Tactile Massage or Relaxation Exercises Do Not Improve the Metabolic Control of Type 2 Diabetics

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Abstract: A 0.8% reduction in glycosylated hemoglobin (hemoglobin A1c) by tactile massage (TM) in patients with diabetes has been shown in a pilot study. The present study was carried out in patients with type 2 diabetes at primary healthcare centers as a parallel-arm clinical study with intention-to-treat analysis, of 10 weeks of TM once/week (n=26) or relaxation using a compact disc once/week (n=27). Anthropometrics were measured, i.e. weight, height, waist and calculation of BMI, blood samples were drawn, i.e. fP-glucose, B-HbA1c, fS-insulin, high-sensitive P-CRP, S-TNF-alpha, S-Interleukin-6, S-Adiponectin, S-Leptin and fP-Ghrelin, urine was collected for 24 hours for catecholamines and cortisol, and questionnaires including lifestyle variables were completed at baseline, after the 10-week intervention and at a follow-up 3 months after the intervention. There was no significant change in HbA1c in either the TM or the relaxation group. Waist circumference was reduced in both groups (p=0.01) but mostly in the TM group, with an adjusted difference between the groups of 4.0 cm (95% confidence interval 1.6-6.4 cm). The S-Adiponectin level increased significantly in the TM group (p=0.0095). TM therapy could not be recommended as a general treatment in subjects with type 2 diabetes. However, further studies in patients with high perceived level of stress and in other patient groups could be of value. The significance of the reduced waist is unclear, but could be of some importance in the long run.

INTRODUCTION

Diabetes is influenced by different factors, one of them is stress. Bjorntorp *et al.* suggested that hypothalamic arousal syndrome with parallel activation of the hypothalamic-pituitary-adrenal axis and the central sympathetic nervous system is responsible for development of endocrine abnormalities, insulin resistance, central obesity, dyslipidemia and hypertension, leading to frank disease, including type 2 diabetes [1]. Thus, it is natural to test stress-reducing therapies as a treatment of type 2 diabetes.

In a study of mindfulness-based stress reduction, HbA1c was reduced by 0.48% and mean arterial pressure by 6 mmHg [2]. In another study where biofeedback and relaxation was used, a reduction of HbA1c of 0.8% was seen, whereas a control group receiving solely diabetes information showed an increase of 0.2% [3]. In a study where another complementary medicine technique, tai chi, was used, no effect on HbA1c was found [4, 5].

For 30 years, a Swedish nurse has developed and practiced a form of contact massage originally called tactile massage (TM). This method involves a pain-free but deliberate, gentle and superficial massage of the skin without manipulation of the underlying muscles [6]. In an observational study in primary care of patients referred to TM for different reasons, mostly pain or sleeping problems, improvements as measured by the Health Index were documented in pain, sleep, relaxation, energy and mood [7].

A 0.8% reduction in glycosylated hemoglobin (hemoglobin A1c) by tactile massage (TM) in patients with diabetes has been shown in a pilot study [8].

The main aim was to study the effect of TM or relaxation exercises using a compact disc (CD) on metabolic control, i.e. HbA1c, in patients with type 2 diabetes, at primary healthcare centers in Stockholm County. The secondary aim was to study stress parameters, i.e. cortisol and catecholamines.

MATERIALS AND METHODOLOGY

The study was performed as a quasi-randomized, parallel-group, superiority trial of TM versus relaxation in type 2 diabetes patients. Outcome assessments were performed blinded. The research was approved by the Regional Ethics Appeal Board in Stockholm, 2007/414-31/4. The trial is registered at ClinicalTrials.gov protocol registration system, NCT 00960674.

Selection of Patients

Four primary healthcare centers (PHCC) in different parts of Stockholm County agreed to participate in the study. Patients with type 2 diabetes and HbA1c of 6-8% according to Swedish standard (corresponding Diabetes Control and Complications Trial, DCCT, standard is 1 percentage unit higher), aged 35-75 years of age, with metformin treatment, were identified at the included PHCC based on information in their medical record, and were randomly offered treatment with TM or relaxation with a CD containing relaxation exercises and soft music. To limit possible effects of genetic differences or effects of migration [9-11], only Swedish-born subjects with Swedish-born parents were included. Besides, the questionnaires and the relaxation exercises were in

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Swedish. Exclusion criteria were: heart failure or renal failure, and insulin treatment.

Altogether 102 persons were eligible. Allocation was performed stratified, by sex and age-group (35-45 years, 46-55 years, 56-65 years and 66-75 years of age) for each PHCC separately. The randomization procedure was performed manually by an independent subject at the research centre, assigning subjects alternately to the TM or the relaxation group, sometimes named as quasi-randomization [12]. By this procedure, 41 subjects were allocated to TM and 38 to relaxation, but 15 and 11 subjects, respectively, did not enter the study for unknown reasons. Thus, 26 and 27 subjects respectively were included in the intention-to-treat analysis. Another 4 and 4 attendants respectively, did not fulfill the study and their last observations were carried forward in the analysis. Additionally, per protocol analysis was also performed using only registered data on subjects fulfilling the study.

Study Design

TM group: The patients received their TM treatment mainly on the same day of the week and at the same time of the day for 10 weeks in order to make the study as standardized as possible. They were asked not to eat or drink for two hours before the treatment. Apart from that, there were no other restrictions regarding their diet or lifestyle.

Relaxation group: The patients were given instructions and received a CD with relaxation exercises and soft music. The CD contained 5 exercises that were each about 7 minutes long. Soft pieces of piano and trumpet music were played before and after each exercise for 3-4 minutes. The total playing time of the CD was 61 minutes. They were instructed to practice the relaxation exercises according to the CD on the same day of the week and at the same time of the day for 10 weeks, in order to follow the procedure of the TM group as closely as possible. They were offered the chance to perform the relaxation exercises at the PHCCs. However, all subjects preferred to perform the relaxation at home.

Measurements in both groups were performed on three occasions: before the intervention (baseline), after they had finished the intervention period of 10 weeks, and 3 months after the intervention. Blood samples were drawn in fasting state. Urine was collected for 24 hours. Questionnaires including questions on lifestyle habits were completed on each of these three occasions.

Intervention

TM group: TM is a form of contact massage in which the underlying muscles are not manipulated [6-8]. Certification as a TM therapist requires one week of combined theoretical and practical education, and an additional 60 hours of documented practice, and finally an examination [6]. The patient lies on a bunk and the TM treatment is given by certain definite smooth movements during one hour. Odorless vegetable oil is used and only the part of the body which is to be massaged is uncovered. The TM treatment starts on the back side of the body with the right and left leg, the back, the nape of the neck and the scalp. It then continues with the face, chest, stomach, arms, hands and fingers, the front of the legs, feet and toes. In order to ensure a calm awakening, the masseur or masseuse

counts calmly down from seven to one. Soft music is played during the whole session.

Relaxation group: The CD lasted for one hour. The participants reported their efforts, stating how often they had practiced the relaxation exercises.

Full treatment was defined as having completed at least 9 TM treatment sessions or relaxation hours.

Side-Effects and Adverse Events

Side-effects were considered unlikely and according to protocol, adverse events were not actively asked for. Four attendants from each group, respectively, did not fulfill their treatment, with two (cancer and fractured thigh-bone, respectively) and one (gall bladder inflammation and myocardial infarction) respectively because of new important diseases. None of these were likely due to side-effects of the intervention.

Blood Samples and Methods of Analysis

The following metabolic and inflammatory markers were analyzed from blood samples: fP-glucose, B-HemoglobinA1c (B-HbA1c) according to mono S standard which is 1% unit lower than DCCT standard, fS-insulin, high-sensitive P-CRP, S-TNF-alpha (ELISA), S-Interleukin-6 (ELISA), S-Adiponectin, S-Leptin and fP-Ghrelin. Catecholamines and cortisol were analyzed from 24-hour urine collections made by each participant in containers prepared by the laboratory. Separate containers had to be used for cortisol and catecholamines. A certified research laboratory performed the analyses and prepared the urine containers (The Laboratory of Clinical Chemistry at Karolinska University Hospital).

Insulin resistance measured by the homeostasis model, HOMA2ir, was calculated [13].

Body Measurements

Weight, height and waist measurements were made with the patient standing up. Waist circumference was measured midway between the lowest rib and the iliac crest following a gentle expiration [14]. Pulse and BP (blood pressure) were measured with the patient sitting after 5 minutes' rest. Measurements were performed in a standardized way, but no inter-observer was calculated. The BMI (Body Mass Index = weight/height²) was calculated based on measured weight and height.

Statistical Data Analysis

For the analysis of the data, the STATA statistical software version 9.1 was used.

Based on the pilot study [8], a power calculation was performed for the main outcome variable, assuming an effect of 0.8% *vs* 0.3% in HbA1c improvement in TM and relaxation groups, respectively, with standard deviation of 0.6, yielding a difference of 0.5 percentage units in improvement, regarded as the smallest clinically relevant effect. With a power=0.8 and alpha=0.05, this difference would need 23 subjects in each group.

Differences at baseline were calculated by Student's t-test, chi-square test or Fisher's exact test. Differences within study groups over time were calculated by ANOVA with

repeated measures. When p-values <0.05 were present, a more conservative approach using Greenhouse-Geisser epsilon was used, indicated with an asterisk (*) in the table. Statistical significance regarding differences within study groups was accepted when p<0.01 due to multiple testing. Between-group differences over time were tested if significant differences within groups were found, i.e. for two variables, with Student's t-test, where the significance level was set at p<0.05. Furthermore, between-group differences over time were tested between groups when p<0.05 was present in models with multiple linear regression. The multiple linear regression models were adjusted for sex, new important disease and changes in diabetes medication, and furthermore for differences over time as regards lifestyle habits, i.e. dietary habits, smoking and physical activity. Correlation coefficient between difference in waist and S-Adiponectin was analyzed by Pearson's test. In these analyses, p<0.05 was accepted as the significance level.

RESULTS

Sample characteristics are shown in Table **1**. BMI was significantly larger among men in the relaxation group. No other significant differences were detected.

Results by intention-to-treat analysis are shown in Table **2**. Within-group comparisons showed significant reduction in waist circumference for both groups, and increase in adiponectin in the TM group when using the significance level p<0.01. Between-group comparison showed only a significantly greater reduction in waist circumference in the TM group relative to the relaxation group.

Some values showed p-values <0.05, but we chose the significance level of p<0.01 due to multiple comparisons, and values nearby 0.01 could be regarded as trend values. CRP showed a trend to increase in the TM group (p=0.012), and four subjects showed increases, reaching above 10 mg/L. BMI showed a trend to decrease in the TM group (p=0.017), parallel to the decrease in waist circumference.

Multiple linear regression was performed in regard to differences over time in the TM and relaxation groups, with adjustment for sex, new important diseases and change in diabetes medication, and also as regard reported changes in lifestyle, i.e. dietary habits, smoking habits and physical activity habits. The only significant difference was found for waist circumference, with the TM group showing a greater reduction after intervention compared to the relaxation group, i.e. 4.0 cm (95% confidence interval 1.6-6.4 cm) in the intention-to-treat and 3.6 cm (95% confidence interval 1.1-6.2 cm) in the per protocol analysis.

Correlation coefficient by Pearson's test for differences between time 1 and time 3 for waist and S-Adiponectin was 0.38 (p=0.065) by intention-to-treat analysis.

DISCUSSION

This study failed to show a significant difference as regards HbA1c and other diabetes-related values, and also as regards stress and inflammatory markers. The only significant change over time between the TM group and the relaxation group concerned waist circumference.

The negative results of TM in this study contrast with the positive effect on HbA1c in the earlier pilot study, where HbA1c decreased by 0.8% [8]. There may be different reasons for this discrepancy, i.e. that the effect of the pilot study was due to non-specific or placebo effects. According to Kaptchuk *et al.* [15], these non-specific effects in a clinical setting could theoretically be separated into three components: a patient's response to observation and assessment (Hawthorne effects), the patient's response to the administration of therapeutic ritual (placebo treatment), and the patient's response to patient-practitioner interaction. When the study was presented at the primary healthcare centers, there was an interest although a rather skeptical attitude to it among the staff and this attitude seemed to be present among the attendants. The high dropout rate after randomization might be explained by this relative skepticism about both methods. The pilot study was performed without

Table 1. **Characteristics of Study Sample, by Intervention (TM=Tactile Massage, Relax=Relaxation with CD) and Sex (Standard Deviation or Percentage in Parentheses)**

	Men		Difference	Women		Difference	All		Difference
	TM	Relax	p-Value	TM	Relax	p-Value	TM	Relax	p-Value
Number	14 (14)	14 (13)		12 (10)	13 (13)		26 (24)	27 (26)	
Age, years	65.0 (5.2)	63.1 (7.2)	0.44	62.7 (9.8)	66.2 (8.4)	0.34	63.9 (7.6)	64.6 (7.8)	0.74
BMI, kg/m^2	26.8 (2.1)	29.4 (3.2)	0.017	28.6 (3.3)	28.6 (4.2)	0.99	27.5 (2.7)	29.3 (9.1)	0.11
Waist, cm	102.0 (9.1)	106.3 (6.5)	0.18	97.9 (10.5)	97.3 (9.0)	0.89	100.3 (9.7)	101.8 (9.0)	0.57
Systolic BP, mm Hg	145.4 (14.5)	138.1 (18.9)	0.27	146.7 (21.6)	144.2 (16.2)	0.76	145.9 (17.4)	141.2 (17.5)	0.34
Diastolic BP, mm Hg	83.0 (9.4)	83.5 (8.3)	0.89	81.4 (6.5)	81.9 (9.0)	0.88	82.3 (8.2)	82.7 (8.5)	0.88
B-HbA1c, % units	6.6 (0.3)	6.8 (0.4)	0.65	6.5 (0.3)	6.6 (0.2)	0.75	6.5 (0.2)	6.7 (0.2)	0.59
Daily smokers, numbers	2 (14.3%)	5 (35.7%)	0.19	3 (25.0%)	4 (30.8%)	0.39	5 (19.2%)	9 (33.3%)	0.24
Regular physical activity, numbers	6/14 (42.9%)	6/14 (42.9%)	1.0	0/9 (0%)	4/12 (33.3%)	0.10	6/23 (26.1%)	10/26 (38.5%)	0.36

BP denotes blood pressure, B denotes blood sample.
Missing values in a couple of subjects, except for age and smoking habits (actual number in parentheses in row for numbers, except for physical activity level).

Table 2.   Results Before the Intervention (with Standard Deviation), After the Intervention Period and After Yet Another Three Months, by Treatment Group and Time. Intention-to-Treat Analysis, with Values Carried Forward (or in Some Cases Backward) in Case of Missing Values

	TM Group				Relaxation Group			
	Time 1	Time 2	Time 3	Trend	Time 1	Time 2	Time 3	Trend
BMI, kg/m^2	27.5 (2.7)	27.1 (2.8)	27.2 (2.7)	0.017*	29.0 (3.7)	29.0 (3.5)	28.9 (3.4)	0.67
Waist, cm	**100.3 (9.7)**	**97.1 (8.8)**	**96.0 (8.4)**	**0.0001***	**101.8 (9.0)**	**101.1 (9.2)**	**100.0 (9.1)**	**0.0053***
Systolic BP, mm Hg	145.9 (17.4)	146.3 (17.2)	144.9 (14.1)	0.90	141.2 (17.5)	146.6 (13.0)	139.5 (14.0)	0.14
Diastolic BP, mm Hg	82.3 (8.2)	82.7 (9.4)	82.8 (8.7)	0.95	82.7 (8.5)	82.5 (9.8)	79.2 (10.4)	0.14
B-HbA1c, % units	6.5 (1.1)	6.4 (1.2)	6.4 (0.9)	0.25	6.7 (1.1)	6.9 (1.2)	6.6 (1.0)	0.061
fP-Glucose, mmol/L	8.8 (1.9)	8.5 (2.8)	8.6 (2.2)	0.53	8.5 (2.4)	8.7 (2.2)	8.1 (2.2)	0.27
fS-Insulin, pmol/L	79.5 (51.2)	99.3 (91.3)	92.2 (72.5)	0.70	91.7 (44.6)	104.4 (54.8)	87.1 (41.2)	0.050*
HOMA2ir	1.66 (1.05)	1.85 (1.61)	1.69 (1.29)	0.77	1.91 (0.99)	2.17 (1.12)	1.77 (0.80)	0.058
P-CRP, mg/L	2.9 (2.8)	3.0 (3.3)	5.5 (6.2)	0.012*	4.9 (10.8)	4.0 (4.4)	4.1 (8.6)	0.89
S-Interleucin-6, ng/L	1.41 (0.77)	1.32 (0.80)	1.61 (0.89)	0.056*	1.70 (1.21)	1.97 (1.21)	2.06 (3.35)	0.44
S-TNF-α, pg/mL	3.1 (3.2)	3.0 (2.5)	5.2 (8.3)	0.055	2.8 (3.7)	2.7 (3.3)	2.8 (2.4)	0.86
S-Adiponectin, mg/L	**6.3 (2.4)**	**6.7 (2.5)**	**7.0 (2.9)**	**0.0095***	6.3 (3.0)	5.9 (2.9)	6.5 (3.3)	0.30
S-Leptin, microg/L	15.4 (10.5)	14.4 (10.4)	15.4 (12.1)	0.96	17.6 (11.0)	17.4 (9.9)	15.3 (10.0)	0.033*
fS-Ghrelin, ng/L	880 (260)	943 (369)	900 (335)	0.045*	740 (239)	754 (245)	758 (252)	0.71
Pt(U)-Cortisol, nmol/d	66.9 (44.3)	76.5 (43.0)	71.9 (42.2)	0.94	72.2 (72.4)	67.0 (42.7)	69.5 (51.4)	0.91
Pt(U)-Noradrenalin, nmol/d	264 (99)	236 (101)	263 (100)	0.47	272 (101)	263 (91)	255 (104)	0.49
Pt(U)-Adrenalin, nmol/d	39.5 (19.9)	27.9 (18.2)	35.3 (27.1)	0.12	27.8 (14.9)	26.2 (19.6)	23.1 (10.2)	0.33
Pt(U)-Dopamin, nmol/d	1607 (444)	1479 (468)	1651 (549)	0.69	1495 (541)	1480 (571)	1348 (398)	0.12

BP denotes blood pressure, B denotes blood sample, f denotes fasting state, P denotes plasma sample, S denotes serum sample, HOMA2ir denotes Homeostatic model 2 insulin resistance, TNF-α denotes Tumor necrosis factor-alpha, Pt(U) denotes quantity in 24-hour urine collection.
Statistical analysis by ANOVA with repeated measures within groups. Asterisk (*) denotes use of Greenhouse-Geisser epsilon in cases with p-levels <0.05 with regular methods. The only statistical significant difference between groups concerned waist circumference change between time 1 and time 3 (p=0.0167 by Student's t-test).

a control group, which may strengthen the emotion of the therapeutic ritual. Furthermore, the pilot study was performed at only one primary healthcare centre, with only a few TM therapists, probably enhancing the positive expectation of the treatment. In addition, most of the attendants of the pilot study were of Turkish origin, and that specific immigrant group in Sweden have been shown to have a high rate of emotional distress [16], and could therefore possibly respond differently than the target group in the present study.

With the negative results on HbA1c in mind, one might argue that the treatment possibly could show effect in patients expressing symptoms of stress, or reporting a higher stress level in a questionnaire, thus identifying subjects with stress induced hyperglycemia. Further studies could be directed to find such persons, rather than perform TM treatment on diabetes subjects in general.

The reason for the finding of a significant reduction in waist circumference in the TM group remains unclear. The measurement of the waist was performed in the same standarized way as at baseline. S-Adiponectin also increased in the TM group, although correlation between change in waist circumference and S-Adiponectin was not significant. BMI also showed a trend to decrease. No other reduction was found in the other biochemical markers, so the

clinical significance of the lower waist circumference is uncertain. If a reduced waist circumference and/or BMI can be shown in additional studies of TM, it would be of value as central obesity and high BMI are associated with hypertension, myocardial infarction and increased mortality [17-19].

Some variables showed borderline statistical significance or trend values, e.g. BMI decreased in the TM group, parallel to the decrease in waist circumference, and CRP increased in the CRP group. As CRP is an unspecific marker of inflammation, concurrent diseases such as virus infections may well influence the results, and the results should be interpreted with caution.

The study has some limitations including dropouts after the allocation. However, they dropped out before baseline measurements were performed, which limits the possible bias this may introduce. The randomization procedure did not follow the CONSORT statement for proper randomization, and could be described as a quasi-randomization with the introduction of possible bias [12]. The interventions could not be blinded by obvious reasons, but the assessments were performed blinded. Besides, the results are only valid for the patient group included in the study, and other groups could possibly react in different ways. We did not use any questionnaire to measure

experienced stress, but solely relied on laboratory parameters. The sample size was smaller than we expected, but yet it had enough power to detect clinical important difference in HbA1c between the two groups. However, the small number of subjects introduced an uncertainty, especially as regards a test such as CRP.

The strength of this study is that it was performed as a parallel-group trial, with a control group receiving relaxation therapy. The analysis was performed and reported by intention-to-treat analysis. However, no important differences were found between intention-to-treat and per protocol analyses of the data.

CONCLUSION

The final conclusion is that TM therapy cannot be used as a general treatment in subjects with type 2 diabetes with the intention to improve metabolic control. Further studies should be directed at identifying subjects with perceived high level of stress and offer TM treatment to them. The clinical significance of the decreased waist circumference is uncertain, but could be important in the long run.

ACKNOWLEDGMENTS

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