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Insulin and Insulin-Like Growth Factor 1 (IGF-1) Increased in Preterm Neonates

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Abstract

Objective—To determine if massage therapy increased serum insulin and insulin-like growth factor 1 (IGF-1) in preterm neonates.

Study Design—Forty-two preterm neonates who averaged 34.6 weeks (M=29.5 weeks gestational age; M birthweight= 1237 gms) and were in the "grower" (step-down) nursery were randomly assigned to a massage therapy group (body stroking and passive limb movements for three, 15-minute periods per day for 5 days) or a control group that received the standard nursery care without massage therapy. On days 1 and 5, the serum collected by clinical heelsticks was also assayed for insulin and insulin-like growth factor-1 (IGF-1), and weight gain and kilocalories consumed were recorded daily.

Results—Despite similar formula intake, the massaged preterm neonates showed greater increases during the 5 day period in: 1) weight gain; 2) serum levels of insulin; and 3) insulin-like growth factor-1 (IGF-1). Increased weight gain was significantly correlated with insulin and IGF-1.

Discussion—Previous data suggested that preterm infant weight gain following massage therapy related to increased vagal activity, which suggests decreased stress, and gastric motility, which may contribute to more efficient food absorption. The data from this study suggest for the first time that weight gain was also related to increased serum insulin and IGF-1 levels following massage therapy.

Conclusion—Preterm infants who received massage therapy not only showed greater weight gain but also a greater increase in serum insulin and IGF-1 levels, suggesting that massage therapy might be prescribed for all growing neonates.

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Keywords

Preterm Infants; Massage Therapy; IGF-1

Massage therapy has consistently led to greater weight gain in preterm neonates (Means range from 28% to 47%), earlier discharge (M=6 days), and a substantial reduction in hospital costs.[1–4] In addition, massaged preterm neonates show more mature motor behavior, more stable state organization, and fewer abnormal reflexes on the Brazelton Neonatal Behavioral Assessment Scale.[2,3] A recent study on potential underlying mechanisms for the massage therapy/weight gain relationship suggested that massage therapy increased vagal activity and gastric motility which were, in turn, related to weight gain.[4]

Massage therapy may also lead to increased weight gain by increasing insulin and IGF-1 inasmuch as insulin promotes the conversion of glucose to both short-term (glucogen) and long-term storage (lipids), and IGF-1 plays an important role in promoting growth by stimulating cell growth and multiplication and inhibiting apoptosis. Stress, which is common in preterm neonates, has been noted to contribute to dysregulation of glucose metabolism in preterm infants including hyperglycemia and insulin resistance.[5, 6] Massage therapy has been noted to reduce stress behaviors and increase calmer states in neonates.[7] This is likely the result of a parasympathetic response elicited by the stimulation of pressure receptors that is, in turn, associated with both decreases in cortisol levels[8] and increases in vagal activity[4] noted in preterm infants who receive massage. Inasmuch as the vagus innervates the stomach and pancreas, increased vagal activity may lead to greater weight gain by increasing gastric activity and promoting the release of insulin. Similarly, by decreasing cortisol, massage therapy may lead to greater weight gain by reducing the inhibitory effects of cortisol on insulin secretion. In addition, by decreasing cortisol, massage therapy may lead to greater weight gain by increasing IGF-1 inasmuch as chronically high levels of cortisol inhibit growth hormone secretion,[9, 10] and growth hormone stimulates the production of IGF-1. Tactile stimulation and increased vagal activity have also been associated with the release of food absorption hormones (e.g. gastrin) which could contribute to more efficient food absorption.[11]

IGF-1 is notably lower in preterm infants.[12] And, in both full-term and preterm infants, IGF-1 is significantly correlated with birthweight, body length and Ponderal index.[13] Inasmuch as a positive relationship has been observed between IGF- 1 levels and subsequent weight gain,[14, 15] IGF-1 might be one of the factors mediating the greater weight gain observed in massaged preterms, and the reverse might also be true, i.e. that weight gain may stimulate insulin and IGF-1.

This study examined the effects of massage therapy on insulin and IGF-1. Following five days of massage therapy, preterm neonates were expected to show greater weight gain and higher concentrations of insulin and IGF-1 than neonates who were not massaged.

Method

Participants

Prior to group assignment, informed consent was obtained from at least one parent and the attending physician of each neonate who met the criteria for being transferred to the "grower" (step-down) nursery including that the neonate was free of medical complications and off the respirator. After the preterm neonates were transferred to the grower nursery, they were randomly assigned to either the massage therapy or a standard treatment control group. Both groups received treatment as prescribed by the attending neonatologists, but the massage group also received massage therapy. Although the parents, staff and researchers were not

informed about the group assignment, "blinding" was not possible. However, any differential special care would likely be given to the control group infants and result in decreased group differences or a more conservative test of the treatment effects.

Preterm neonates were specifically excluded if: (a) they had genetic anomalies, congenital heart malformations, and/or central nervous system dysfunction; (b) they were HIV-positive; (c) they had been exposed to illicit drugs (confirmation of drug use through medical records and a drug screen); (d) they required surgery; or (e) they had unstable BPD, IVH, NEC, sepsis or other serious morbidities as well as intubation.

A power analysis based on our most recent preterm infant massage study suggested a sample size of 18 per group for power of .80 at $p<.05$.[4] We recruited 45 neonates to accommodate an expected attrition rate of 20% although only 3 neonates did not complete the study, yielding a sample size of 42. The forty-two preterm neonates (N=29 females) were born to lower SES mothers (M=4.1 which is low socioeconomic status on the Hollingshead Index) who averaged 27.6 years of age and who were distributed 53% Hispanic, 41% Black and 6% Caucasian. The neonates' gestational age averaged 29.5 weeks (s.d. =2.6), their birthweight averaged 1236 grams (s.d. =317.8), and their Ponderal index averaged 2.1 (s.d. =.31) (see table 1). At the time of the study, the infants averaged 34.6 weeks gestation, and they had spent an average of 27.7 days in the NICU. The groups did not differ on these measures.

Procedure & Measures

Massage Therapy—The massage therapy protocol developed by Field et al.[1] was used in this study, with the sessions beginning on the day of transfer to the intermediate care nursery, or as soon after as parental consent was obtained, and the sessions continued for 5 consecutive days. The massages were provided for three 15-minute periods per day. As in our earlier studies, the first treatment session occurred approximately one hour after the morning feeding, the second about one-half hour after the mid-day feeding, and the third approximately 45-minutes after the completion of the second treatment session. Vital signs were measured 15 minutes before, 15 minutes during and 15 minutes after the massage procedure. Heart rate was recorded for those time intervals and converted to vagal activity (high frequency component of heart rate variability).

Each session consisted of tactile stimulation for 5 minutes, followed by kinesthetic stimulation for 5 minutes and concluding with another 5 minutes of tactile stimulation. The sessions were conducted with the infant in an isolette or a crib. The therapist warmed his/her hands prior to the start of the treatment and remained silent during the 15-minute session.

The tactile stimulation segment was conducted with the infant in a prone position. Moderate pressure stroking was done with the flats of the fingers of both hands. Each area (the head, shoulders, back, legs and arms) was stroked for six 10-second strokes for a total of 5 minutes. For the kinesthetic phase, the infant was placed in a supine position. The limbs were moved into flexion and extension six times (10 seconds each time) in the following sequence: (a) right arm, (b) left arm, (c) right leg, (d) left leg, and (e) both legs simultaneously for a total of 5 minutes. The tactile segment was then repeated with the infant in a prone position.

Nursing Notes—Nursing notes were examined daily for weight gain and formula intake. The neonates were weighed daily prior to the 8 am feeding. Kilocalories (Kcals) per Kilogram were calculated based on the caloric content of the formula and the weight of the neonate.

Serum Blood Samples—On Days 1 and 5, 1.5 mL of blood was taken from the clinical heelstick blood sample. These heelsticks were performed by a phlebotomist at 5–6 am prior to the first feeding. These samples were then taken to the lab of one of the authors (A.K.) for

assays. Serum insulin and IGF-1 levels were assayed by radioimmunoassay and non-extraction IRMA respectively, using commercial kits (Diagnostic System Laboratories, Webster, Texas). For the insulin assay, 100 μL sample serum was treated with 100 μL insulin antibody, and the mixture was incubated for 16 hours at 2–8°, and the complex was treated with precipitating reagent, incubated for 15 minutes, centrifuged, drained, and the radioactivity 7 (I-125) in the precipitated complex was counted using the gamma counter (Perkin Elmer, Dual Channel, Model 1450). For the IGF-1 assay, a sample of 50 μL serum was pipetted at the bottom of the tube and immediately mixed with 200 μL of anti-IGF-1 reagent, incubated at room temperature for two hours on a shaker decanted, and treated 3x with wash solution, and radioactivity in the complex was counted using a gamma counter as above. Quantification of insulin and IGF-1 was carried out using pre-programmed computer generated standard curves obtained with varying concentrations of insulin and IGF-1 standards. The sensitivity of the method for insulin was 1.3 μ IU/mL and intra- and inter-assay coefficients of variance (% CV) were 4.5–8 and 4.7–12.2 respectively. For IGF-1, the sensitivity of the assay was 2pg/tube or 2ng/mL plasma/serum, and % CV for intra- and inter-assays were between 4–7% and 4–8% respectively.

Results

A Chi Square analysis suggested that the groups did not differ on ethnicity. A MANOVA revealed that the groups did not differ on other demographic variables including (see table 1): 1) mothers' age; 2) mothers' SES; and 3) parity. A MANOVA on birth measures suggested that the groups did not differ on (see table 2): 1) gestational age (weeks); 2) birthweight (grams); 3) birth length (cms); 4) head circumference (cms); 5) Ponderal Index (birthweight/length^3 × 100); and 6) Obstetric and Postnatal Complications Scale Scores. In addition, ANOVAs revealed no significant differences between the massage and control infants with respect to 1) days since birth; 2) days in the NICU; 3) weight at start of the study; and 4) kilocalories consumed. However, the control group showed greater (p=.02) weight gain on the two days prior to group assignment (see Table 2). Thus this variable was entered as a covariate.

Vagal activity significantly increased during the massage therapy (M= 3.85 to M = 4.30, F (1,35)= 12.54, P< 0.001). This increase suggests that massage therapy enhanced parasympathetic activity.

As can be seen in table 3, although the groups did not differ on calorie consumption (Kcal/Kg) during the study period, the massage group versus the control group showed: 1) a greater increase in weight gain (F= 6.07, p= 0.02); 2) a greater increase in insulin (F= 4.75; p= 0.001); and 3) a greater increase in IGF-1 (F=4.93, p= 0.05)

Correlation analyses suggested significant relations between these growth variables for the massage group but not for the control group as follows: 1) weight gain was related to increased insulin, r=.60, p=.05; and 2) in weight gain was related to increased IGF-1, r= .46, p=.02. Calorie consumption was not related to any of these variables.

Discussion

In an earlier study we documented increased vagal activity and gastric motility following massage therapy, and these two variables were, in turn, related to weight gain.[4] Inasmuch as moderate pressure massage led to those effects, while light pressure massage did not, we concluded that stimulation of pressure receptors may lead to enhanced vagal activity and, in turn, increased gastric motility.

In the present study, increased IGF-1 was associated with weight gain, consistent with other studies.[7, 8] The increased insulin and IGF-1 levels and the associated weight gain in massaged preterm infants in the present study might also be mediated by increased vagal activity.

Enhanced vagal activity has been associated with increased production of food absorption hormones including gastrin, as reported by at least one group,[8] suggesting vagal activity as a potential mediating mechanism.

Massage therapy could also contribute to weight gain by increasing insulin and IGF-1 given that insulin promotes the conversion of glucose to both short-term and long-term storage, and IGF-1 stimulates cell growth and multiplication. Stress, which is frequently experienced by preterm neonates, can contribute to dysregulation of glucose metabolism in preterm infants including hyperglycemia and insulin resistance,[5, 6] and massage has reduced stress behaviors and increased calmer states in preterm neonates.[7] This is likely associated with both the decreased cortisol levels[8] and increased vagal activity[4] noted in preterm infants following moderate pressure massage. Increased vagal activity may lead to greater weight gain by both increasing gastric activity and promoting the release of insulin. Further, massage therapy may lead to greater weight gain by reducing the inhibitory effects of cortisol on insulin secretion. In addition, massage therapy may lead to greater weight gain by decreasing cortisol and in turn, increasing IGF-1, as chronically high levels of cortisol inhibit growth hormone secretion,[9, 10] and growth hormone stimulates the production of IGF-1

Future studies might evaluate other aspects of the IGF system such as various IGF-1 binding proteins. In addition, research on larger samples may enable the use of more sophisticated statistical models to address pathways for relationships between massage therapy and the potential mediating variables of vagal activity, gastric motility, insulin, and IGF-1 for preterm newborn weight gain. In the interim, the clinical implications of these data are that massage therapy might be prescribed for all growing preterm neonates to lower their stress,[7] enhance vagal activity and gastric motility, and increase their insulin and IGF-1 levels and associated weight gain.

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Table 1

Means for demographic variables (standard deviations in parentheses)

Variables[1]	Groups	
	Control	Massage
Ethnicity (%)		
Hispanic	58	48
Black	38	44
Caucasian	4	8
Mothers' Age	29.2	25.9
	(5.8)	(6.6)
Mothers' SES	4.2	4.0
	(0.9)	(1.5)
Parity	1.1	1.5
	(1.1)	(1.4)

[1] none of the group differences were statistically significant.

Table 2

Means for birth measures and baseline growth measures (standard deviations in parentheses)

Birth Measures[1]	Groups	
	Control	Massage
Gestational Age (wks)	29.8	29.3
	(2.5)	(2.7)
Birth Weight (grams)	1292.5	1178.5
	(305.1)	(330.6)
Birth Length (cms)	39.0	37.3
	(3.4)	(2.6)
Head Circumference (cms)	27.2	26.4
	(2.3)	(2.8)
Ponderal Index	2.0	2.2
	(0.3)	(0.3)
Obstetric Complications Scale[2]	71.0	75.8
	(14.9)	(13.2)
Postnatal Complications Scale[2]	74.9	76.5
	(9.7)	(12.0)
Baseline Growth Measures		
Days since Birth	30.9	38.7
	(17.6)	(25.1)
Days in NICU	26.6	28.9
	(17.4)	(24.2)
Weight at start of study (grams)	1640.5	1655.0
	(220.8)	(251.8)
Kilocalories Consumed[3]	110.8	106.8
	(11.3)	(14.1)
Weight Gain (grams)[3]	27.9	15.9
	(21.6)	(13.5)

[1] none of the group differences were statistically significant

[2] higher score is optimal

[3] mean for 2 days prior to start of study

Table 3

Means for changes in growth variables (standard deviations in parentheses)

Variables[1]	Groups	
	Control	Massage
Kcal /Kg Consumed	115.9	115.1
	(10.8)	(9.8)
Change in Weight Gain (grams)	−.47	13.6[2]
	(24.1)	(16.0)
Change in insulin (μU/mL)	.42	.95[3]
	(.11)	(.24)
Change in IGF-1 (ng/ mL)	.33	.72[1]
	(.49)	(.74)

[1] Superscripts denote statistically significant group differences

[1] $p < 0.05$

[2] $p < 0.02$

[3] $p < 0.001$.