Ten-year follow up on microvascular complications and risk factors for developing cardiovascular diseases: The Danish arm of Anglo-Danish-Dutch study of Intensive Treatment of people with Newly diagnosed diabetes in primary care (ADDITION-Denmark)

Investigators

Professor Annelli Sandbæk, Senior Researcher Morten Charles, Senior Researcher Else-Marie Dalsgaard, Professor Daniel Witte, Senior Researcher Nanna Borup., Professor Knut Borch-Johnsen, Professor Marit Eika and Professor Torsten Lauritzen, Department of Public Health, University of Aarhus, Denmark

Background

Type 2 diabetes mellitus (T2DM) is a common disease in Denmark. The prevalence is increasing 5% annually due to sedentarism, unhealthy lifestyle, and the demographic change towards more elderly in the Danish population. It is expected that around half a million Danes will have T2DM in 2020 (1). Since T2DM is associated to a substantial burden of premature mortality, morbidity, suffering and economical expenses to society (2), prevention of diabetes and it's complications are advocated by many stakeholders.

Most patients with T2DM are treated in general practice, and the general practitioner is therefore a key person in preventing diabetic macro- and microvascular complications, e.g. myocardial infarction, retinopathy, neuropathy. Treatment of individual risk factors such as blood pressure, cholesterol, and glucose is effective and may be more pronounced when achieved early in the course of the disease(8). Recommendations in Denmark for the prevention of diabetic complications includes early detection of diabetes, promotion of healthy lifestyle, and intensive pharmacological treatment from the diagnosis of T2DM (3). However, opinion leaders among general practitioners in Denmark has questioned the need for early intensive pharmacological treatment of hyperglycemia, as the evidence for this is based on a study performed more than two decades ago (4). In this way, uncertainties on the decision of early intensive pharmacological treatment can arise among practitioners. However, evidence from trials of intensive treatment of hyperglycaemia suggests that beneficial effects can be seen for microvascular outcomes even in the short term among patients with longstanding diabetes (5-7).

But, the evidence of treating these risk factors early in the trajectory of diabetes has so far been sparse.

The ADDITION study (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care) was the first study on early detection and intensive multifactorial treatment of type 2 diabetes in general practice. It was planned on basis of findings from the Steno 2 trial, where patients with longstanding diabetes had substantial benefits from multifactorial intensive treatment. The ADDITION study consisted of two phases: (i) a screening phase, and (ii) a pragmatic, cluster-randomized parallel group trial. The ADDITION trial was set-up to investigate whether intensive multifactorial treatment improved outcomes compared to routine care when commenced in the lead time between detection by screening and clinical diagnosis. Intensive treatment was associated with a small but significant improvement in HbA_{1c}, blood pressure and cholesterol and a non-significant 17% reduction in the composite cardiovascular endpoint over 5.3 years compared to routine care (8). General practitioners from Denmark, Holland, and England participated in the study.

Most of our knowledge of diabetic neuropathy (DN) stems from cross-sectional studies of selected diabetic populations. Suggested risk factors for DN in T1D include increased age, longer diabetes duration, poor glycemic control, hypertension, obesity, and cigarette smoking (9), whereas less is known about risk factors for DN in T2DM (10). In spite of earlier diagnosis and more aggressive treatments over the last decade, more than 60% of all T2DM patients still develop DN. It remains unclear why some patients with T2DM develop DN and others do not. Similarly, the reasons that only a proportion of patients with DN develop pain are unknown (11). While the metabolic syndrome has been shown to be associated with DN, studies investigating the role of specific components of the metabolic syndrome have yielded inconsistent results, and even the importance of glycemia is likely less than previously believed. In T1D, enhanced glycemic control substantially reduces the incidence of DN, but a recent meta-analysis of glycemic control in T2D failed to show a reduction in DN despite large trials (12). To improve the diagnosis, prevention, and treatment of DN, large-scaled population-based studies are needed to clarify the determinants of DN

development and prognosis in T2DM, including information on lifestyle factors, biomarkers, metabolic factors, drug use, and comorbidities.
In the Danish arm of the ADDITION study, patients were further examined for presence of diabetic neuropathy at the 5-year follow up examination. We found that in spite of early detection and intensive treatment around 1/3 of the patients in ADDITION Denmark had signs of diabetic peripheral neuropathy while around 1/5 had signs of cardiac autonomic neuropathy (13;14). Furthermore, we did not find a statistically significant difference between treatment groups in the presence of DN. However, outcomes tended to favor more intensive treatment. This trend is also found in results on nephropathy and retinopathy (15). Therefore, the 5 year duration of follow-up may have been too short to detect potentially clinically important differences between the two treatment groups. Further follow-up of the trial cohort may be justified, to examine whether early intensive multifactorial treatment reduces microvascular and macrovasucular risk in the long term as seen in the UKPDS and Steno2 studies (16;17).

Aims

We aim to assess whether the differences in intensity of treatment achieved in the first five years after diagnosis are associated with a reduction in microvascular complications over ten years among individuals with screen-detected diabetes in the *ADDITION-Denmark* trial cohort.

Our primary objective is to evaluate the effect of early intensive multifactorial treatment among people with screen-detected diabetes on presence of microvascular complications (neuropathy, nephropathy, retinopathy) and intermediate outcomes.

Our secondary objective is to identify risk factors for the development of diabetic complications with primary focus on diabetic neuropathy.

Methods

Study design

This is a two arm, cluster (general practice) randomised, open-label, parallel group, pragmatic trial of intensive multifactorial therapy in people with screen-detected type 2 diabetes in primary care. The methods have been reported (11, 14). Following recruitment, all participating practices in each centre were independently randomised to intensive treatment (IT) or routine care (RC). We undertook a program of population-based stepwise screening in participating practices among people aged 40 to 69 years who were not known to have diabetes (15). Individuals at high risk of diabetes were initially identified using self-administered questionnaires in Denmark (16). A stepwise process of screening using random glucose measurements and HbA_{1c}, followed by fasting glucose and OGTT as diagnostic tests was undertaken. Participants were diagnosed with diabetes according to the WHO criteria (20) including the requirement for confirmatory tests on separate occasions.

Study population

By the end of the screening phase of the *ADDITION* study, 182 GP practices had undertaken blood glucose screening of 28,031 in Denmark (15). In total 1,533 patients were recruited to the *ADDITION* study. In total 1278 persons, found to have type 2-diabetes by screening in the period 2001-2006 and who are still alive 1st of January 2015, will be invited to take part in the follow-up examination. The examination will include measurements of blood pressure, height, weight, waist circumference, retinopathy (ictures of retina), examination for prescence of cardial and peripheral neuropathy, nephropaty, hypercholesterolaemia and glucosemetabolism. Furthermore blood and urine will be collected and stored in a biobank and participants will be asked to answer a questionnaire on lifestyle and disease specific questions.

	Kbh	Århus	Sønderborg	Holstebro	Esbjerg	Total
N survivors Invited for basis examination	284	432	195	239	128	1278
Invited for extended neuropathy ex.	284	432	0	0	0	716
Invited for pulsewave velosity	284	0	0	239	0	523

Study intervention

Patients with screen-detected diabetes were cluster-randomised to routine care (according to national guidelines for the management of type 2 diabetes and prevention of CVD in primary care which were broadly similar across centres), or intensive treatment. In the intensive treatment group, practitioners received group or practice-based education and training in the provision of intensive multifactorial treatment according to agreed guidelines. This included lifestyle advice (concerning diet, physical activity, smoking cessation and medication adherence) with supporting educational materials for patients, prescription of aspirin, and stepwise increases in drug treatment of blood glucose, blood pressure and lipids in order to achieve and maintain lower levels of these risk factors than were recommended in national treatment guidelines (see study website for further details: http://www.addition.au.dk/).

Medical examinations to be used in the effect studies:

Microvascular:

- Retinopathy (ETDRS scale)
- Nephropathy (Albumin Creatinin Ratio, eGFR)
- Neuropathy (more examinations on peripheral and autonomic neuropathy)

Macrovascular:

- Pulse Wave Velocity
- Ankle Brachial Index

Other:

- HbA1c
- Total, HDL and LDL cholesterol and triglycerides
- Weight
- Waist
- Height
- Blood pressure

Patientreported, GP reported and register information to be used in the studies:

Patientreported from questionnaires:

- Mood (CES-D)
- Pain (BP1-SF Danish)
- Perception of help from therapists (PACIC)
- Health literacy (HLS-EU-Q16)
- Own role in treatment (PAM)

GP reported information for each participant:

- Results from blood and urine analysis as close to Dec. 31th 2014 as possible: HbA1c, P-Creatinine, lipid profile and Urine Alb/Creat ratio.
- Pharmaceutical treatment in the end of the year 2014

Register information will be obtained on:

- Comorbidities (from The National Patient Register)
- Medication use (from The Danish National Prescription Registry)
- Health care utilisation (from The National Health Service Registry and The National Patient Register)

Data collection

During 2015 and 2016 all participants will be invited to a follow up examination in a centre near the patient (Holstebro, Aarhus, Esbjerg, Sønderborg, Copenhagen). Data from examinations will be reported in electronic versions of Case Record Forms virtually placed at a server at Health AU (behind firewalls). Questionnaires will be given the patients in printed versions during the session together with a form for having the transport costs covered and an envelope with prepaid postage to be returned to the study coordinator.

Statistical analysis

Descriptive analyses

For continuous variables, means and standard deviations will be presented, unless the variable has a highly skewed distribution, in which case, medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of individuals within each category will be presented. For each variable (continuous or categorical), the % of missing values will be reported. No p-values will be calculated.

Analyses of study endpoints

For binary endpoints the number and percentage of individuals experiencing the endpoint will be presented, by randomised group. The denominator for calculating the percentage will be the number of individuals with data on that particular outcome. A logistic regression model will be used to estimate the odds ratio and 95% confidence interval for the comparison of the intervention group with the routine care group.

For continuous endpoints (eg e-GFR, Michigan score), a normal errors regression model will be used to estimate the difference in the expected value of the endpoint, and 95% confidence interval, comparing the intervention group with the routine care group. Where the endpoint is also available at baseline or at five years follow up (eg e-GFR), the difference in mean change from baseline will be modelled including the baseline measure as a covariate in the model.

Ethical and research governance considerations

All participants gave written informed consent to undergo screening for diabetes and to take part in the *ADDITION-Europe* study, and permitted access to information contained in medical records. The study has been undertaken according to Good Clinical Practice (GCP) guidelines. We will seek scientific ethics committee and research and development approval. The study is approved by the Danish Data Protection Agency (Datatilsynet journalnummer: 2014-54-0704).

Side effects

The follow-up examination has no side effects. There might be some discomfort in having taken the blood sample and the retinopathy test might have the inconvenience that for the next 1-3 hours things are seen less bright and sun light might impede. The electrophysiological procedures may cause slight discomfort due to the use of electrical stimulation.

Respect for physical and mental integrity

Participant in the examination are protected by the law for treatment of personal data and ‘Sundhedsloven’. All personal information is protected by patient confidentiality. The study is approved by the Danish Data Protection Agency (Datatilsynet journalnummer: 2014-54-0704). Information on health, medication and examination results will be stored anonymized.

Economic conditions

This examination is a 10 year follow-up of a cohort previous examinated initiated by Professor Torsten Lauritzen and Professor Annelli Sandbæk, Section for General Practice, Department for Public Health, Aarhus University. The follow-up examination is budgeted to 4 million DKK and is financed through funding from Novo Nordic Foundation. The person responsible for the examination has no economic connection to companies or funds.

Publication of research results

Results from the studies will be released at international research conferences and published in international peer reviewed journals. Both positive, negative and inconclusive results will be published.

Informed consent retrieval

All persons who were identified with type 2 diabetes in the ADDITION-study will be mailed a letter containing information on the 10-year follow-up examination with an invitation to take part in an elaborating, oral information meeting. The letter also holds a copy of the 'Informed consent'. Information on the examination will be repeated and elaborated oral at presence on the examination center. The oral information will be given individually and in an undisturbed environment. The participant is invited to bring a companion.

If the invited gives written informed consent to participate in the examination he/she will be offered an examination on the same day or the examination will be scheduled to a future date.

Compensation

The examination will be offered on a public hospital clinic and the participants are therefore covered by the patient insurance (Patientforsikringsordning). Participants will be compensated for travel expenditure.

Reference List

1. Stovring H, Andersen M, Beck-Nielsen H, Green A, Vach W (2003) Rising prevalence of diabetes: evidence from a Danish pharmaco-epidemiological database. Lancet 362: 537-538

2. Laakso M (2010) Cardiovascular disease in type 2 diabetes from population to man to mechanisms: the Kelly West Award Lecture 2008. Diabetes Care 33: 442-449

3. Type 2 diabetes - et metabolisk syndrom. 2012. Dansk Selskab for Almen Medicin. (GENERIC)Ref Type: Report

4. Anonymous(1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352: 854-865

5. Patel A, MacMahon S, Chalmers J, et al (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N.Engl.J.Med. 358: 2560-2572

6. Ismail-Beigi F, Craven T, Banerji MA, et al (2010) Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 376: 419-430

7. Duckworth W, Abraira C, Moritz T, et al (2009) Glucose control and vascular complications in veterans with type 2 diabetes. N.Engl.J.Med. 360: 129-139

8. Griffin SJ, Borch-Johnsen K, Davies MJ, et al (2011) Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 378: 156-167

9. Tesfaye S, Chaturvedi N, Eaton SE, et al (2005) Vascular risk factors and diabetic neuropathy. N.Engl.J.Med. 352: 341-350

10. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL (2012) Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 11: 521-534

11. Peltier A, Goutman SA, Callaghan BC (2014) Painful diabetic neuropathy. BMJ 348: g1799

12. Callaghan BC, Little AA, Feldman EL, Hughes RA (2012) Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane.Database.Syst.Rev. 6: CD007543

13. Charles M, Ejskjaer N, Witte DR, Borch-Johnsen K, Lauritzen T, Sandbaek A (2011) Prevalence of Neuropathy and Peripheral Arterial Disease and the Impact of Treatment in People With Screen-Detected Type 2 Diabetes: The ADDITION-Denmark study. Diabetes Care 34: 2244-2249

14. Charles M, Fleischer J, Witte DR, et al (2013) Impact of early detection and treatment of diabetes on the 6-year prevalence of cardiac autonomic neuropathy in people with screen-detected diabetes: ADDITION-Denmark, a cluster-randomised study. Diabetologia 56: 101-108

15. Sandbaek A, Griffin SJ, Sharp SJ et al (2014) Effect of early multifactorial therapy compared with routine care on microvascular outcomes at 5 years in people with screen-detected diabetes: a randomized controlled trial: the ADDITION-Europe Study. Diabetes Care. 2014 Jul;37(7):2015-23.

16. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N.Engl.J.Med. 359: 1577-1589

17. Gaede P, Pedersen O (2004) Intensive integrated therapy of type 2 diabetes: implications for long-term prognosis. Diabetes 53 Suppl 3: S39-S47