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Psychological Distress Predicts HbA1c Trajectories among Type 1 Diabetic Adolescents*

El estrés psicológico predice las trayectorias de HbA1c en adolescentes diabéticos tipo 1

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ABSTRACT
Diabetic adolescents have poor metabolic control. We aimed to characterize the longitudinal association between the stress-related domains of emotional burden (EB), physician related-distress (PD), regimen-related distress (RD), diabetes-related interpersonal distress (ID), and hemoglobin glycosylated (HbA_{1c}) trajectories among Type 1 diabetics Chilean adolescents. Thirty-two Type 1 diabetic adolescents (M_{age}=15.97; SD=3.45) were followed for one year. HbA_{1c} was assessed at three time points, and a stress measure was obtained. Using a longitudinal growth curve modeling, a marginal overall negative linear trend was found in HbA_{1c} ($b = -0.23$, $p = 0.096$). There was an interaction between time and PD ($b = -0.33$, $p < 0.05$), and a main effect of EB, RD, and ID on HbA_{1c}. Psychological stress domains predict metabolic control trajectories. Monitoring diabetes specific stress may be a useful tool to identify adolescents at risk for poor control, and interventions that reduce such stress might lead to better management of diabetes in adolescents.

Keywords
Adolescent Diabetes; Psychological Stress; Metabolic Control.

RESUMEN
Los adolescentes diabéticos tienen un pobre control metabólico. El propósito de este estudio fue caracterizar la asociación longitudinal entre el estrés emocional (EB), estrés con el médico (PD), estrés con el tratamiento (RD) y estrés interpersonal (ID), con trayectorias de hemoglobinas glicosiladas (HbA_{1c}) en adolescentes diabéticos tipo 1 (DM1). Treinta y dos adolescentes DM1 (M_{edad} = 15.97, DE = 3.45) fueron seguidos un año. Se obtuvo la HbA_{1c} tres veces en el año, más un auto-reporte de estrés. Análisis de curvas de crecimiento predijeron una tendencia lineal negativa en la trayectoria de HbA1c ($b = -0.23$, $p = 0.096$). Hubo una interacción entre el tiempo y PD ($b = -0.33$, $p \leq 0.05$) y los efectos principales de EB, RD, e ID en HbA_{1c}. Se concluye que el estrés psicológico predice trayectorias de HbA_{1c}. Monitorear dominios específicos de estrés podría ser útil para identificar adolescentes con riesgo

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de tener pobre HbA_{1c}, e intervenciones que reduzcan el estrés podrían ayudar a manejar la diabetes en adolescentes.

Palabras clave
Diabetes; Adolescentes; Estrés Psicológico; Control Metabólico.

Adolescence has been described as a complex evolutionary stage, characterized by greater biological, psychological and social changes (Helgeson, Escobar, Siminerio, & Becker, 2010; Holmbeck, Friedman, Abad & Jandasek, 2006), each of which may generate greater stress levels. Previous studies have reported elevated psychological stress among adolescent population (Pouweret al., 2013; Romeo, 2013). Further, the diagnosis of a chronic disease such as Type 1 diabetes during adolescence in addition to the treatment demands may lead to increased stress levels in this population. The psychological and behavioral challenges imposed by Type 1 diabetes and its treatment have been related to greater risk for depressive symptoms (Anarte et al., 2011; Baucom et al., 2015; McGrady, & Hood, 2010), low treatment adherence (Moström, Ahlén, Imberg, Hansson, & Lind, 2017; Patton, 2011), and poor metabolic control (Ortiz & Myers, 2014) among diabetic patients.

Several studies have reported positive associations between psychological stress and raised glucose levels (Faulenbach et al., 2012; Pyatak, Sequeira, Peters, Montoya, & Weigensberg, 2013; Ortiz, Ortiz, Gatica, & Gómez,, 2011), however these studies have limitations such as defining psychological stress as a general factor (one-dimensional construct), assessing chronic life stress, life-events, or self-reported perceived stress instead of a specific diabetes-distress related measure, and testing the cross-sectional association between psychological stress and glucose levels. The following study aimed to test the longitudinal association between diabetes-distress and metabolic control, using the Polonsky, Fisher, Earles, & Dudl (2005) Diabetes Distress Scale (DDS), a specific measure developed for a diabetic population. In addition, the DDS allows for the identification of four-specific domains: emotional burden, physician related-distress, regimen-related distress, and diabetes-related interpersonal distress. Diabetes related distress might emerge as a consequence of the diabetes diagnosis, being afraid of micro and macro-vascular complications, having unsupportive family/friends and health providers (Gonzalez, Fisher, & Polonsky, 2011). High emotional burden may be expected as a consequence of living with diabetes, and high physician related-distress and high regimen-related distress may be associated with the behavioral demands imposed by treatment. Because Type 1 diabetes treatment permeates all the adolescents' domains, including school and social relationships, it can be expected that there will be high diabetes-related interpersonal distress in adolescents living with Type 1 diabetes.

The purpose of this study was to test the longitudinal association between the stress-related domains of emotional burden, physician related-distress, regimen-related distress, diabetes-related interpersonal distress, and hemoglobin glycosylated trajectories among a unique sample of Type 1 diabetic Chilean adolescents.

Method

Participants

Thirty-two Chilean Type 1 diabetic adolescents were recruited from the Chilean Juvenile Diabetes Foundation. Twelve participants were recruited from Santiago city and 20 from Temuco city. All the participants were in low socioeconomic status, users of the Chilean public health system, and were treated with an intensified insulin treatment.

The ethics committee of the Servicio de Salud Araucanía Sur approved this research. All participants voluntarily consented to participate in the study. All the participants and their parents/tutors signed a written informed consent. Participants were economically compensated

with $10 U.S. dollars (5000 Chilean pesos) at each time point examination.

Instruments

Stress was assessed using the four subscales from the Diabetes Distress Scale (Polonsky et al., 2005). All the subscales of the DDS are specific to the domain of diabetes. The subscales were *emotional burden* (EB; e.g., "feeling that diabetes is taking up too much of my mental and physical energy every day", Cronbach's $\alpha = 0.89$), *physician-related distress* (PD; e.g., "feeling that my doctor doesn't know enough about diabetes and diabetes care", Cronbach's $\alpha = 0.78$), *regimen-related distress* (RD; e.g., "not feeling confident in my day-to-day ability to manage diabetes", Cronbach's $\alpha = 0.90$), and *diabetes-related interpersonal distress* (ID; e.g., "feeling that friends or family are not supportive enough of my self-care efforts (e.g., planning activities that conflict with my schedule, encouraging me to eat the 'wrong' foods)", Cronbach's $\alpha = 0.79$).

Glycosilated Hemoglobine (HbA_{1c}) % was collected at three different time points, roughly three months apart, using the Siemens/ Bayer DCA 2000+ equipment. Higher HbA_{1c} percentages indicate worse metabolic control. After the exam was conducted, the results were communicated immediately to each participant.

Participant age, sex, years living with diabetes, and whether or not they played sports (a proxy for physical activity) were collected via self-report.

Data Analysis

Data were analyzed using longitudinal growth curve models (Singer, & Willett, 2003) with R version 3.0.2. Growth models allow for flexible handling of time and account for non-independence from repeated measures on each participant. In addition to the usual linear regression parameters, growth models can have a random intercept, capturing the variability between participants in starting points (in our models, individual differences in baseline HbA_{1c}) and random slopes, capturing the variability between participants in change over time (in our models, the trajectory of HbA_{1c}). The models also allow the intercept and slope to be correlated, which indicates the degree of correlation between an individual´s starting point and his/her change over time. For example, a strong negative correlation would indicate that the higher baseline levels of HbA_{1c} a participant had, the more they decline over time.

All models included a random intercept and time slope that were allowed to correlate. Time was coded as 0, 1, and 2. Participant age in years, sex, number of months living with diabetes, and whether or not they played any sports were included as covariates in all analyses. In addition, the focal variables, time and stress were entered into all models. We tested whether each type of stress interacted with time (time x stress interaction). If the interaction term was not significant, we dropped it and report estimates from the final model without the interaction. Effects were considered statistically significant at $p < 0.05$. Confidence intervals were calculated using 1,000 samples from a parametric bootstrap.

Results

Subject Characteristics

Participant demographics as well as descriptive statistics for study variables are reported in Table 1. The participants' mean age was 15.97 (SD = 3.45), and on average they were living with diabetes 53.31 months (SD = 48.26). Forty-seven percent of the participants were female, and 78% reported playing a sport.

Table 1
Subjects Characteristics

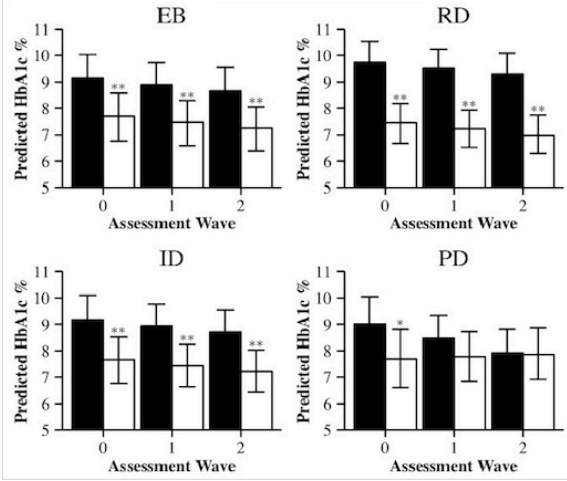
Variable	N [%] or M [SD]	Range
Sex (female/male)	15 / 17 [47% / 53%]	
Play a sport (yes/no)	25 / 7 [78% / 22%]	
Age (in years)	15.97 [3.45]	10 – 21
Months living with diabetes	53.31 [48.26]	3 – 168
EB	2.27 [1.01]	1 – 5
PD	1.85 [0.94]	1 – 5
RD	2.36 [1.10]	1 – 5
ID	2.20 [1.07]	1 – 4.67
HbA_{1c} Time 1 % (mmol/mol)	8.89 (74) [1.80 (19.7)]	6.7 (50) – 13.6 (125)
HbA_{1c} Time 2 % (mmol/mol)	8.63 (71) [1.49 (16.3)]	6.3 (45) – 14.0 (130)
HbA_{1c} Time 3 % (mmol/mol)	8.43 (69) [1.82 (19.9)]	6.0 (42) – 12.4 (112)

Note. EB = Diabetes Distress Scale (DDS) emotional burden, PD = DDS physician-related distress, RD = DDS regimen-related distress, ID = DDS interpersonal distress.

First, we examined a growth model over time and covariates but not stress to characterize the overall trajectory. For this baseline model, the estimate for the intercept was b = 8.8, and the random effect, EC 1 = 1.67, indicating that the overall mean intercept was 8.8 and the standard deviation of individual subject variability about that mean was 1.67. The overall time effect was not statistically significant (b [95% CI] = -0.23 [-0.50, 0.04], p = 0.096), although the trend was for a decrease in HbA_{1c} levels over the course of this study. The random effect for the time slope was EC 2 = 0.55, which is large relative to the mean, suggesting that although the trend was a slight decrease, there is substantial individual variability in linear time slope. The estimated correlation between the random intercept and time slope parameters was -0.59, indicating that subjects who were above the mean at baseline tended to have more negative time slopes. None of the covariates (age, sex, whether play sports, and months with diabetes) approached statistical significance.

Next we tested whether each of the diabetes specific stress measures predicted the trajectory of HbA_{1c}. There was a significant interaction between time and physician-related distress (b [95% CI] = -0.33 [-0.60, -0.06], p < 0.05) such that at baseline, participants who were significantly higher in physician-related distress had higher HbA_{1c} levels, but there were no significant differences for the second and third assessments (Figure 1). The time x stress interaction was not statistically significant for emotional burden, regimen-related distress, or interpersonal distress (Table 2).

Figure 1
Predicted HbA_{1c} % over time for high and low diabetes distress



Note. EB = Diabetes Distress Scale (DDS) emotional burden, PD = DDS physician-related distress, RD = DDS regimen-related distress, ID = DDS interpersonal distress. Black bars = +1 *SD* above the mean, white bars = -1 SD below the mean (white bars) for each stress variable. Bars show predicted means holding covariates at the mean or mode with 95% bootstrapped confidence intervals. Asterisks indicate whether the difference between +1 *SD* and -1 *SD* are statistically significant. *$p < 0.05$ **$p < 0.01$

Table 2
Longitudinal Growth Curve Models Predicting HbA_{1c}% from Diabetes Distress

Predictor	EB	RD	ID	PD
Intercept	9.23** [7.04, 11.41]	10.39** [8.47, 12.30]	9.63** [7.39, 11.86]	8.49** [5.97, 11.00]
Age (in years)	-0.04 [-0.18, 0.10]	-0.11† [-0.23, 0.01]	-0.07 [-0.21, 0.07]	0.01 [-0.15, 0.16]
Female (ref = male)	0.84 [-0.24, 1.92]	0.66 [-0.24, 1.55]	0.74 [-0.33, 1.80]	0.68 [-0.52, 1.89]
Play sports (ref = yes)	0.36 [-1.02, 1.73]	-0.07 [-1.25, 1.10]	0.55 [-0.79, 1.89]	0.96 [-0.52, 2.43]
Months with Diabetes	-0.00 [-0.01, 0.01]	0.00 [-0.01, 0.01]	-0.00 [-0.01, 0.01]	-0.00 [-0.02, 0.01]
Time	-0.23† [-0.50, 0.04]	-0.23† [-0.50, 0.04]	-0.23† [-0.50, 0.04]	-0.23† [-0.48, 0.02]
Stress	0.71** [0.25, 1.17]	1.04** [0.64, 1.44]	0.70** [0.25, 1.15]	0.70* [0.06, 1.36]
Time x Stress				-0.33* [-0.60, -0.06]
$\sigma_{intercept}$	1.46	1.16	1.53	1.57
σ_{time}	0.55	0.55	0.55	0.47
$r_{intercept,\ time}$	-0.55	-0.52	-0.64	-0.48
$\sigma_{residual}$	0.78	0.78	0.78	0.78

Note. † p < 0.10, * p < 0.05, ** p < 0.01. EB = Diabetes Distress Scale (DDS) emotional burden, PD = DDS physician-related distress, RD = DDS regimen-related distress, ID = DDS interpersonal distress, σintercept = estimated standard deviation of subject variability in intercept, σ = estimated standard deviation of subject variability in parameter, r = estimated correlation between parameters.

There were significant main effects of emotional burden, regimen-related distress, and

interpersonal distress on HbA_{1c} levels, such that higher stress scores were significantly associated with higher HbA_{1c} levels across all three time-point examinations (all *ps* < 0.01, see Table 2 and Figure 1).

Discussion

Our study tested the longitudinal association between psychological stress and HbA_{1c} trajectories in a unique sample of Type 1 diabetic Chilean patients. To our knowledge, few studies have tested HbA_{1c} trajectories among Type 1 diabetic patients, using specific diabetes distress-related domains as predictors. As previously mentioned, most studies testing the association between psychological stress and metabolic control in Type 1 diabetes have been cross-sectional, or have used non-specific diabetes distress related measures such as chronic life stress or perceived stress. Our study addressed these limitations by testing the longitudinal association between specific diabetes distress-related domains and HbA_{1c} trajectories. In addition, the relations were tested among a unique sample of low socioeconomic, Chilean adolescents.

As expected, the four stress domains tested were associated with HbA_{1c} at baseline, such that higher stress scores were significantly related to higher HbA_{1c} levels. Although participants who were high in emotional burden, regimen-related distress, and interpersonal distress had worse metabolic control across all three time points, the association between physician-related distress and HbA_{1c} was significant at baseline only, but not at the end of the assessment.

These results are consistent with previous studies that demonstrated a longitudinal association between psychological stress and metabolic control in Type 1 diabetic patients, (Helgeson et al., 2010; Helgeson, Honcharuk, Becker, Escobar, & Siminerio, 2011). Type 1 diabetes is a stressful chronic disease that requires adoption of new behaviors, changes in lifestyle behaviors, and a constant self-monitoring that can result in elevated stress levels, especially in adolescents. Furthermore, it is not surprising that participants scoring high on these four specific distress domains had worse metabolic control than those reporting low diabetes-related distress. Adolescence is characterized as an evolutionary stage in which social life and food are central elements (Borus, & Laffel, 2010). The diet restrictions, the insulin treatment, and the blood sugar self-monitoring, among other behavioral demands imposed by the diabetic treatment may overwhelm adolescents and lead to emotional burden, regimen related-distress, and interpersonal-distress (Monaghan, Helgeson, & Wiebe, 2015).

Similarly, patients reporting high physician-related distress also had worse metabolic control than those reporting low physician-distress at baseline. This result is particularly relevant in this unique sample. Given their low socioeconomic status, these participants only have access to the Chilean public health system with the restriction that they can neither choose nor change their diabetic care physician, if they are unsatisfied with their care. Previous studies have shown that the relationship between patients and health care professionals is crucial to achieving good diabetic control (Beverly, Worley, Court, Prokopakis, & Ivanov, 2016; Bundesmann, & Kaplowitz, 2011). If the patient negatively evaluates the relationship with health care professionals, it may affect other processes such as communication and satisfaction with caregivers, and these may interfere with treatment adherence and thus indirectly alter metabolic control (Jones et al., 2014).

Although the overall time effect was not statistically significant, a trend for a decrease in HbA_{1c} levels over the course of this study was found. As part of our procedure, all participants received an oral and written report with their HbA_{1c} levels at the end of each visit. This immediate feedback may have had a beneficial effect on the participants' metabolic control. In fact, previous studies have reported that immediate feedback has positive effects on Type 1 diabetes metabolic control (Li, Zhou, Chen, Song, & Xue, 2012; Polonsky et al., 2011).

This study had some limitations. Treatment adherence was not measured so it was not possible to test the association between these specific psychological distress domains, and the behaviors requested by the diabetic treatment, making it harder to estimate if the psychological stress was related to HbA_{1c} via a behavioral pathway or physiological dysregulation pathway. It is well known that psychological stress may exert its effect on HbA_{1c} directly, for instance, through the hypothalamic-pituitary-adrenal axis or sympathetic-adrenal-medullary system dysregulation (Ortiz, Willey, & Chiang, 2014) or altering adherence to health behaviors considered pillars for diabetic treatment, such as increasing sugary food consumption and decreasing physical activity. Another limitation was the small sample size of this unique sample, which suggests caution in the interpretation of these findings. This study also has several strengths including the use of longitudinal growth curve modeling, the measure of a robust biomarker for metabolic control in Type 1 diabetic patients, the use of a well-validated measure for diabetes related distress, and the study of a unique sample of Chilean adolescents.

Future research should include a large sample size and include understudied populations such as adolescents or culturally diverse backgrounds to generalize results to the population. Our results demonstrate a relationship between psychological stress and HbA_{1c}; interventions targeting psychological stress among Type 1 diabetic adolescents may be beneficial to demonstrate whether there is a causal association between psychological stress and HbA_{1c}. Furthermore, a study targeting psychological stress among Type 1 diabetic adolescents that includes daily techniques will allow a better understanding of the relationship of psychological stress with HbA_{1c}.

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Notes

* Research article.