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Interventions in Type 1 Diabetes: A Systematic Review and Meta-Analysis Examining Factors
that Lead to Improved Glycemic Control

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Interventions in Type 1 Diabetes: a systematic review and meta-analysis examining factors that lead to improved glycemic control

Abstract: Uncontrolled type 1 diabetes puts adolescents at an increased risk for cardiovascular disease, retinopathy, neuropathy, reduced brain mass, and reduced life expectancy among other symptoms. Clinically, behavioral interventions are staged for patients with uncontrolled type 1 diabetes. Meta-analyses of these interventions have yielded non-significant differences in overall glycemic control, and have yet to identify any significant moderators of outcomes. The goal of this study was to update and improve upon past meta-analyses, and evaluate potential moderators. 28 RCTs of behavioral interventions in type 1 diabetes evaluating glycemic control were identified. Variables within interventions were collected and reviewed systematically, separating interventions into groups based on operational intensity, and time investment. Significant differences in effect size between groups separated by intervention administrator, training of administrators, and contact time were observed, marking those variables as potential effect moderators. However, more stringent meta-analytic tests concluded no evidence for moderation by any of the identified variables. Future studies regarding the science of intervention development should aim to limit demographic variance, and identify articles with large sample sizes, in order to discover significant moderators in improving glycemic control within behavioral type 1 diabetes interventions.

Type 1 diabetes is a chronic and incurable disease wherein the pancreas does not produce insulin, a hormone that helps regulate the level of glucose in the blood⁵. Uncontrolled diabetes in pediatric patients is generally defined as having a hemoglobin A1c (HbA1c) greater than 9.5%⁶⁴, although specific targets vary by age. HbA1c is the measure of hemoglobin in red blood cells that are attached to glucose. Given the longer life span of red blood cells (~120 days), the HbA1c is effectively a measure of average blood glucose over a period of ~3 months. This measurement has been historically established as the primary indicator of diabetes, although it may not be wholly reliable⁷⁴.

The rates of Type 1 diabetes are increasing world wide⁵⁰, it is the third most common chronic illness in teenagers⁵², and afflicted adolescents display the worst glycemic control compared to other age-groups^{3, 11, 21, 27, 57} due to a variety of demographically unique social, familial, and developmental stressors^{27, 31, 38, 47}. Poor glycemic control among these adolescents can reduce their life expectancy by up to 15 years compared to same-age healthy individuals^{61, 20}, negatively affects their emotional well being³⁹, is associated with vast medical-resource usage and healthcare expenses^{53, 54}, is associated with adolescents' psychiatric comorbidities⁸, and

tends to persist into young adulthood⁷. Even a single episode of ketoacidosis (caused by prolonged hyperglycemia) is associated with lower cognitive functioning and reduction in brain mass in young children⁸⁷. The favorable management of these adolescents' glycemic control can prevent both serious and long-term medical complications (severe hypoglycemia, ketoacidosis, retinopathy, nephropathy, neuropathy, cardiovascular disease)^{85, 69, 20}.

Adolescents are an at-risk population for Type 1 diabetes because it requires continuous attention to care plans established by specialized diabetic endocrinologists or healthcare providers⁵⁵. Social, familial, and developmental stressors in adolescents' lives lead to their low-adherence to care plans^{27, 31, 39, 48}. Psychologists, physicians, and diabetic endocrinologists often work together to intervene in situations where diabetes is uncontrolled by adjusting the behavior of patients, their parents/support system, and/or healthcare providers. Research on medical interventions into the treatment of chronic-diseases has found that personable, communication-driven, patient-clinician relationships improve disease outcomes⁸⁸. Type 1 Diabetes related behavioral interventions present a uniquely complicated intersection of obstacles, mixing the chronic, intensive care required of diabetes with the complex developmental phase of adolescence. The structure, targets, goals, duration, and populations of these interventions can differ¹⁴. Research suggests stronger outcomes for psychological versus educational interventions⁷², and outlines factors within strong intervention that effectively promote self-management⁹. Such results indicate that more engagement, or time investment in an intervention, could be related to its success. However, previous meta-analyses of behavioral type 1 diabetes interventions have not found significant results in improving glycemic control, or significant moderators of outcomes^{9, 13, 25, 33, 51, 72, 83}.

There is not yet a comprehensive meta-analysis of all prior behavioral interventions into adolescent Type-1 diabetic glycemic control. Furthermore, prior meta-analyses have been limited in their analysis of potential moderator effects. The present paper attempts to address both of these concerns to advance future research.

Methods:

A review of existing literature across databases PubMed, Cochrane Library, PSYCHInfo, Research Gate, Elsevier, NIH, and Google Scholar was conducted for the following: Interventions related to the glycemic control of Type 1 diabetic adolescents who have been diagnosed for >6mo, and that measured HbA1c at baseline and follow-up after 6-15 months (keywords used: “Type 1 diabetes,” “RCT,” “intervention,” “pediatrics,”). This search yielded 315 results. Articles were then screened for their adherence to PRISMA guidelines for meta-analyses⁶⁷. 73 articles were selected for reading based on title relevance and abstract screening, 4 were duplicates, and 6 were meta-analyses or systematic reviews. Selection criteria was indiscriminate of behavioral intervention style or population subset. After review, 28 RCT’s of behavioral Type 1 diabetes interventions were identified, detailing 35 separate interventions.

Data collected included every operational variable identified in the articles, as well as demographic information. An inductive analysis of the articles revealed 4 potential moderator variables, which are described and operationalized below: *Intervention style, degree of intervention administrator, length of training for intervention administrator, and contact time with adolescents.*

Intervention Style:

Six different styles of intervention were identified, with some studies involving multiple styles: (1) education only; (2) behavioral therapy; (3) motivational interviewing; (4) behavioral family systems training; (5) case management; and (6) multi-systems therapy. Guided by Deborah Christie’s work¹⁴, intervention style was coded dichotomously as either ‘0’/less intensive (Styles 1-3, above) or ‘1’/more intensive (Styles 4-6, above).

Degree of Intervention Administrator:

Interventions were administered by people with varying levels of academic degrees, which is a proxy for level of qualification. Intervention administrator was coded dichotomously as either ‘0’/less qualified (i.e., people without post-doctoral training or medical degrees, such as nurses and some clinicians) or ‘1’/more qualified (i.e., people with post-doctoral training or a relevant medical degree, such as physicians, therapists, or Ph.D.-holding intervention developers).

Length of Training for Intervention Administrator:

The training of administrators regarding how to implement interventions varied in terms of length of time. *Length of training for intervention administrator* was coded dichotomously as either '0'/less time (i.e., administrators given < 5 hours of in-person training, or who relied solely on literature) or '1'/more time (i.e., ≥ 5 hours of in-person training).

Length of Contact Time with Adolescents

Interventions involved varying amounts of total intervention-contact time with adolescents, which was comprised of: (1) the frequency with which administrators met with patients (e.g., per week, month); (2) the duration of each meeting (e.g., minutes, hours); and (3) the duration of the entire intervention (e.g., 6 months, 12 months). For each intervention, these data were used to a total length of contact time with adolescents (in minutes). According to a median split, length of contact time with adolescents was coded dichotomously as either '0'/less time (i.e., < 540 minutes) or '1'/more time (i.e., ≥ 540 minutes).

Systematic Review

A systematic review was conducted by running t-tests on each intervention result (i.e., change in HbA1c and effect size r) according to the dichotomous moderator groups described above. While there were no significant differences for *Intervention Style* (Table B), for the variables of *Intervention Administrator* (Table C), *Training of Administrators* (Table D), and *Contact Time* (Table E), the 'more intense' groups (e.g. 1's) were significantly associated with a decrease in HBA1c change and an increase in effect size r .

These three variables – *Intervention Administrator*, *Training of Administrators*, and *Contact Time* – were then used to generate an ordinal, overall 'intensity' score for each individual intervention. Specifically, each individual intervention was assigned 1 point for each of these three variables when they were 'more intense' (vs. 'less intense') in that intervention. As a result, each individual intervention was assigned a 0-3 score. Interventions were then dichotomized into two groups: 'more intense' (a score of 2-3) and 'less intense' (a score of 0-1).

A t-test showed that, compared to ‘less intense’ interventions, ‘more intense’ interventions were significantly associated with a decrease in HBA1c change and an increase in effect size r (Table F).

Meta-Analysis

The meta-analysis was conducted using Hunter-Schmidt Meta-Analysis Programs⁷³. The Hunter-Schmidt method³⁷ assumes a random-effects model. This effect compares the change seen in the experimental group to the change seen in the control group. This comparison is the strongest test of the effect, as it accounts for changes in control group that may indicate threats to validity (e.g., history effects, maturation). A total of $n = 27$ effect sizes were extracted from the literature. The total meta-analysis sample size was $N = 1751$, with a mean sample size per intervention of $N = 64.85$ ($SD = 71.48$).

Results:

Table A:

Demographic characteristics of this study	
Number of youths identified in studies	2,418
Average age	13.9
Average diabetes duration	6 years
Average baseline A1c	9.46 (1.04)
Average follow-up A1c	9.24 (0.90)
Average intervention effect size (r)	-0.063

Results of Systematic Review:

Table B: *=significant result difference at 0.05 confidence level

Intervention style	Change in A1c	Average effect (r)
0 (<i>n</i> =17)	-0.181764706	-0.055699789
1 (<i>n</i> =18)	-0.262777778	-0.069294669
ttest	0.618567873	0.800266922

Table C:

Intervention administrators	Change in A1c	Average effect (r)
0 (<i>n</i> =19)	-0.068947368	-0.016360484
1 (<i>n</i> =16)	-0.406875	-0.117709453
ttest	*0.025913701	*0.042698066

Table D:

Training of Administrators	Change in A1c	Average effect (r)
0 (<i>n</i> =16)	-0.020625	-0.007375427
1 (<i>n</i> =19)	-0.394210526	-0.109273348
ttest	*0.01385259	*0.046124654

Table E:

Contact Time	Change in A1c	Average effect (r)
0 (<i>n</i> =18)	-0.029444444	-0.002689037
1 (<i>n</i> =17)	-0.428823529	-0.126223399
ttest	*0.010867236	*0.016480113

Table F:

Sum of variables with significant differences	Change in A1c	Average effect (r)
sum 0-1 (<i>n</i> =20)	0.017	0.013671689
sum 2-3 (<i>n</i> =15)	-0.544	-0.164508949
ttest	*0.000293242	*0.000362056

To confirm these significant results, *Intervention Administrator*, *Training of Administrators*, and *Contact Time* were explored as intervention effect moderators through a more stringent, meta-analytic test.

Results of Meta-Analysis:

The meta-analysis indicated that interventions had a marginally significant effect on A1c levels relative to control groups. The observed mean effect size was $r = .07$ (observed $SD = .13$), $d = .14$, and the sample-size weighted mean correlation was $\rho = .04$, ($SD_{\rho} = .10$, 95% CI [-.00,

.07], 80% Credibility Interval [-.09, .16]), $\delta = .08$. The results also indicated that 100% of the variance in effect sizes was due to sampling error, indicating that there were no moderators of this effect. However, this sampling error calculation assumes independent groups, and thus overestimates the true sampling error for a repeated measures design⁷³.

Adjusting the sample size to account for the lower levels of sampling error resulted in an adjusted total sample size of $N = 40,021$ (mean $N = 1482$). Using the adjusted sampling error calculations, the sample-size weighted mean effect size was not statistically significant, $\rho = .02$ ($SD_{\rho} = .09$, 95% CI [-.01, .05], 80% Credibility Interval [-.09, .13]), $\delta = .04$. In this case, however, the results indicated that sampling error could account for only 8.99% of the variance in effect sizes, indicating other artifacts and/or moderators exist, as proposed by the systematic review.

No corrections for other artifacts were performed. Studies indicate that A1c measures have a test-retest reliability of approximately $r = .93$, which is quite high⁷⁴. All of the studies use the same measure of HbA1c, so this artifact cannot explain additional variance in effect sizes.

Analyses of potential moderators *Intervention Administrator*, *Training of Administrators*, and *Contact Time*, as well as the other proposed non-significant moderators; *Intervention style*, *baseline A1c*, *average patient age at baseline*, and *intervention delivery in groups of patients* ($y=1$ or $n=0$), were conducted in an attempt to explain additional variance in effect sizes.

Table G:

<i>Intervention Administrator</i>	1	0
Weighted mean effect size (SD)	0.09	0.01
95% CI	[0.03-0.15]	[-0.03-0.05]

Table H:

<i>Training of administrators</i>	1	0
Weighted mean effect size (SD)	0.08	<-0.01
95% CI	[0.03-0.13]	[-0.02-0.02]

Table I:

<i>Contact time</i>	1	0
Weighted mean effect size (SD)	0.05	0.01
95% CI	[-0.01-0.11]	[-0.03-0.05]

None of the proposed moderators were able to explain additional variance. In many cases the credibility intervals for groups overlap (Tables G, I, and moderators not shown), and the percentage of variance explained increased minimally. The *Training of Administrators* moderator (Table H) saw a difference in effect size, but the credibility intervals still constitute minimal overall effect, even at the upper range, and the variable explained little additional variance (8.99% -> 15.92%), suggesting no evidence for moderation by this variable. The same analyses were conducted on a second set of studies, which were representative of repeated measure designs with no classical control group^{23, 30, 79}, and the results were virtually identical.

Discussion: Interventions in type 1 diabetes for juvenile patients are incredibly important in avoiding acute and chronic health complications^{20, 69, 85, 87, 8}. Between ages 12-18, type 1 diabetics see significant increases in HbA1c⁵⁵. These interventions cost providers time, staff, and resources, and thus constitute significant investment, even at low levels of engagement. This makes it increasingly frustrating and wasteful when interventions do not provide desired results. In the systematic review, significant outcome differences within the administrator-training and contact-time variables suggest that resource investment is directly correlated with better glycemic outcomes in patients. This finding should incentivize and provide justification for the development of more ‘hands-on’ and involved interventions. Despite the fact that studies produced moderate effect sizes without meeting the outlined criteria⁴⁵, and others found no results while meeting criteria^{66, 80}, the systematic analysis suggests that administrators, administrator training, and contact time are related to positive intervention outcomes. However, the meta-analytic data suggests no significant relationship between any of the variables and

improved glycemic outcomes. This lack of findings is possibly explained by sampling error and/or publication bias.

One reason why the meta-analytic weightings and adjustments diluted significant results may involve interventions' low sample sizes, which likely contributed to a wide range in standard deviations for changes in glycemic scores. Low sample sizes are likely due to the expense associated with intervention expenses. For instance, larger sample sizes mandate increased, and thus costly, healthcare resources (e.g., time of providers, technicians, and specialists, increased materials, etc.). The pressure to keep costs down incentivizes: (1) interventions with lower sample sizes; and/or (2) interventions that are less 'intense.' In both of these cases, the potential for interventions' success, and the meta-analytic ability to adequately assess this success, is diminished. In sum, rather than concluding that interventions are non-efficacious, it might be concluded that the 35 interventions examined do not accurately reflect the research community's strongest intervention efforts.

Economic analyses of interventions should be conducted in order to justify them (or not). For example, quality interventions, although expensive to conduct, may actually result in cost savings when their longer-term healthcare benefits are considered, such as reducing patients' healthcare usage (and thus reducing testing and medication costs, etc.). Modern interventions utilizing technology like Skype have shown great promise in creating hands-on interventions that require less investment³⁰.

Perhaps the biggest source of error, across all analyses of diabetic interventions, comes from how HbA1c change is conceptualized. Currently, all HbA1c changes are considered to be equivalent and thus comparable. However, patients' ability to reduce A1c is affected by their baseline A1c levels. For example, it is easier for diabetics to reduce their A1c from 12mmol/mol to 10mmol/mol than it is from 10mmol/mol to 8mmol/mol, suggesting that HbA1c changes are not equivalent and comparable. Future studies examining HbA1c change need to develop a logarithmic adjustment in order to statistically account for this fact.

Future research also needs to pay more attention to patient demographics. Intervention participants' families are largely low-to-middle class, and socio-economic status likely affects patients' abilities to control diabetes⁶⁸. Intervention participants are also overwhelmingly Caucasian, and we know that rates and levels of diabetes vary along cultural lines^{14, 6, 4}.

How to move forward

I think the field, and its inherent problems in finding significant results with meta-analytic power, relate to the eclectic nature of palliative interventionism as an imperfect science. Diabetic interventions, for example, are much more relevant to clinical endocrinology than they are to retrospective research into the science of their development and composition. These interventions cannot be tested *in vitro* or in mice. Pilot study or borne out psychosocial methodology, these interventions are implemented in clinical diabetes care with real patients to which they will have real effects on their healthcare and well-being. Once an intervention is shown to have significant results via pilot study and receives funding for implementation, it's active. There's no longer an ethical justification for the kind of randomized controlled trial that's included in these analyses, where some patients are randomized to a non-treatment group. "X" is shown to work, so in a clinical setting it gets put to use, not many additional studies are conducted to see if "X" is still working, unless they're given a reason to believe it isn't.

Additionally, with healthcare interventions, results are much more likely to be treated as subjected to the individual, not failures of the intervention. Thus, for many interventions, longitudinal studies with bigger populations are hard to justify, and conduct. Therefore, the obstacle these diabetic intervention meta-analyses run into with low effect sizes, high sampling error, are very difficult to overcome.

I think that future meta-analyses in pediatric type 1 diabetes can address inherent obstacles through inclusion criteria. Trying to control for as many variables as possible like socioeconomic status, family structure, etc. reduces confounding moderators. Also, consideration should be given to non-RCT publications that evaluate large scale utilization of certain interventions. Perhaps clinical standards, or HbA1c trends by age^{31, 55} could be utilized like control groups. The ultimate goal being explicit guidelines for intervention development in type 1 diabetes.

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