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Massage Improves Growth Quality by Decreasing Body Fat Deposition in Male Preterm Infants

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Abstract

Objectives—To assess the effect of massage on weight gain and body fat deposition in preterm infants.

Study design—Preterm infants (29–32 wk) were randomized to Massage (n=22, 12F/10M) or Control (n=22, 12F/10M). Treatment was masked with Massage or Control administered twice-daily by licensed massage therapists (6 d/wk for 4 wk). Body weight (g), length (cm), ponderal index (PI g/cm^3), body circumferences (cm), skinfold thickness (triceps TSF, mid-thigh MTSF, and subscapular SSF; mm) were measured. Circulating IGF-1, leptin, and adiponectin were determined by ELISA. Daily dietary intake was collected.

Results—Energy and protein intake as well as increase in weight (g/kg/d), length, and body circumferences were similar. Massage male infants had smaller PI, TSF, MTSF, and SSF, and increases over time than Control male infants ($p<0.05$). Massage female infants had larger SSF increase than Control females ($p<0.05$). Circulating adiponectin increased over time in Control male infants (group X time X sex interaction, $p<0.01$) and was correlated to PI ($r=0.39$, $p<0.01$).

Conclusions—Twice daily massage did not promote greater weight gain in preterm infants. Massage did, however, limit body fat deposition in male preterm infants. Massage decreased circulating adiponectin over time in male infants with higher adiponectin concentrations associated with increased body fat. These findings suggest that massage may improve body fat deposition, and in turn growth quality, of preterm infants in a sex-specific manner.

Keywords

preterm infant; infant massage; growth; growth quality; body fat; IGF-1; adiponectin; leptin

Massage therapy is advocated for stress attenuation in preterm infants (<37 weeks postmenstrual age).[1] Preterm infants admitted to the newborn intensive care unit (NICU) are exposed to numerous stressful events.[2] Stressful events elicit neuroendocrine release of

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glucocorticoid which suppress the IGF-1 axis, and in turn, weight gain in preterm infants.[3,4] We found improved autonomic nervous system function, and in turn stress response, in male preterm infants who received twice-daily massage.[5] Infant massage is also reported to increase circulating IGF-1 [6] and weight gain [7]. Stress attenuation by massage therapy, therefore, may help optimize weight gain of hospitalized, preterm infants.

Optimal weight gain is essential for survival and long-term health of preterm infants. Preterm infant weight gain alone, however, is a poor indicator of growth quality.[8] Growth encompasses simultaneous changes in body length, lean tissue, and fat mass. Fat tissue deposition may be abnormally higher in hospitalized, preterm infants. Excess endogenous glucocorticoid exposure, as a result of chronic stress, alters growth quality by promotion of fat storage.[4] Preterm infants are lighter and shorter at term (40 weeks postmenstrual age; PMA) than term-born infants, but their total body [9, 10] and inter-abdominal fat mass [11] is up to 70% greater. These alterations to body fat deposition impair growth quality, and may result in part, from the numerous stressful events associated with preterm birth.

To date, how stress attenuation by massage relates to growth quality of preterm infants is unknown. Therefore, we evaluated weight gain, body fat deposition, and circulating leptin and adiponectin levels in preterm infants randomized to receive a twice daily Massage program compared with preterm infants randomized to receive standard NICU care (Control). We hypothesized that Massage would decrease body fat deposition in preterm infants. We also tested the relationships between massage, body fat deposition, and circulating leptin and adiponectin in preterm infants.

Methods

Preterm infants admitted to the NICU at University of Utah Hospital or Intermountain Medical Center and born between 28 4/7 and 32 3/7 wk post-menstrual age confirmed by maternal dates, mid-pregnancy 2-D fetal ultrasound, and physical exam at birth and with birth weight, length, and head circumference between the 10^{th} to 90^{th} percentiles for gestational age were eligible for study. At the time of informed parental consent, infants were stratified by sex and randomized to Massage or Control. Exclusion criteria included abnormal intrauterine growth, congenital anomalies, intravenous nutrition at 14 days of age, or other conditions known to affect growth. Infants entered the study protocol when tolerating enteral feeding volumes >100 ml/kg/d. This study was approved by the University of Utah Institutional Review Board for Human Subjects. This trial was registered with ClinicalTrials.gov (NCT00722943).

The Massage and Control treatments were performed for 20 min twice daily at 0700h and 1900 h, 6 d/wk (Monday-Saturday) for a maximum of 4 weeks. The Massage and Control treatments were performed behind a privacy screen by a licensed massage therapist. The Massage treatment was modeled after the Infant Massage USA® protocol and modified for preterm infants by eliminating massage of the abdomen. Although there is no evidence that massage of the abdomen is associated with the development of necrotizing enterocolitis or other abdominal injury, we eliminated massage of the abdomen as a precautionary measure.[5] The Massage protocol consisted of the application of six soft-tissue compression strokes to the following areas of the supine infant: (1) top of thighs to ankles and feet; (2) chest over ribcage; (3) shoulders down the arms to hands; (4) head from crown to neck; and (5) along the back from the neck to the waist.[5] Range-of-motion to the arms and legs as described was delivered following the massage. During the range-of-motion phase, each arm and each leg moved away from (extension) and back toward (flexion) mid-line against the infant's own resistance. Extension/flexion movements were repeated five times for each arm and

each leg. The Control treatment required the licensed massage therapist to stand quietly by the infant's bedside for 20 min twice daily at 7:00 a.m. and 7:00 p.m.

Nine licensed massage therapists, certified in infant massage, provided all Massage and Control treatments. All massage therapists were trained to recognize clinical signs of distress. A rotation schedule assured equal distribution of the therapists' within study subjects and between treatments. The lead massage therapist (SH) randomly observed the treatment protocol every 20 treatments as administered by the massage therapists to ensure treatment fidelity.

Both Massage and Control were administered behind a privacy screen to maintain 'masking' of the infant's study assignment to parents and NICU clinical staff. In addition, study personnel responsible for anthropometric measurements or biochemical analyses (the clinical studies coordinator and two research assistants) were masked to the infant's study assignment to minimize bias during data collection. Only the massage therapists and the study PI (LMM) were aware of the infant's study assignment.

Anthropometric measures included body weight, length, body circumferences (head, abdominal, mid-arm and –thigh), and skinfold thickness at Days 1, 8, 15, 22, and 29 (baseline through week 4). Body weight on an electronic infant scale (Air Shields, Vickers, OH) was recorded to the nearest g. Body length (Infant Length Board, Ellard Instrumentation, Inc., Seattle, WA) and body circumferences (head, abdomen, mid-upper arm and thigh) using a disposable paper tape were measured to the nearest 0.1 cm as described by Koo.[16] Measures of infants body fat included skinfold thickness (triceps TSF, mid-thigh MTSF, and subscapular, SSF; mm) [17] by caliper (Lange; Beta Technologies, Santa Cruz, CA) and ponderal index (PI, g/cm^3). Enteral feeding volume was recorded daily. Calories (g/kg/d) and protein, fat, and carbohydrate (all g/kg/d) based on the feeding source (human milk + commercial fortifier or preterm infant formula) was determined.

Spot blood samples were collected onto filter paper using standard heelstick technique at baseline, 2 and 4 weeks. Samples were immediately processed and stored. IGF-1, leptin, and adiponectin were extracted [18] and concentrations determined in duplicate by ELISA (Signosis, Inc., Sunnyvale, CA). The intra- and inter-rater coefficients of variation for all assays were <2% and <5%, respectively.

Statistical Analyses

The sample size of five infants per treatment group and sex to achieve a power = 0.80 with alpha le;0.05 was based on an expected +2.8 ± 1.6 g/kg/d average daily weight gain difference between Massage and Control at the completion of the 4 week study period.[7] Independent t-test and *Chi*-square were used to test for differences between Massage and Control infant's characteristics at birth and study entry. The generalized estimating equations (GEE) procedure was employed to determine the effect of treatment (Massage or Control) on anthropometric measures, growth rate, and serum measures for all infants. A random intercept for each infant and a random slope for study day were included in the model to estimate individual trajectories for change over time. Goodness of fit was achieved for the positively skewed independent variables using the Gamma distribution. The GEE test accommodates the dependent nature of repeated measures data. Similar to an ANOVA-derived F distribution, the GEE test uses the Wald χ^2 to test the true value of the measurement of interest. Sex was included in the modeling due to its known recognized influence on weight gain, body fat, and serum variables of interest. The three-way interaction (treatment X study day X sex) was our primary effect of interest. Weekly average energy (Kcal/kg/d) and protein (g/kg/d) were cofactors for anthropometric comparisons

whereas biochemical measures were adjusted or infant body weight (g). Pearson *r* controlling for time was used to test the relationships between measures of growth and serum biomarkers. SPSS v.20.0 (IBM Corporation, Armonk, NY) was used for all analysis with significance set at $p \leq 0.05$.

Results

Informed, parental permission was obtained for 62 infants who were randomized to Massage (n=30) or Control (n=32). Eighteen infants (8 Massage and 10 Control) had incomplete data collection before day 15 of study. Data collection was complete through study week 2 for 44 infants (22 Massage, 22 Control), 30 infants (15 Massage, 15 Control) through study week 3, and 21 infants (11 Massage) through study week 4. Sex distribution was consistent between treatment groups during the study period. Ethnic distribution as well as post-menstrual age and body weight at birth, study entry, and study completion were similar for Massage and Control infants (Table I).

The predominant feeding source was human milk with fortification to 24/kcal/oz (79.5%) for both groups. No differences were detected between Massage and Control for weekly energy and protein intakes (Table I). The overall average daily weight gain was 16.8 ± 4.8 g/kg/d Massage compared with 16.4 ± 5.5 g/kg/d Control (Table I). The average weekly weight gain was similar between groups. The overall or weekly changes in body length, or body circumferences were not influenced by treatment group, time, sex, or their interactions. The mean weekly change for body weight, length, and head circumference were within established growth guidelines for preterm infants (Table I).[7]

Baseline PI, TSF, MTSF, and SSF measurements did not differ between Massage and Control infants (Table II). All measures increased over time ($p<0.001$). Treatment X time interactions were not significant. Significant treatment X time X sex interactions were detected for PI and skinfold thickness from baseline to 4 weeks. In Massage males, the PI, TSF, MTSF, and SSF increases were smaller than Control male infants ($p<0.05$). Massage females had a larger SSF increase compared with Control female infants ($p<0.001$).

Circulating IGF-1, leptin, and adiponectin results at baseline, 2 and 4 weeks are presented in Table II. Both groups of infants had similar IGF-1 and leptin concentrations at each measurement interval. Female infants had higher leptin levels than male infants independent of treatment group (31.56 ± 2.15 ng/ml female and 26.40 ± 1.10 ng/ml male; Wald $\chi^2=4.315$, $p<0.001$). Circulating adiponectin levels increased from baseline to week 2 and remained elevated in male Control compared with male Massage infants ($p<0.01$). There was no significant treatment X time X sex interaction detected for circulating IGF-1 or leptin.

The correlations between growth and biochemical measures are in Table III. Weekly body weight gain, PI, TSF, and MTSF were negatively related to circulating leptin ($p<0.05$). Circulating leptin was also inversely related to circulating IGF-1 ($p<0.05$). Positive correlations were found between circulating leptin and SSF ($p<0.05$) as well as PI and circulating adiponectin ($p<0.05$).

Discussion

Although advocated to improve weight gain [6,7], we did not find a massage benefit to weight gain in our study cohort of preterm infants. Recent investigations of massage and preterm infants are inconsistent with only 50% reporting greater weight gain.[19–26] The lack of agreement between these studies may be due to variability in the degree of prematurity, birth weight, and inclusion of intrauterine growth restricted (IUGR; birth

weight <5th percentile) infants. For example gestational age and birth weight of earlier investigations ranged from 28 to 35 weeks PMA [26] and 0.5 to 2.0 kg [19, 21], respectively. Weight gain trajectories are higher in less mature (<29 week PMA) and IUGR infants.[8] The inclusion of less mature [20] or IUGR infants [19–22,25] may bias weight gain comparisons in preterm infants. We minimized this bias by limiting our study cohort to preterm infants born at 29 to 32 week PMA without evidence of IUGR. The similar dietary intake provided to our homogeneous study cohort, increased our ability to control for the confounding effect of diet on changes in weight when investigating the effects of massage on weight gain.

IGF-1, the predominant postnatal growth factor, has been linked to greater weight gain in massage treated preterm infants.[6] Although positively associated with body weight, we did not detect differences in circulating IGF-1 between our Massage and Control cohorts. Both circulating IGF-1 concentrations and weight gain may be influenced by energy and protein intake. Average daily energy and protein intake, provided at advised levels for preterm infants [8], did not differ between Massage and Control infants.

Weight gain alone, however, is a poor indicator of the changes to body fat. For that reason we evaluated body fat deposition by PI and regional skinfold thickness measurements.[16] Despite similar weight gain, Massage male infants had lower PI change, an indicator of total body fat, as well as skinfold-determined peripheral (TSF and MTSF) and central (SSF) subcutaneous fat deposition than Control male infants. This finding suggests massage promotes lean mass over fat mass in male preterm infants. In female infants, massage was associated with greater central subcutaneous fat deposition increase than Control females. This does not, however, mean that massage promotes abnormally higher central subcutaneous fat mass in female preterm infants. Intrauterine central subcutaneous deposition, measured by skinfold thickness at 33 to 41 weeks PMA, is greater in female compared with male newborn infants.[26] Thus, the higher central subcutaneous fat deposition in female Massage as well as the lower peripheral and central subcutaneous fat deposition in male Massage infants suggests sex-specific responses to Massage in preterm infants. Therefore, we speculate twice-daily massage affected fat mass deposition in both male and female preterm infants.

Cortisol levels are higher in preterm infants than term infants due to immaturity of the hypothalamic-pituitary axis which impedes stress recovery.[13] Chronic cortisol exposures alter body composition by increasing lean tissue catabolism and fat deposition.[3,4] Total body fat as well as intra-abdominal visceral fat tissue is higher in preterm infants at term adjusted age (40 wk PMA) compared with term newborn infants.[9–11]. Infant massage decreases post-massage cortisol levels as well as blood pressure.[7] Further we have shown improved autonomic nervous system maturation and parasympathetic activity in massage infants with a greater response noted in male compared with female preterm infants.[5] We now present evidence that twice-daily massage decreases subcutaneous fat deposition in male preterm infants. Together, our data may suggest a mechanism by which twice-daily massage improves growth quality by decreasing stress-driven fat deposition in male preterm infants. The unexpected sex-specific response may reflect greater vulnerability to stress in male preterm infants and warrants further investigation.

The stable circulating adiponectin concentrations with massage treatment support the theory that massage attenuates stress-driven body fat acquisition in male preterm infants. Male Massage infants' adiponectin concentrations decreased over time in contrast to a significant, sustained increase in male Control infants. Our Control infant as well as female Massage infant results are in concordance with those of Saito et al [14] who observed a significant increase in circulating adiponectin levels from birth at 32–35 weeks to term corrected age in

hospitalized, preterm infants. Although infant weight gain was positively related to the rise in circulating adiponectin ($r=0.37$, $p<0.001$) in this study, we did not detect a similar relationship. Rather we found a similar positive relationship between circulating adiponectin and infant PI, an indicator of infant body fat. In obese adults, higher body fat is associated with lower circulating adiponectin.[12] The discrepancy in the body fat and adiponectin relationship is attributed to mature adipocyte hypertrophy in adults versus increased pre-adipocyte number in preterm infants.[27] In neonatal animals, exposed to the acute stress of a hypoxic insult, pre-adipocytes increase adiponectin secretion.[28] Thus, we attribute the increased circulating adiponectin of our male Control infant cohort to stress-driven body fat deposition. Importantly, massage attenuation of stress-driven body fat deposition is supported by the decreased circulating adiponectin in Massage treated infants.

The circulating leptin results for Massage and Control infants are in agreement with Ng et al who reported no change in circulating leptin despite significant weight gain over a five week period in <34 week PMA, AGA preterm infants.[15] Although circulating leptin was unrelated to body weight or weight gain in this investigation[15], we noted weak inverse relationships between weight gain and measures of body fat and circulating leptin.

There were several potential limitations to the study. Data collection was limited to 44 preterm infants born 29–32 weeks gestation. Our small sample size was offset by 1) restricting eligibility to medically stable, preterm infants to insure a more homogeneous cohort in regard to growth and body composition and 2) using a prospective, longitudinal study design to increase statistical power. Our study was designed to insure protocol compliance and limit study-related bias by masking to infant treatment assignment of all personnel involved in measurements and testing.

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List of Abbreviations

GEE	General estimating equation
MTSF	Mid-thigh skinfold (mm)
PI	Ponderal index (kg/cm^3)
PMA	Postmenstrual age (weeks)
SSF	Subscapular skinfold (mm)
TSF	Tricep skinfold (mm)

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Table 1

Subject Characteristics by Treatment Group

	Massage	Control
N		
Baseline to 2 week	22	22
Baseline to 3 week	15	15
Baseline to 4 week	11	10
Sex % male	50%	50%
Ethnicity		
Non-Hispanic, White	64 %	68 %
Hispanic	36 %	32 %
Gestational Age (wk)	31.4 ± 0.9	31.0 ± 0.8
Birth Weight (g)	1574 ± 232	1618 ± 231
Birth Length (cm)	41.0 ± 2.2	41.2 ± 2.0
Birth Head Circumference (cm)	28.8 ± 1.3	29.1 ± 1.1
Body Weight at Study Entry (g)	1522 ± 238	1598 ± 278
Body Weight at Study End (g)	2186 ± 35	2265 ± 338
Age at Study Entry (PMA, wk)	32.7 ± 0.8	32.3 ± 0.7
Age at Study End (PMA, wk)	35.9 ± 0.9	35.4 ± 0.9
Feeding Source (24 kcal/oz)		
Human Milk + fortifier	77.3%	81.8%
Preterm Formula	22.7%	18.2%
Caloric Intake (Kcal/kg/d)		
Week 1	111.4 ± 11.5	118.6 ± 8.9
Week 2	112.4 ± 10.1	114.6 ± 9.6
Week 3	112.2 ± 16.3	114.7 ± 14.2
Week 4	117.1 ± 5.0	110.7 ± 7.4
Protein Intake (g/kg/d)		
Week 1	2.8 ± 0.8	2.9 ± 0.9
Week 2	3.3 ± 0.3	3.3 ± 0.3
Week 3	3.4 ± 0.5	3.3 ± 0.6
Week 4	3.4 ± 0.8	3.5 ± 0.2
Anthropometric Changes *		
Body Weight (g)		

	Massage	Control
Baseline	1522 ± 238	1598 ± 278
Study completion	2186 ± 352	2265 ± 337
Δ per week (g/kg/d)	16.8 ± 4.8	16.4 ± 5.5
Length (cm)		
Baseline	41.1 ± 2.1	41.5 ± 2.1
Δ per week	1.3 ± 0.4	1.1 ± 0.6
Head Circumference (cm)		
Baseline	28.5 ± 1.2	29.0 ± 1.6
Δ per week	1.0 ± 0.3	0.9 ± 0.4
Abdominal Circumference (cm)		
Baseline	23.7 ± 1.5	23.9 ± 1.8
Δ per week	1.1 ± 0.4	1.0 ± 0.5
Mid-Arm Circumference (cm)		
Baseline	7.0 ± 0.6	7.1 ± 0.7
Δ per week	0.4 ± 0.1	0.4 ± 0.1
Mid-Thigh Circumference (cm)		
Baseline	9.8 ± 0.9	10.0 ± 0.9
Δ per week	0.7 ± 0.3	0.9 ± 0.3

Percent or Mean ± SD. Chi-square, independent t-test, or

*GEE test for treatment, time, sex, and their interactions with body weight and energy (Kcal/kg/d) as covariates.

Table 2

PI, Skinfold Thickness, and Serum Results at Baseline, 2 and 4 Weeks for Treatment Group by Sex

	Massage		Control	
	Males	**Females**	**Males**	**Female**
PI (kg/cm^3)				
Baseline	2.27 ± 0.06	2.21 ± 0.03	2.23 ± 0.05	2.18 ± 0.04
Δ per week	0.05 ± 0.01[a]	0.10 ± 0.02	0.07 ± 0.02	0.06 ± 0.01
TSF (mm)				
Baseline	2.4 ± 0.1	2.6 ± 0.1	2.6 ± 0.1	2.4 ± 0.1
Δ per week	0.2 ± 0.1[b]	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.1
MTSF (mm)				
Baseline	2.4 ± 0.2	2.7 ± 0.1	2.7 ± 0.1	2.7 ± 0.2
Δ per week	0.3 ± 0.1[c]	0.4 ± 0.1	0.6 ± 0.1	0.4 ± 0.1
SSF (mm)				
Baseline	2.8± 0.1	3.0 ± 0.2	3.0 ± 0.2	2.9 ± 0.2
Δ per week	0.1 ± 0.1[d]	0.5 ± 0.1[d]	0.3 ± 0.1	0.3 ± 0.1
IGF-1 (ng/mL)				
Baseline	197.6 ± 23.5	150.1 ± 22.5	195.2 ± 56.1	198.6 ± 20.8
Week 2	214.9 ± 27.8	151.3 ± 25.5	277.0 ± 78.5	253.8 ± 49.4
Week 4	222.6 ± 42.0	247.2 ± 47.5	241.7 ± 80.0	236.4 ± 35.1
Leptin (ng/mL)				
Baseline	31.2 ± 3.4	28.8 ± 3.3	30.0 ± 1.6	31.9 ± 3.9
Week 2	27.4 ± 3.4	21.7 ± 2.6	28.7 ± 0.8	27.9 ± 5.0
Week 4	23.2 ± 2.2	20.3 ± 2.9	26.8 ± 2.8	27.2 ± 5.0
Adiponectin (pg/mL)				
Baseline	25.9 ± 11.0	22.7 ± 6.1	22.6 ± 6.1	15.4 ± 4.7
Week 2	27.1 ± 13.0	17.1 ± 2.1	33.6 ± 15.0	23.8 ± 5.4
Week 4	10.3 ± 2.0[e]	38.7 ± 13.6	34.8 ± 11.0	27.6 ± 5.4

Estimated mean ± SE. GEE test with average weekly energy (Kcal/kg/d) and protein intake (g/kg/d) as cofactors for PI and skinfold thickness analysis while biochemical measures were adjusted for body weight.

[a] PI: treatment X time x sex Wald χ^2 = 433.027, p<0.001; Massage male < Control male.

[b] TSF: treatment X time X sex interaction Wald χ^2 = 7.599, p<0.05; Massage male < Control male.

[c] MTSF: treatment X time X sex interaction Wald χ^2 = 7.949, p<0.05; Massage male < Control male.

[d] SSF: treatment X time X sex interaction Wald χ^2 = 24.451, p<0.001; Massage male < Control male and Massage female > Control female.

[e] Adiponectin: treatment X time X sex interaction Wald χ^2 = 20.860, p<0.01; Massage male < Control male.

Table 3

Correlations for Anthropometric and Biochemical Measures

	IGF-1 (ng/mL)	Leptin (pg/mL)	Adiponectin (ng/mL)
Leptin (pg/mL)	0.22 *		
Adiponectin (ng/mL)	0.05	−0.16	
Weight gain (g/kg/d)	0.15	−0.23 *	−0.14
Ponderal Index (g/cm^3)	0.07	−0.32 *	0.37 *
TSF (mm)	0.04	−0.31 *	−0.03
MTSF (mm)	0.16	−0.53 **	0.02
SSF (mm)	−0.14	0.26 *	0.13

Pearson *r* correlation test with time as cofactor;

* $p<0.05$;

** $p<0.01$