerosis development (Binder 2003). Furthermore, plasma from these mice had the ability to block uptake of oxLDL to macrophages (Binder 2003).

The lower titers of IgM among the women with diabetes and/or MI in the present study are in accordance with previous and subsequent studies where acute (Tsimikas 2003) or prior MI (Hulthe 1998) was associated with lower IgM titers than in controls. Furthermore, in patients with ACS, but not in patients with stable angina or in controls, a considerable increase in IgM titers following the acute event was registered (Tsimikas 2003). Moreover, in healthy subjects, IgM titers were inversely associated with carotid artery atherosclerosis (Hulthe 2001, Karvonen 2003). Thus the higher titer of IgM to oxLDL among the healthy women in the present study might reflect a protective function of the immune system.

In contrast with titers of IgM, IgG titers were higher in women with MI and/or diabetes than in controls in the present study. This is in agreement with a previous study including both men and women, in which levels of IgG antibodies to MDA-LDL were significantly higher in patients with coronary artery diasease and/or diabetes than in controls (Griffin 1997). It is also in accordance with other studies, reporting elevated titers of IgG antibodies to MDA-LDL in men with accelerated carotid atherosclerosis compared to controls without progress (Salonen 1992), in men with a previous MI (Tornvall 2003), and in patients with angiographically verified multivessel coronary artery disease or ACS compared with controls (Inoue 2001). Patients with acute MI were also demonstrated to have higher IgG antibody titers than controls (Inoue 2001, Tsimikas 2003). However, other studies showed no association between IgG titers and coronary atherosclerosis (McDowell 2002, van de Vijver 1996), or carotid intima-media thickness (Uusitupa 1996, Hulthe 1998).

Different techniques and different types of antibody preparations probably explain the conflicting results of the association of antibody titers to

oxidized LDL and atherosclerotic disease. Accordingly, during the last years, methods of analysing plasma levels of oxidized LDL by ELISA techniques based on the use of monoclonal antibodies have been developed. However, this technique was not available at the time of our study.

Subsequent studies including both men and women have shown that plasma oxLDL levels are positively associated with presence of coronary artery disease (Holvoet 2001), and severity of ACS (Ehara 2002). Increased levels of circulating oxLDL were demonstrated in subjects with impaired glucose tolerance compaired with normal glucose tolerance (Kopprasch 2002), and in diabetic compared with non-diabetic subjects with unstable angina (Ehara 2002). Furthermore, plasma levels of oxLDL were associated with carotid atherosclerosis (Hulthe 2002), and the metabolic syndrome, as well as LDL size in middle aged men (Sigurdadottir 2002). Kopprasch also reported a strong korrelation of oxLDL with levels of LDL cholesterol and triglycerides (Kopprasch 2002). Possibly, the difference in IgM titers between women with MI and/or DM and controls in the present study reflects an early, protective, immune response to the atherogenesis (Griffin 1997), while IgG titers may reflect atherosclerosis that is already manifest.

CRP

In recent years, the view of diabetes has widened from a disturbance in glucose regulation only to also include cardiovascular and inflammatory disburbances (Dandona 2004). Several lines of evidence suggest that inflammation plays an important role in atherosclerosis (Libby 2002). The presence of inflammation, as indicated by elevated CRP levels, predicts diabetes (Freeman 2002, Pradhan 2001, Hu 2004) and stroke (Rost 2001). Prior studies of the association of CRP to CVD were mainly limited to men. However, CRP is a strong, independent risk factor for CVD also in women, with the risk for MI or stroke being 7-fold in the highest quartile of CRP (Ridker -98). In accordance with this, the present study showed the highest CRP levels in diabetic women with MI, a group with high risk of recurrent CVD and death. Furthermore, the significantly higher CRP levels among the non-diabetic women without MI compared with controls, probably contributes to their increased future risk for MI (Haffner 1998), calling attention to the importance of careful prophylactic measures in this group of patients. In fact, Ridker reported CRP to be a stronger predictor of CVD events than LDL-cholesterol, at least in women (Ridker 2002).

Chronic inflammation is considered to be a component of the metabolic syndrome (Festa 2000). Accordingly, CRP levels were elevated in

prediabetic subjects with insulin resistance but not in those with a primary defect in β-cell function (Festa 2003). CRP was also reported to be higher in men with established or newly diagnosed diabetes compared with healthy controls (Sigurdadottir 2004).

It is probable that the positive association of CRP with body mass index, waist/hip ratio, systolic blood pressure and triglycerides and negative association with HDL cholesterol, in confirmation of previous studies (Mendall 1996, Rohde 1999), do contribute to the increased CVD risk. The positive correlation between HbA_{1c} and CRP in the present study, and reported previously by others (King 2003, Schillinger 2003), might indicate that a poor glycaemic control contributes to atherosclerosis not only by glycation but also by increased inflammation. Indeed, the Center for Disease Control and American Heart Association recently recommended assessment of CRP in patients at intermediate risk for CVD, for guidance in further treatment (Pearson 2003). Furthermore, in the present study CRP was inversely associated with IgM–antibodies to oxLDL, which strengthens the putative protective role of IgM antibodies.

Multiple risk factors

In the present study women with both diabetes and MI carried a very substantial risk factor burden (Paper I). Another finding was that women with diabetes but no prior MI had similar levels of CVD risk factors and inflammatory markers as the non-diabetic women who had suffered a MI (Paper I and II). This is in accordance with previous studies, where diabetic patients without prior MI had comparable risk of a primary MI as non-diabetic subjects with prior MI to develop a reinfarktion (Haffner 1998). Similar results were reported for mortality after MI (Mukamal 2001) and unstable angina and non-Q-wave MI (Malmberg 2000, Svensson 2004). However, these conclusions have been challenged by others, reporting a history of prior MI to be a more potent predictor of cardiovascular events than diabetes (Simons 1998, Lotufo 2001, Evans 2002).

A third novel observation from the present study was the association of even slightly elevated triglycerides with future diabetes. Furthermore, triglycerides are inversely correlated with HDL cholesterol (Turner 1998). In the prospective Tromsø study (Njolstad 1998), and in the MONICA Augsburg cohort (Meisinger 2002) low HDL-cholesterol was a significant risk factor for incident diabetes. Hence, the dyslipidemia preceding diabetes might contribute to the increased risk of myocardial infarction seen in diabetic women, and explain why diabetes duration and metabolic control are not so strongly associated with macrovascular complications in diabetes type 2 (Turner 1998, Fuller -01).

The association between serum triglycerides and diabetes found in the present study was independent of obesity and high blood pressure but BMI $\geq$ 27 kg/m^2 and SBP $\geq$ 145 mmHg at base-line were also independent predictors of diabetes. Increased triglyceride levels, obesity and hypertension constitute important components of the metabolic syndrome, which is a strong risk factor for major cardiovascular events and death in women (Kip 2004). This is important, reinforcing the fact that the risk of developing CVD in prediabetic women is increased already before the onset of diabetes (Hu 2002).

In accordance with the present study, an accumulation of CVD risk factors among men and women with diabetes, particularly dyslipidemia, hypertension and obesity, is well known from previous reports (Manson 1991, Stamler 1993, Adlerberth 1998, Hanefeld 1996, Vilbergsson 1998, Turner 1998, Fuller-01). Indeed, in the Multiple Risk Factor Intervention Trial, comprising a very large cohort of diabetic men but not including women, s-cholesterol, blood pressure and smoking accounted for two thirds of the excess deaths from CVD in diabetics (Stamler 1993) and findings in middle aged Göteborg men were similar (Rosengren 1989). In women with known CHD, the risk of reinfarction or death from coronary heart disease increased markedly in the presence of multiple CVD risk factors (Vittinghoff 2002).

Metabolic control

Tight metabolic control reduces the risk of microvascular complications in both type 1 (Holman 1983, Feldt-Rasmussen 1991, Reichard 1996, DCCT 1993) and type 2 diabetes (UKPDS 33, Gaede 2003). Logically, an improved glycemic control would reduce the risk for future macrovascular diabetic complications as well. However, until recently an unequivocal effect by improved glycemic control on macrovascular complications had not been demonstrated (Knatterud 1978, Abraira 1997). In the Diabetes Control and Complications Trial (DCCT), intensive insulin treatment of young patients with type 1 diabetes did indeed reduce the incidence of cardiovascular events by 40 %. Still, the difference was not significant, probably due to the relatively young age of the participants and a small number of events during the 6.5 years mean follow-up time (DCCT 1995). Similarly disappointing results were reported from the United Kingdom Prospective Study of newly diagnosed type 2 diabetic patients. Intensive treatment resulted in a reduction of glycated hemoglobin by 0.9 % during the 10 year follow-up. However, the risk reduction for MI of 16 % was not significant (p=0.052), and stroke incidence was not improved at all (UKPDS 33).

In order to prevent CHD in patients with diabetes, tight glycemic control, although beneficial in other respects, is inadequate. Indeed, treating dyslipidemia and hypertension seems to be at least as important, if not more, in type 2 diabetes (Turner 1998). Accordingly, a recent study from the Steno Diabetes Center showed that intensive multiple risk factor intervention in patients with type 2 diabetes with microalbuminuria significantly reduced the risk of cardiovascular events by 50 % during 7.8 years follow-up (Gaede 2003). Furthermore, according to Collins (Collins 2003), several recent studies, such as the HPS study, the UKPDS and the HOPE studies, clearly illustrate the importance of controlling macrovascular risk factors beyond hyperglycemia in subjects with diabetes.

Prevention

One of the objectives of the present study was to explore the reasons for the loss of the female protection against CHD among women with diabetes. A conspicuous feature were the high risk factor levels among women with both MI and diabetes (Tables 4 and 5). Smoking and hypertension were more common, triglycerides higher, levels of HDL cholesterol lower, and plasma fibrinogen higher. In accordance with the SCORE project (Conroy 2003), a CVD risk estimation system based on a large European pool of datasets from general population samples, this accumulation of risk factors may well explain the 2-3 times increased risk of CVD among diabetic women.

Some risk factors for diabetes and CVD, such as elevated fasting glucose, overweight and low physical activity, are potentially reversible. Recent studies have shown that it is possible to reduce risk factors by life style intervention. Metabolic and lipid abnormalities improve with weight loss, exercise, smoking cessation and dietary modification. Previous studies of Swedish men (Eriksson 1991) and of Chinese men and women (Pan 1997) indicated that changes in diet and increased physical activity did prevent development of diabetes. These results were confirmed by the Finnish Diabetes Prevention Study (Tuomilehto 2001) and by the American Diabetes Prevention Program (Knowler 2002), showing that lifestyle intervention was particularly effective, as development of diabetes was reduced by 58 % in both men and women with impaired glucose tolerance. In a Swedish study of middle-aged women at risk for diabetes, one single counselling session on life-style changes resulted in beneficial effects in body mass index, blood pressure, physical activity, and dietary habits compared with a control group (Lidfeldt -03). Furthermore, life style changes in obese women without previous disease, resulted in weight loss and reduction in markers of inflammation and insulin resistance (Esposito

2003). Therefore, life style modification is the first line of therapy in patients at risk for, and with already developed, type 2 diabetes.

Limitations of the study

Study group size

A weakness of the present study is the limited number of women with both DM and MI in Papers I and II. As the prevalence of MI increases with age, the studied groups could have been larger if the upper age limit had been higher. However, the rationale for selecting 64 years as the upper limit was the advantage of using the MI-register and MONICA-population when recruiting patients and controls for the study. The MI register made it possible for us to identify all women who had been hospitalised for an MI during 1994-96, including not only those who were admitted to the coronary care unit (CCU). The MONICA population is well suited to serve as a control group, as it is a random sample of the general population. However, neither the MI register nor the MONICA-population comprises subjects older than 64 years.

The selection process resulted in a lower mean age in control women than in women with DM and/or MI, as the proportion of women aged 45 to 50 years was higher among controls than in the other groups with consecutively included women. To handle this, we did not match the patients and controls for age, but adjusted for age and other relevant factors in the analyses when appropriate.

Previous studies have shown that total cholesterol and LDL-cholesterol levels increase when women become postmenopausal (Lindquist 1985, Jensen 1990. Matthews 1994, Hall 2002). However, because of the very strong intercorrelation between menopause and age, there was in the present study no independent effect of menopause. Therefore we adjusted for age but not menopause in the analyses. Furthermore, no studies have shown a rise in CVD morbidity or mortality at menopause, and consequently it seems that age rather than menopause influences coronary risk in women (Tunstall-Pedoe 1998, Barrett-Connor 1997).

Even if the risk of MI is considerably increased in women with diabetes, the number of surviving women who were possible to include in Study I and II during the three years was limited. We have no information on mortality before hospital admission among women in the studied population. Prehospital mortality was reported to be higher in men than in women (Sonke 1996, Rosengren 2001, Macintyre 2001), but did not differ between diabetic and non-diabetic subjects with a first MI (Lehto 1994).

Also, Miettinen reported similar prehospital mortality in women with and without diabetes (Miettinen 1998). If an increased prehospital mortality contributed to the low number of women in the present, it would probably have underestimated, rather than exaggerated the differences.

Definiton of diabetes

In both cohorts of patients with MI/ACS of the present study (Paper I-II and IV), diabetes was defined by self report or by registration in medical records, which is a limitation. However, this is the method used in most studies of diabetes and CHD. With a more sensitive method for diagnosis, i. e. an oral glucose tolerance test (OGTT), the prevalence of diabetes would most probably have been higher. However, for screening purposes in large populations, such as in the ACS study, OGTT is difficult. For the case-control study (Paper I-II) an OGTT was not included. A proportion of patients in the present study with undiagnosed DM was therefore probably classified as non-diabetic. However, this potential misclassification would rather have attenuated than exaggerated the differences between the groups.

Combining type 1 and type 2 diabetes

An objection to our study could be that women with both type 1 and type 2 diabetes were included. Age at onset and method of treatment are somewhat arbitrary criteria for classification of type 1 and 2 diabetes. However, only five women in the present study (Papers I and II), all without MI, were diagnosed with diabetes after age 35 and starting insulin treatment within one year of diagnosis. The classification of type 1 diabetes in these cases was subsequently confirmed by analyses of GAD-antibodies showing elevated levels.

Although macrovascular disease is the major complication of type 2 diabetes, one out of four, or 26 %, of the women with both diabetes and MI in Paper I and II of the present study had type 1 diabetes. This reflects the increased risk of MI also in type 1 diabetes, and is in accordance with previous studies (Borch-Jensen 1987, Rossing 1996, Laing 2003). Moreover, in the study by Laing et al, mortality rates in women with type 1 diabetes were not only greater than for non-diabetic women, but were also considerably higher than for men without diabetes. In addition, in type 1 diabetic patients below age 40, coronary mortality was similar in women and men. At ages over 40 years, mortality was higher in diabetic men than in women with diabetes, but the difference was smaller than among non-diabetic subjects (Laing 2003). Similar rates of cardiovascular mortality in men and women with type 1 diabetes were also reported by others (Borch-Jensen 1987, Rossing 1996, Krolewski 1997). The mean age of 56 years and a diabetes duration of 30 years among the type 1 women of the present

study is in accordance with previous studies, reporting diabetes duration (Koivisto 1996, Lehto 1999), and age (Krolewski 1987, Koivisto 1996, Rossing 1996) as risk factors for CHD in type 1 diabetes. However, in the Steno study, diabetes duration in type I diabetes was not related to cardiovascular mortality (Borch-Johnsen 1987).

The effect of other risk factors for CHD, such as high blood pressure (Rossing 1996. Fuller 2001), smoking (Rossing 1996), and disturbed lipid levels (Koivisto 1996), seem to be similar in both types of DM. Accordingly, a recent study of type 1 diabetic patients showed that except age and albumin excretion rate, fasting triglycerides, HDL-cholesterol and blood pressure were signifikant predictors of CHD in women (Soedamah 2004). Because both types of diabetes carry increased CHD risk, and as separating the diabetes types would have limited group sizes even more, the women in the study were considered together, irrespective of diabetes type.

Implications for the future

The present data indicate that the atherosclerotic process, with a concomitant inflammatory response, might already be well under way in women with diabetes even in the absence of clinical signs of atherosclerosis. Furthermore, increased levels of CVD risk factors in the pre-diabetic phase might be of great importance for the subsequent risk of MI in subjects who later develop diabetes. Therefore, elevated triglycerides should be concerned at least in women. The accumulation of modifiable CVD risk factors in women with diabetes, and in women at risk of diabetes, indicate the importance of implementing well-known non-pharmacological and pharmacological measures directed towards metabolic control, weight reduction, increased physical activity, smoking cessation, and effective treatment of hyperlipidemia and hypertension to attenuate the risk for future cardiovascular disease. Both primary and secondary preventive measures are therefore of considerable importance to decrease morbidity and mortality among women with diabetes. Furthermore, as symptom presentation, clinical course and prognosis differ between the sexes, it is important to analyse men and women separately in studies on diabetes and ACS.

CONCLUSIONS

- Women with diabetes who have manifested a MI carry a very substantial cardiovascular risk factor burden.

- The findings also indicate a pronounced inflammation and differentiated immune response against modified LDL that might result in a more aggressive atherosclerotic process in women with diabetes and/or MI.

- Women with diabetes but no MI have a similar risk factor profile as non-diabetic women with manifest coronary disease.

- Among previously healthy middle-aged Swedish women even slightly elevated triglyceride levels and moderately increased blood pressure and body mass index have a strong influence on diabetes risk independent of other factors.

- The accumulation of unfavourable risk factors in women long before diabetes has developed, might contribute to the increased risk of cardiovascular disease found in women with diabetes.

- In patients admitted to hospital with ACS, women with diabetes more often present with ST-elevation, are more likely to develop Q-wave MI, and have a worse prognosis than non-diabetic women, whereas the difference between men with and without diabetes is less pronounced. These findings suggest a different effect of diabetes on the pathophysiology of ACS based on the patient's sex.

- The results of the present study emphasize the importance of analysing men and women separately in studies on ACS and diabetes.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: Diabetes mellitus är en metabol sjukdom som orsakar förhöjt blodsocker beroende på för liten insulinproduktion, nedsatt insulinkänslighet eller en kombination av båda dessa faktorer. Förekomsten av framför allt typ 2 diabetes, som ofta har samband med övervikt, låg fysisk aktivitet, förhöjda blodfetter och högt blodtryck, ökar kraftigt. Beräkningar visar att diabetesfrekvensen kommer att fördubblas till år 2030, då man förväntar att ca 350 miljoner människor i världen kommer att vara drabbade.

Kardiovaskulär sjukdom, dvs hjärtinfarkt, stroke och andra åderförkalkningssjukdomar, är den största enskilda orsaken till sjuklighet och död hos diabetiker. Medan förekomsten av diabetes i befolkningen är 3-6%, finner man att 20-25% av patienter med hjärtinfarkt har känd diabetes, en nästan lika stor andel har tidigare odiagnosticerad diabetes och ytterligare en andel har nedsatt glukostolerans, ett förstadium till diabetes. Studier har visat att bara ca 1/3 av patienter med hjärtinfarkt har normal glukosomsättning.

Diabetiker löper således en avsevärt ökad risk för hjärtinfarkt och kardiovaskulär död jämfört med icke-diabetiker. Vidare tycks kvinnor med diabetes vara särskilt drabbade. I Västvärlden har dödligheten i kranskärlssjukdom minskat de senaste årtiondena. Emellertid har dödligheten minskat i mindre grad bland män med diabetes, medan den inte har minskat, eller, enligt vissa forskare, till och med har ökat, bland kvinnor med diabetes.

Det är välkänt att rökning, högt blodtryck, övervikt och blodfettrubbning har stor betydelse för utvecklingen av ateroskleros, en process där även immunsystemet och inflammatorisk aktivitet tycks spela en viktig roll. Diabetiker har en mer uttalad ateroskleros än icke-diabetiker och karaktäriseras ofta av ett ogynnsamt kardiovaskulärt riskfaktormönster. Oftast finner man ingen skillnad mellan diabetiker och icke-diabetiker vad gäller nivåer av total- och LDL kolesterol, medan förhöjda triglycerider och sänkt HDL-kolesterol är vanligare hos diabetiker. Förhöjt LDL kolesterol medför visserligen samma ökade risk för hjärtinfarkt hos diabetiker och ickediabetiker, men den absoluta risken är avsevärt högre hos diabetiker. Emellertid finns det inte så många studier där man undersökt hur dessa faktorer bidrar till risken för hjärtinfarkt hos kvinnor med diabetes.

Vid akut koronarsyndrom (ACS), dvs hjärtinfarkt och instabil kärlkramp, tycks diabetiker uppvisa annorlunda symtom, sjukdomsförlopp och prognos än icke-diabetiker, men den kliniska bilden hos speciellt kvinnor med diabetes är inte så väl belyst.

Syfte: Syftet med projektet är att belysa frågan om varför diabeteskvinnor förlorar skyddet mot hjärtinfarkt. Vi undersökte därför kardiovaskulära riskfaktorer som karaktäriserar kvinnor med diabetes och genomgången hjärtinfarkt i jämförelse med infarktkvinnor utan diabetes, diabeteskvinnor utan infarkt och friska kontroller. Vi studerade också sambandet mellan immunsvaret, speglat av antikroppstitrar mot oxiderat LDL-kolesterol, CRP, som markör för inflammation, diabetes och hjärtinfarkt hos kvinnor. Vidare undersökte vi faktorer av betydelse för risken att utveckla diabetes och effekten av diabetes på kliniska symtom, sjukdomsförlopp och prognos hos kvinnor och män med ACS.

Metodik: Kvinnor med (n=29) och utan (n=64) diabetes som haft hjärtinfarkt 1994-96 jämfördes med diabeteskvinnor som inte haft hjärtinfarkt (n=46) och friska kontroller (n=125). Riskfaktorer för hjärt-kärlsjukdom registrerades med hjälp av frågeformulär, mätningar av kroppsmått och blodtryck och blodanalyser (studie I). Vidare bestämdes antikroppar mot oxiderat LDL-kolesterol och CRP som mått på immunsvar och inflammatorisk aktivitet (studie II).

1979-81 undersöktes 1351 ur befolkningen slumpvist utvalda, tidigare friska kvinnor, 39-65 år gamla, med frågeformulär, kroppsundersökning och blodanalyser. Utveckling av diabetes i denna grupp studerades vid en uppföljning 1997-98 (studie III).

Vidare undersöktes inom ramen för Euro Heart Survey ACS 6488 män (21,2% diabetes) och 2809 kvinnor (28,7% diabetes) som vårdats på europeiska sjukhus med diagnos ACS. Symtom, vårdförlopp och prognos bedömdes med hjälp av registerdata (studie IV).

Resultat: Diabeteskvinnor med hjärtinfarkt hade kraftigt förhöjda nivåer av konventionella riskfaktorer. De var i högre utsträckning rökare och mer fysiskt inaktiva än de övriga kvinnorna, hade signifikant högre midje/stuss omfång och s-triglycerider, och signifikant lägre HDL-kolesterol än diabeteskvinnor utan hjärtinfarkt. Infarktkvinnor utan diabetes hade intermediära värden för dessa parametrar. Såväl kvinnor med diabetes som de med hjärtinfarkt hade ett rubbat immunsvar med signifikant högre titrar av IgG och lägre titrar av IgM antikroppar mot oxiderat LDL. Vidare hade de högre CRP nivåer än de friska kontrollkvinnorna.

Förhöjda triglycerider, övervikt, högt blodtryck och låg fysisk aktivitet ökade risken för senare utveckling av diabetes. Även lätt förhöjda triglycerider, dvs nivåer som normalt inte anses indikera ökad risk för kardiovaskulär sjukdom, medförde avsevärt ökad risk för diabetes oberoende av övriga faktorer.

Vid ACS påverkade diabetes sjukdomsbilden på olika sätt hos män och kvinnor. Kvinnor med diabetes utvecklade signifikant oftare ST-höjning på EKG, Q-vågs infarkt och hade också ökad sjukhusmortalitet jämfört med kvinnor utan diabetes. Män med diabetes hade större benägenhet att utveckla instabil kärlkramp och icke-Q-vågs infarkt jämfört med män utan diabetes, men skillnaden var inte signifikant vid justering för bakgrundsfaktorer.

Slutsats: Diabeteskvinnor med genomgången hjärtinfarkt har avsevärt förhöjda nivåer av kardiovaskulära riskfaktorer. Fynden indikerar också en förändrad immunrespons mot modifierat LDL-kolesterol och en mer uttalad inflammation hos kvinnor med diabetes och/eller hjärtinfarkt jämfört med friska kvinnor.

Diabeteskvinnor utan hjärtinfarkt har en riskfaktorprofil som mer liknar infarktkvinnorna än de friska kvinnorna.

Bland tidigare friska medelålders kvinnor innebär även lätt förhöjda triglycerider en betydligt ökad risk för diabetes under 18 års uppföljning, oberoende av ålder, vikt, blodtryck och fysisk aktivitet.

Förekomst av rubbade riskfaktornivåer redan innan diabetes diagnostiseras skulle kunna bidra till den ökade hjärtinfarktrisken hos kvinnor med diabetes.

Vid ACS medför diabetes en högre sannolikhet för ST-höjning på EKG, utveckling av Q-vågs infarkt och sämre prognos hos kvinnor, medan skillnaderna mellan män med och utan diabetes är mindre uttalade. Detta skulle kunna tala för att diabetes har olika effekt på patofysiologin vid koronarsjukdom hos kvinnor och män.

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