

Muscle strength, mobility and quality of life in patients with diabetic polyneuropathy : the influence of a functional strength and gait training

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strength. We did observe a moderate loss of compound muscle action potential (CMAP) in the DPN patients, suggesting some loss of muscle mass. However, the parallel loss of muscle strength in both patients with or without mild to moderate DPN suggest that in these patients other factors than loss of motor nerve function are responsible of the reduction in muscle strength.

The data presented in chapter 4 suggest that exercise regimes have a limited positive effect on lower extremity muscle strength in patients with mild to moderate DPN. We observed a significant increase in ankle joint plantar flexor strength after 12 weeks of training. No further increase was observed after 12 and 24 weeks. Importantly, after the half-year follow-up the plantar flexor muscle strength remained 44% higher in the intervention group than in the control group, indicating a long-term beneficial effect. However, no improvements in muscle strengths of the ankle joint dorsal flexor strength, knee extensor and flexor strength were found. In addition, muscle fatigueability of the lower extremities did not improve over time. All together, our findings suggest that a 24 week training program can improve muscle strength in patients with mild to moderate DPN; however the effects are limited.

Mobility

In **chapter 3 and 4** a study is presented in which we examined mobility in relation to DM2 and mild to moderate DPN. We showed that the effect of the diabetic state per se was associated negatively with mobility. A six minute walk test (6MWT), timed get up and go test (TUGT), and the Physical Activity Scale of the Elderly (PASE) questionnaire were used to determine mobility. Walking speed and self-reported daily activity were lower in our groups of patients compared to healthy age matched elderly. However, both mobility outcome measures did not differ between patients with and without DPN.

We also demonstrated in **chapter 4** that 24 weeks of physical training can improve walking speed in patients with DPN. An increase of 27 meters is considered clinical relevant during the 6MWT (4), patients with mild to moderate DPN improved their distance walked at the 6MWT with 30 meters (6%) after 12 weeks of training. Improvement in walking speed remained the same after 24 weeks of training and after the half-year follow-up. No improvement in walking speed at the TUGT and the score at the PASE questionnaire was found after the intervention. In a questionnaire specifically developed for our randomized controlled trial (**chapter 4**) to evaluate the experiences of the subjects, participants reported subjective improvement in physical fitness.

In conclusion, a 24 week intervention as described in **chapter 4 and 5** can improve walking speed in patients with DPN who are able to complete the training; this effect was long lasting. Also, patients who followed the 24 week intervention felt physically fitter.

Health related quality of life

As described in **chapter 3 and 4**, the SF36 questionnaire was used to determine health related quality of life (HR-QoL). This questionnaire contains 36 items. It measures health on nine multi-item dimensions based on functional status, well being and overall evaluation of health. Patients with mild to moderate DPN scored six out of the nine SF36 items lower than the healthy elderly. Patients with DM2 but without DPN scored seven of the nine SF36 items lower. Both groups scored lower on items such as: physical and social functioning, pain, vitality and health perception compared to healthy elderly. But, no differences were observed in perceived HR-QoL between both groups of patients.

We showed that there was a clear correlation between HR-QoL and muscle strength and mobility outcome measures, such as plantar flexor strength of the ankle and distance walked at the 6MWT at baseline. Despite the fact that these parameters improved during the intervention, no intervention effects were found in the HR-QoL. Although we expected that the intervention would lead to less physical dependence and improved health perception, we did not find such improvements.

Methodological considerations

Study populations and designs – external validity

The participants that were included in the studies described above consisted of a selected group of elderly (≥ 50 years) Caucasian individuals. There is evidence that there are ethnic differences in cardio-metabolic risk profile (5, 6) and the development of long-term diabetic complications, such as DPN (7). In addition cultural differences could have an impact on for example HR-QoL. Additional studies with participants from other ethnicities are necessary to confirm our findings in these populations.

We excluded patients with DM1 the reason for this was twofold. Since DM1 usually occurs at a younger age (during childhood), DPN frequently develops at a younger age than in patients with DM2. Secondly, different disease processes play a role in the development of DM1 and DM2, each with a theoretically different effect on nerve integrity. For instance, the development of DM2 is closely associated with several cardiovascular risk factors, such as central obesity and hypertension which are also risk factors for DPN (8). Moreover, subjects with DM2 tend to have a sedentary life style, reduced mobility and loss of muscle strength (9) as also showed in this thesis. Including patients with DM1 and DPN would lead to a less homogeneous group of subjects considering the effect of aging and diabetes on for example muscle strength. Theoretically, in order to determine the interaction between muscle strength and nerve function loss, the inclusion of patients with DM1

would probably have been more preferable from a scientific point of view. From a clinical point of view, however, given the much larger number of subjects with DM2, we have chosen to include only patients with DM2. Whether the results found in this dissertation can be extrapolated to a population with DM1 is therefore unclear and needs further investigation.

For our main study (**chapter 3 and 4**) diabetic nurses selected the patients with DPN. Only patients who were known to the general practitioner or internist were contacted. We have opted for the diabetic nurses to make the initial contact with the potential subjects as these nurses play an important role in their daily care.

Overall, the majority of the subjects in our studies had mild to moderate DPN which could explain the fact that we did not find differences in the loss of muscle strength between patients with DM2 and with or without DPN. The distribution of the CNE score in our group of patients was: 64% mild DPN (CNE score of 5-14), 33% moderate DPN (CNE score of 15-24) and 3% had severe DPN (CNE score of ≥ 25). It is not known what the normal distribution of the severity of DPN is in a general population of patients with DPN, but given the exclusion criteria applied, it is reasonable to assume that patients with severe DPN are under-represented in our study. We excluded subjects who had severe cardiac disease, renal insufficiency (creatinine $> 180 \mu\text{mol/l}$), cerebrovascular disease, muscular disorders, rheumatoid arthritis, foot ulcers in the last six months prior to the intervention and subjects that were not able to walk 6 minutes without walking aids. As diabetic complications tend to cluster, these exclusion criteria might have resulted in a selective loss of patients with more severe DPN (10-12). Upon diagnosis with diabetes, 10 to 20% of the patients have already some signs of nerve damage (13, 14). This indicates how important it is to screen elderly for DPN. As mentioned above, severe leg muscle weakness was in particular observed in patients with severe, symptomatic DPN and not in patients with asymptomatic mild to moderate DPN (10, 15). The data described in **chapter 2, 3 and 4** are in line with these observations as we could not observe loss of strength which could be ascribed to loss of nerve function. We did observe loss of muscle strength in both patients with DM and mild to moderate DPN, that is probably the result of both loss of muscle mass and decreased muscle quality. These changes are likely multifactorial of origin, and related to changes in e.g. muscle composition, aerobic capacity and metabolism (16-19). With the benefit of hindsight, less strict exclusion criteria for patients to participate in our study might have been better, although this would have increased the risk of drop out. But, by including these more severely ill patients it could have been possible to gain more insights in the effect of muscle strength training in patients with severe DPN.

Study populations and designs – internal validity

Selection bias

In randomized controlled trials selection bias may obscure true associations and thus hamper interpretations of obtained results. Selection bias can occur if a proper randomization of subjects is not achieved. In addition, this form of bias often results from selective dropout of the unhealthiest participants. Our randomized trial (**chapter 4**) had a high dropout: 53% of the intervention group participants did not complete the one year trial, in part because of intervention related injuries. However, dropout rate was also high in the control group (36%), and was probably a consequence of the relative poor general health status of these individuals. Patients who dropped out had marginal but significantly higher CNE scores in comparison to patients who did not: 14 and 11 points respectively. This could mean that patients with more severe DPN have a higher risk for dropout, possibly due to the more frequent presence of co-morbidities or greater susceptibility to complications of the training due to more severe sensory loss. Also relatively more women than men dropped out during the study: 50 vs 44%. Men and women did not report different reasons for leaving the trial, suggesting that the women might have been less motivated but no firm conclusions can be drawn. No further differences were observed between subjects who dropped out and those subjects who did not. Seven patients (14%) from the intervention group dropped out because of intervention related injuries (two subjects with ulceration and five with knee complaints), seven patients (14%) because of injuries that were not related to the intervention (e.g. cardiac complaints, cancer and cataract surgery), six (12%) stopped because of lack of motivation and seven patients (14%) had various other reasons to quit. Eight subjects (17%) from the control group refrained because of physical impairments (e.g. cardiac and pulmonary complaints), three (6%) had motivational problems and six patients (13%) had other reasons to quit. Overall, half of all subjects that refrained from the study gave physical complaints as a reason to quit, indicating that patients with mild to moderate DPN, who appear to be relatively fit, are yet physically vulnerable. In addition, 20% of all subjects who refrained from the study indicated motivational problems. Dropout rates were higher than in other, smaller studies (20-26) where the dropout rates were between 0 and 33% as described in **chapter 6**. We cannot explain the differences between our study and the other mentioned studies, but one of the reasons could be that our participants suffered more from co-morbidities. Another reason for the differences in dropout rates could be that in these aforementioned relatively small studies mostly very motivated subjects were included and lack of motivation was never indicated as reason for dropout in these studies. In one large intervention study including patients with DM2 dropout rates were comparable to the rates we observed (27). The high dropout rates in this latter study and in our study indicate that it is crucial not to underestimate the vulnerability of patients with DM2 and DPN when offering them a physical

training program and its implications will be discussed below. In future studies, it is important to gain more insight in the reason why subjects drop out in order to prevent including patients to a training intervention who are physically or mentally not able to participate in a long term exercise program or alternatively to individualize the intervention in such a way that it better fits with the limitations of the participants.

We analyzed the data of the subjects who dropped out and those who completed the intervention separately; with this per protocol analysis there is a clear risk for selection bias. The reason that we have nevertheless chosen to use this approach is we tried to determine the possible benefits for those patients who are able to follow a prolonged intervention.

Information bias

Information bias arises in a clinical study because of misclassification of the level of exposure or errors in the measurements and hence bias in data interpretation. In the present studies, there was a risk for information bias for both the intervention and the measurements that were performed.

The subjects assigned to the intervention were divided over 5 sub-groups to receive weekly plenary training for 24 weeks. The groups were guided by different physical therapists. In order to prevent differences in execution of the exercises both subjects and physiotherapists received an exercise manual with a description and photo's of the exercises. In addition, to prevent different interpretations of the exercises the physiotherapists were supervised by a member of the research team. Subjects of the intervention group had to train twice a week at home; although we asked repeatedly, almost none of the subjects filled out their training diary. Therefore, it is not clear if and how often the subjects performed exercises at home. The use of more objective activity monitors, such as tri-axial accelerometers, can in future studies give more insight in the fact whether a person has actually trained. Although such accelerometers also have clear limitations in detecting muscle strength trainings of isolated extremities.

Lower extremity muscle training was performed at a moderate intensity at 40 to 60% of one repeated maximum (performing 12-16 repetitions). As DPN patients frequently have multiple co-morbidities with elevated risk of injuries and cardiac problems, a moderate training intensity was chosen, it is possible that the training intensity was too low to improve muscle strength in the lower extremities. As described in **chapter 4** only strength of the plantar flexor muscle around the ankle improved after training. However, it seems that strength training at a moderate intensity can be successful and sometimes even equally effective as strength training at a high intensity (28). Factors other than training intensity may affect the lack of training response on dorsal flexor strength of the ankle and upper leg strength. Difficulties in execution of the exercises could be one of the reasons

that no improvement in for example dorsal flexor strength of the ankle was observed in contrast to the plantar flexor strength. The training sessions consisted of general walking exercises and exercises that were aimed to improve specific muscle groups. In order to improve plantar flexion strength, subjects were instructed to perform 'raising heels' exercises and dorsal flexion against resistance. To improve dorsal flexor strength subjects were instructed to perform walking on heels exercises and to pull up their foot against the resistance of an elastic band. Several participants reported that these latter exercises were more difficult to execute and could not always be performed because of imbalance during the exercises. To improve dorsal flexor function, exercises which are easier to execute for DPN patients may be necessary in future training regimens. In addition, maximal strength of isolated muscles was measured in a fixed position with a dynamometer. Perhaps tests that measure muscle strength in a more functional way, which is more related to the daily life exercises that our subjects performed during the training sessions, are easier to perform for patients with DPN and are therefore more able to observe improvements. An example of a standardized functional strength test is the "five times sit to stand test". In one study on the effect of whole body vibration, this test was used in DPN patients and an increase of 22% in functional strength was determined (22). The TUGT was one of the instruments that was used in the current studies to determine mobility. Although we did not find an intervention effect, a time effect was observed; both the control and intervention group improved their walking speed over time. This finding suggests that a learning effect probably occurred. To get a better overview of mobility behavior during the day, the use of an objective tool, like an activity monitor, is recommended (29).

The aim of our study was to evaluate the effects of functional resistance and mobility training on lower limb muscle strength, mobility and HR-QoL in patients with DPN. Balance was not addressed in our attempt to reverse this physical and psychological spiral. Balance is disturbed in patients with DPN (30-32) and, as described in **chapter 6**, recent literature suggests that balance plays an important role in the mobility and HR-QoL of patients with DPN (21, 33-35). Unsteadiness leads to an increase in fall risk and is a major determinant for depression in patients with DPN (33, 36). Although balance was not measured in the intervention study, participants reported that they felt less unsteady and were less afraid to trip and fall when walking on the street after the intervention. This is in line with earlier studies in which the authors concluded that muscle strength is an important factor in keeping balance (37). Improving muscle strength and balance could lead to decreased risk of falling in patients with DPN (38). In addition, changes in both body sway and stance phase of gait in patients with DPN indicate a more impaired static and dynamic control of balance (25). Diminished somatosensory input from the smaller muscle fibers and muscle weakness can both play an important role in the modulation of the support phase of gait (35). It seems possible to improve

balance in patients with DPN (21, 22, 24, 25) and therefore, we recommend including balance exercises in future physical training programs for patient with DPN.

Apart from loss of muscle strength and impaired balance, loss of mobility in DPN could also be related to neuropathic pain. This neuropathic pain can have a major impact on gait (39) and with that decreasing general activity and HR-QoL (33, 40-42). Perhaps pain relief with medication may assist patients with painful DPN in obtaining better results during a physical intervention that aims to improve mobility, but this remains to be studied in future interventions (13, 14, 43, 44).

We did not succeed in improving the HR-QoL of patients with DPN after 24 weeks of physical intervention. Perhaps the objectively measured increases in muscle strength and walking speed were too small to lead to an improvement in the subjective HR-QoL, at least as detectable with the SF36 questionnaire. In addition, including balance exercises in future intervention to improve balance and coordination could perhaps have a positive effect on outcome measures such as “physical functioning” and “general health perception”, determined with the SF36 questionnaire. Theoretically, it is also possible that an intervention as described and the improvement in muscle strength and mobility do not affect the outcome measures as determined with the SF36 questionnaire, but for instance a supervised exercise training program in subjects with DM2 was associated with a marked increase in various domains of the SF-36 questionnaire (45).

Clinical implications and valorisation

The primary goal of this dissertation was to evaluate whether a physical intervention program could counterbalance the downward spiral of loss in muscle strength, mobility and HR-QoL. In addition, we wished to gain more insight into the complex physical and mental problems faced by patients with DPN.

The data obtained in this dissertation show that the loss of muscle strength, mobility and HR-QoL was comparable between patients with DM2 and patients with mild to moderate DPN and was mainly caused by DM2 per se and not by mild to moderate DPN. However, patients with DPN suffer from (severe) co-morbidities (13, 44, 46, 47), disturbed passive and dynamic balance (30-32) and, at a later stage, this deteriorated balance can for example increase the risk of falls (33, 36, 38). It has been shown that physical interventions can improve balance in patients with DPN (21, 22, 24, 25). Therefore, it is recommended to prescribe an individualized exercise program for patients with DPN aiming to improve balance and based on the trainability and personal goals of the patient. Subjects who completed the intervention evaluated the intervention positively. Participants experienced exercising with fellow patients as pleasant and they would recommend this intervention to other

patients. In addition, participants reported that they felt physically fitter after the intervention and they looked forward to go to the plenary sessions. These data indicate that potentially there is a opportunity for patients with DPN to break the downward spiral of reduced muscle strength, loss of mobility and loss of fitness, after following a physical intervention of several weeks.

As described in **chapter 6**, it is currently not clear which intervention is the most beneficial. But based on the feedback of the subjects and the data obtained in this dissertation, it seems important to offer patients with DPN a physical training program of functional strength and balance exercises so they can improve their physical fitness and self-confidence. It is recommended to train patients twice a week for several weeks in small groups with fellow patients under supervision of a physiotherapist. However, several patients with DPN will not be able to follow a physical training program. Patients with DPN are vulnerable and intrinsic motivation is lacking often, strategies are also necessary to enhance this motivation and willingness to stick to the exercise program. Pre-screening on physical and mental capabilities is recommended to increase the success of a training program for patients with DPN.

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