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Narrative Review Article

# Prediabetes and macrovascular disease: Review of the association, influence on outcome and effect of treatment

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ABSTRACT

Prediabetes is an intermediate metabolic state between normal glucose metabolism and diabetes mellitus. Patients with prediabetes have an increased risk (of up to 70%) of developing type 2 diabetes. Prediabetes is highly prevalent in patient with macrovascular disease including coronary artery disease, stroke and peripheral artery disease, persisting in the post-acute phase, which suggests true disturbance of glucose metabolism rather than a temporary reflection of stress. Moreover, the clinical and functional outcome in these patients is worse compared to patients with normal glucose metabolism. As the prevalence of prediabetes is growing rapidly, prediabetes might become an important modifiable therapeutic target in both primary and secondary prevention. Concerning primary prevention, lifestyle modification and to a lesser extend antidiabetic drugs decrease the risk of developing type 2 diabetes in patients with prediabetes. Furthermore, long-term follow-up studies showed that intensive lifestyle intervention, and/or medical treatment of cardiovascular risk factors reduced the incidence of macrovascular mortality and all-cause mortality in these patients as well.

As to secondary prevention, there is only little evidence that treatment of prediabetes in patients with macrovascular disease decreases the recurrence of macrovascular complications and improves outcome.

This review focuses on the association of prediabetes with outcome in patients with macrovascular disease, and the effect of treatment of prediabetes on the risk of developing macrovascular disease (in primary prevention) as well as on the outcome in patients with established macrovascular disease (secondary prevention).

## 1. Introduction

Prediabetes is an intermediate metabolic state between normal glucose metabolism and diabetes mellitus. Following diabetes mellitus, the prevalence of prediabetes is growing worldwide (up to 30% when aged 60 years or more). It is well known that prediabetes increases the risk of type 2 diabetes to up to 70% [1–3]. In addition, prediabetes is highly prevalent in patients with macrovascular disease. As macrovascular diseases like coronary artery disease, heart failure, stroke and peripheral artery disease are the leading cause of morbidity and case fatality in developed countries, treatment of associated risk factors like prediabetes could significantly lower this burden. However, whether prediabetes leads to an adverse outcome in patients with macrovascular disease and whether treatment of prediabetes leads to prevention of macrovascular disease in primary prevention as well as in secondary prevention, is less known.

This review focuses on the association of prediabetes with outcome in patients with macrovascular disease, and the effect of treatment of prediabetes on the risk of developing macrovascular disease (in primary prevention) as well as on the outcome after macrovascular diseases (secondary prevention).

## 2. Methods

A search of the literature was performed in the databases Medline, Embase, Cochrane Library and Web of Science.

Prediabetes was defined as an impaired fasting glucose of 5.6–6.9 mmol/L (100–125 mg/dL) and/or impaired glucose tolerance of 7.8–11.0 mmol/L (140–199 mg/dL) and/or HbA1C ranges of 38–46 mmol/mol (5.7%–6.4%) [4]. Also, the higher threshold for IFG of 6.1 mmol/L used by the WHO-criteria was included [5].

In Table 1 you will find the most important studies we used for this review, describing the prevalence of prediabetes, outcomes and limitations in different forms of macrovascular diseases.

## 3. Prevalence of prediabetes and association with outcome in macrovascular disease

The prevalence of prediabetes in patients with coronary artery disease varies between 19 and 36% in several studies, persisting in the

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**Table 1**
Summary of most important included studies.

| Study | Population | Event | Intervention | Glucose assessment | Number of patients | Prediabetes, n (%) | Outcome | Limitations |
|---|---|---|---|---|---|---|---|---|
| Bartnik [7] | Europe | Coronary artery disease | – | OGTT or FPG | 4196 (2107 acute and 2854 elective consultations) | 332 (36%) of acute CAD without known diabetes | Majority of patients with CAD have abnormal glucose metabolism and OGTT is needed to disclose these patients | The OGTT was only performed in 56% of patients without known diabetes |
| Norhammar [8] | Europe | Myocardial infarction | – | OGTT or FPG | 181 | 58 at discharge (35%) and 58 after 3 months (40%) | Prevalence of prediabetes (see column left) | Small sample size, no control group without myocardial infarction |
| Thrainsdottir [13] | Europe | Heart failure | – | OGTT or FPG | 19.381 | 1977 (10%) | The incidence of heart failure in prediabetic patients is 6% versus 3.2% in normal glycemic patients and 11.8% in diabetic patients | Older study (includes inhibitants of Reykjavik in 1966) with other criteria for heart failure and prediabetes |
| Berry [15] | Europe | Acute heart failure | – | Nonfasting plasma glucose levels (glucose at admission 8.0–10.99 mmol/L) | 454 | 60 (13%) | In hospital mortality and mortality and morbidity long term (median follow-up 812 days), were higher in patients with abnormal glucose tolerance and diabetes | No use of FPG or OGTT to determine IGT. |
| Kernan [25] | USA | Ischemic stroke and TIA | – | FPG & OGTT | 98 | 30 (31%) | Prevalence of prediabetes (see column left) | Small sample size. No repetition of glucose tests |
| Ivey [26] | USA | Ischemic stroke | – | FPG & OGTT | 216 | 37 (46%) | Prevalence of prediabetes (see column left) | Small sample size. No repetition of glucose tests |
| Vermeer [32] | Europe | Ischemic stroke and TIA | – | Nonfasting plasma glucose levels | 317 | 165 (5%) | IGT was associated with higher risk of future stroke, not with myocardial infarction or cardiac death. | No use of FPG or OGTT to determine IGT. No repetition of glucose tests. |
| Osei [34] | Europe | Ischemic and hemorrhagic stroke | – | FPG | 1007 | 213 (21%) | Prediabetes was associated with poor functional outcome or death and with no discharge to home. | Glucose levels measured in the acute phase after stroke, possibly reflecting an acute stress response. No repetition of glucose tests. |
| Golledge [37] | Australia | Peripheral arterial disease | – | FPG | 1637 | 460 (28.1%) | Patients with prediabetes had similar outcomes (mortality and PAD intervention) to patients without diabetes | No OGTT performed, relatively short follow-up of 2 years |
| Liu [42] | Asia | Metabolic syndrome and cardiovascular diseases | – | FPG | 30.378 | 6415 (21.1%) | The risk of cardiovascular diseases in patients with prediabetes and diabetes was higher in patients who also had the metabolic syndrome | No OGTT performed |
| Knowler [47] | USA | – | Metformin vs placebo vs lifestyle modification | OGTT and FPG | 3234 | All patients had prediabetes | Incidence reduction of diabetes 58% with lifestyle intervention and 31% with metformin (compared to placebo) | No information about confounders like weight loss, dietary changes and increased physical activity. |
| Perreault [50] | USA | – | Metformin vs placebo vs lifestyle modification | OGTT or FPG | 2775 | All patients had prediabetes | Using the Framingham score for 10-year CVD risk, the mean scores were highest in prediabetes group during 10 year follow-up. Restoration to normal glucose regulation and medical treatment of CVD risk factor can reduce the CVD risk. | No results op hard CVD outcome yet. Variability in glucose measures. |
| Li [51] | Asia | – | Lifestyle modification vs control group | OGTT | 577 | All patients had prediabetes | Lifestyle intervention in prediabetes can reduce incidence of cardiovascular diseases and all-cause mortality and diabetes | Different follow-up methods were used. Lack of information about changes in behavior and cardiovascular risk factors after lifestyle intervention (blood pressure, cholesterol etc.) |

CAD = coronary artery disease. OGTT = oral glucose tolerance test. FPG = fasting plasma glucose. IGT = impaired glucose tolerance. TIA = transient ischemic attack. PAD = peripheral arterial disease. CVD = cardiovascular disease.