

Epidemiology of risk factors for cardiovascular disease in diabetes and impaired glucose tolerance

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Abstract

Diabetes mellitus is a strong risk factor for all manifestations of atherosclerotic vascular disease, coronary heart disease (CHD), cerebrovascular disease and peripheral vascular disease. Diabetes can be classified into two main subtypes, insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus (NIDDM). This review focuses only on NIDDM. Also, in impaired glucose tolerance (IGT), a precursor stage of diabetes, the risk of macrovascular disease is substantially increased. NIDDM and IGT are known to be associated with several adverse cardiovascular risk factors, including hypertension, obesity, central obesity, hyperinsulinemia and serum lipid and lipoprotein abnormalities, characterized mainly by elevated serum total triglycerides and low high-density lipoprotein cholesterol. Practically no information is available on the role of different cardiovascular risk factors to predict macrovascular complications in subjects with IGT. The role of different cardiovascular risk factors with respect to the risk of CHD, stroke and peripheral vascular disease will be discussed. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Diabetes mellitus increases the risk for all manifestations of atherosclerotic vascular disease (ASVD), coronary heart disease (CHD), cerebrovascular disease and peripheral vascular disease (PVD) [1]. CHD mortality and morbidity rates are two to four times higher in diabetic patients than in non-diabetic subjects. Also milder abnormalities in glucose tolerance are associated with an increased risk of CHD.

Diabetes can be classified into two main subtypes, insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus (NIDDM). It is generally believed that NIDDM is preceded by a precursor phase of asymptomatic hyperglycemia of variable duration. This prediabetic stage includes impaired glucose tolerance (IGT), a category between normal and diabetic glucose tolerance.

Both NIDDM and IGT are known to be associated with several adverse cardiovascular risk factors, including hypertension, obesity, central obesity, hyperinsulinemia and serum lipid and lipoprotein abnormalities, characterized mainly by elevated serum total triglycerides and low high-density lipoprotein (HDL) cholesterol [2–5]. Although much of the excessive CHD risk in these subjects can be accounted for by the high prevalence of these risk factors, a significant proportion of it remains unexplained. This implies that the excessive occurrence of CHD and other cardiovascular complications, particularly in NIDDM must be partly caused by diabetes itself or factors related to it or factors not yet classified.

2. Occurrence of atherosclerotic vascular disease in abnormal glucose tolerance

Several studies have indicated that in subjects with IGT the risk for macrovascular disease is substantially increased [1]. However, in the following review the

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emphasis will be given to NIDDM and on the role of different risk factors in predicting CHD, cerebrovascular disease and peripheral vascular disease in patients with NIDDM because data on IGT is limited in this respect.

2.1. CHD

Diabetic patients with myocardial infarction (MI) have a 2–3-fold higher mortality than non-diabetic subjects [6]. A major part of this excess mortality is explained by higher in-hospital mortality [7–9]. The most important mechanism increasing the mortality rate after MI in diabetic patients is cardiac failure. This has been found in studies conducted before [10] and during the thrombolytic era [11]. MI is more often silent in diabetic patients, leading to delayed diagnosis and treatment [12]. Despite evidence that infarct size is similar in diabetic and non-diabetic patients, the prognosis for diabetic patients after MI is worse [7,13].

The risk of fatal and non-fatal CHD is increased in diabetic patients compared to non-diabetic subjects, particularly among women [14–16]. The Framingham Study reported a relative risk (RR) for CHD mortality of 1.7 in diabetic men relative to non-diabetic men and 3.3 in diabetic women compared with their non-diabetic counterparts [17]. The age-adjusted incidence of CHD in the Multiple Risk Intervention Trial [18] was four times greater in diabetic patients than in non-diabetic subjects.

We have recently completed a study including 1059 patients (581 men, 478 women) with NIDDM, aged 45–64 years from two areas of Finland. The formation of this patient population has been described previously in detail [19]. These patients were followed for up to 7 years with respect to CHD events. Altogether 16.7% of the male and 12.8% of the female NIDDM patients died of CHD and 26.8% of the male and 20.9% of the female patients had a serious CHD event (death from CHD or non-fatal myocardial infarction) [20]. Diabetic men had 3–4 fold higher and diabetic women 8–11-fold higher risk for CHD than corresponding non-diabetic subjects ($P < 0.001$).

In another study from the Kuopio area [21] an excess CHD mortality was also found in elderly subjects with NIDDM. During the 3.5-year follow-up, 3.4% of non-diabetic and 14.8% of NIDDM subjects died from CHD or had a non-fatal MI.

2.2. Cerebrovascular disease

Higher mortality after stroke in diabetic patients, than in non-diabetic individuals, has been previously found in several studies [22]. Also population-based studies have indicated that the risk for stroke is considerably elevated in NIDDM.

The Multiple Risk Factor Intervention Trial determined the 12-year stroke mortality in 5163 men aged 35–57 years who reported taking medication for diabetes and in 324 815 men without a history of diabetes [23]. The risk of fatal non-hemorrhagic stroke was 3.8-fold (95% CI 2.7–5.3) higher among diabetic patients compared those without diabetes, independently of age, race, income, blood pressure, cigarette smoking and other CHD risk factors. In the Honolulu Heart Program [24] the relative risk of thromboembolic stroke for diabetic patients compared to non-diabetic subjects was 2.0 (95% CI 1.4–3.0).

In our study on 1059 patients with NIDDM, diabetic men had a 2–3-fold higher and diabetic women a 5-fold higher risk for stroke during 7-year follow-up than corresponding non-diabetic subjects [25]. Ischemic stroke was the most common cause of stroke in non-diabetic subjects and NIDDM patients in both areas.

In our 3.5-year follow-up study of elderly patients with NIDDM 3.4% of the non-diabetic subjects and 6.1% in NIDDM subjects had a fatal or non-fatal stroke [26]. The incidence of stroke was 2-fold higher in diabetic women compared to non-diabetic women.

2.3. Peripheral vascular disease

Several epidemiologic studies have shown a higher prevalence of absent peripheral leg and foot pulses in patients with diabetes than in non-diabetic subjects [27]. Exercise-induced leg pain, known as intermittent claudication, is strong evidence for PVD. In the Framingham Heart Study, the 34-year age-adjusted incidence of intermittent claudication was 2.7 times higher in male diabetic patients and 3.4 times higher in female diabetic patients than in men and women without diabetes [28].

Patients with NIDDM have 10–15-fold higher risk for lower extremity amputation than non-diabetic subjects [29,30]. Despite its clinical importance, amputation is probably the least well studied among all of the complications of diabetes.

In our study on 1059 NIDDM patients the incidence of amputation during the 7-year follow-up was similar in both genders (5.6% in men and 5.3% in women) [31]. Of the 58 first amputations performed during the study period, 31 (53.5%) were amputations of toes, 17 (29.3%) amputations were performed below the knee, and 10 (17.2%) above the knee.

Medial artery calcification (known also as Mönckeberg's arteriosclerosis (MAC)) is a condition which leads to the stiffening of the elastic layer of the arterial wall, but it does not obstruct the arterial lumen, in contrast to intimal artery calcification [32]. Whereas intimal calcification represents an advanced state of atherosclerosis, MAC has been related to aging and diabetes, especially to a long period of diabetes and its complications [33].

We have investigated the predictive value of medial artery calcification in relation to a 7-year cardiovascular disease mortality, CHD events, stroke and lower extremity amputation in 1059 patients with NIDDM [34]. Diabetic patients with medial artery calcification had significantly higher total mortality (38.0 vs. 22.3%; $P < 0.001$), CHD mortality (20.3 vs. 11.1%; $P < 0.001$) and stroke mortality (4.6 vs. 2.3%; $P < 0.05$) than patients without medial artery calcification.

2.4. Abnormalities in cardiovascular risk factors in subjects with IGT and NIDDM

Subjects with IGT and NIDDM have multiple abnormalities in cardiovascular risk factors including dyslipidemia, elevation of blood pressure, obesity, hemostatic factors, hyperinsulinemia and hyperglycemia.

2.4.1. Serum lipids and lipoproteins

In patients with NIDDM, the most common dyslipidemia is hypertriglyceridemia. This reflects an increase in the number of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein particles [2,3,35,36], already in IGT triglyceride and VLDL triglyceride levels tend to be elevated [37–39]. Hyperinsulinemia, insulin resistance and abdominal obesity [40] which are essential features of NIDDM and IGT, apparently play a central role in the development of increased hepatic VLDL triglyceride production.

The results concerning serum total and low-density lipoprotein cholesterol (LDL) levels in patients with NIDDM have been conflicting, some studies reporting elevated levels and other studies normal levels in patients with newly or previously diagnosed NIDDM, compared to serum total and LDL cholesterol levels in corresponding control subjects [1]. In subjects with IGT, plasma total and LDL cholesterol levels have been reported to be elevated [41] or normal [42] compared with those found in normoglycemic subjects. Compositional changes in LDL particles occur in NIDDM. The most important of these is the predominance of small, dense LDL particles, which have been associated with increased risk for CHD. In the Framingham Study population the impact of serum total cholesterol on the risk of cardiovascular disease was similar in diabetic patients and in non-diabetic subjects [43].

Most studies have shown a decrease in serum HDL cholesterol levels in patients with NIDDM compared to non-diabetic subjects of the same age and sex [1,44]. A decrease in the HDL₂ subfraction is responsible for the decrease of HDL cholesterol level in NIDDM [44].

2.4.2. Blood pressure

The prevalence of essential hypertension in patients with NIDDM is greater than in the general population [45]. The cause of higher risk of hypertension in patients with NIDDM is unknown but it is associated with insulin resistance and hyperinsulinemia [46].

2.4.3. Obesity

Obesity is a modifiable cardiovascular risk factor that is far more prevalent in patients with NIDDM than in the general population [47]. Obesity [48] and upper body (central or abdominal) obesity, measured as waist-to-hip ratio, increases the risk for NIDDM in both cross-sectional and prospective studies [49]. Obesity has an important role in the development of plasma lipid and lipoprotein abnormalities, hypertension and hyperinsulinemia in diabetic subjects.

2.4.4. Hemostatic factors

Hemostatic abnormalities have been shown to be associated with NIDDM as well as the insulin resistance syndrome [1]. Several studies have demonstrated an increase of plasma PAI-1 in patients with NIDDM [50]. In addition, increased von Willebrand factor levels have been found in patients with NIDDM [51].

2.5. Association of cardiovascular risk factors with atherosclerotic vascular disease in NIDDM

There is practically no data available on cardiovascular risk factors predicting atherosclerotic complications in IGT and therefore the following review will focus solely on NIDDM.

2.5.1. Total and LDL cholesterol

In the Multiple Risk Factor Intervention Trial, the age-corrected incidence of CHD in diabetic patients was 4-fold that in non-diabetic subjects at any level of cholesterol [18]. Other population-based studies, including the Framingham Study [43] and the Whitehall Study [52], which also included women, have demonstrated that the predictive value of total cholesterol with respect to the risk of CHD death is similar in diabetic and non-diabetic subjects. In our study including 1059 middle-aged patients with NIDDM total and LDL predicted CHD events (Fig. 1) [53].

Contradictory results have been reported on the importance of high total cholesterol as a risk factor for stroke in patients with NIDDM. In our study high cholesterol predicted stroke events (Fig. 2) [25].

Hypercholesterolemia has been shown to be related to an increased occurrence of intermittent claudication in diabetic patients [54]. Lee et al. [55] found high serum cholesterol levels to be a positive predictor of LEA in American Indian women with NIDDM, but not in men. A non-significant trend toward increased

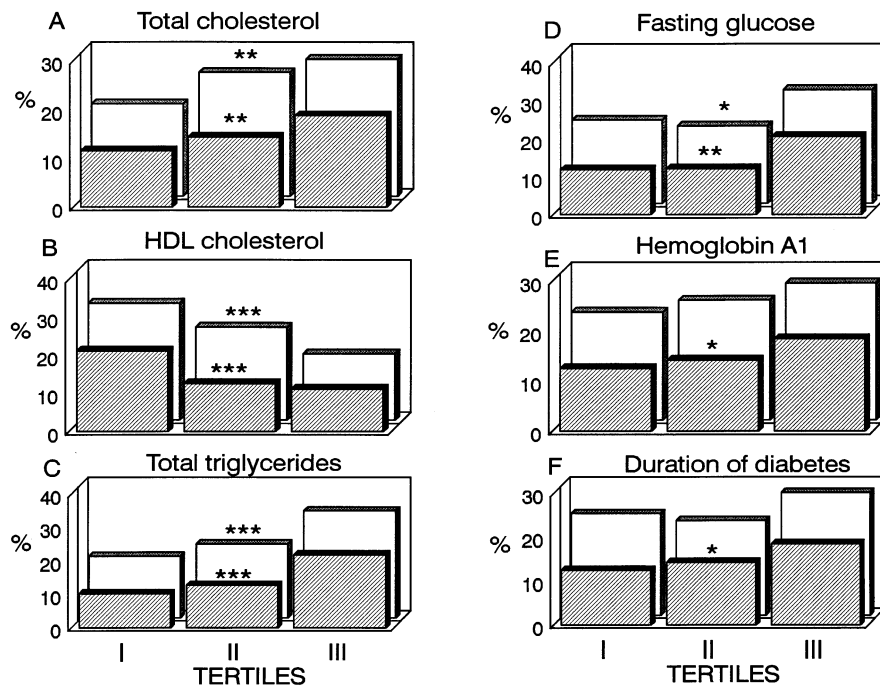


Fig. 1. A 7-year age-adjusted incidence (%) of CHD mortality (front panel) and all CHD events (CHD death or non-fatal myocardial infarction) (back panel) with respect to the tertiles of serum lipids, plasma glucose, glycated hemoglobin A₁ (GHbA₁) and the duration of diabetes: I, lowest; II, middle; and III, highest tertile. (A) Total cholesterol (low < 5.94 mmol/l; middle 5.94–7.20 mmol/l; high > 7.20 mmol/l). (B) HDL-cholesterol (low < 1.02 mmol/l; middle 1.02–1.30 mmol/l; high > 1.30 mmol/l). (C) Total triglycerides (low < 1.51 mmol/l; middle 1.51–2.60 mmol/l; high > 2.60 mmol/l). (D) Plasma glucose (low < 9.6 mmol/l; middle 9.6–13.4 mmol/l; high > 13.4 mmol/l). (E) Glycated hemoglobin A₁ (low < 8.9%; middle 8.9–10.7%; high > 10.7%). (F) Duration of diabetes (low < 6.0 years; middle 6.0–9.0 years; high > 9.0 years). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, for the trend over the tertiles. Adapted from Lehto et al. [53].

risk with higher cholesterol levels was also observed among Pima Indians. In our study hypercholesterolemia did not predict LEA (Fig. 3) [31].

2.5.2. HDL cholesterol

Several studies indicate an inverse relationship between HDL cholesterol and the risk of CHD in non-diabetic subjects [56] and in patients with NIDDM [57]. Our study, in which all lipoprotein fractions were determined by ultracentrifugation techniques in 313 NIDDM patients, demonstrated that the most powerful single lipoprotein risk factor for CHD was low HDL cholesterol. Low HDL cholesterol increased the risk of CHD death 4-fold and the risk of all CHD events, 2-fold [5].

An inverse association between HDL cholesterol and stroke has been reported in non-diabetic subjects [58]. Our study demonstrated that low HDL cholesterol is a predictor of stroke in patients with NIDDM (Fig. 2) [25].

HDL cholesterol levels are inversely related to PVD in non-diabetic subjects [59] and in patients with NIDDM [54,60]. Also in our study low levels of HDL cholesterol were weakly associated with the risk for LEA (Fig. 3) [31].

2.6. Blood pressure

The relationship of blood pressure to cardiovascular disease morbidity and mortality has been reported to be similar in diabetic patients and in non-diabetic subjects [1]. The recent study, including 4714 diabetic patients aged 35–55 years and participating in the WHO Multinational Study, demonstrated that patients with NIDDM and hypertension and proteinuria had a 5-fold mortality risk among men and a 8-fold mortality risk among women compared with those without hypertension and proteinuria [61]. According to several studies, hypertension and particularly elevated systolic blood pressure are dominant risk factors for CHD both in non-diabetic and in diabetic subjects [18].

Hypertension is the single most important risk factor for stroke in non-diabetic subjects [62] as well as in diabetic patients [63]. Also our own study confirmed the finding that hypertension is an important risk factor for stroke in NIDDM patients [25].

High blood pressure level is a significant risk factor for amputation in NIDDM [55]. Selby and Zhang [64] found in their large case-control study, including 10 068 diabetic patients (primarily non-insulin-dependent) with on average 13.2 years follow-up, that baseline systolic blood pressure was an independent predictor of ampu-

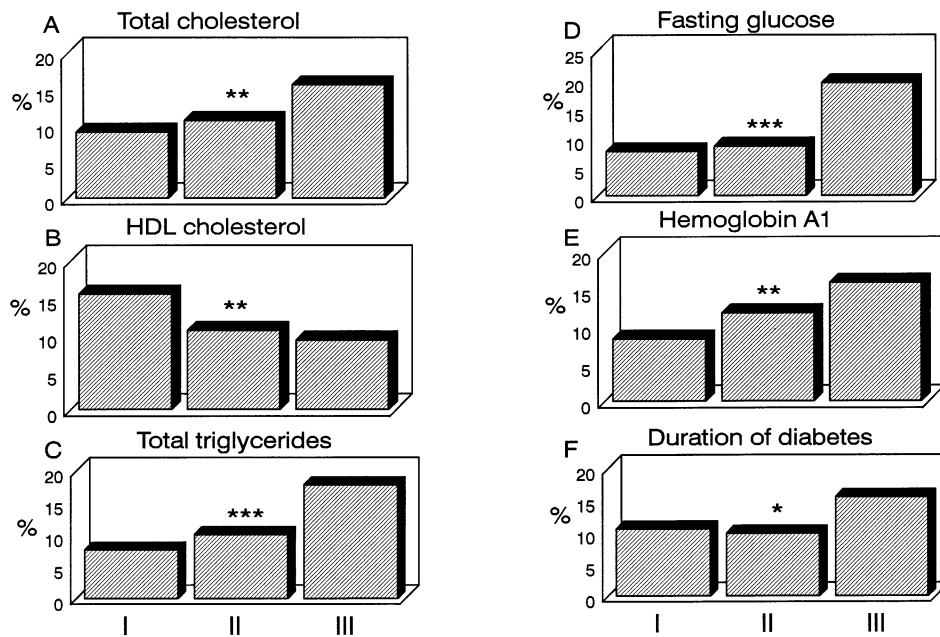


Fig. 2. A 7-year incidence (%) of fatal or non-fatal stroke according to the tertiles of serum lipids, plasma glucose, glycated hemoglobin (GHbA₁) and duration of diabetes: I, lowest; II, middle; and III, highest tertile. (A) Total cholesterol (low < 5.94 mmol/l; middle 5.94–7.20 mmol/l; high > 7.20 mmol/l). (B) High-density lipoprotein (HDL) cholesterol (low < 1.02 mmol/l; middle 1.02–1.30 mmol/l; high > 1.30 mmol/l). (C) Total triglycerides (low < 1.51 mmol/l; middle 1.51–2.60 mmol/l; high > 2.60 mmol/l). (D) Plasma glucose (low < 9.6 mmol/l; middle 9.6–13.4 mmol/l; high > 13.4 mmol/l). (E) GHbA₁ (low < 8.9%; middle 8.9–10.7%; high > 10.7%). (F) Duration of diabetes (low < 6.0 years; middle 6.0–9.0 years; high > 9.0 years). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ comparison over tertiles. Adapted from Lehto et al. [25].

tation ($P = 0.004$). Moreover, it has been suggested that hypertension is independently associated with the progression of PVD [65].

2.6.1. Obesity

The importance of obesity as an independent risk factor for CHD remains controversial. Some [43,66], but not all [67], large long-term follow-up studies in non-diabetic subjects have shown an association between these two. Central obesity has predicted CHD in prospective studies independently of overall obesity in diabetic patients [68].

Obesity and especially central obesity are risk factors for stroke in non-diabetic subjects [66,69]. The impact of obesity and central obesity as risk factors for stroke or PVD in patients with diabetes has not been evaluated.

2.6.2. Microalbuminuria

The risk of cardiovascular mortality has been found to be associated with an increased urinary albumin and protein excretion rate independently of classic cardiovascular risk factors in patients with NIDDM [70,71]. The mechanisms behind this association are poorly understood. Increased urinary albumin excretion rate is often associated with adverse changes in cardiovascular risk factors [71,72]. Interestingly, a simultaneous occurrence of hyperinsulinemia and microalbuminuria identifies a group of subjects with a highly increased risk for

CHD [73].

Only a few studies have previously been published regarding the association between proteinuria and stroke. In Japanese and European prospective studies on diabetic patients, proteinuria predicted cerebrovascular disease [74,75]. On the other hand, Gall et al. found no significant relationship between baseline albuminuria and the mortality from stroke in their study based on a 5-year follow-up of NIDDM patients [70].

In our study of 1056 middle-aged NIDDM patients in whom total urinary protein concentration was available from the morning spot urine specimen cardiovascular mortality was higher in NIDDM subjects with clinical proteinuria than in those without proteinuria [76].

2.6.3. Glycemic control

Several studies have examined the relationship of fasting glucose levels to atherosclerotic complications in non-diabetic subjects [1,77]. In some studies a positive association between glycemia and atherosclerotic complications has been found, whereas other studies have not reported a significant association.

Several recent prospective studies have indicated that poor metabolic control could increase the risk of cardiovascular disease. Uusitupa et al. carried out a 10-year prospective study on newly detected patients with NIDDM aged 45–64-years in Kuopio, in eastern Finland [78]. High fasting blood glucose significantly predicted cardiovascular mortality in multiple logistic

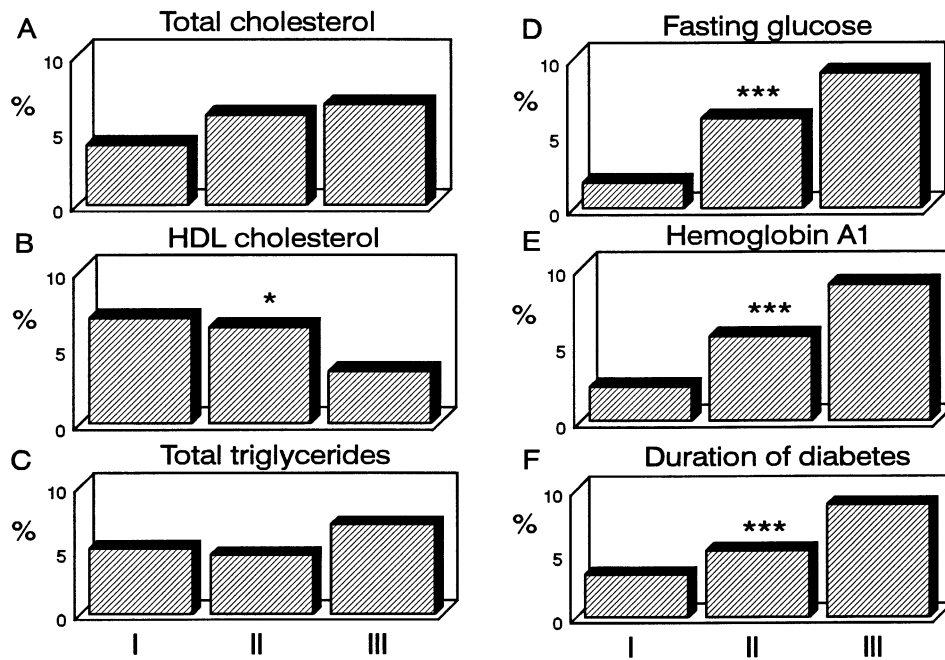


Fig. 3. A 7-year incidence (%) of lower extremity amputation according to the tertiles of serum lipids, plasma glucose, glycated hemoglobin A_{1c} and duration of diabetes: I, lowest; II, middle; and III, highest tertile. (A) Total cholesterol (low < 5.94 mmol/l; middle, 5.94–7.20 mmol/l; high > 7.20 mmol/l). (B) HDL cholesterol (low < 1.02 mmol/l; middle 1.02–1.30 mmol/l; high > 1.30 mmol/l). (C) Total triglycerides (low < 1.51 mmol/l; middle, 1.51–2.60 mmol/l; high, > 2.60 mmol/l). (D) Plasma glucose (low < 9.6 mmol/l; middle 9.6–13.4 mmol/l; high > 13.4 mmol/l). (E) Glycated hemoglobin A_{1c} (low < 8.9%; middle 8.9–10.7%; high > 10.7%). (F) Duration of diabetes (low < 6.0 years; middle 6.0–9.0 years; high > 9.0 years). * $P < 0.05$, *** $P < 0.001$ comparison over tertiles. Adapted from Lehto et al. [31].

regression analysis independently of other risk factors. Cardiovascular mortality was increased 3-fold in NIDDM patients included in the highest blood glucose tertile compared to the lowest blood glucose tertile irrespective of the mode of treatment.

Andersson studied the influence of long-term glycaemic control measured as annual values of fasting blood glucose in a cohort of all newly detected NIDDM patients diagnosed between 1972 and 1987 ($n = 411$) in a small Swedish community [79]. Glycaemic control was significantly related to survival and cardiovascular mortality.

In our study on elderly patients with NIDDM, hyperglycemia was significantly associated with the risk of CHD [21]. In that study there was a significant dose-response relationship between GHbA_{1c} and the risk of CHD death. A long duration of diabetes without concomitant high GHbA_{1c} increased CHD event rate considerably less than did high GHbA_{1c} with a short duration of diabetes. Also in another study by us including middle-aged patients with NIDDM high fasting glucose predicted CHD events (Fig. 1) [53].

Hyperglycemia predicts poorer prognosis after stroke and worsens the ischemic brain damage from a stroke in diabetic patients [80]. In the Wisconsin Epidemiological Study of Diabetic Retinopathy, high HbA_{1c} levels were significantly associated with stroke mortality in diabetic patients [81]. In our studies of middle-aged [25]

and elderly patients with NIDDM [26] poor metabolic control was a significant and independent predictor of stroke.

Studies on Pima Indians and Oklahoma Indians and the recent study from Nauru have shown that high fasting glucose and a long duration of diabetes are associated with a high risk of LEA [30,55,82]. This was also true in the study by Selby et al. [64], a prospective analysis of risk factors for LEA in a cohort of 10 068 patients with NIDDM. Klein [81] has demonstrated that high glycated hemoglobin was significantly associated with an increased risk of amputation in younger- and older-onset diabetic groups. Our study is consistent with these studies showing that high fasting glucose and a long duration of diabetes are associated with a high risk of LEA [31]. High GHbA and high fasting glucose were associated with a 2-fold risk for LEA.

2.6.4. Hyperinsulinemia and insulin resistance

Three prospective population studies in non-diabetic subjects, the Helsinki Policemen Study, the Paris Prospective Study and the Busselton Study, have independently shown that high plasma insulin is associated with an increased risk of CHD independently of other risk factors [1]. Similar results were obtained in a recent prospective study of CHD-free men in Quebec [83]. However, several other studies have failed to demonstrate an association between hyperinsulinemia and cardiovascular events [84].

The majority of patients with NIDDM are hyperinsulinemic, but information from prospective studies on high plasma insulin as a predictor of CHD in patients with NIDDM is limited and controversial [85]. Our unpublished results of the 7-year follow-up study indicate that in patients with NIDDM, hyperinsulinemia was associated with risk of death from cardiovascular disease and CHD, especially in men. No studies are available on the association between hyperinsulinemia and the risk for stroke or PVD in patients with NIDDM.

2.6.5. Hemostatic factors

The role of hemostatic factors as a risk factor for CHD has been established by several large prospective studies in non-diabetic subjects [86]. High levels of fibrinogen, PAI-1 activity, factor VII and von Willebrand factor predict CHD [87,88]. There are no studies on the impact of hemostatic factors on the risk of CHD, stroke or PVD in diabetic patients.

3. Summary of contribution of different cardiovascular risk factors to the risk of macrovascular disease in NIDDM

The relative contribution of different risk factors for macrovascular disease in NIDDM is possible to assess only in studies in which cardiovascular risk factors have been measured and correlated with the risk of CHD, stroke and PVD. As far as we know our study on 1059 middle-aged patients with NIDDM is the only study including a comprehensive evaluation of the role of different cardiovascular risk factors for macrovascular disease [19].

With respect to CHD, dyslipidemias, low levels of HDL cholesterol and high levels of total and LDL cholesterol as well as total triglycerides, are important risk factors (Fig. 1). Also poor metabolic control significantly predicts CHD events. The risk factor profile for stroke is somewhat different (Fig. 2). Hypertension and also dyslipidemias (particularly high cholesterol, low HDL cholesterol, high triglycerides) are significant predictors of stroke. The role of poor metabolic control in predicting stroke events is relatively more important than it is with respect to CHD. The most important risk factor for PVD is poor metabolic control (Fig. 3). In contrast to other manifestations of macrovascular disease, dyslipidemias do not consistently increase the risk for PVD.

In the prevention of macrovascular disease in patients with IGT and NIDDM, classic risk factors are as important as they are in non-diabetic subjects. Therefore, treatment for high cholesterol and blood pressure and the stopping of smoking should reduce the risk for all atherosclerotic complications although trial evidence

for this notion is still limited. In addition, high levels of triglycerides and low levels of HDL cholesterol should be a target of intervention. Because subjects with IGT and NIDDM are often obese, weight loss and physical activity should be encouraged. Finally, accumulating evidence indicates that poor metabolic control is associated with an increased risk for all manifestations of macrovascular disease. Therefore, the achievement of optimal glucose control should also be one of the cornerstones of treatment of diabetic patients, not only in the prevention of microvascular complications, but also in the prevention of atherosclerotic vascular disease in patients with NIDDM.

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