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REVIEW ARTICLE

Average Daily Risk Range as a Measure for Clinical Research and Routine Care

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Abstract

There is emerging evidence suggesting that glycemic variability may relate to risk for diabetes-related complications. This article provides a description of average daily risk range (ADRR), a diabetes-specific measure of risk for hyperglycemia and hypoglycemia, and provides a summary of research using ADRR and clinical applications of ADRR. Average daily risk range is a variability metric that is based on "risk" values obtained from glucose levels that are mathematically transformed to give equal weight to hyperglycemic and hypoglycemic excursions. It can be calculated using self-monitoring of blood glucose or continuous glucose monitoring (CGM) data. The ADRR is scored based on risk categories: low risk, 0–19; moderate risk, 20–40; and high risk, 40 and above. Research using ADRR has found it to be a reliable predictor of extreme blood glucose values regardless of diabetes type and patients' age. Moreover, in treatment studies, ADRR presents as a very conservative measure of variability. Clinically, ADRR can provide meaningful data related to patients' risk for hyperglycemia and hypoglycemia that is not available from glycated hemoglobin values. Average daily risk range scores may also help clinicians to identify patients who may be overtreating blood glucose levels, leading to very high or low values. To expand the utility of ADRR, future research should examine the validity of existing risk cutoff scores for pediatric patients, determine if ADRR cutoff scores need to be modified for CGM data, and investigate whether patients' ADRR scores also relate to the development of long-term complications, including retinopathy and microalbuminuria.

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Introduction

Diabetes is a serious chronic illness associated with both acute and long-term complications related to glycemic control.[1] Treatment for diabetes involves daily attention to diet, blood glucose monitoring, and insulin administration.[1] The requirement of exogenous insulin places patients with diabetes at risk for wide variations in glycemic control.[1] Whether glycemic variability can increase a patient's risk for complications has been a matter of some debate. However, emerging evidence from cell culture studies suggests that intermittent high glucose concentrations may activate intracellular stress signaling, increase oxidative damage, and lead to cellular dysfunction and cell death more than that

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Abbreviations: (ADRR) average daily risk range, (CGM) continuous glucose monitoring, (CSII) continuous subcutaneous insulin infusion, (GRADE) glycemic risk assessment diabetes equation, (HbA1c) glycated hemoglobin, (LBGI) low blood glucose index, (MAGE) mean amplitude of glycemic excursion, (MDI) multiple daily injection, (SDT) total standard deviation, (SMBG) self-monitoring of blood glucose

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induced by sustained hyperglycemia.[2–9] Likewise, some *in vivo* studies in humans have associated glycemic variability with intravascular oxidative damage[10–12] and at least one study has identified glycemic variability as a potential risk factor for the development of diabetic retinopathy in patients with type 1 diabetes.[13]

Glycated hemoglobin (HbA1c), the primary benchmark for assessing glycemic control in diabetes, does not measure glycemic variability.[1,14] However, there are over 25 measures that have been developed to assess glycemic variability.[14,15] Conceptually, these measures can be classified as those that capture variance (e.g., standard deviation and its derivatives, coefficient of variation, interquartile range), those that measure mean variability across time either within days (e.g., continuous overall net glycemic action) or between days (e.g., lability index, mean of daily differences), those that measure frequency of crossing physiologically relevant thresholds (e.g., excursion frequency),[15] and those that measure quality of the blood glucose profile by measuring deviations beyond the target range [e.g., M value, J index, mean amplitude of glycemic excursion (MAGE), average daily risk range (ADRR), high blood glucose index, low blood glucose index (LBGI), blood glucose risk index, index of glycemic control, and glycemic risk assessment diabetes equation (GRADE) metrics], which may not be a measure glycemic variability in the strictest sense, but does reflect the influence of glycemic variability on patients' control.[14] While some measures can be applied to self-monitoring of blood glucose (SMBG; e.g., standard deviation and ADRR), others are limited in that they can only be applied to continuous glucose monitoring (CGM) data (e.g., excursion frequency).[15] However, Rodbard[14] has noted significant correlation between some of these measures, particularly among measures within the same class, making it likely that some are interchangeable.

Average daily risk range is a metric developed by Kovatchev and coauthors[16] to measure risk for hyperglycemia and hypoglycemia based on the presence of extremely high and low blood glucose levels. To calculate ADRR, blood glucose values are first transformed mathematically into "risk" values; this transformation gives equal weight to hyperglycemic and hypoglycemic excursions.[16] This is a departure from other familiar measures of variability, which are more highly affected by episodes of hyperglycemia than hypoglycemia because of the inherent asymmetry of both the blood glucose scale and the distribution of blood glucose values among patients with diabetes.[14,16] The ADRR can be calculated based on either SMBG or CGM data,[16–18] and there are several glucometer software programs that automatically calculate the ADRR for patients. Interestingly, while there has been some research using ADRR for patients with type 1 and type 2 diabetes, it is unclear how deeply this measure has penetrated into clinical practice and whether physicians and diabetes educators use ADRR in combination with HbA1c when making treatment management decisions. The purpose of this review is to describe ADRR, outline its development and validation, discuss limitations of ADRR, review research that has used ADRR, and present information to help demonstrate appropriate clinical applications of ADRR in youths with type 1 diabetes.

Average Daily Risk Range

As noted previously, the ADRR was developed as a diabetes-specific measure of glycemic variability.[16] Original scoring rules required a minimum of 14 days of blood glucose data with an average frequency of at least three blood glucose levels per day. These scoring rules also allowed for data use from nonconsecutive days, provided these days were all within the same month. However, other studies have calculated an ADRR score using less than 14 days of data.[19–21]

Average daily risk range corresponds to the overall average of daily risk ranges for the measurement period, with risk values defined relative to a predefined target (112.5 mg/dl).[16] The specific formula for calculating ADRR is available in the original article and from the authors.[16] However, once the ADRR is obtained, these values are interpreted based on risk categories: low risk, 0–19; moderate risk, 20–40; and high risk, 40 and above. These cutoff scores are based on the distribution of ADRR scores for 70 adult patients (39 with type 1 diabetes), and they have been confirmed based on correlations with the number of extreme hypoglycemic and hyperglycemic events recorded by the patients prospectively over 3 months, $r = 0.40$ and $r = 0.53$, respectively.[16]

The authors note some design advantages specific to the ADRR as a clinical measure of variability.[16] First, ADRR appears equally sensitive in predicting future episodes of extreme hypoglycemia and hyperglycemia. Second, ADRR is less

sensitive to variability within the target blood glucose range (70–150 mg/dl, for adults), which is consistent with the clinical expectation that some within-target variability is expected. Third, each very high or low blood glucose value confers additional risk, which is reflected in an increasing ADRR score. Thus, unlike simply counting the occurrence of these events, the ADRR implies there is greater risk when the amplitude of high or low blood glucose values is greater. Fourth, unlike calculating a standard deviation, ADRR is not a relative measure and is therefore amenable to clinical cutoff scores. Finally, because the ADRR can use SMBG data and does not require data from consecutive days, it may be very amenable to the amount/type of data typically obtained from patients in a routine diabetes clinic appointment. It also may be easily calculated using a spreadsheet and basic computer.[16]

However, challenges to using ADRR have also been noted.[15] First, in follow-up studies, ADRR has shown a very weak correlation with the percentage of values within range for adult patients.[22] This is likely because ADRR was designed to be more sensitive to occurrences of extreme variability versus moderate or within-range variability. Second, because ADRR reflects risk for both high and low blood glucose levels, it is possible that ADRR risk scores may be compromised if patients trend toward spending a majority of time stably above or below the target range. Third, there has been some concern that calculating an ADRR score based on CGM data may result in less-sensitive scores.[17] Fourth, ADRR has been criticized for being relatively insensitive to treatment effects.[22,23] Again, it is likely this may occur because ADRR is biased toward capturing extreme glycemic variability and is relatively blind to within-target variability and to modest reductions in extreme variability. Fifth, because the ADRR combines the high blood glucose index and LBGI, which alternatively account for the ADRR's correlation to future hyperglycemic and hypoglycemic events, ADRR has been criticized for being less sensitive than either of these component indices in predicting either hyperglycemia or hypoglycemia.[14] The ADRR has also been criticized for being less sensitive to hyperglycemia and hypoglycemia than the hyperglycemia and hypoglycemia indices and the $GRADE_{hyperglycemia}$ and $GRADE_{hypoglycemia}$ scores, respectively.[14] Sixth, there have been no studies to demonstrate whether ADRR risk scores longitudinally associate with the development of microvascular complications in patients with diabetes. Finally, while normative references for ADRR exist for nondiabetic adults of various ethnicities (ADRR reference range 0.0–8.7 overall),[24] age-tailored cutoff risk scores for youths have not yet been published.[25] Therefore, clinicians using ADRR scores in the management of their pediatric patients currently do not have age-specific reference ranges for low, moderate, and high levels of glycemic variability. It also remains to be determined whether the established reference ranges require adjustment if using CGM data.[18]

Research Using Average Daily Risk Range

The available research using ADRR can be divided into assessment and treatment outcomes research. In the category of assessment research, five studies have been published.[18,19,25–27] Kohnert and coauthors[19] published ADRR scores for a sample of 114 adults with type 2 diabetes (53 women, mean age 63.5 ± 8.3 years). In this study, ADRR scores were calculated based on up to three days of CGM data. Subjects had a mean ADRR score of 18.1 (range 14.8–22.6), and researchers found ADRR to be the only measure to correlate ($r = 0.37$; $p < .001$) with the time patients spent below the target glucose range (hypoglycemia). In another study recruiting a sample of 34 adults with type 1 diabetes (14 women, mean age 37 ± 2.1 years), researchers looked at the relations between ADRR and patients' insulin sensitivity and epinephrine response.[26] Patients participating in this study collected SMBG data for 1 month and then completed inpatient hyperinsulinemic–euglycemic and hyperinsulinemic–hypoglycemic clamps. The results showed patients' ADRR scores correlated positively with their insulin sensitivity ($r = 0.50$; $p = .002$) and negatively with their release of epinephrine (counter-regulatory response; $r = -0.40$; $p = .029$), suggesting that both higher insulin sensitivity and lower epinephrine responsiveness during hypoglycemia are associated with higher levels of glycemic variability. Kim and coauthors[27] conducted an assessment of ADRR in a sample of 124 Asian adults with type 1 diabetes (86 women, mean age 33 years). Subjects had a mean ADRR score of 33 (range 25–44). There was a positive correlation between patients' ADRR scores and their HbA1c levels ($r = 0.53$; $p < .01$) and a negative correlation between patients' ADRR scores and their C-peptide levels ($r = -0.31$; $p < .05$), suggesting that decreased residual beta-cell function may be associated with increased glycemic variability. Finally, there have been two pediatric studies that have measured ADRR scores.[18,25] In the first study, 48 young children with type 1 diabetes were recruited (22 girls, mean age 5.1 ± 1.2 years), and ADRR scores were calculated based on both CGM (ADRRc) and SMBG data (ADRRs).[18] Children had a mean ADRRc of

55 ± 12 and a mean ADRRs of 46 ± 11, indicating a high risk for variability based on Kovatchev and coauthors'[16] cutoff scores. Children's ADRRc correlated positively with the percentage of glucose readings below 80 mg/dl ($r = 0.29$; $p = .05$) and the percentage of glucose readings above 200 mg/dl ($r = 0.49$; $p = .01$), suggesting that ADRR does relate to extreme hypoglycemic and hyperglycemic events in young children. In the second study, ADRR scores were calculated for 116 young children (62 girls, mean age 5.44 ± 1.3 years).[25] Seventy-two percent of children were classified as high-risk based on Kovatchev and coauthors'[16] cutoff scores, and like the first study, children's ADRR scores correlated positively with the percentage of glucose readings below 70 mg/dl ($r = 0.20$; $p = .05$) and percentage of readings above 200 mg/dl ($r = 0.70$; $p < .01$). Children's ADRR scores also correlated positively with number of emergency department visits ($r = 0.28$; $p < .01$).

In addition to the discussed studies, modified ADRR scores have been calculated using <14 days of SMBG data and evaluated for their ability to predict mortality in the critical care setting. In one study, 18,563 consecutive patients with acute myocardial infarction were evaluated.[21] While ADRR (calculated over 2 days) predicted the risk for inpatient mortality in unadjusted analyses, ADRR was no longer a significant predictor after multivariable adjustment. A second study evaluated the ability of ADRR to predict mortality in a burn intensive care unit.[20] After matching on multiple characteristics, 346 surviving or nonsurviving subjects were classified based on ADRR (calculated over 8 days), with mortality increasing progressively across increasing ADRR risk groups [25% in the low-risk group to 60% in the high-risk group ($p < .001$)]. *Post hoc* analysis revealed that nonsurvivors exhibited higher ADRR ($p < .01$) than survivors.

There are currently four studies that have used ADRR as a treatment outcome measure in diabetes.[23,28–30] Three of these studies recruited adult patients (type 1 or type 2 diabetes),[22,28,29] and one study recruited children with type 1 diabetes.[23] In the first study, 39 adult patients with type 1 diabetes (mean age 38.1 ± 9.3 years) participated in a randomized crossover clinical trial comparing insulin pump [continuous subcutaneous insulin infusion (CSII)] therapy with lispro to multiple daily injection (MDI) therapy with lispro and glargine.[28] Glycemic variability [namely, ADRR, total standard deviation (SD_T), MAGE, and lability index] was the primary outcome, with HbA1c and other biomarkers as secondary outcomes. The results showed lower glycemic variability for patients when using CSII versus MDI based on the MAGE and lability index score, but a nonsignificant group difference based on SD_T and ADRR (mean ADRR = 25.5 ± 7.9 and 26.9 ± 6.9 for CSII and MDI, respectively).[28] Likewise, Rodbard and coauthors[22] found ADRR to be relatively insensitive to treatment change in their interventional study of real-time CGM. The researchers retrieved 7 days of CGM data for three consecutive weeks from 85 adult patients. In week 1 of the study, patients were blind to the CGM data. However, in weeks 2–3, patients received the CGM data in real time. The results showed a decrease in variability during the unmasked phase based on patients' MAGE, mean of daily differences, continuous overall net glycemic action, and SD_T scores. However, there was no difference found based on patients' ADRR and LBGI scores and on their percentage of low glucose values (<80 mg/dl).[22] Another research group used ADRR to compare the effects of exenatide and glargine on risk for acute blood glucose extremes in a sample of adult patients with type 2 diabetes ($n = 549$, ages 30–75 years).[29] Adults were randomly assigned to either the exenatide or glargine treatment group, and ADRR scores were generated based on at least 14 days of SMBG data at six study appointments (out to 26 weeks postbaseline). Overall, the adults had ADRR scores in the low-risk category. However, the researchers found that adults treated with exenatide achieved slightly lower ADRR scores than the adults treated with glargine (mean ± standard error of the mean, 16.3 ± 0.45 and 18.5 ± 0.49, exenatide and glargine, respectively).[29] Finally, in a pediatric study, ADRR was used to assess glycemic variability for 13 children (7 girls, mean age 7.6 years) who participated in a telemedicine clinic.[23] Children participated in telemedicine appointments every 2 weeks for up to 3 months. Then children participated in 4 months of an assessment-only phase without regular telemedicine follow-up. While the results showed a reduction in children's HbA1c during the telemedicine period ($p = .012$), there was no change in children's ADRR scores across the study (mean ± standard deviation, 33.6 ± 5.4, 32.3 ± 6.7, 34.8 ± 6.3, baseline, telemedicine, assessment-only phases, respectively).[23]

While the research is limited, existing studies suggest that ADRR is a reliable predictor of extreme blood glucose values regardless of diabetes type and patients' age. In treatment studies, ADRR presents as a very conservative measure of glycemic variability. Without focused attention to normalizing all blood glucose values, it is unlikely that ADRR will show an improvement, because it is more strongly weighted toward extreme values.

Clinical Use of Average Daily Risk Range

Within clinical practice, ADRR may help to identify youths with suboptimal glycemic control. As noted previously, HbA1c is not sensitive to glycemic variation. Thus, two patients could have the same HbA1c level but very different ADRR scores if one patient was experiencing significant glycemic variation.[16] Moreover, elevated ADRR scores would suggest that the patient was experiencing extreme high and low blood glucose values, which is more clinically meaningful than variation within the target range. Youths with higher ADRR scores should receive intensive counseling and diabetes education, as these values suggest youths are at higher risk for an extreme hypoglycemic or hyperglycemic event, which is potentially dangerous.[18,25] Higher ADRR scores may indicate problems with diabetes management. Perhaps youths are overtreating their blood glucose levels, leading to values that are too low because of excessive insulin use or exercise or to values that are too high because of underdosing of insulin, consumption of large snacks, or outdated insulin-to-carbohydrate ratios or sensitivity factors. An ADRR score would be more sensitive to these problems than HbA1c. Youths who own software that calculates an ADRR score may be able to track their values independently, which presents an exciting opportunity for diabetes management and counseling. Similar to tracking individual blood glucose values, youths may be able to track their ADRR scores every two weeks and, through regular monitoring, target a lower ADRR score to achieve less glycemic variability. However, if counseling families to monitor ADRR scores, it is important to advise them to look at these scores no more frequently than semi-monthly, as the ADRR is unlikely to change over short durations. Also, because we do not know how ADRR compares with other measures of glycemic variability, it is important to counsel patients not to overgeneralize ADRR scores.

Conclusion

The ADRR is a measure of quality of glycemic control that reflects a patients' risk for extreme hypoglycemic and hyperglycemic events.[16] It has a number of advantages for research and clinical application, but to date, there has been only limited research using ADRR, and it is unclear whether physicians and diabetes educators currently use ADRR in routine diabetes management. To broaden the utility of ADRR, future research should focus on validating ADRR cutoff scores for pediatric patients, determining whether existing ADRR cutoff scores need to be adjusted when using CGM versus SMBG data, determining how self-care behaviors impact ADRR as well as other measures of glycemic variability, and examining the correlation between any measure of glycemic variability and the occurrence of chronic adverse outcomes (namely, retinopathy and microalbuminuria). Clinically, it is expected that integrating ADRR scores into routine diabetes care will yield more meaningful data than simply monitoring patients' HbA1c levels over time. Glycemic variability is masked by HbA1c, but counseling patients based on their ADRR scores may help them to achieve more normalized blood glucose levels and improve their quality of life and health outcomes.

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