Mastication training in adult patients with mitochondrial diseases: an explorative study

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Abstract

Background: Fatigued muscles during mastication is a frequently reported clinical symptom in patients with mitochondrial diseases (MD). In general, long-term training will improve exercise capacity and mitochondrial function. Currently, no disease specific training is available for mastication in this patient group.

Aim and research question: The aim is to explore the effect of low intensity mastication training on mastication related outcome measures. Research question: Is there an effect of low intensity mastication training using chewing gum on masticatory performance, bite force, efficiency and endurance in adult patients with MD?

Design: Quasi-experimental explorative study.

Method: Twenty participants cooperated: 10 in the intervention and 10 in the control group, matched on sex and age. The intervention consisted of an 8-weeks low intensity (3 times a day, 20 minutes each) mastication training at home, using sugar-free chewing gum. Examination took place at baseline and directly after the intervention. The following masticatory measures were used: (1) performance using bicolour chewing gum samples; (2) bite force using the VU Bite Force gauge (VU-BFG); (3) efficiency using the Test of Mastication and Swallowing of Solids (TOMASS); (4) endurance, using the 6 minutes mastication test (6MMT).

Results: In the intervention group, masticatory efficiency - number of masticatory cycles needed to eat a cracker - significantly changed. Masticatory performance, bite force and endurance did not change. In the control group, no significant changes were observed.

Conclusion: Mastication training using chewing gum in patients with MD improved masticatory efficiency. Findings contribute to developing a disease specific training program to reduce oral phase impairment.

Recommendations: Further research is recommended to investigate the optimal frequency and duration of mastication training, along with the long-term effects of training.

Keywords: Mitochondrial Diseases, mastication, chewing gum, clinical-trial.

Background

Mitochondrial diseases (MD) include a heterogenous group of anomalies of the mitochondria in the human body.[1] Mitochondria are organelles of the cells that have a primary role in generating energy (adenosine triphosphate - ATP). ATP is a form of energy which powers many of the cell activities and is required for cells to function normally. Mitochondria are also involved in other physical processes in the human body. Therefore, damage to mitochondria can have extensive consequences.[2] Most of the problems emerge in organs that require loads of energy, for instance the hart, brain and muscles. A recent study in the United Kingdom showed that MD are affecting 1 in 4,300 adults.[3] MD can reveal at different ages and can be of inherent or acquired dysfunctional origin.[4] Most of the patients with MD display a cluster of clinical symptoms that are linked to specific phenotypes, such as chronic progressive external ophthalmoplegia (CPEO) and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).[5] Most of the MD are (slowly) progressive, although symptoms can be stable for years. Patients with MD often complain about fatigue, muscle pain, loss of muscle strength and diminished endurance in physical activities.[6,7] Also dysphagia is a common problem in patients with MD.[8] For instance, easily fatigued muscles during mastication is a frequently reported clinical symptom.[6,9] Mastication efficiency is defined as the number of chewing cycles required to crush food between the teeth and the manipulation of the resulting particles to form a food bolus to swallow.[10,11] A mastication movement is described as a chewing cycle with an opening and closing phase. Adult patients with MD showed a decreased total amount of chewing cycles compared to healthy participants and complained more about fatigue and pain during the 6-minute mastication test (6MMT).[9] Current usual care of these complaints during mastication is the adaption of food or eating more smaller meals a day. For example, eating pureed food instead of solid slices, or eating six times a day a half-portion instead of three times a full portion.

Although current usual care is based on compensatory strategies, literature showed that mitochondrial function and exercise capacity, like cycling, in patients with MD will improve by long-term (3 months), low intensity training, which appears to be safe.[12–14] For example, aerobic training (cycling) was found to have meaningful effects in skeletal muscle endurance in patients with MD, with no adverse effects of training.[15] In addition, a study on efficacy of aerobic mastication training using chewing gum was performed in patients with Duchenne muscular dystrophy. Results showed improvement of the masticatory performance after a 4 week training.[16]

Problem statement and aim

Mastication training is considered to be low intensity.[16] It is hypothesized that mastication training will improve masticatory functions in adult patients with MD. This hypothesis is based on positive results of aerobic training in patients with MD combined with improvement of masticatory performances after mastication training in patients with Duchenne muscular dystrophy.[15,16] Before starting a disease specific training program on mastication, it is important to know the dominant benefits on masticatory performances and experiences of mastication training in patients with MD. To the authors' knowledge, applicability of mastication training in patients with MD has not been described. Therefore, the aim of this study is to explore the effect on masticatory performance, bite force, masticatory efficiency and endurance of low intensity mastication training.

Research question

Is there an effect of low intensity mastication training using chewing gum on masticatory performance, bite force, efficiency and endurance in adult patients with MD?

Method

Design

The design of this study was a quantitative quasi-experimental explorative study.

Participants

Participants were recruited from the Radboud Center for Mitochondrial Medicine (RCMM). The inclusion criteria were: (1) genetically confirmed MD, (2) aged over 16 years. Exclusion criteria were: (1) not able to participate on the measurements at baseline due to physical problems, (2) having a long beard, (3) a Functional Oral Intake Scale (FOIS) score of 1-4[17], because safety of the intervention could not be guaranteed in case of moderate to severe dysphagia.

Thirty eligible participants were informed about the study by their medical specialist of the RCMM. They received an information letter with an invitation to participate in the study. Participants were contacted by the researcher. A total of 20 participants approved to participate. Data were collected between February and May 2018. Informed consent was obtained from all participants. Registration of research data took place anonymously. A unique fictive code was used to trace back data.

Intervention

When included, participants were assigned to: the intervention, or control group. The intervention consisted of 8 weeks low intensity mastication training at home using sugar-free chewing gum (22 gram, Stimorol sugar-free; Dandy AS, Denmark). Instructions for training were: 1 piece of sugar-free chewing gum per exercise, 3 exercises a day of each 20 minutes, 5 days a week. Participants were free to choose the time of training, with an interval of at least 2 hours between two exercises. Five days instead of seven days a week has been chosen to increase compliance. Participants were asked to keep a diary to check for compliance and potential complications. Participants assigned to the control group were asked to do nothing additional to their daily routine. They were allowed to continue their compensatory strategies, if necessary.

Procedures

This explorative study tested different primary outcomes: masticatory performance, bite force, masticatory efficiency and endurance. Secondary outcomes were: patient reported mandibular function, and patient reported experiences of training. Participants were examined at baseline (T_1) and after 8 weeks (T_2). All participants underwent the same clinical examination, which took place at the Radboudumc or at the participant's home. At baseline, participant characteristics were gathered. These included data of sex, age, body height, bodyweight, mtDNA mutation, syndrome, and percentage of heteroplasmy (if applicable).

The following clinical examinations were performed (in this order at T_1 and T_2) for both the intervention and control group:

1. Masticatory performance.

   Masticatory performance was assessed using bicolour chewing gum samples according to the spatial heterogeneity method.[18,19] A four-gram sample made of purple and pink chewing gum (Bubblicious Ultimate Original and Grape; Cadbury, London, United Kingdom) was given to the participants, with the instruction to chew naturally. Samples were chewed 15 times and afterwards retrieved and flattened to a slice of 1mm height. Pictures of both sides of the slice were taken with a Canon 750D EOS DSLR camera; Canon lens 50 mm; ISO 100, F2.8. Pictures were taken in a white closed portable studio box lit by a side mounted MCOplus Pro series LED Macro Ring Light (MP-MRF32) 32 LED lights at 5500K highest brightness (Hongkong, China). The spread of the colour intensities is the measure of mixing: 'DiffPix' score. A higher score indicates more differences in color intensity, thus less

mixing. This measure has been processed using the Wolfram Mathematica Algorithm.[19]

2. Maximum bite force.

   Maximum bite force was measured using the VU University Bite Force gauge (VU-BFG). The VU-BFG was placed centrally between the incisors. Participants were instructed to bite 3 times as hard as possible for 3 seconds, with a rest period of 30 seconds between the attempts.[18] The highest score of the three attempts was used.

3. Mandibular function impairment.

   To capture the effect of the intervention in participants' daily lives, participants were asked to fill in a Dutch questionnaire: mandibulaire functiebeperking vragenlijst (MFV).[20] This questionnaire consisted of 17 statements, providing information on mandibular function. Each statement was rated on a 5-point Likert scale varying from 'not at all'(1) to 'excessively'(5).

4. Masticatory efficiency.

   The Test of Mastication and Swallowing Solids (TOMASS) was used to measure masticatory efficiency.[21,22] Following the standardised protocol, participants were asked to drink 100 ml of water. Afterwards, a small standardised cracker was eaten as quickly as comfortably possible. When finished, participants had to call out their own name. This test was videotaped from lateral position with a good view on the mandibular movements. Standardised values were calculated for total bites, total masticatory cycles, total swallows and total time.[22]

5. Masticatory endurance.

   Participants had to chew on a 15 cm chewing tube of resistance level 4 (Theratube©), following the standardised protocol of the 6-minutes mastication test (6MMT).[9] Participants were asked to chew on the tube during 6 minutes on the preferred side of the teeth. They were allowed to swallow their saliva, by temporary removing the tube. The test was videotaped laterally with a good view on the mandibular movements. The total number of chewing cycles and the percentage difference between minute 1 and minute 6 were determined afterwards. An additional qualitative rating was given on rhythm of mastication (rhythmic, variable, not rhythmic) and magnitude of masticatory movements (normal, big, small). A numeric visual analogue scale (VAS 0-10) to assess masticatory muscle pain and

fatigue was used directly after the test and after 5 minutes.

In addition to the examination as described above, participants in the intervention group had to fill in one other questionnaire at T_2 in order to express their experiences about the training. Participants were asked to evaluate the intervention by reviewing 5 statements (Appendix A). They specified their level of agreement to a statement on a 5-point Likert scale varying from “strongly disagree”(1) to “strongly agree”(5).

Sample size

A hypothetical sample size of N=20 was used in this study, based on the explorative design. Effects of mastication training in patients with MD have not been described before. Therefore, it was unethical to conduct a fully powered clinical trial.

Allocation of participants

A matching strategy based on sex and age, divided 20 participants into 2 groups: intervention (n=10) and control (n=10). In order to establish similar groups, matching was found to be appropriate because of the small number of subjects in this study.[23] Participants were assigned to the intervention by the researcher, and were matched on age with a five-years range. Participants with dental implants who therefore avoid chewing gum, were assigned to the control group. Since receiving chewing gum is part of the intervention, participants and the researcher were not blind for the intervention. To limit bias the procedures were standardised, and one researcher examined all participants. Besides, objective measures were chosen as primary outcomes.

Statistical analysis

Descriptive statistics were used to document participant characteristics and data of the questionnaires. The qualitative rating of the masticatory movements and data of the numeric VAS-scores (6MMT) were presented by descriptive statistics as well.
The two-sided Wilcoxon signed-rank test was used to assess possible differences between timepoints T_1 and T_2 for both intervention and control group. Differences were assed for the level of masticatory performance, bite force, efficiency and endurance. Normal values described as z-scores were calculated for efficiency and endurance. Data were analysed with IBM Statistics 23 software[24], and statistical significance was defined as p=.05. No correction for multiple testing was applied, as this was an explorative study.

Results

Data of 19 participants were used for statistical analysis (Figure 1). One participant of the control group was lost to follow-up because of bad health. One participant allocated to intervention refused training and therefore was replaced to the control group. Characteristics of participants in the intervention and control group are indicated in Table 1. A detailed description of clinical symptoms presented in both groups is depicted in Appendix B.

Masticatory performance

One participant of the control group did not perform the bicolour chewing gum test, because of diet restriction due to diabetes. A complete case analysis has been done as this was an explorative study. Masticatory performance did not change significantly after 8 weeks mastication training (z=-0.770, *p*=.441) (Table 2). Masticatory performances in the control group did not change either (z=-0.889, *p*=.374).

Maximum bite force

Data of one participant of the intervention group was missing at T_2 due to dental problems. Complete case analysis has been done.

In the intervention group, no differences were determined between T_1 and T_2, regarding the maximum bite force (z=-0.420, *p*=.674). Also, in the control group medians at T_1 and T_2 did not change (z=-0.663, *p*=.508) (Table 2).

Masticatory efficiency

To eat a cracker, participants in the intervention group needed a significant lower number of masticatory cycles after mastication training than before (z=-2.106, *p*=.035). Besides, a decrease in the number of bites, swallows and time needed was observed, but changes were not significant (respectively *p*=.144; *p*=.129; *p*=.203). Values of the median and range are depicted in Table 2. In the control group, the number of masticatory cycles needed to eat a cracker did not change (z=-0.153, *p*=.878). A decrease in the number of bites, swallows and time, as seen in the intervention group, was not observed in the control group. In contrast, the median of time showed a slight, not significant, increase (*p*=.260).

Masticatory endurance

In the intervention group, at T_2, one participant stopped the 6MMT after 3 minutes, because of severe cramps in masticatory muscles. In the control group, at T_1, two participants stopped the 6MMT after respectively 2 and 4 minutes, because of severe

cramps in masticatory muscles. At T_2 these two participants both stopped the 6MMT after 1 minute, for the same reason as described before. Another participant stopped after 3 minutes, to avoid severe cramps and headache. For analysis, the number of chewing cycles was scored as 0 in case of a minute that was not performed.
In the intervention group the total number of chewing cycles after 6 minutes and the percentage difference between minute 1 and 6 did not significantly change between T_1 and T_2 (respectively p=.575; p=.767). Also, in the control group the total number of chewing cycles after 6 minutes and the percentage difference between minute 1 and 6 did not significantly change between T_1 and T_2 (respectively p=.799; p=.263) (Table 2).
The qualitative ratings of rhythm and magnitude of the masticatory movements are presented in Table 3. In the intervention group, an increase of movements with a normal magnitude was observed between T_1 and T_2. This change was not observed in the control group. In both groups, rhythmic masticatory movements were most frequent and did not change between T_1 and T_2.
In the intervention group, mean scores of the numeric VAS scores for fatigue directly after the 6MMT showed a small decrease (5.6%) between T_1 and T_2 (Table 4). In contrast, mean scores for pain directly after the 6MMT increased with 28.6%.
In the control group, mean scores for fatigue directly after the 6MMT also showed a decrease (19.4%) between T_1 and T_2. Mean scores for pain directly after the 6MMT showed an increase of 17.1% between T_1 and T_2.

Mandibular function impairment

In the intervention group at T_1, 66.7% of the participants reported that they experienced no problems of pain and fatigue during drinking. After mastication training (T_2), the percentage of participants that experienced no problems during drinking was 100%. Furthermore, no explicit changes were observed between T_1 and T_2 for both the intervention and control group (Table 5).

Experiences about the training

Five out of nine participants (56%) agreed that the training had an acceptable level of time investment. Eight out of nine participants (89%) agreed that training took little extra energy effort. The same percentage was observed on the statement if training easily fits in daily life. Five out of nine participants (56%) would recommend this training to others.

Compliance and adverse events

Analysis of the diaries showed that all participants in the intervention group completed the 8-week training program. The compliance was high, resulting in an average of 97% of the required training time. For one participant of the intervention group, examination took place 8 days after ending the training program. No serious adverse events were observed or reported during the study.

Discussion

The present study explored the effect of mastication training using chewing gum in patients with MD, by assessing the level of masticatory performance, bite force, masticatory efficiency and endurance. Mastication training significantly improved masticatory efficiency measured by the number of masticatory cycles needed to eat a cracker. The number of bites, swallows and time to eat a cracker improved as well, but not significant. Masticatory performance, bite force and endurance showed no differences.

Masticatory performances of patients in the intervention group were found to be comparable to the masticatory performances of healthy adults (Appendix C). Thus, masticatory performances of the participants with MD in this study were not affected in advance. In line with findings of van Bruggen et al.[16] it therefore is logical that the level of performance showed no difference after training.

Performing many chewing cycles during training, the movement of the jaw was primary trained. It stands to reason that skills of coordination and motor control would be directly affected by training. As clenching the incisors was not part of the training program, it seems reasonable that bite force did not change. From previous studies it is known that harder foods require more muscle activities.[10] As a soft type of chewing gum was used for training, it is a natural consequence bite force was not affected. Furthermore, clenching is not considered as a low intensity aerobic exercise.[16]

The significant improvement of masticatory efficiency points out the results of directly training the skills of coordination and motor control. Patients with MD need significant more masticatory cycles, swallows and time when compared with normal values.[25] Also in the current study masticatory efficiency turned out to be disturbed, and therefore is likely to be affected by training. The improvement of the number of masticatory cycles needed to eat a cracker, indicates positive effects of low intensity, aerobic mastication training in patients with MD. Results are in line with findings of Jeppesen et al. showing an improvement of maximal oxygen uptake and workload after 12-weeks of low intensity, aerobic cycling training.[12]

In the current study, mastication training was modified for frequency and duration: 3-

times a day during 8 weeks. A 12-week training program might possibly lead to even better outcomes for the number of bites and time. However, only 56% of the participants in this study agreed that the 8-week training had an acceptable level of time investment. Presumably, when increasing the duration of training this rate might drop resulting in less compliance.

After performing a total of 40 hours mastication training, an improvement of endurance was hypothesized as, on the 6MMT, the total amount of chewing cycles and the percentage difference between M_1-M_6 were below the mean of normal values.

In both groups z-scores <-2 were found for the total amount of chewing cycles (31.6%) and for the percentage differences between M_1-M_6 (21.1%). This is in line with findings reported by Van den Engel-Hoek et al., where 20% of patients with MD had z-scores <-2 for the total amount of chewing cycles.[9] Individual test performances may be influenced by changing complaints ('bad days and better days') and might explain why less participants completed the 6MMT at T_2. In addition, the repeated measure may possibly be an explanation why endurance did not change. At T_2, participants may have been more aware of their reduced ability to complete the 6MMT and may have used compensatory strategies to reduce their amount of chewing cycles. This phenomenon is seen before in previous research on the 6MMT in patients with MD.[9]

In order to interpret the findings of this study, some limitations need to be considered. First, no sample size calculation has been done because of the explorative design of this study. A fully powered study, randomly allocating subjects to intervention or control group, would give more strength to the results. Besides, it is considered possible that more significant results might be found in case of a fully powered study. Second, the environment of the clinical examination was not standardized. Participants experienced travelling as a burden, because of the lack of energy which is a hallmark symptom of MD. Seventy-five percent of the participants preferred clinical examination at home. In some cases, video-taped chewing movements were difficult to count because of weak light source and visible noise. Third, dentures seemed to influence the workability of the mastication training. Participants with dentures (15%) were aligned as controls if they refused training. Although it is possible to chew chewing gum when wearing dentures, most of the people avoid it because of the risk of adherence to dentures. Therefore, in further research or training, it is considered to use a non-adhesive chewing gum base composition for mastication training.

This study also has several strengths. First, different phenotypes of MD were included. This diversity positively affects generatability of the results. Second, a standardized approach was used for examination to limit observer bias.

Results of this study are the first step in developing a training program on mastication for patients with MD. Mastication training might be relevant as problems with solid food intake are a common symptom in patients with MD.[26] This study showed a significant better score after mastication training on the number of masticatory cycles needed to eat a cracker. Thus, mastication training may improve masticatory efficiency in patients with MD and consequently may reduce oral phase impairment. If less masticatory cycles are needed, in daily life patients may be able to eat more solid slices and increase the size of a portion. In addition, fewer masticatory cycles needed might influence the experience of fatigued masticatory muscles during eating. Indirectly, these benefits may be linked to a better quality of life. Therefore, patients with MD might take advantage from a training program on mastication.

Conclusion

An 8-weeks low intensity mastication training using sugar-free chewing gum in patients with MD improved masticatory efficiency. Masticatory performance, bite force and endurance did not change. Findings can contribute to developing a disease specific training program to reduce oral phase impairment.

Recommendations

Based on the results of this study, for future training it is recommended to focus on improvement of masticatory efficiency, as this might influence the experience of fatigue during eating. In order to give more strength to the results, it is recommended to conduct a fully powered study where subjects are randomly allocated to intervention, or control group. Further research is recommended to investigate the optimal frequency and duration of mastication training. In addition, long-term effects of training should be investigated before starting a widespread mastication training program in patients with MD.

Ethical approval

This study was approved by the Committee on Research Involving Human Subjects of Arnhem and Nijmegen, the Netherlands (registration number 2017-3822).

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Conflict of interest

The authors declared that they have no conflicts of interest.

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Table 1. Characteristics of the participants with Mitochondrial Disease in the intervention group (n=9) and control group (n=10).

	Intervention group (*n*=9)	Control group (*n*=10)
Sex *N*(%)		
men	3 (33.3)	2 (20.0)
women	6 (66.7)	8 (80.0)
Age in years mean (range)	47 (25-65)	47 (29-64)
Body height in cm mean (SD)	170 (5)	167 (13)
Body weight in kg mean (SD)	72 (18)	62 (14)
% Heteroplasmy in urine mean (range)	55 (23-92)	62 (17-100)
% Heteroplasmy in blood mean (range)	32 (7-88)	33 (14-100)
mtDNA† *N*(%)		
3243A>G	6 (66.7)	8 (80.0)
4267A>G	1 (11.1)	-
7472	-	1 (10.0)
8334A>G	1 (11.1)	-
2 heterozygote POLG	1 (11.1)	-
Twinkle C.G1435A:p.E479k	-	1 (10.0)
Syndrome‡ *N*(%)		
CPEO	1 (11.1)	1 (10.0)
MELAS	3 (33.3)	4 (40.0)
MERRF	1 (11.1)	-
MIDD	3 (33.3)	4 (40.0)
SANDO	1 (11.1)	-
Unknown	-	1 (10.0)
FOIS level§ *N*(%)		
3¶	-	1 (10.0)
5	-	-
6	1 (11.1)	2 (20.0)
7	8 (88.9)	7 (70.0)
normal frequency of chewing on chewing gum *N*(%)		
never	7 (77.8)	9 (90.0)
once a month	1 (11.1)	-
once a week	1 (11.1)	1(10.0)
daily	-	-
>3 times a day	-	-

Note.
†mtDNA = mitochondrial DNA. A genotype-based classification.
‡Classification system based on phenotype.
§FOIS, Functional Oral Intake Scale: scored as 3 = tube dependent with consistent intake of liquid or food; 5 = total oral diet with multiple consistencies but requiring special preparation or compensations; 6 = total oral diet with multiple consistencies without special preparation, but with specific food limitations; 7 = total oral diet with no restriction.
¶Tube dependency, but not related to functional oral intake.

Table 2. *Z* statistics and *p*-values obtained from a two-sided Wilcoxon signed rank test between the 2 timepoints: T_1 (baseline measure) and T_2 (after 8 weeks), for intervention and control group, at the level of masticatory performance, bite force, efficiency and endurance.

Group	Measurements Median (range)	T_1	T_2	Z	p
Intervention	Performance† (*n*=9)	0.143 (0.123;0.164)	0.142 (0.117;0.163)	-0.770	0.441
	Maximum bite force‡ (*n*=8)	18.75 (7.93;36.96)	17.30 (11.02;38.24)	-0.420	0.674
	Efficiency§ (*n*=9)				
	Time	0.85 (0-0.52;5.62)	0.39 (-0.52;3.33)	-1.272	0.203
	Bites	0.42 (-1.25;2.29)	-0.42 (-1.25;2.92)	-1.461	0.144
	Masticatory cycles	0.12 (-0.64;1.80)	-0.30 (-1.23;1.21)	-2.106	0.035*
	Swallows	0.33 (-0,78;3.67)	0.33 (-0.78;0.33)	-1.518	0.129
	Endurance¶ (*n*=9)				
	Total in 6 minutes	-0.80 (-3.27;0.46)	-1.01 (-3.30;0.74)	-0.560	0.575
	Percentage difference between M_1-M_6	-0.07 (-0.97;0.75)	-0.29 (-5.88;3.52)	-0.296	0.767
Control					
	Performance (*n*=9)	0.153 (0.143;0.170)	0.147 (0.112;0.188)	-0.889	0.374
	Maximum bite force (*n*=10)	13.36 (0.21;24.46)	14.25 (4.48;29.62)	-0.663	0.508
	Efficiency (*n*=10)				
	Time	1.59 (0.12;10.21)	2.05 (0.12;13.79)	-1.126	0.260
	Bites	0.42 (-0.42;1.56)	0.42 (-1.25;2.08)	-0.175	0.861
	Masticatory cycles	1.17 (0.29;5.75)	1.51 (-0.30;7.68)	-0.153	0.878
	Swallows	1.44 (-0.78;7.00)	1.44 (-0.78;5.89)	-0.170	0.865
	Endurance (*n*=10)				
	Total in 6 min	-1.28 (-4.00;0.37)	-0.98 (-4.29;1.15)	-0.255	0.799
	Percentage difference between M_1-M_6	-0.11 (-5.88;4.66)	-0.57 (-5.88;2.45)	-1.120	0.263

Note. Two-sided Wilcoxon signed rank test between T_1 and T_2.
*Significant difference between T_1 and T_2: p <0.05.
†Performance: DiffPix-scores calculated according to the spatial heterogeneity method.
‡Maximum bite force: Anterior Maximum Voluntary Bite Force in kg. Maximum vertical bite forces between the central incisors of the upper and lower jaw.
§Efficacy: z-scores calculated based on eating a small standardized cracker as quickly as comfortably possible (TOMASS). Z-scores are calculated using the equitation: (measured value – normal value)/standard deviation of normal value.
¶Endurance: z-scores calculated based on 6 minutes of mastication on a chewing tube (6MMT). Z-scores are calculated using the equitation: (measured value – normal value)/standard deviation of normal value.

Table 3. Qualitative ratings of the masticatory movements during the 6MMT for intervention and control group at T_1 (baseline measure) and T_2 (after 8 weeks).

	Intervention group (*n*=9)		Control group (*n*=10)	
Qualitative rating	T_1	T_2	T_1	T_2
Rhythmic, *N* (%)	9 (100.0)	7 (77.8)	8 (80.0)	6 (60.0)
Variable[†], *N* (%)	-	1 (11.1)	-	2 (20.0)
Not rhythmic, *N* (%)	-	1 (11.1)	2 (20.0)	2 (20.0)
Normal movements, *N* (%)	2 (22.2)	5 (55.6)	4 (40.0)	3 (30.0)
Big movements, *N* (%)	1 (11.1)	-	-	1 (10.0)
Small movements, *N* (%)	6 (66.7)	4 (44.4)	6 (60.0)	6 (60.0)

Note. 6MMT, 6-min mastication test.
[†]Masticatory movements were qualified as variable if the rhythm was changing over time.

Table 4. Mean VAS scores for pain and fatigue for intervention and control group, directly after the test and after 5 minutes at T_1 (baseline measure) and T_2 (after 8 weeks).

	Intervention group (*n*=9)		Control group (*n*=10)	
VAS scores	T_1	T_2	T_1	T_2
VAS scores pain directly after the test (SD)	4.2 (2.7)	5.4 (3.3)	4.1 (3.1)	4.8 (3.6)
VAS scores pain after 5 min (SD)	2.3 (2.8)	2.4 (2.1)	2.3 (2.0)	2.8 (2.4)
VAS scores fatigue directly after the test (SD)	5.3 (3.4)	5.0 (3.6)	6.7 (2.6)	5.4 (3.7)
VAS scores fatigue after 5 min (SD)	2.4 (2.1)	2.8 (3.6)	4.4 (3.1)	3.9 (3.1)

Note. VAS, visual analogue scale (0-10).

Table 5. Patient reported outcomes of the MFV for mandibular function impairment for intervention and control group at T_1 (baseline measure) and T_2 (after 8 weeks).

		Intervention group (*n*=9)		Control group (*n*=10)	
MFV† statement		T_1	T_2	T_1	T_2
1. Social activities, *N*(%)	not at all	6 (66.7)	8 (88.9)	5 (50.0)	6 (60.0)
	sometimes	3 (33.3)	-	3 (30.0)	2 (20.0)
	usually	-	1 (11.1)	-	1 (10.0)
	very often	-	-	2 (20.0)	1 (10.0)
	excessively	-	-	-	-
2. Talking, *N*(%)	not at all	6 (66.7)	6 (66.7)	2 (20.0)	5 (50.0)
	sometimes	3 (33.3)	2 (22.2)	5 (50.0)	3 (30.0)
	usually	-	1 (11.1)	3 (30.0)	2 (20.0)
	very often	-	-	-	-
	excessively	-	-	-	-
3. Biting something sizeable, *N*(%)	not at all	4 (44.4)	4 (44.4)	1 (10.0)	3 (30.0)
	sometimes	3 (33.3)	4 (44.4)	4 (40.0)	4 (40.0)
	usually	2 (22.2)	-	3 (30.0)	2 (20.0)
	very often	-	1 (11.1)	1 (10.0)	-
	excessively	-	-	1 (10.0)	1 (10.0)
4. Eating solid food, *N*(%)	not at all	5 (55.6)	3 (33.3)	2 (20.0)	3 (30.0)
	sometimes	2 (22.2)	5 (55.6)	4 (40.0)	4 (40.0)
	usually	1 (11.1)	-	2 (20.0)	2 (20.0)
	very often	1 (11.1)	-	1 (10.0)	-
	excessively	-	1 (11.1)	1 (10.0)	1 (10.0)
5. Eating soft food, *N*(%)	not at all	7 (77.8)	7 (77.8)	8 (80.0)	8 (80.0)
	sometimes	2 (22.2)	2 (22.2)	1 (10.0)	1 (10.0)
	usually	-	-	-	1 (10.0)
	very often	-	-	1 (10.0)	-
	excessively	-	-	-	-
6. Daily activities, *N*(%)	not at all	6 (66.7)	8 (88.9)	5 (50.0)	8 (80.0)
	sometimes	3 (33.3)	-	4 (40.0)	1 (10.0)
	usually	-	1 (11.1)	-	1 (10.0)
	very often	-	-	1 (10.0)	-
	excessively	-	-	-	-
7. Drinking, *N*(%)	not at all	6 (66.7)	9 (100.0)	6 (60.0)	6 (60.0)
	sometimes	3 (33.3)	-	2 (20.0)	3 (30.0)
	usually	-	-	-	1 (10.0)
	very often	-	-	2 (20.0)	-
	excessively	-	-	-	-
8. Laughing, *N*(%)	not at all	8 (88.9)	8 (88.9)	5 (50.0)	5 (50.0)
	sometimes	1 (11.1)	1 (11.1)	-	4 (40.0)
	usually	-	-	3 (30.0)	1 (10.0)
	very often	-	-	2 (20.0)	-
	excessively	-	-	-	-
9. Mastication of tough food, *N*(%)	not at all	3 (33.3)	3 (33.3)	2 (20.0)	2 (20.0)
	sometimes	3 (33.3)	4 (44.4)	3 (30.0)	3 (30.0)
	usually	1 (11.1)	1 (11.1)	2 (20.0)	4 (40.0)

	very often	2 (22.2)	-	2 (20.0)	-
	excessively	-	1 (11.1)	1 (10.0)	1 (10.0)
10. Yawn, *N*(%)	not at all	7 (77.8)	6 (66.7)	5 (50.0)	4 (40.0)
	sometimes	1 (11.1)	3 (33.3)	2 (20.0)	4 (40.0)
	usually	1 (11.1)	-	2 (20.0)	1 (10.0)
	very often	-	-	1 (10.0)	1 (10.0)
	excessively	-	-	-	-
11. Kissing, *N*(%)	not at all	8 (88.9)	8 (88.9)	3 (30.0)	5 (50.0)
	sometimes	-	1 (11.1)	4 (40.0)	4 (40.0)
	usually	1 (11.1)	-	2 (20.0)	1 (10.0)
	very often	-	-	1 (10.0)	-
	excessively	-	-	-	-
12. Eating solid biscuits, *N*(%)	not at all	7 (77.8)	5 (55.6)	6 (60.0)	4 (40.0)
	sometimes	-	3 (33.3)	1 (10.0)	3 (30.0)
	usually	2 (22.2)	1 (11.1)	1 (10.0)	2 (20.0)
	very often	-	-	2 (20.0)	-
	excessively	-	-	-	1 (10.0)
13. Eating meat, *N*(%)	not at all	4 (44.4)	4 (44.4)	3 (30.0)	3 (30.0)
	sometimes	3 (33.3)	3 (33.3)	4 (40.0)	3 (30.0)
	usually	1 (11.1)	1 (11.1)	-	1 (10.0)
	very often	1 (11.1)	-	2 (20.0)	2 (20.0)
	excessively	-	1 (11.1)	1 (10.0)	1 (10.0)
14. Eating raw carrot, *N*(%)	not at all	5 (55.6)	4 (44.4)	5 (50.0)	2 (20.0)
	sometimes	2 (22.2)	3 (33.3)	1 (10.0)	4 (40.0)
	usually	1 (11.1)	1 (11.1)	1 (10.0)	1 (10.0)
	very often	1 (11.1)	1 (11.1)	2 (20.0)	1 (10.0)
	excessively	-	-	1 (10.0)	2 (20.0)
15. Eating French bread, *N*(%)	not at all	6 (66.7)	4 (44.4)	2 (20.0)	5 (50.0)
	sometimes	-	3 (33.3)	3 (30.0)	1 (10.0)
	usually	2 (22.2)	1 (11.1)	3 (30.0)	3 (30.0)
	very often	1 (11.1)	-	2 (20.0)	-
	excessively	-	1 (11.1)	-	1 (10.0)
16. Eating peanuts, *N*(%)	not at all	6 (66.7)	6 (66.7)	4 (40.0)	4 (40.0)
	sometimes	2 (22.2)	2 (22.2)	4 (40.0)	3 (30.0)
	usually	1 (11.1)	1 (11.1)	-	1 (10.0)
	very often	-	-	1 (10.0)	1 (10.0)
	excessively	-	-	1 (10.0)	1 (10.0)
17. Eating an apple as a whole, *N*(%)	not at all	4 (44.4)	4 (44.4)	2 (20.0)	2 (20.0)
	sometimes	4 (44.4)	4 (44.4)	3 (30.0)	3 (30.0)
	usually	1 (11.1)	-	2 (20.0)	1 (10.0)
	very often	-	1 (11.1)	2 (20.0)	2 (20.0)
	excessively	-	-	1 (10.0)	2 (20.0)

Note.

†MFV, Mandibulaire functiebeperking vragenlijst: Dutch questionnaire consisting of 17 statements providing information on mandibular function.

Figure 1. Sampling and flow of participants

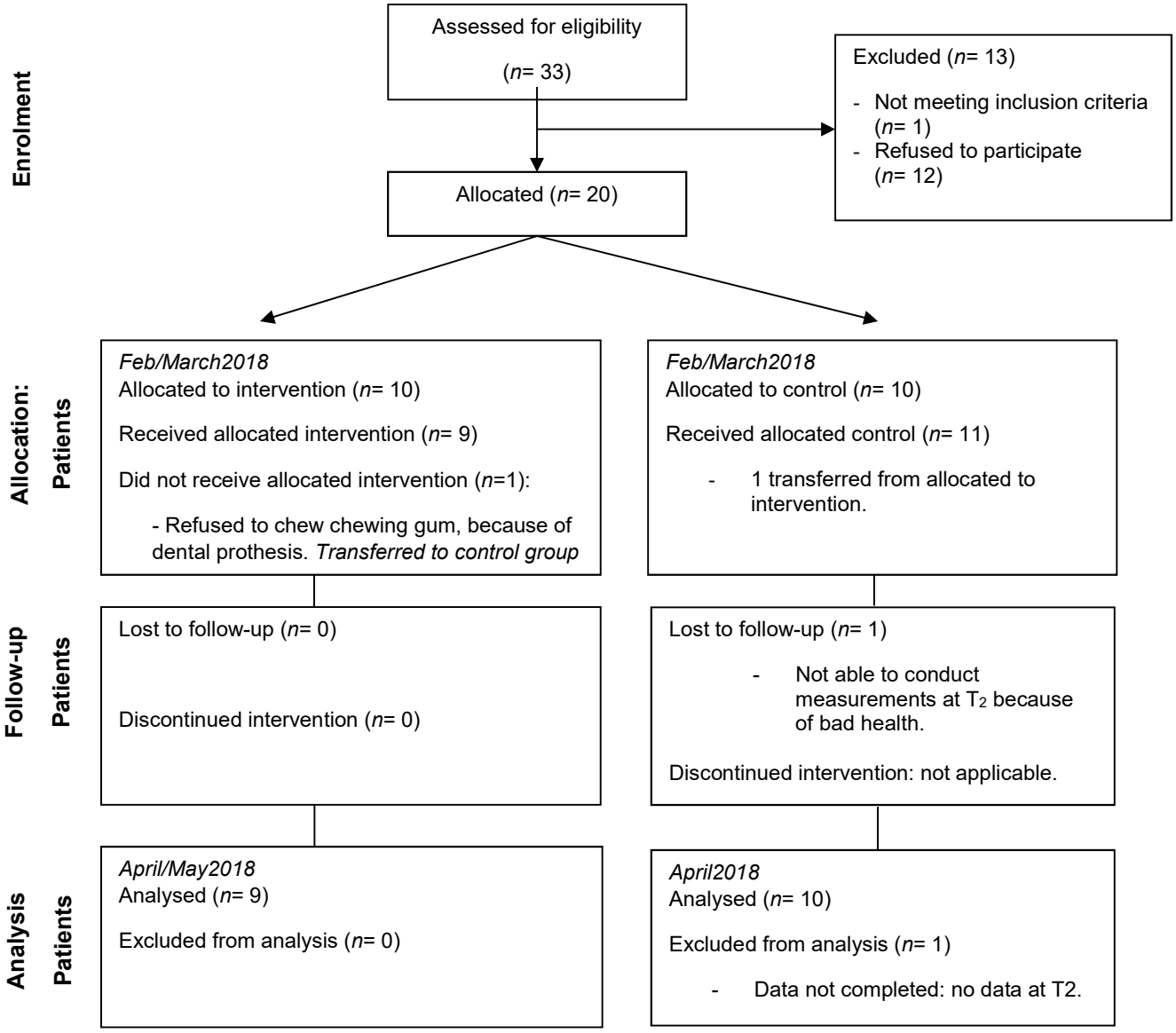

Figure 1. Participant flow chart following the Consolidated Standards of Reporting Trials. Adapted from the CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments.[27]

Dutch summary/ Nederlandse samenvatting

Titel: Kauwtraining bij volwassenen met een mitochondriële aandoening: een exploratieve studie.

Achtergrond: Kauwproblemen (pijn en vermoeidheid) komen vaak voor bij mensen met een mitochondriële aandoening. Uit onderzoek is gebleken dat laag intensieve training (fietsen) een positief effect heeft op de aandoening. Op dit moment is er nog geen trainingsprogramma beschikbaar gericht op kauwproblemen bij mensen met mitochondriële aandoeningen.

Onderzoeksvraag: Heeft kauwtraining met een lage intensiteit, waarbij gebruik wordt gemaakt van kauwgom, effect op de kauwprestatie, bijtkracht, kauwefficiëntie en duurvermogen bij mensen met een mitochondriële aandoening?

Methode: Een groep van 20 patiënten uit het Radboudumc Nijmegen heeft deelgenomen aan de studie: 10 in de interventiegroep en 10 in de controlegroep. Groepen waren ingedeeld op basis van geslacht en leeftijd. De interventie bestond uit een laag intensieve kauwtraining met suikervrije kauwgom. De training duurde 8 weken en kon thuis worden uitgevoerd. Er heeft een voormeting en een nameting plaatsgevonden, zowel bij de interventie- als de controlegroep. De volgende onderzoeken zijn daarbij afgenomen: twee-kleuren-kauwgom volgens de spatial heterogeneity methode, de Test of Mastication and Swallowing of Solids, de 6 minuten kauwtest en de VU-bijtkrachtmeter. Aanvullend is de mandibulaire functiebeperking vragenlijst afgenomen. De participanten uit de interventiegroep hebben tijdens de nameting 5 stellingen over de uitvoerbaarheid van de training beoordeeld op een 5-puntsschaal.

Resultaten: In de interventiegroep is de efficiëntie, met betrekking tot het aantal kauwbewegingen, significant verbeterd na de kauwtraining. Op het niveau van prestatie, duurvermogen en bijtkracht is geen verandering gemeten. In de controlegroep zijn geen verschillen gevonden tussen de voor- en nameting.

Conclusie: Kauwtraining verbeterd de efficiëntie: er zijn minder kauwbewegingen nodig voor het eten van vast voedsel. Resultaten van deze studie dragen bij aan het ontwikkelen van een specifiek kauwtrainingsprogramma voor mensen met mitochondriële aandoeningen, om zo kauwproblemen te verkleinen.

Aanbevelingen: De optimale duur en frequentie van de kauwtraining dient verder te worden onderzocht, evenals de lange termijneffecten.

Appendices

Appendix A Questionnaire to evaluate experiences of the intervention

Vragenlijst uitvoerbaarheid van de training

Geef aan in hoeverre u het met onderstaande stellingen eens bent.

1= totaal oneens

2= oneens

3= neutraal

4= mee eens

5= totaal mee eens

1. Ik vond 3 keer per dag, 20 minuten kauwgom kauwen gedurende 8 weken goed vol te houden.

1 – 2 – 3 – 4 – 5

2. De training kostte mij weinig extra energie.

1 – 2 – 3 – 4 – 5

3. De training is goed in te passen in mijn dagelijks leven.

1 – 2 – 3 – 4 – 5

4. Ik zou anderen aanraden om deze training te volgen.

1 – 2 – 3 – 4 – 5

<u>Opmerkingen:</u>

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……
……
……

Appendix B Reported clinical symptoms for both intervention and control group.

Intervention group:

Fatigue, restricted exercise tolerance, gait instability, muscle weakness, muscle aches, ptosis, ophthalmoplegia, vision disorder, hearing loss, ataxia, gastro-intestinal symptoms, cardiac arrhythmia, diabetes mellitus, neuropathic pain, status epilepticus, obstructive sleep apnea, myopathy, lipomatosis, gout, microalbuminuria.

Control group:

Fatigue, restricted exercise tolerance, muscle weakness, muscle aches, ptosis, ophthalmoplegia, hearing loss, malnutrition, underweight, anorexia, depression, concentration problems, migraines, ataxia, gastro-intestinal symptoms, diabetes mellitus, hyperparathyroidism, lactic acidosis, dysphagia, dysarthria, myalgia, proximal myotonic myopathy, maculopathy, microalbuminuria.

Appendix C DiffPix vs chew times in healthy adults – The bicolor chewing gum test

Figure 2: Values of DiffPix versus chew times, in 6 healthy adults measured with the bicolor chewing gum test by R.A.F. Weijenberg (PhD, Department of Clinical Neuropsychology, VU University Amsterdam, The Netherlands). (Results not published)