Effects of tactile massage on metabolic biomarkers in patients with type 2 diabetes

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Received 8 October 2012; received in revised form 5 February 2013; accepted 5 February 2013

Abstract

Aim. – Tactile massage (TM) is a gentle and superficial form of massage. A pilot study of patients with type 2 diabetes in primary care reported a reduction of 0.8% in glycosylated haemoglobin (HbA1c), whereas a randomized study comparing the effects of 10 weeks of TM once per week with relaxation exercises performed once per week as per instructions on a CD found no effects of TM on HbA1c in an intention-to-treat analysis. However, a significant reduction in waist circumference (WC) was found between the groups.

Methods. – This was a secondary per-protocol analysis of the effect of TM (n = 21) compared with relaxation (n = 25) on other metabolic biomarkers. Anthropometrics (BMI and WC) and metabolic factors (HbA1c, S IGF, fS insulin, S adiponectin, S leptin and fP ghrelin) were assessed, insulin resistance (IR) was determined by modified homeostasis model assessment (HOMA2–IR) using fP glucose and fS insulin, and ratios of adiponectin-to-leptin, adiponectin-to-HOMA–IR, adiponectin-to-WC and adiponectin-to-HbA1c were calculated at baseline, and at 10 weeks and 6 months after the intervention.

Results. – Significant results adjusted for age, gender and changes in lifestyle and medical factors were shown for WC in women (−6.2 cm [95% CI: −10.4, −1.9]), but not in men. In addition, improvements in the TM group were found for adiponectin and ratios of adiponectin-to-leptin and adiponectin-to-HbA1c levels.

Conclusion. – Our data indicate that TM therapy may affect metabolic markers in type 2 diabetes despite the lack of significant effects on HbA1c. The clinical implications of our findings need to be evaluated in further studies.

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Keywords: Complementary/alternative medicine; Relaxation; Tactile massage; Diabetes mellitus; Primary health care; Sweden

Résumé

Effets des massages sur les marqueurs métaboliques dans le diabète de type 2.

Objectif. – L’effet des massages doux sur l’équilibre glycémique reste mal connu. Une étude pilote chez les personnes diabétiques de type 2 en soins primaires a rapporté une réduction de 0.8 % du taux d’hémoglobine glycosylée (HbA1c), alors qu’une étude randomisée comparant les effets de dix semaines de massages une fois par semaine à des exercices de relaxation effectués une fois par semaine, suivant les directives sur ces exercices enregistrés sur un CD, n’a trouvé aucun effet sur l’HbA1c.

Méthodes. – L’effet des massages sur les marqueurs métaboliques a été testé versus relaxation. Les paramètres anthropométriques (IMC et tour de taille), et les facteurs métaboliques (HbA1c, insulin, adiponectine, leptine et ghreline), index de résistance à l’insuline HOMA ont été évalués, au départ à dix semaines et à six mois après l’intervention.

Résultats. – Une diminution significative du tour de taille a été observée après ajustement pour l’âge et les modifications du style de vie chez les femmes (−6,2 cm [95 % CI: −10,4, −1,9]), mais pas chez les hommes. Une augmentation de l’adiponectine était également notée.
Conclusion. — Nos données indiquent que les massages doux modifient certains paramètres métaboliques dans le diabète de type 2, malgré l’absence d’effets significatifs sur l’HbA1c. Les implications cliniques de nos résultats doivent être évaluées dans des études ultérieures.

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Mots clés : Approches complémentaires/parallèles en santé ; Relaxation ; Massage tactile ; Le diabète sucré ; Les soins de santé primaires ; En Suède

1. Introduction

Stress can affect the development of type 2 diabetes through activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic central nervous system, both of which have been suggested to be involved in insulin resistance (IR), central obesity, dyslipidaemia and hypertension [1]. For this reason, stress-reducing therapies have been considered beneficial for the treatment of type 2 diabetes, and some studies have demonstrated this with glycosylated haemoglobin (HbA1c) reductions of 0.5–0.8% [2,3], whereas others have failed [4,5].

Tactile massage (TM) is a special type of massage that entails gentle and superficial massaging of the skin without involving the underlying muscles [6]. TM has been shown to have positive effects on pain, sleep, relaxation, energy and mood [7]. In a pilot study of TM in patients with type 2 diabetes, a reduction of 0.8% was found in HbA1c levels [8]. In a randomized trial where the effects of TM were compared with those of relaxation exercises, no effect on HbA1c levels was found in the intention-to-treat (ITT) analysis [9]. However, secondary effects on waist circumference (WC) and adiponectin were detected.

In fact, HbA1c may be too insensitive a measure to assess the effects of stress-reduction therapies on metabolic function, and beneficial metabolic effects may occur in the absence of any improvement in HbA1c [10]. Adiponectin, leptin and ghrelin are all biomarkers that have been closely associated with metabolic abnormalities and cardiovascular risk [11–16]. It has been proposed that biomarker ratios might be better markers of metabolic disturbances than each biomarker on its own [17–23]. To investigate the metabolic effects of TM on different biomarkers, a per-protocol (PP) analysis is preferable to an ITT analysis, the effects of which may be diluted due to poor compliance and missing laboratory values.

The main aim of the present study was to assess the effect of TM and relaxation exercises on metabolic variables other than HbA1c in patients with type 2 diabetes attending primary healthcare centres in Stockholm County.

2. Materials and methodology

The study was performed as a quasi-randomized, parallel-group, superiority trial in type 2 diabetes patients to compare the effects of TM vs. relaxation. Researchers performing the outcome assessments were blinded to the patients’ allocations. The study had the approval of the regional Research Ethics Appeal Board in Stockholm (2007/414-31/4). The trial was registered on the ClinicalTrials.gov protocol registration system (NCT 00960674).

2.1. Selection of patients

Four primary healthcare centres (PHCC) located in different parts of Stockholm County participated in the study. Patients with type 2 diabetes and HbA1c levels of 6–8%, according to the Swedish standard (the corresponding Diabetes Control and Complications Trial [DCCT] standard is 1 percentage unit higher), aged 35–75 years and treated with metformin, were identified based on their medical records. Patients were randomized into two groups. One group was given TM while the other was offered relaxation based on a CD containing relaxation exercises and soft music. To limit any possible effects of differences because of genetics or migration [24–27], only Swedish-born subjects with Swedish-born parents were included. This was decided also because the questionnaires and relaxation exercises were given in Swedish. Exclusion criteria were heart failure, renal failure and insulin treatment.

Altogether, 102 patients were eligible and 79 were included in the randomization. The recruited patients at each PHCC were further stratified by gender and age (35–45 years, 46–55 years, 56–65 years and 66–75 years). The randomization procedure was done manually by an individual other than the researchers who assigned subjects alternately to either the TM or relaxation group in a quasi-randomized fashion [28]. By this procedure, 41 subjects were allocated to TM and 38 to relaxation. However, 15 participants in the TM group and 11 in the relaxation group withdrew from the study after giving no reasons. Thus, the TM and relaxation groups comprised 26 and 27 participants, respectively, in the ITT analysis. However, due to missing values for different variables, only 21 and 25 participants in the TM and relaxation groups, respectively, were included in the PP analysis (Table 1).

2.2. Study design

All participants in the TM group received treatment on the same day of the week and at the same time of day for 10 weeks in total. They were all asked not to eat or drink anything for 2 h before treatment. No other restrictions on the participants’ diet or lifestyle were applied.

All participants in the relaxation group were given a CD recording of the relaxation exercises and soft music. They were instructed to perform the relaxation exercises on the CD on the same day of the week and at the same time of day for 10 weeks in total. Although participants could perform the relaxation exercises at the PHCC, all preferred to do the exercises at home.

Fasting blood glucose samples were taken and questionnaires were handed out to participants at baseline (before the...
intervention), and also at 10 weeks after the intervention and after a further 3 months (around 6 months after the intervention).

### 2.3. Interventions

TM is a gentle form of massage that exerts its effects through relaxation and not by working directly on the muscles [6–8]. To become a certified TM therapist requires a week-long educational program that combines theory and practical exercises, and 60 h of post-education documented practice followed by an examination [6]. A TM session typically lasts an hour. Odourless vegetable oil is used and only the specific body part to be massaged is exposed. At the beginning of a TM session, the patient lies face down and the therapist applies gentle pressure on the backs of the right and left legs, the back, the nape of the neck and the scalp. The patient then lies on his back while the therapist gently massages the face, chest, stomach, arms, hands and fingers, front of the legs, feet and toes. The therapist revives the patient by counting down from seven to one. Soft music plays in the background during the session.

Participants in the relaxation group received an hour-long CD recording of five exercises, each one lasting about 7 min. In general, soft piano and trumpet music plays in the background before and after each exercise that typically last for 3 to 4 min. The participants were asked to record how often they performed the relaxation exercises.

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

### 2.4. Side-effects and adverse events

The occurrence of side-effects with either treatment was considered unlikely and therefore was not accounted for. Four participants in each group did not complete their treatment for reasons such as cancer, a fractured thigh bone, gallbladder inflammation and myocardial infarction. None of these was likely to be a side-effect of the interventions.

### 2.5. Blood samples and methods of analysis

The following metabolic and inflammatory markers were analyzed from blood samples: fasting plasma glucose (FPG); HbA1c (originally measured by the Swedish [mono-S] standard, which is 1 percentage unit lower than the DCCT standard, but translated to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) HbA1c value assessed in mmol/mol), free serum insulin, serum insulin-like growth factor (IGF)-1, serum adiponectin, serum leptin and free plasma ghrelin were measured. A certified research laboratory at Karolinska University Hospital performed the analyses.

### 2.6. Metabolic ratios

Modified homoeostasis model assessment for IR (HOMA2–IR) [29], which involves measuring levels of FPG and fasting insulin in the blood, was used to assess IR. Adiponectin-to-leptin [18] and adiponectin-to-HOMA2–IR ratios [17] were calculated. Also calculated were ratios between markers of abdominal obesity and metabolic control such as adiponectin-to-WC and adiponectin-to-HbA1c.

### 2.7. Body measurements

Weight, height and WC measurements were taken with the patient standing up. WC was measured after a gentle breath out
Table 2
Per-protocol analysis showing differences within treatment groups between values at baseline and after 6 months as logarithmic and anti-logarithmic values.

<table>
<thead>
<tr>
<th></th>
<th>Tactile massage</th>
<th>Relaxation exercises</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Baseline</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>17</td>
<td>27.5 (3.0)</td>
</tr>
<tr>
<td>WC, cm</td>
<td>17</td>
<td>99.7 (1.1)*</td>
</tr>
<tr>
<td>B HbA1c IFCC (mmol/mol)</td>
<td>21</td>
<td>59.0 (12.4)</td>
</tr>
<tr>
<td>S IGF, mcg/L</td>
<td>19</td>
<td>137.8 (1.2)*</td>
</tr>
<tr>
<td>fS insulin, pmol/L</td>
<td>19</td>
<td>78.9 (1.7)*</td>
</tr>
<tr>
<td>HOMA2–IR</td>
<td>19</td>
<td>1.67 (1.69)*</td>
</tr>
<tr>
<td>S adiponectin, mg/L</td>
<td>19</td>
<td>5.77 (1.62)</td>
</tr>
<tr>
<td>S leptin, mcg/L</td>
<td>19</td>
<td>12.45 (2.09)*</td>
</tr>
<tr>
<td>fS ghrelin, ng/L</td>
<td>19</td>
<td>791 (1)*</td>
</tr>
<tr>
<td>Adiponectin/leptin</td>
<td>19</td>
<td>0.44 (2.15)*</td>
</tr>
<tr>
<td>Adiponectin/HOMA2–IR</td>
<td>19</td>
<td>3.31 (1.90)*</td>
</tr>
<tr>
<td>Adiponectin/WC</td>
<td>15</td>
<td>0.060 (0.018)</td>
</tr>
<tr>
<td>Adiponectin/HbA1c IFCC</td>
<td>19</td>
<td>0.101 (0.040)</td>
</tr>
</tbody>
</table>

Data presented are results of paired t tests expressed as arithmetical means (SD) or geometric means when log transformation was used (with back-transformed SD); *geometric means (back-transformed SD); significant findings are in bold. WC: waist circumference; B: blood sample; IFCC: International Federation of Clinical Chemistry and Laboratory Medicine; S: serum sample; fS: fasting serum sample; HOMA2–IR: modified homoeostasis model assessment for insulin resistance.

by placing the measuring tape around a point halfway between the lowest rib margin and tip of the iliac crest [30]. Body mass index (BMI) was calculated by dividing the patient’s weight by the square of the height (kg/m²).

2.8. Statistical data analysis

For this analysis, STATA data analysis and statistical software (version 11.0) was used. The study sample size was calculated to show a difference in HbA1c of 0.8% vs. 0.3% (SD 0.6) with a power of 0.8 and α = 0.05 [31] — in other words, 23 people in each group — with assumptions based on a pilot study [8].

Testing for possible skewed distributions of the variables showed that the following were significantly skewed at baseline in men: insulin; HOMA2–IR; leptin; adiponectin-to-leptin ratio; and adiponectin-to-HOMA2–IR ratio. In women, the skewed variables were: adiponectin-to-leptin ratio; adiponectin-to HOMA2–IR ratio; and adiponectin-to-WC ratio. When considering both TM and relaxation groups with women and men combined at baseline or at the 6-month follow-up, the following variables were significantly skewed: WC; IGF; insulin; HOMA2–IR; ghrelin; adiponectin-to-leptin ratio; adiponectin-to-HOMA2–IR ratio; and adiponectin-to-WC ratio.

Log-transformed values were used for these variables when calculating mean differences within the groups by paired t tests and between the groups by unpaired t tests. These values are presented in Tables 1 and 2 as arithmetical means with standard deviations (SD); where logarithmic transformations were done, the back-transformed mean values (geometric means) and back-transformed SD were also calculated. Lifestyle factors were registered for smoking habits (daily smoking or not), physical activity (four categories: sedentary; now and then; regular during leisure time; and physical training — shown in Table 1 as ‘regular or not’ and dietary adherence (four categories: not at all; a little; mostly; and always — shown in Table 1 as ‘mostly or not’). Differences at baseline were calculated by Fisher’s exact test. For medications, only changes were noted and, for differences over time, statistically significant skewness was found for BMI, HbA1c, insulin, HOMA2–IR, ghrelin, adiponectin-to-leptin ratio and adiponectin-to-HOMA2–IR ratio. Multiple linear regression models used the differences between values at baseline and at 6 months, respectively, as dependent factors; and age, gender, changes in diabetes medication and changes over time in lifestyle habits (dietary habits, smoking and physical activity) as independent factors. In addition, the interaction between gender and treatment allocation was tested. Results are shown as beta coefficients and 95% confidence intervals (CI). The statistically significant level was set at P < 0.05.

3. Results

Characteristics of the study participants are shown in Table 1. Men in the TM group had a significantly lower BMI and a borderline significant value for WC, but higher IGF and ghrelin levels than men in the relaxation group.

Results according to PP analysis for within-group comparisons showed significant reductions in WC in both groups and significant increases in adiponectin values, as well as in adiponectin–leptin, adiponectin–WC and adiponectin–HbA1c (IFCC) ratios in the TM group (Table 2).

Results for between-group comparisons of Δ values (differences between baseline and follow-up at 6 months) are shown in Table 3. For the WC Δ values, a significant interaction between gender and treatment effect was found (P = 0.041) when only results according to gender were included in the calculations. As for differences between men and women in terms of treatment effect, this was only found for WC, with changes of −6.2 cm (95% CI: −10.4, −1.9) in women and 0.2 cm (95% CI: −4.8, 5.2) in men.
Table 3
Treatment results by per-protocol analysis between tactile massage (TM) and relaxation exercise (Relax) groups using linear regression models adjusted for gender, age, changes in diabetes medication and differences over time in lifestyle (dietary habits, smoking and physical activity).

|                  | Δ values between TM and Relax groups |<ref>
| Body mass index, kg/m² | −0.3 (−1.0, 0.4) |<ref>
| B HbA₁c, IFCC (mmol/mol) | −1.6 (−6.8, 2.8) |<ref>
| S IGF, mcg/L | −12.9 (−30.2, 4.3) |<ref>
| fS insulin, pmol/L | 22.5 (−6.4, 51.5) |<ref>
| HOMA2–IR | 0.53 (−0.13, 1.18) |<ref>
| S adiponectin, mg/L | 0.65 (−0.25, 1.55) |<ref>
| S leptin, mcg/L | 0.77 (−2.55, 4.08) |<ref>
| fS ghrelin, ng/L | 48 (−40, 136) |<ref>
| Adiponectin/leptin | 0.18 (−0.04, 0.40) |<ref>
| Adiponectin/HOMA2–IR | 0.36 (−1.08, 1.80) |<ref>
| Adiponectin/WC | 0.010 (−0.001, 0.021) |<ref>
| Adiponectin/HbA₁c, IFCC | 0.012 (−0.006, 0.030) |<ref>

B: blood sample; IFCC: International Federation of Clinical Chemistry and Laboratory Medicine; S: serum sample; fS: fasting serum sample; HOMA2–IR: modified homeostasis model assessment for insulin resistance.

<ref>
| a Difference between follow-up values at 6 months and baseline values, expressed as beta coefficients (95% CI); for waist circumference (WC), a significant interaction was found between treatment allocation and gender (results shown only in text by gender).

4. Discussion

In the present study, TM appeared to have positive metabolic effects compared with a relaxation programme using exercises recorded on a CD. The effect was a reduction in WC with TM that was also in accord with changes noted by secondary analyses in the ITT analysis [31], albeit only in women. In addition, within-group analysis indicated an effect in the TM group as regards adiponectin, adiponectin–leptin, adiponectin–WC and adiponectin–HbA₁c (IFCC) ratios.

Measuring the effects on different ratios such as the relationship between adiponectin and leptin, and on metabolic disturbances such as the metabolic syndrome [32], as well as changes in BMI, triglycerides, high-density lipoprotein (HDL) cholesterol [18] and incident type 2 diabetes [19] could be of clinical significance. Moreover, the adiponectin-to-HOMA2–IR ratio has also been associated with the metabolic syndrome [17]. Our study found an increase of 25% in adiponectin–leptin ratio within the TM group and a treatment effect of 48% for TM vs. relaxation that nonetheless was not significant. This result can be compared with that of a study from Korea reporting 80% higher values for adiponectin-to-leptin ratios in healthy subjects compared with those who had the metabolic syndrome [32]. The adiponectin–leptin ratio has been shown to correlate better with clamp-derived insulin sensitivity than with other surrogate markers of insulin sensitivity, including HOMA, in people with diabetes [20]. The adiponectin-to-leptin ratio was also found to be a better marker of IR than either adiponectin or leptin alone in a study of Japanese diabetic patients [18]. In addition, adiponectin has been positively associated with HDL cholesterol in patients with type 2 diabetes [33].

There are several possible explanations for the effects seen here with TM. First, the effects of relaxation therapy on the HPA axis [1] may be able to reverse stress-related increases in cardiometabolic risk parameters [2,3]. Our pilot study found a tendency towards lower cortisol levels [8], but this was not confirmed in the present study [9]. Second, the superiority of TM vs. relaxation exercises in the present study may perhaps be explained by the putative release of oxytocin induced by the gentle manipulation [34]. However, the pilot study mentioned above showed no significant effects on oxytocin levels with TM [8]. Third, visiting the healthcare centre once a week for 10 weeks of TM sessions may have induced a non-specific treatment effect [35]. Finally, participating in the TM arm of the study may have encouraged lifestyle changes that were not measured by the study questionnaires.

As the measurement of WC was performed using established methods, it is unlikely that the significant reduction observed among participants in the TM group was due to measuring errors [30]. As a large WC, a sign of central obesity, is associated with hypertension [24] and myocardial infarction [36], this reduction may have clinical value. Studies to support this idea include a cohort study in which a decreasing WC was beneficially associated with a reduction in features of the metabolic syndrome after 9 years [37]. In yet another study, an intervention combining nutritional advice with psychological support and regular physical activity demonstrated that a smaller waistline was associated with a lower Framingham risk score after 10 years [38]. Interestingly, the effect of TM on WC was seen only among women and not among men. This finding needs to be confirmed in further studies.

The HOMA2–IR [29] is an established surrogate assessment of IR, although strictly speaking, as insulin is released in pulses, insulin values should be entered as the mean of two or more assessments, which is not the case in most studies. However, as our study sample was rather small and insulin was measured only once at each opportunity, the results of the HOMA2–IR assessments should be interpreted with caution.

The present study has yet other limitations. Even if the sample size had been sufficient for the prespecified treatment effect — finding an effect of 0.5% units of HbA₁c (equal to 5 mmol/mol in HbA₁c IFCC), it would still not be enough to compare effects in men vs. women. Also, IR was previously shown to be associated with high leptin levels in men and low ghrelin levels in women, but these differences could not be further explored in our study due to the small sample size [39]. In addition, the randomization procedure did not follow the CONSORT statement for proper randomization and is described here as quasi-randomization with the possible introduction of bias [28]. Furthermore, the potential effect of TM on diabetic patients receiving other types of treatment is uncertain. No questionnaire was used to measure experienced stress. The analyses were performed per protocol in contrast to the main evaluation of the study [9], although no important differences were found between the ITT and PP data analyses.
The main strengths of our study were that it was performed as a parallel-group trial with a control group receiving relaxation therapy and that it involved a wide range of measured biomarkers.

5. Conclusion

TM therapy appeared to have metabolic effects in patients with type 2 diabetes, despite showing no effect on HbA1c. Researchers should be aware of metabolic effects other than the effect on HbA1c when assessing interventional effects in diabetes. Ratios such as adiponectin-to-WC and adiponectin-to-HbA1c may have clinical value, but their superiority over their individual components in other settings and in relation to other clinical variables has yet to be established.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

This study was supported by grants from Stockholm County Council. We would also like to thank the participants in the study, the nurses who performed TM and the participating healthcare centres in Stockholm County.

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