Original Research Article

Effect of Intensive Therapy Versus Routine Care on Peripheral Arterial Disease and Neuropathy in Patients with Type 2 Diabetes

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ABSTRACT
Background: There is limited evidence on how intensive multifactorial treatment (IT) improves outcomes of diabetes when initiated in the lead time between detection by screening and diagnosis in routine clinical practice.
Objective: We examined the effects of early detection and IT of type 2 diabetes in primary care on the prevalence of diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) 6 years later in a pragmatic, cluster-randomized parallel group trial.
Methods: We screened diabetic patients and divided our study into two phases. All the diabetic patients were grouped into two to receive either routin e care and intensive treatment. In the second phase we followed-up all patients and observed the diabetes related parameters and assessed the effect on peripheral artery disease and peripheral diabetic neuropathy.
Results: The mean duration of follow-up was 2.8 years for the control group and 3.5 years for the intensive treatment group. However, a modest reduction in HbA1c levels was seen in the intervention group. Both groups saw a notable decrease in systolic and diastolic blood pressure, as well as total cholesterol levels, which was consistent across the groups. During the follow-up period, there was a general rise in the percentage of individuals who utilised medicine. The effect on PAD and DPN was in favour of intensive therapy.
Conclusion: In a population characterised by the detection of type 2 diabetes by screening, it was shown that the implementation of intensive therapy subsequent to screening resulted in a statistically significant variation in the occurrence of DPN and PAD three years following the first diagnosis.
Keywords: Type 2 diabetes, diabetic peripheral neuropathy, peripheral arterial disease, Intensive therapy, Clinical outcome

INTRODUCTION

Diabetes mellitus (DM), which affects people from all socioeconomic backgrounds and continues to grow to pandemic proportions. Nearly half a billion people worldwide have diabetes, and in the following 25 years, that number is projected to rise by more than 50% [1]. The disease's numerous chronic consequences cause heavy economic, psychological, and physical costs. The primary vascular problems result in microvascular sequelae unique to diabetes in the retina, nerves, and glomerulus. Other conditions include atherosclerotic macrovascular disease in the heart, lower limbs, and brain [2]. With an estimated global frequency of 1.8% [3], lower extremity issues in diabetic patients are widespread, are on the rise, and impact roughly 131 million people globally. They have a major negative effect on the morbidity and mortality of DM patients, occasionally resulting in leg ulcers and amputations, which are typically accompanied by physical impairment, decreased productivity, and mental disorders. Peripheral artery disease (PAD) is a significant factor to the development of leg ulcers and amputations, despite the fact that neuropathy has received much attention as a cause [4]. As a result, PAD may not be properly identified or treated. A total or partial obstruction of one or more peripheral arteries in the upper or lower limbs that are not connected to the heart or the brain is referred to as PAD and may cause tissue loss or diminished blood flow [5]. Although embolism, thrombosis, fibromuscular dysplasia, or vasculitis can also cause it, atherosclerosis of the vascular wall is the

primary cause [5]. Systemic atherosclerosis in non-indicated by atherosclerotic PAD. The DM mostly affects the arteries in the lower extremities, particularly the distal arteries, particularly the dorsalis pedis artery[6]. Another major diabetic complication is a collection of clinical symptoms brought on by harm to the peripheral and autonomic nerve systems which are often known as various types of neuropathies [7]. These are brought on by diffuse and localised nerve system injury and affect up to half of all diabetics [8]. In the 'stocking and glove' distribution of distal symmetric polyneuropathy, the hands and lower limbs are frequently afflicted [9]. A constellation of autonomic neuropathies, such as cardiac autonomic neuropathy, gastrointestinal dysmotility, diabetic cystopathy, and impotence, can also manifest as widespread neuropathies related to peripheral intra-cerebral and coronary arteries may be diabetes [9. Focal neuropathies, however less frequent, include nerve root dysfunction that results in radiculopathy or polyradiculopathy or isolated mononeuropathies of the peripheral nervous system [10]. The available trial evidence on the prevention of diabetic peripheral neuropathy (DPN) and PAD in individuals with diabetes is currently insufficient. The objective of our study was to examine the impact of early detection and intensive multifactorial treatment (IT) on the prevalence of DPN) and PAD in patients with screen-detected type 2 diabetes. It is important to note that the existing knowledge on PAD and DPN in diabetes primarily comes from patients with clinically diagnosed and often long-standing diabetes. However, the prevalence of PAD and DPN in patients with screen-detected diabetes remains unknown.

MATERIALS AND METHODS

We divided our study in two distinct phases, namely a screening phase and a pragmatic, cluster-randomized parallel group trial. This study conducted in a single center having OPD for diabetic patients and all other facilities to detect the diabetes related parameters. Diabetic patients (40-69 years) were selected for study. The diagnosis of diabetes in these individuals was made based on the criteria established by the World Health Organisation (WHO), as previously outlined. A total of 286 peoplewith screen-detected diabetes in the randomised control group and 245 individuals in the intervention group, consented to participate in the experiment. A total of 80 individuals only sought medical care from their primary care physician, while five individuals were excluded from the study due to lack of participation in the administered tests and questionnaires. The individuals in question were eliminated from our analysis, resulting in a research sample size of 400 participants for the analysis given in this work (control 210 and intensive treatment190**Intervention**

The goal of the intensive treatment was to offer primary care patients the greatest possible evidence-based care. Based on the step-by-step procedure employed in the study our goal was to inform and assist general practitioners and practise nurses in target-driven treatment (using medication and promoting a healthy lifestyle) of hyperglycemia, blood pressure, and cholesterol. A number of new elements were added to diabetes care to enhance intensive treatment. Patients received instructional materials from the practise personnel, and when yearly check-up appointments were past due, patients received reminders. Although treatment goals were established and medication classes were advised, choices on prescriptions, including the choice of particular medications, were determined by practitioners and patients. General practitioners in the locations on each foot (plantar aspect of the great toe and first, third, and fifth metatarsal heads). Atypical control group only received the findings of diagnostic tests. Patients with diabetes who had been found by screening got the conventional pattern of diabetes management.

Measurements

According to normal operating protocols, centrally trained staff (blind to research group assignment) performed health evaluations at baseline and follow-up that included biochemical, anthropometric, and questionnaire measurements.

Demographics

Information on sociodemographic traits (education, employment, and ethnicity), dietary habits (smoking status and alcohol consumption), and self-reported cardiovascular disease (previous myocardial infarction, stroke, or operation/instrumentation on the heart) was gathered using standardised self-report questionnaires.

Blood pressure

Using Omron blood pressure recorders, participants were sat with the cuff on their right arm resting at the level of the heart. Blood pressure was measured as the mean of three measures taken after at least 10-min of rest.

Body mass index

sing a Tanita scale and a fixed rigid stadiometer, light indoor attire and no shoes were worn for the measurements of height and weight.

Urine analysis

At baseline and follow-up, all biochemical measurements were examined at the pathology department. Men's and women's albumin/creatinine ratios on spot urine were used to define microalbumiuria, whereas macroalbuminuria was classified as being >25 mg/mmol [11].

Sensory testing

A Semmes-Weinstein 10 g/5.07 monofilament was used for light touch sensory testing at four test behaviour was defined as the inability to feel one or more of the test locations (12). This is a single

predetermined threshold that is used to identify clear insensitivity. Following a routine methodology, the vibration detection threshold (VDT) was assessed on the dorsal side of the great toe next to the nail on both feet using a CASE IV and the 4-2-1 stepping algorithm (13).

Ankle brachial index

A Doppler MiniD900 med Huntleigh Transducer EZ8 Widebeam was used by qualified technicians to evaluate the ankle brachial index (ABI). Two measurements of brachial systolic blood pressure were taken in each arm after a 10-min nap in the supine position. After that, the arteria dorsalis pedis and the arteria tibialis posterior on each foot were alternately measured twice for distal systolic blood pressure (or three times if there was a difference of more than 10 mmHg). The maximum distal blood pressure divided by the highest brachial blood pressure from each side was used to determine ABI for each foot. Low ABI was outlined as being at least 0.9.

Assessment of neuropathy

The Michigan Neuropathy Screening Instrument (MNSI)'s questionnaire portion was given to the patients, who were then rated in accordance with their responses. Scores below 7 were deemed abnormal (14). Additionally, patients filled out a brief questionnaire for the Brief Pain Inventory (15). Patients were considered to have painful diabetic neuropathy if they reported suffering from pain in both of their arms or both of their legs (from the elbow down).

RESULTS

Table 1 displays the initial and subsequent attributes of the participants. The mean duration of follow-up was 2.8 years for the control group and 3.5 years for the intensive treatment (IT) group. There was no significant change in the median HbA1c levels over the follow-up period for both groups. However, a modest reduction in HbA1c levels was seen in the intervention group. Both groups saw a notable decrease in systolic and diastolic blood pressure, as well as total cholesterol levels, which was consistent across the groups. During the follow-up period, there was a general rise in the percentage of individuals who utilised medicine. In the control group, there was a notable rise in the number of individuals who were prescribed antihypertensive medicines, rising from 17.6% to 49.04% over the follow-up period. The proportion of individuals utilising lipid-lowering medications had a notable rise, surging from 15.2% to 31.9%. Within the IT group, the respective proportions experienced a growth from 30.5% to 63.2% and from 27.9% to 46.3%. During the follow-up period, 55% of participants in the control group and 67% of participants in the intervention group reported the use of antiglycemic medicines. There was a notable decrease in the prevalence of smoking among participants in both groups, with no statistically significant difference seen between the groups. Additionally, there was a decrease in overall alcohol intake. A decrease in the body mass index (BMI) was seen compared to the initial measurement.

Table 2 displays the incidence rates of low ankle-brachial index (ABI) and several assessments of diabetic peripheral neuropathy (DPN). The impact of intervention is quantified in terms of an odds ratio. The average values of the normal deviates of VDT in each foot were found to be greater in the RC group when compared to the IT group. However, it is important to note that this difference did not reach statistical significance. The baseline measures of neuropathic pain symptoms, as assessed by the NPSI, showeda significant difference between the control versus intensive treatment group.3). By the fourth week, a notable distinction emerged between the intensive treatment and routine care groups in terms of overall pain score ($P \leq 0.001$), superficial spontaneous pain ($P \leq 0.001$), deep pain ($P = 0.03$), paroxysmal pain ($P \leq 0.001$), and paraesthesia ($P = 0.01$). Significant differences were seen at the follow-up for all sub-scores, including overall pain ($P \leq 0.001$), superficial pain ($P \leq 0.001$), deep pain ($P = 0.002$), paroxysmal pain ($P \leq 0.001$), and paraesthesia ($P \leq 0.001$

Table 1: Disease related Basic characteristics at baseline and at follow-up

Patient characteristics	Baseline		Follow-up (3 years)	
	Control	Intensive Treatment	Control	Intensive Treatment
No. of patients	210	190	210	190
Male, *N* (%)	140 (66.6)	132 (69.5)	140 (66.6)	132 (69.5)
Age (years)	61.5 (5.4)	60.6 (5.9)	64.5 (5.4)	63.6 (5.9)
Glycosylated Hb (% of Hb)*	6.9 (0.7)	8.9 (1.1)	7.0 (0.8)	8.3 (0.9)
Systolic blood pressure (mmHg)	129.2 (12.3)	157.5 (20.2)	125.1 (10.3)	151.1 (13.2)
Diastolic blood pressure (mmHg)	86.4 (10.3)	92.5 (11.1)	83.4 (8.3)	84.5 (8.1)
Weight (kg)				
Female (Mean ± SD)	63.7±6.5	81.4±7.2	60.1±5.1	72.8 ± 5.4
Male (Mean ± SD)	75.1±7.6	86.1±8.9	70.2±5.6	78.4 ± 6.6
Height (cm)				
Female (Mean ± SD)	156.1±10.5	156.4±11.2	156.1±10.5	156.4 ± 11.2
Male (Mean ± SD)	167.3±11.6	167.1±12.3	167.3±11.6	167.1 ± 12.3
BMI				
Female (Mean ± SD)	23.7±0.5	27.1±0.8	22.3±0.3	24.6±0.4
Male (Mean ± SD)	24.1±0.6	29.4±1.2	22.2±0.4	24.9±0.9
Total cholesterol (mmol/L)	6.47 (0.95)	8.03 (0.98)	5.12 (0.65)	7.12 (0.71)
HDL (mmol/L)	1.81 (0.41)	1.06 (0.06)	1.71 (0.61)	1.26 (0.04)
Triglycerides (mmol/L)*	1.7 (1.0; 2.8)	2.5 (1.2; 4.4)	1.62 (1.0; 2.6)	2.3 (1.2; 4.1)
Smoking, *N* (%)	81 (38.5)	84 (44.2)	52 (24.7)	44 (23.15)
Alcohol, N (%)	90 (42.8)	93 (48.9)	71 (33.8)	78 (41.05)
Microalbuminuria, *N* (%)	30 (14.3)	41 (21.6)	29 (13.8)	40 (21.05)
Macroalbuminuria, *N* (%)	3 (1.42)	5 (2.63)	3 (1.42)	7 (3.68)
Antihypertensive drugs (%)	37 (17.6)	58 (30.5)	103 (49.04)	120 (63.2)
Lipid-lowering drugs (%)	32 (15.23)	53 (27.9)	67 (31.9)	88 (46.3)

Table 2: Prevalence (% of examined population) of different measures of DPN and low ABI in control and intensive treatment group

Variable	*N*	Control (95% CI)	Intensive Treatment (95% CI)	Odd Ratio
ABI ≤0.9 (%)	126/307	8.9 (5.8; 10.2)	6.9 (5.3; 8.8)	0.87
Light touch, 1/8 (%)	132/267	18.3 (14.3; 23.1)	15.9 (12.1; 20.2)	0.91
VDT, >95th percentile (%)	87/195	23.1 (17.1; 34.1)	22.4 (16.6; 27.5)	0.93
Light touch + VDT (%)	102/199	33.5 (26.9; 41.2)	29.3 (25.0; 33.2)	0.96
MNSI questionnaire, cut ≥7	231/421	8.7 (7.1; 11.5)	7.9 (6.1; 9.3)	0.84
Pain (%)	128/281	3.6 (1.9; 7.1)	4.9 (3.1; 7.1)	0.97

DISCUSSION

Our found statistically significant impact of intensive treatment (IT) in general practise on the prevalence of DPN and PAD in individuals with type 2 diabetes detected through screening. This IT intervention involved providing education and support to general practitioners and practise nurses in evidence-based, target-driven management, as well as following strict treatment targets and algorithms. To yet, intervention trials conducted on individuals diagnosed with type 2 diabetes have yielded relatively moderate outcomes in terms of preventing DPN. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial revealed that intensive glycemic control had a discernible effect on the occurrence of neuropathy [17]. The study observed a significant disparity between treatment groups in terms of light touch sensation, as measured by a monofilament test. The findings of the UK Prospective Diabetes Study demonstrated that maintaining tighter glycemic control had a positive impact on the development of microvascular problems. However, it did not show any significant influence on surrogate end points related to DPN [16]. The Steno-2 trial found no significant disparity in the incidence of peripheral neuropathy, as assessed by biothesiometry, across the various therapy groups [6]. The UK Prospective Diabetes Study findings suggest that dyslipidemia and blood pressure may be modifiable risk factors for the onset of peripheral vascular disease in individuals diagnosed with type 2 diabetes [18]. The Fremantle Diabetes trial provided prospective results indicating that the use of statins or fibrates may potentially offer protection against the onset of DPN [19]. Nevertheless, the results of the study indicated that the risk estimations for multifactorial intervention were in favour. This observation might potentially be attributed to the fact that people with previously undetected diabetes are identified through screening during the early stages of the illness. It is plausible to consider that, given the current state of the disease development underlying PAD and DPN, a more extended period of IT may be required in order to notice any discernible impact. Previously, the ADDITION trial in Denmark, saw significant treatment improvements in both groups from baseline to follow-up. These improvements coincided with the development of general population treatment recommendations over the same time period (7,8). The existing body of information regarding PAD and DPN in individuals with diabetes has primarily been acquired via studies conducted on people who have received conventional diagnoses and, in some cases, have had diabetes for an extended period of time. The surveys utilised the Michigan Neuropathy Screening Instrument (MNSI) score of greater than 2 to identify cases of DPN. The results indicated that DPN had a frequency of 32% among a sample of 190 patients with diabetes. Additionally, the surveys also assessed the prevalence of ankle-brachial index (ABI) values below 0.9, which is indicative of peripheral arterial disease. Within the same cohort, the incidence of DPN as determined by a MNSI score greater than 2 was found to be 32%. The implementation of evidence-based, target-driven management and strict treatment targets/algorithms among general practitioners and practise nurses did not result in a statistically significant variation in the occurrence of diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) in a population of individuals with screen-detected type 2 diabetes, when compared to the delivery of routine care (RC) in accordance with national recommendations. Given the correlation between both diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) with the occurrence of foot ulcers and cardiovascular disease, it is imperative for physicians to be cognizant of these elevated prevalence rates while managing patients diagnosed with diabetes through screening.

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