ARIABILIDAD
GLUCEMICA.

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Servicio de Endocrinología
Nutrición.

VARIABILIDAD GLUCEMICA

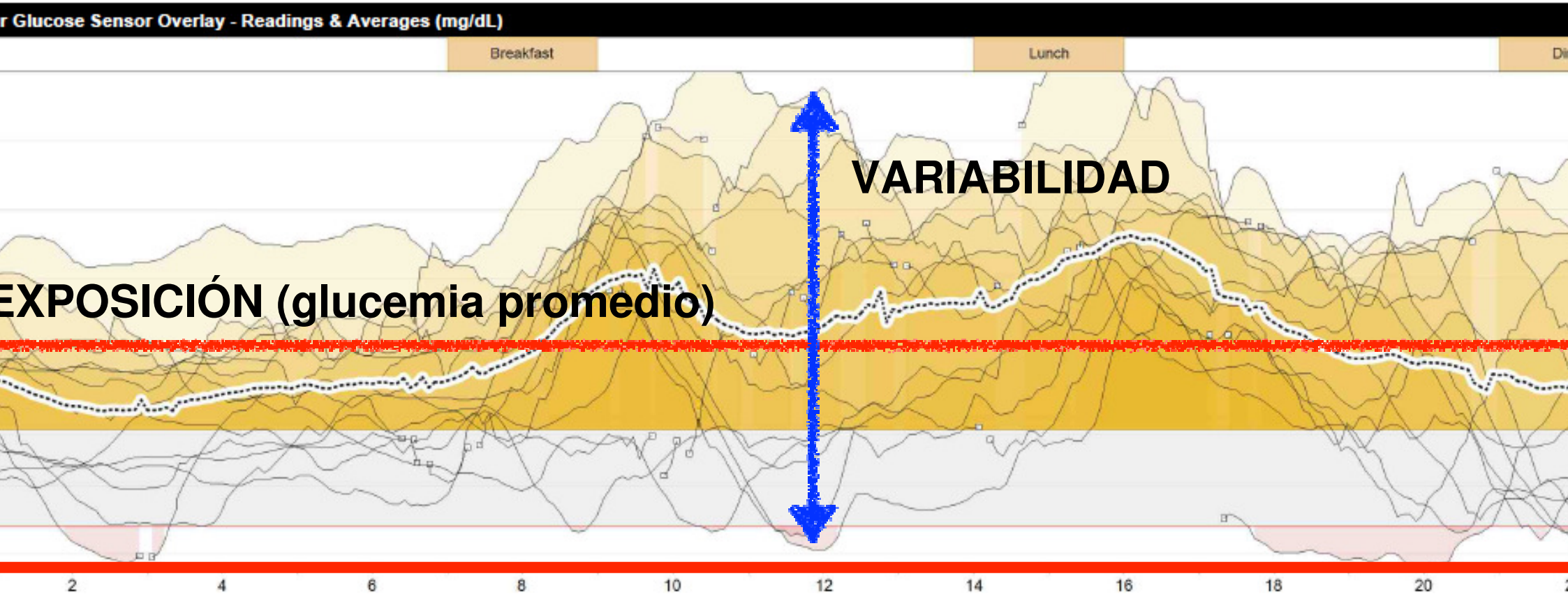
DEFINICION

IMPORTANCIA

TENEMOS HERRAMIENTAS SUFICIENTES COMO
PARA DETECTARLA/CUANTIFICARLA?

COMO PODEMOS DISMINUIRLA?

DEFINICIÓN

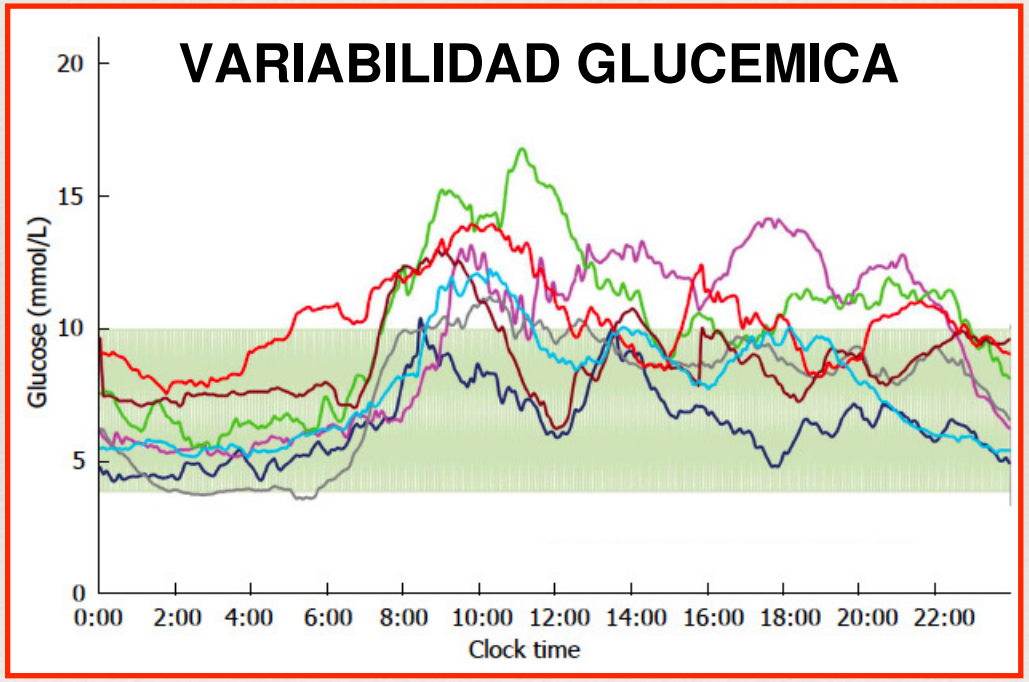


DOS DIMENSIONES DE LA

DEFINICION

CURSIONES HIPERGLUCEMICAS POSTPRANDIALES

HIPOGLUCEMIAS

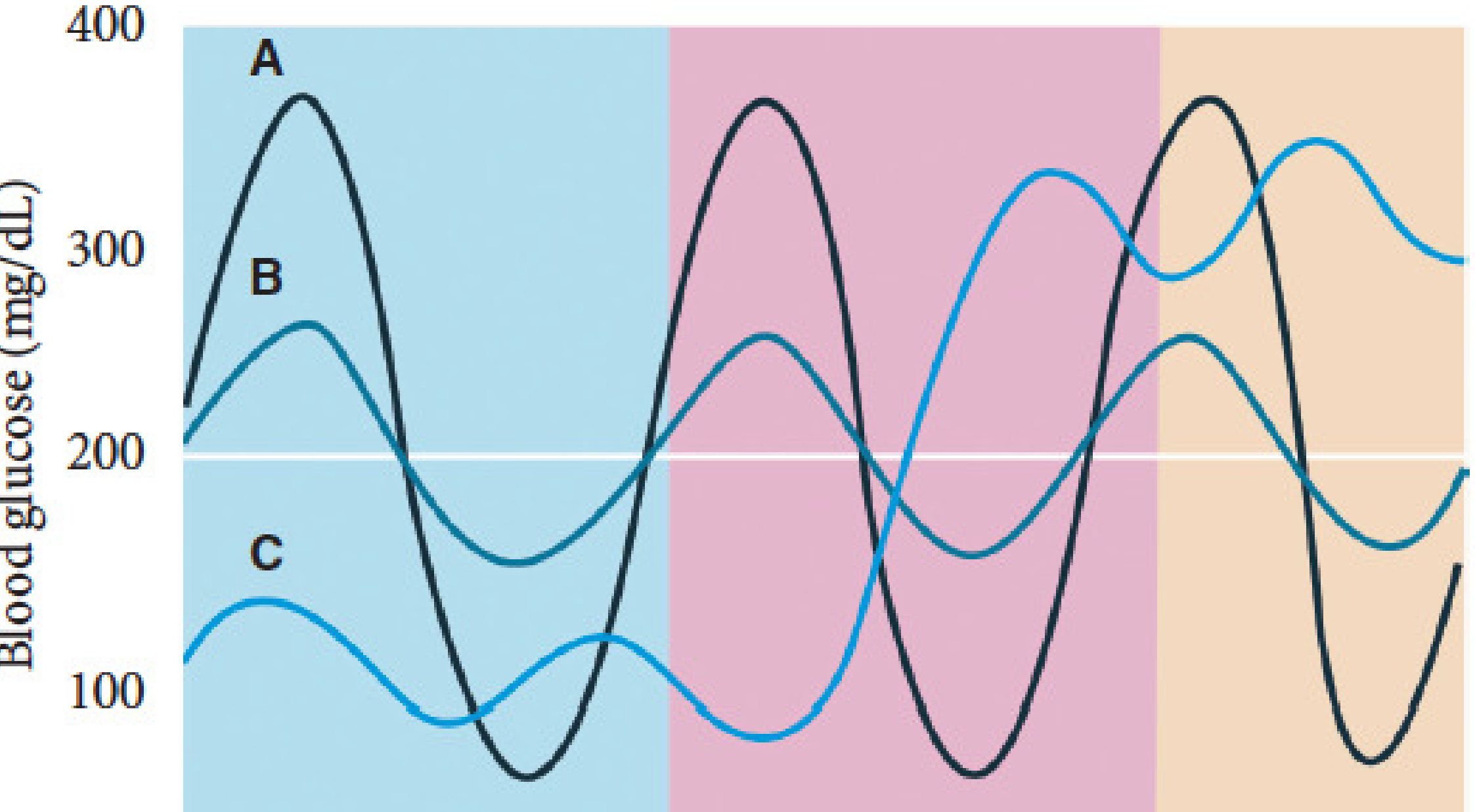


VARIABILIDAD INTRADIA

VARIABILIDAD INTERDIA

UCTUACIONES GLUCEMICAS A LA MISMA HORA

ucemia media vs Variabilida



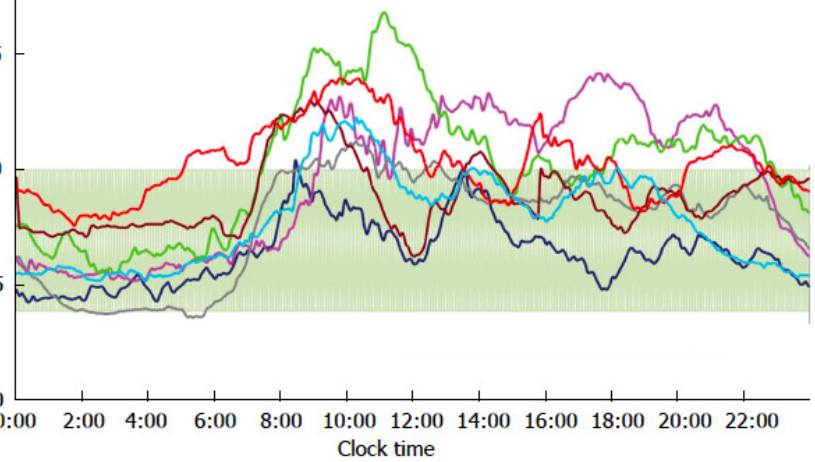
IMPORTANCIA LN1

COMPLICACIONES CRÓNICA

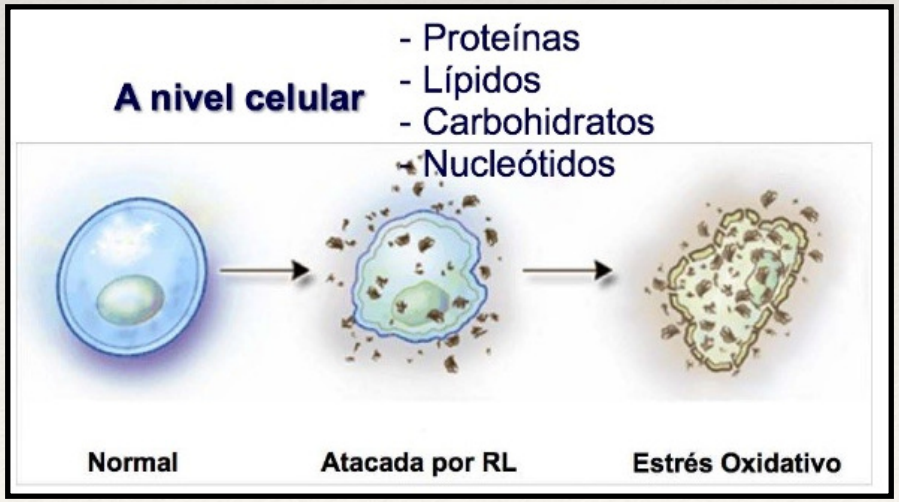
Kilpatrick et al. A1C variability and the risk of microvascular complicatio
1 diabetes: data from the Diabetes Control and Complications Trial. Diab

CULTAD PARA DEFINIR EL ROL DE LA VG COMO FACT
NDEPENDIENTE DE LAS COMPLICACIONES CRONICAS LN2

VARIABILIDAD GLUCEMICA



HIPOGLUCEMIA



Diapositiva 6

LN1 Data from the Diabetes Control and
Complications Trial showed that long term fluctuations in glycemia expressed as SDs of HbA1c independently relate
to the development of retinopathy and nephropathy.
Lia Nattero; 19/05/2016

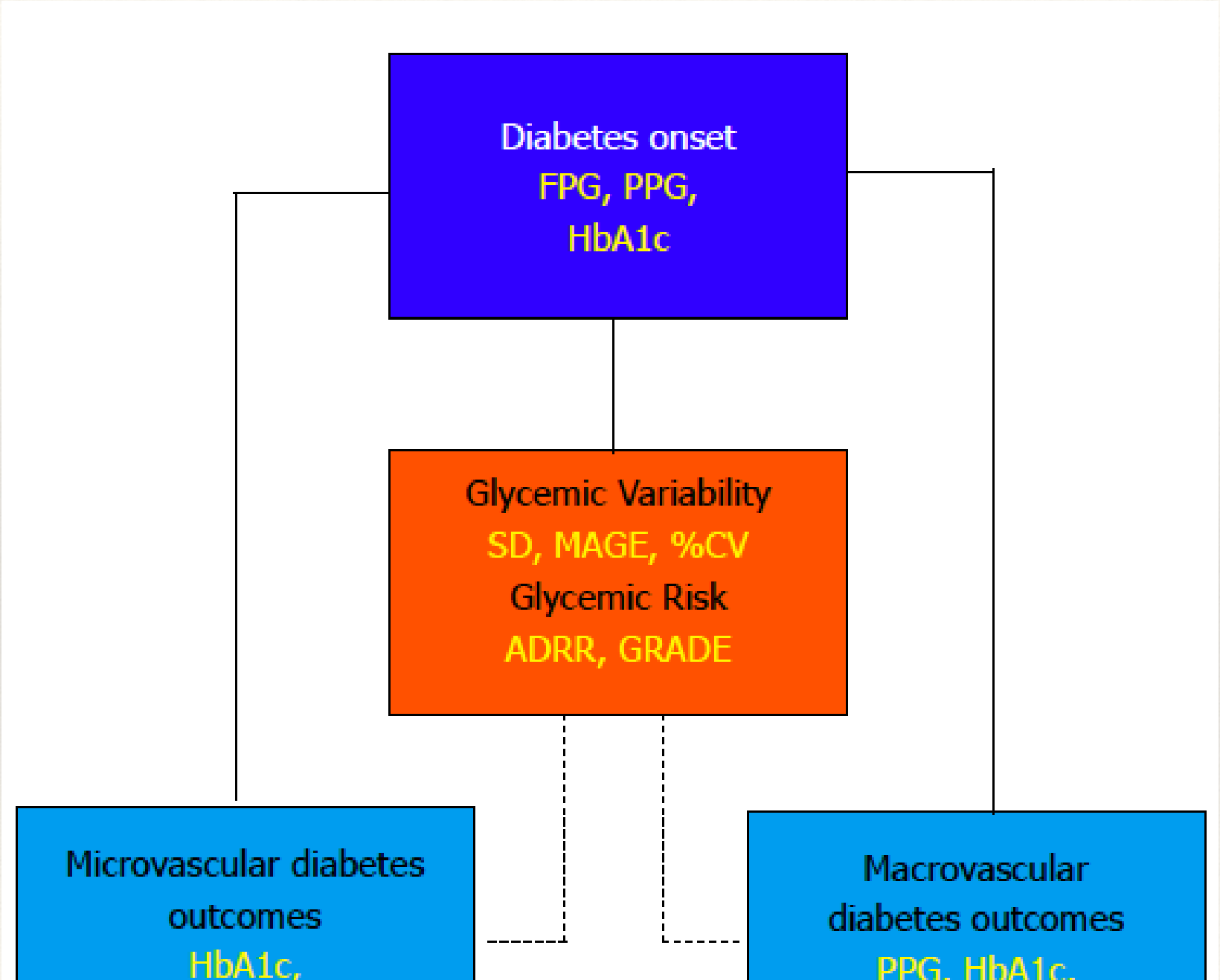
LN2 Because traditional measures of GV,
with the exception of % CV, are closely correlated with mean glucose, it remains difficult to define an independent role for GV in the development of diabetes complications
Lia Nattero; 19/05/2016

LN3 In an 11-year followup study, Bragd et al found that GV measured by SD of blood glucose was a predictor of the prevalence of peripheral neuropathy. Moreover, Snell-Bergeron reported subclinical atherosclerosis to be associated with glucose levels and glucose SD in men with type 1 diabetes. The potential importance of GV for the development of microvascular complications has been corroborated by Soupal et al in a recent cross-sectional study of type 1 diabetes patients. This study showed significantly increased values for GV indices, such as SD, CV, and MAGE, for patients with microvascular complications as compared to those without complications.
Lia Nattero; 19/05/2016

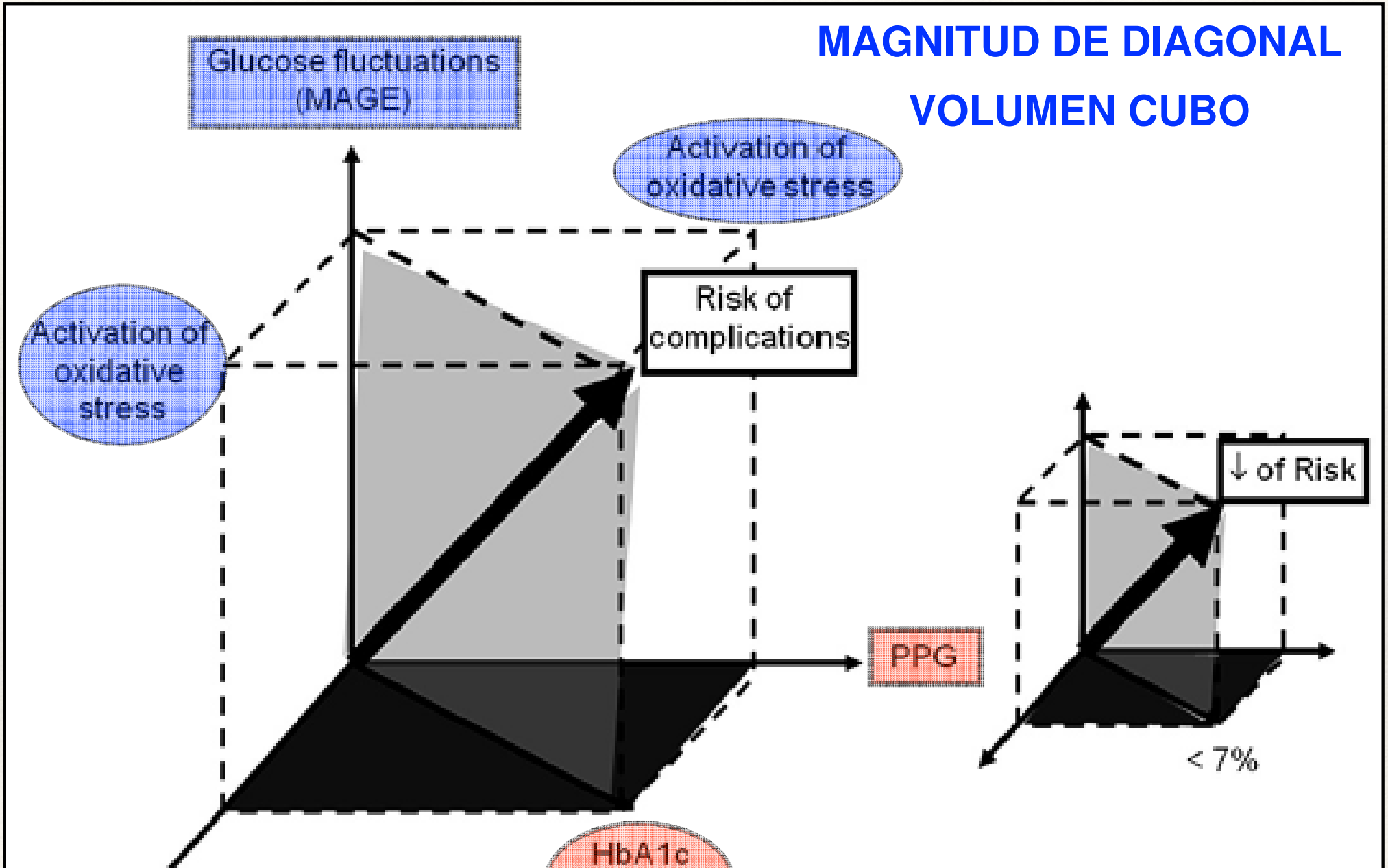
IMPORTANCIA

“El hecho de que un aumento en la VG es un potente
redictor del ***riesgo de hipoglucemia***, y se asocia a u
mal control glucémico, es probablemente la razón d
mayor peso en el momento actual, para detectarla e
intentar minimizarla”.

Glycemic Markers and Risk of Diabetic Complications



EL TERCER COMPONENTE DE LA DISGLICEMIA?



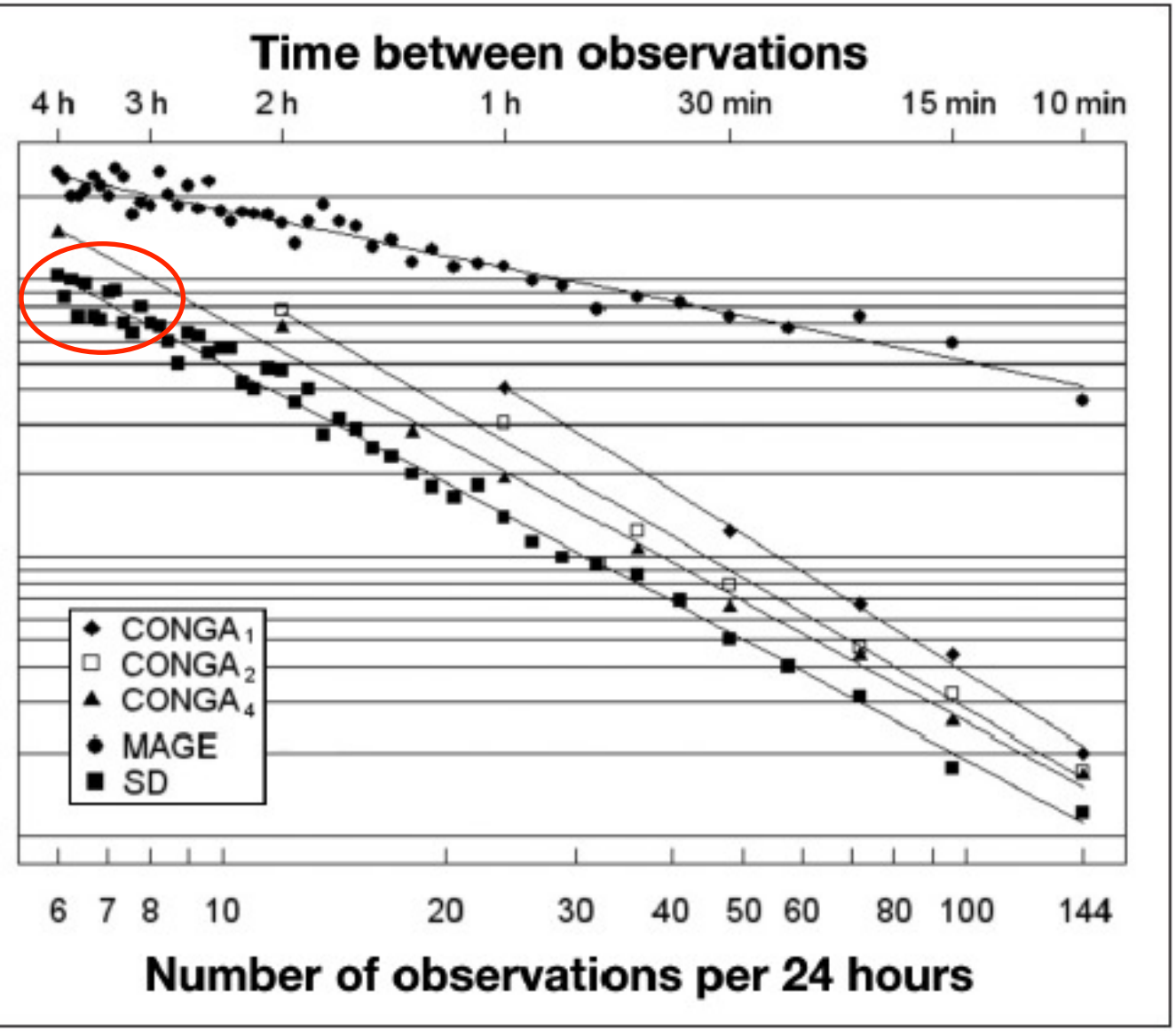
Diapositiva 9

LN4 Model suggested for illustrating the pathophysiological impacts of the excessive glycation of proteins and the activation of oxidative stress on the risk of diabetic complications (diagonal solid arrow). The contributions of the three components of dysglycemia, i.e., hyperglycemia at fasting (FPG), hyperglycemia during postprandial periods (PPG), and acute glucose fluctuations (MAGE), are indicated on the x, y, and z axes, respectively.

Lia Nattero; 18/06/2016

COMO DETECTARLA?

Minimum Frequency of Glucose Measurements from W
Glycemic Variation Can Be Consistently Assessed



Percentage Error in Measures of Glycemic Variability According to the Spacing betw Glucose Measurements

Measure of GV	Spacing between successive gluc		
	1 h	2 h	
SD	1.4	3.8	
$CONGA_4$	2.0	5.5	
$CONGA_2$	2.6	7.7	n
$CONGA_1$	4.1	not applicable	n
MAGE	11.0	16.1	

MEDIDAS DE VARIABILIDAD

NTRADIA

ESVIACION ESTANDAR DE A MEDIA

COEFICIENTE DE ARIACION

ANGO INTERCUARTIL

AGE

ONGA

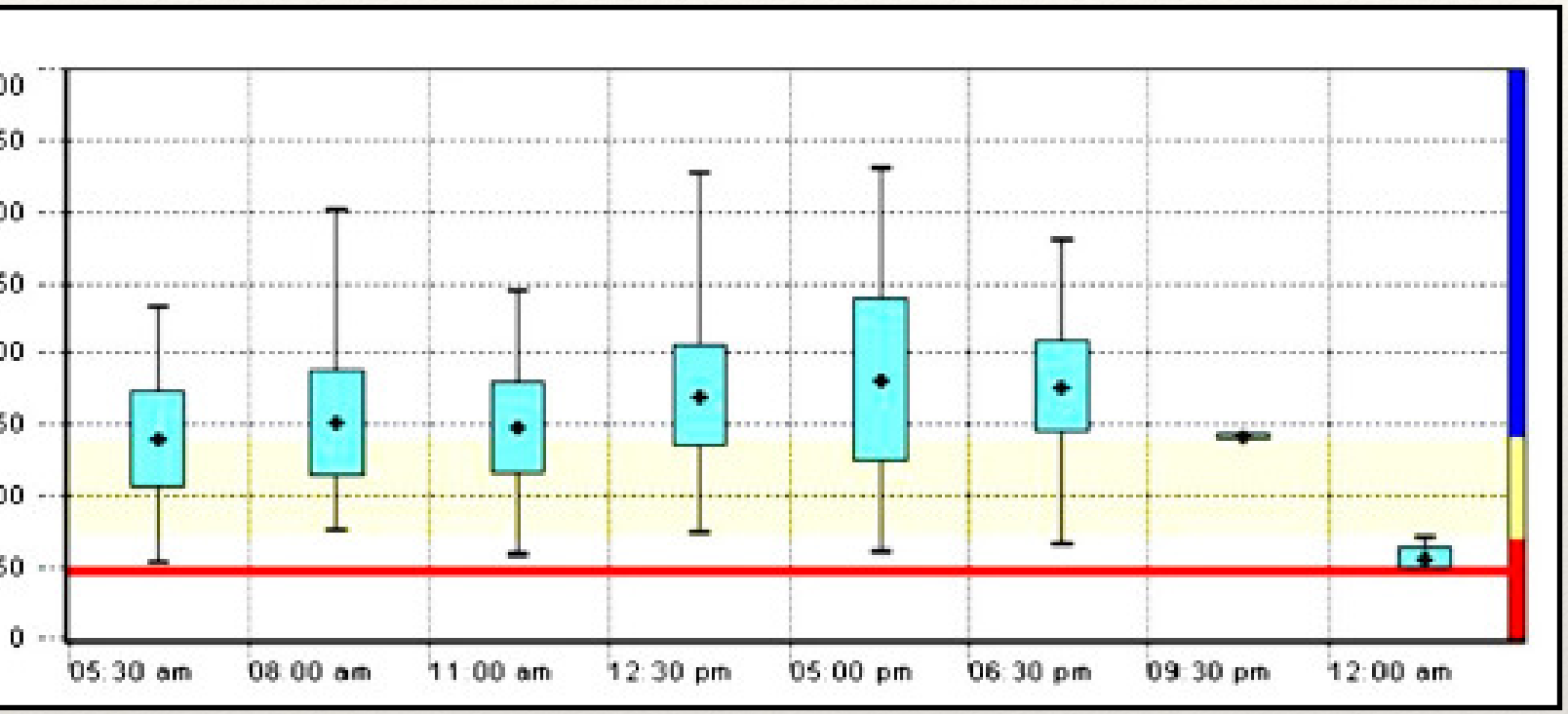
NTERDIA

I. DE RIESG

- **HBGI**
- **LBGI**
- **MDRR**

DESVIACION ESTANDAR

Irl Hirsch en 20



GLUCOSA NO T
UNA DISTRIBU
NORMAL
LAS MUESTRAS
SON AL AZAR (
SESGADAS)

G puede considerarse “baja” si el DS se encuentra 3 veces por deba
sa promedio (en DM1 aceptable alcanzar DS x 2 < glucosa promedio).

DESVIACIÓN ESTÁNDAR

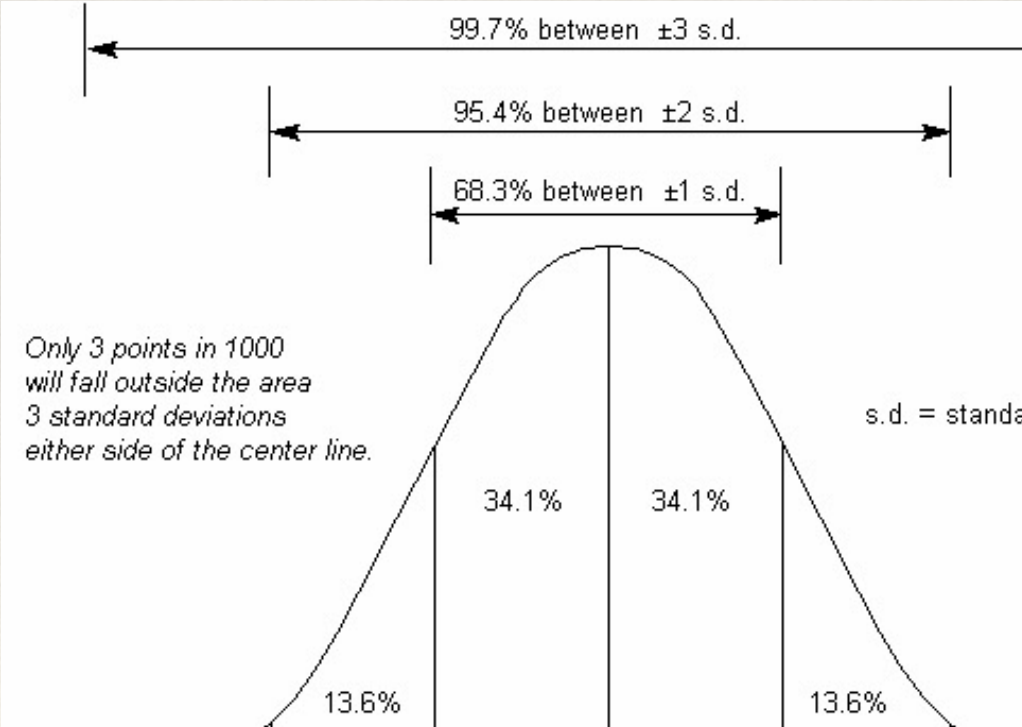
	Desayuno		Almuerzo		Merienda		Cena	
	Antes	2 Hs. Después	Antes	2 Hs. Después	Antes	2 Hs. Después	Antes	2 Hs. Después
	80	120	80	120	80	120	80	120

…. Vamos a ignorar esos supuesto
importantes y calcular el SD para un
típico de un diabético …

Digamos que tienes la suerte que eso s
y al acostarse tiene 80 mg/dl.

romedio de 100 y una desviación
estándar de 20 mg/dL.

o tanto, te esperarías que el 99,74% de
s lecturas este entre 160 y 20 mg/dL?



% COEFICIENTE DE VARIACIO

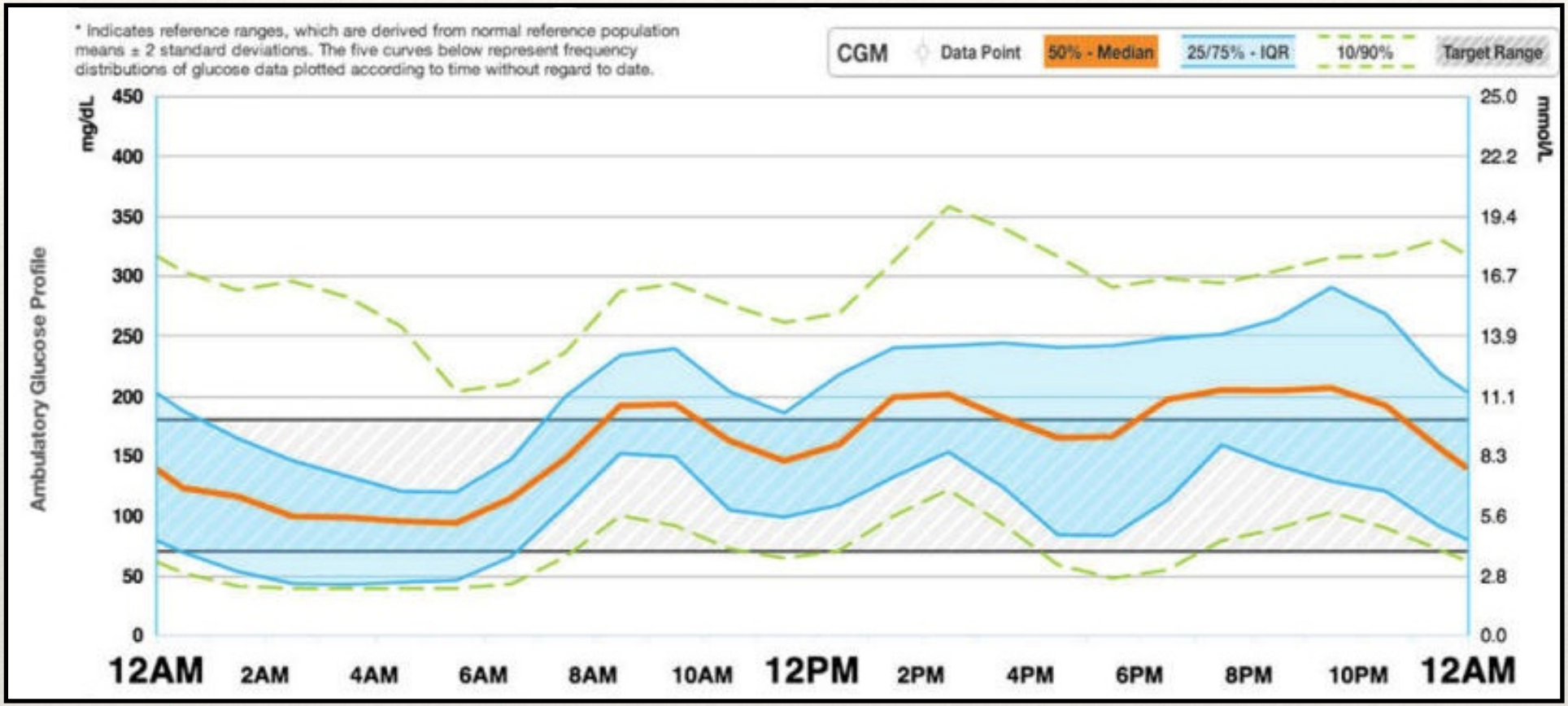
Bergenstal et al. (

Deriva de la desviación estándar.

$$\%CV = \frac{100SD}{MBG}.$$

OS: Simple. Método estadístico clásico. Relativamente, ***r***
nstante que otras medidas.

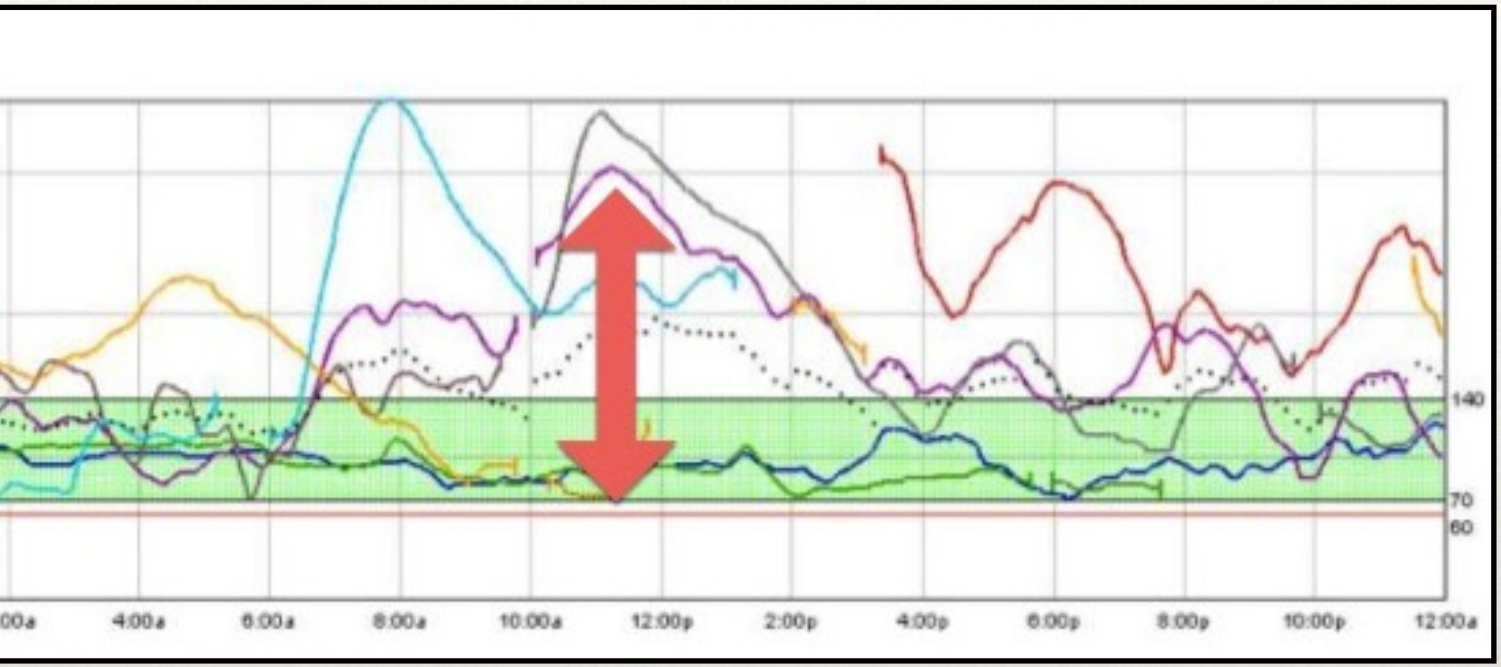
RANGO INTERCUARTIL



ICION: Diferencia entre percentil 75th y 25th.

MAGE

Hill et al. en 19

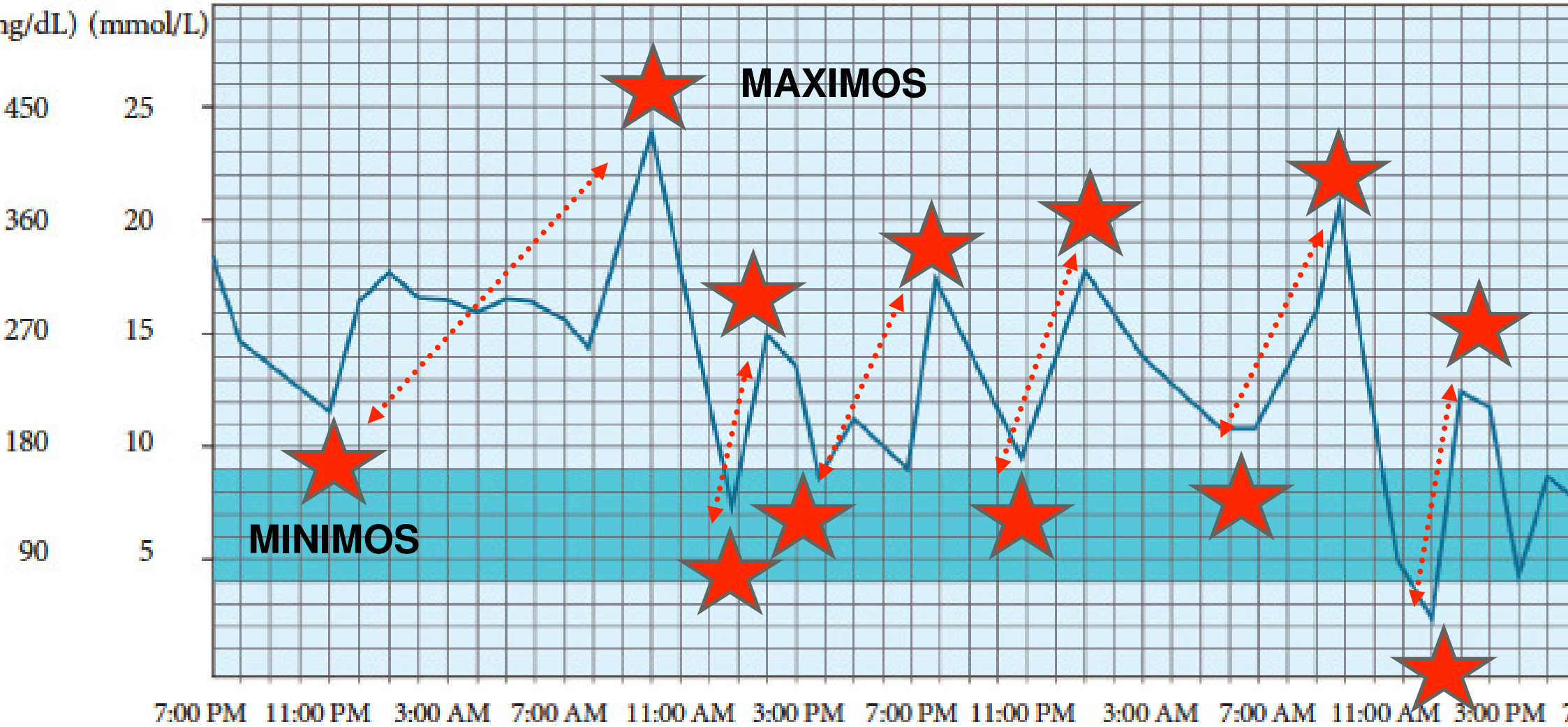


M ean (promedio)
A mplitud (Amplitud)
G licemic (Glucémica
E xcursions (Excursio

$22 \leq MAGE \leq 60$ sanos,
$60 < MAGE \leq 90$ diab. estab
$90 < MAGE \leq 200$ diab. ines

ICION: media aritmética del punto más bajo hasta los picos, cuando la dife
e la DE.

RAS: Incluye sólo las oscilaciones grandes. Se asocia débilmente c
ucemia, está inherentemente sesgado hacia la hiperglucemia.



Mean glucose (mg/dL) 243 | SD 75 | MAGE 172

	Time	Glucose nadir (mg/dL)	Time	Glucose peak (mg/dL)	ΔG>
1	11:00 PM	209	10:00 AM	432	22
2	1:00 PM	137	2:00 PM	272	13
3	4:00 PM	157	8:00 PM	317	16
4	11:00 PM	173	1:00 AM	322	14

Diapositiva 18

LN5 Calculation of MAGE: In the first step, all the local maximum/minimum values are determined. The next step is an assessment of maximum/minimum pairs against the SD. If the difference from minimum to maximum is greater than the SD, this variation from mean measure is retained. If the local maximum/minimum is less than 1 SD it is excluded from further calculations. These troughs are retained and summed to achieve the MAGE.
Lia Nattero; 18/06/2016

LN6 The measurement can be made either in the peak-to-nadir or nadir-to-peak direction, the direction being selected by the first upward or downward glucose excursion that is greater than one SD.
Lia Nattero; 18/06/2016

CONGA

Mc Donnell CM et al., en 2

ontinuos (continua)
verall (general)
et (neta)
ycemic (glicemica)
ction (Acción)

$$CONGA_n = \sqrt{\frac{\sum_{i=n+1}^{N}(D_i - \overline{D})^2}{N-1}}$$

BG medida en mmol/L.

NICIÓN: Se calcula sobre la DE de las diferencias entre los va
glucosa, medidos a intervalos regulares de tiempo (para
rvación de las n primeras horas, se calcula la diferencia ent
rvación actual y la n observaciones después. La CONGA se d
o la DE de estas diferencias).

MODD

Molnar et al. en

an (promedio)
(de)
ly (diarias)
erences (diferencias)

$$MODD = \frac{1}{(K(m-1))} \sum_{i=1}^{N-K} |BG_i - BG_{K+i}|$$

BG medida en mmol/L.

$0.3 < MODD \leq 0.5$ sanos
$0.5 < MODD \leq 2$ diab. e
$MODD > 2$ diab. inestab

INICIÓN: Media de la diferencia absoluta 2 valores tomados e
mo tiempo, de dos días consecutivos (mide la variación de la ter
a día).

NTRA: Limitado por la representatividad restringida de los val
o durante dos días consecutivos).

OS: Altos valores de MODD indican hábitos de irregularidad en c

MEDIDAS DE RIESGO GLUCEMICO

Kovatchev et al. en 2

HBGI

$HBGI \leq 4.5$ riesgo bajo,
$4.5 < HBGI \leq 9$ riesgo medio,
$HBGI > 9$ riesgo alto.

LBGI

$LBGI \leq 1.1$ riesgo mínimo,
$1.1 < LBGI \leq 2.5$ riesgo bajo,
$2.5 < LBGI \leq 5$ riesgo medio,
$LBGI > 5$ riesgo alto.

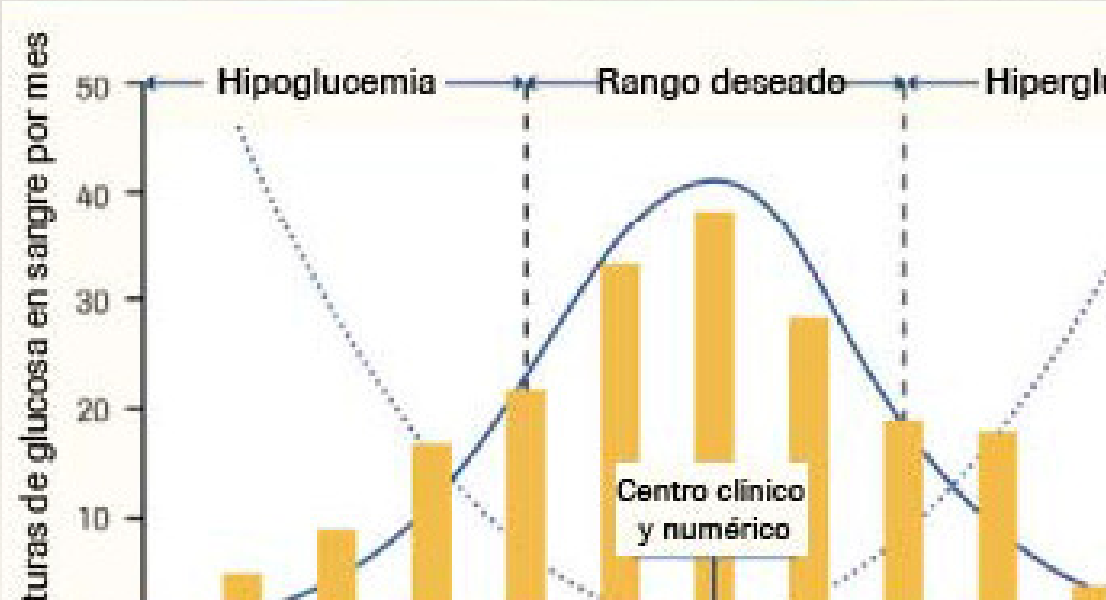
ADRR (average daily risk ange).

$ADRR < 10$ riesgo mínimo,
$10 \leq ADRR < 20$ riesgo bajo,
$20 \leq ADRR < 40$ riesgo medio,
$ADRR \geq 40$ riesgo alto.

Convierten valores de glucosa en scores. Cu
el RIESGO de EXTREMOS (min, max) glucém

No miden "per se" VG, sino CONSECUENCIAS.

Cálculo del índice de HBGI/LBGI.



Diapositiva 21

LN7 El "índice de nivel bajo de glucosa en sangre" (LBGI) y el "índice de nivel alto de glucosa en sangre" (HBGI): El primero es una medida de la frecuencia y la extensión de las lecturas de niveles bajos de glucosa en sangre, basada en la sección de hipoglucemia del espacio de riesgo de glucosa en sangre (ver la figura 3, rama izquierda de la parábola). El segundo calcula la frecuencia y la extensión de las lecturas de niveles altos de glucosa en sangre, en la sección de hiperglucemia del espacio de riesgo de glucosa en sangre (ver la figura 3, rama derecha de la parábola).
Lia Nattero; 03/06/2016

MEDIDAS DE RIESGO GLUCEMICO

Hill et al. en 20

RADE (glycemic risk assessment diabetes equation)

uación de evaluación de riesgo glucémico en la diabe

$$median(425(\log_{10}(\log_{10}(BG/18) + 0.16)^2)$$

BG medida en mmol/L.

$GRADE < 5$ buen co

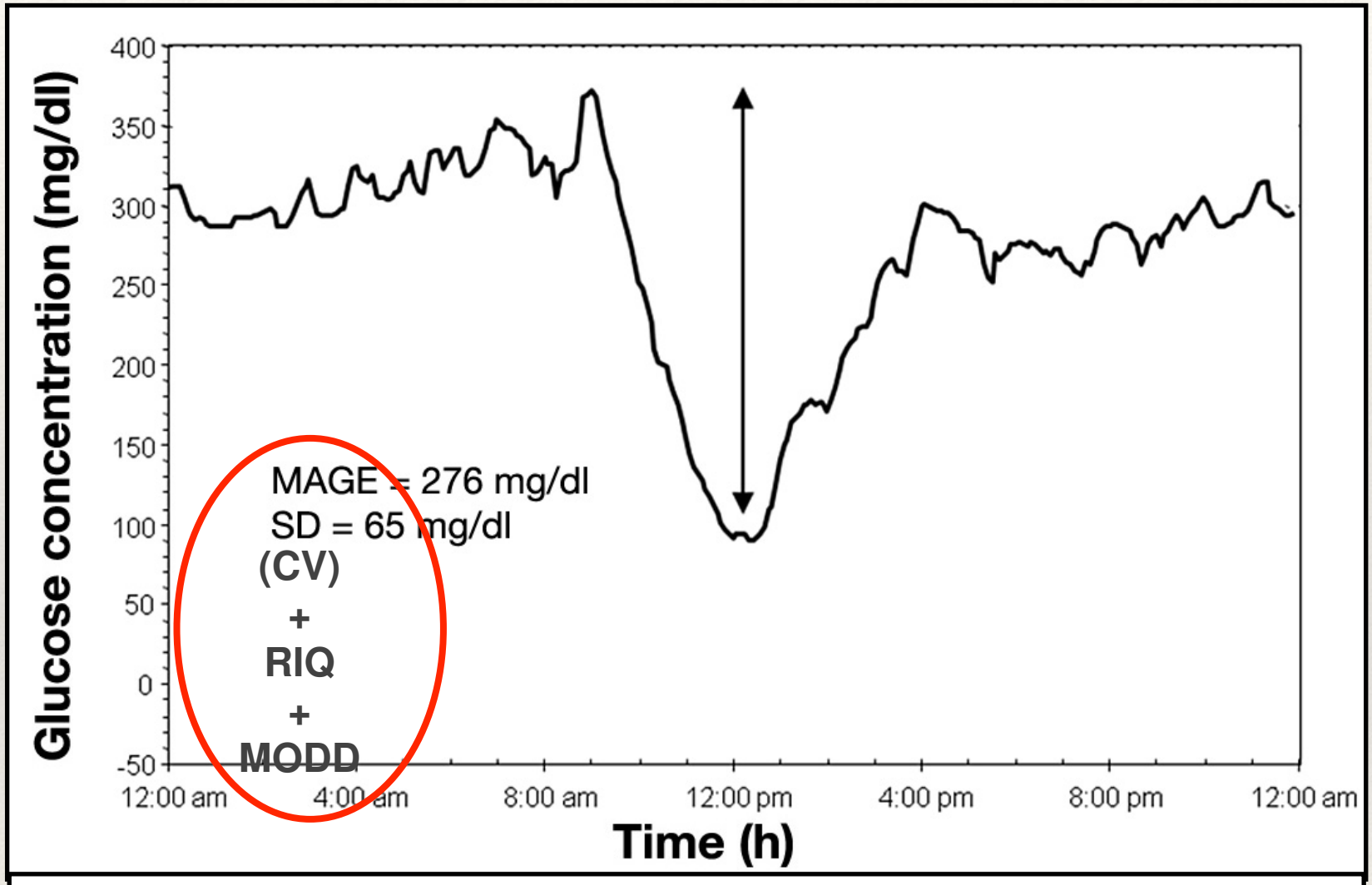
empo en un range en un rango especificado:

ADE hypoglycemia (% of GRADE score attributable to glucose < 70 mg/dL)

ADE euglycemia (% OF GRADE score atrtributable to glucose 70-140 mg/dL)

ADE hyperglycemia (% of GRADE score attributable to glucose > 140 mg/dL)

CUAL ES EL MAS UTIL?



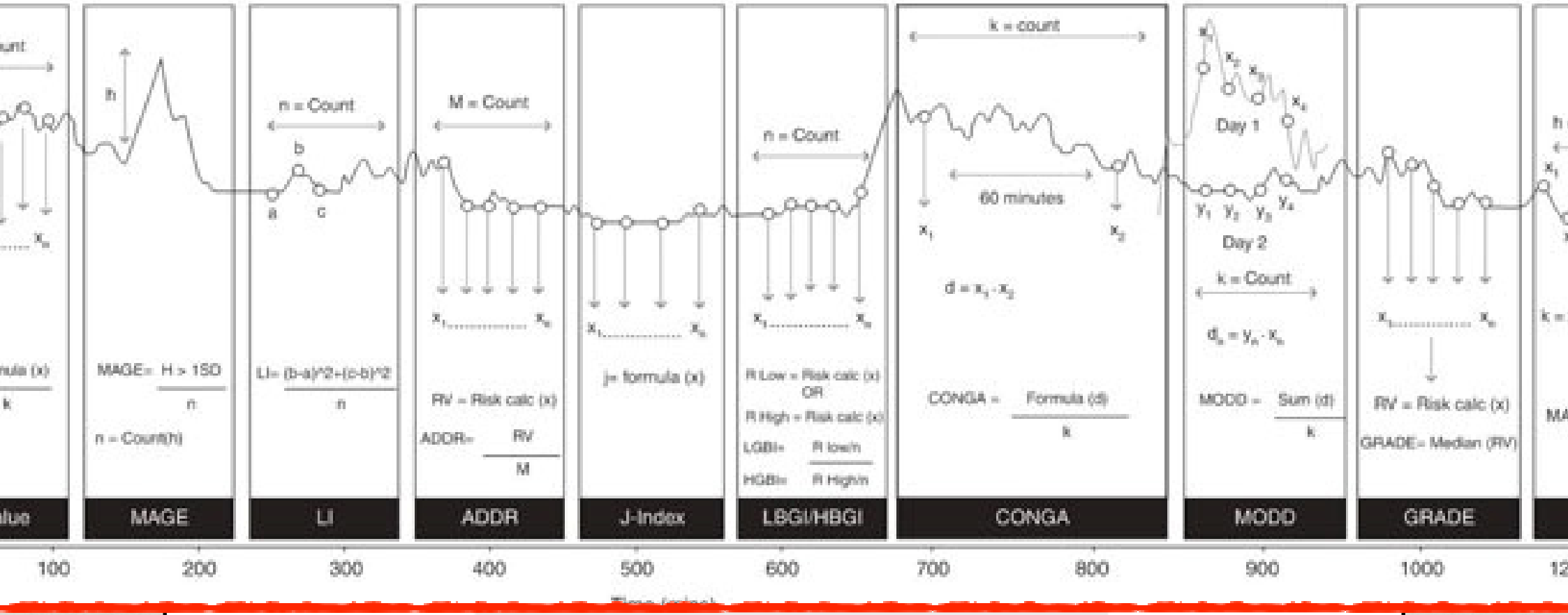
MCG 24h. DM 1 en tratamiento con MDI.

Diapositiva 23

LN8 This patient had small glucose fluctuations throughout the day but exhibited a rapid and unpredictable glucose drop after breakfast. The nadir was reached at noon with a further glucose increase after lunch and a return to a high stable glucose value at 4:00 pm. In this patient, the calculation showed a profound discrepancy between the SD that remained at a modest level (65 mg/dl), while the MAGE was greatly increased (276 mg/dl, 15.3 mmol/liter). This type of profile, which is encountered in unstable type 1 diabetes, seems to indicate that the SD may minimize the effect of sudden, very large changes in individuals with overall modest fluctuations.

Lia Nattero; 18/06/2016

Diabetes labil/inestable

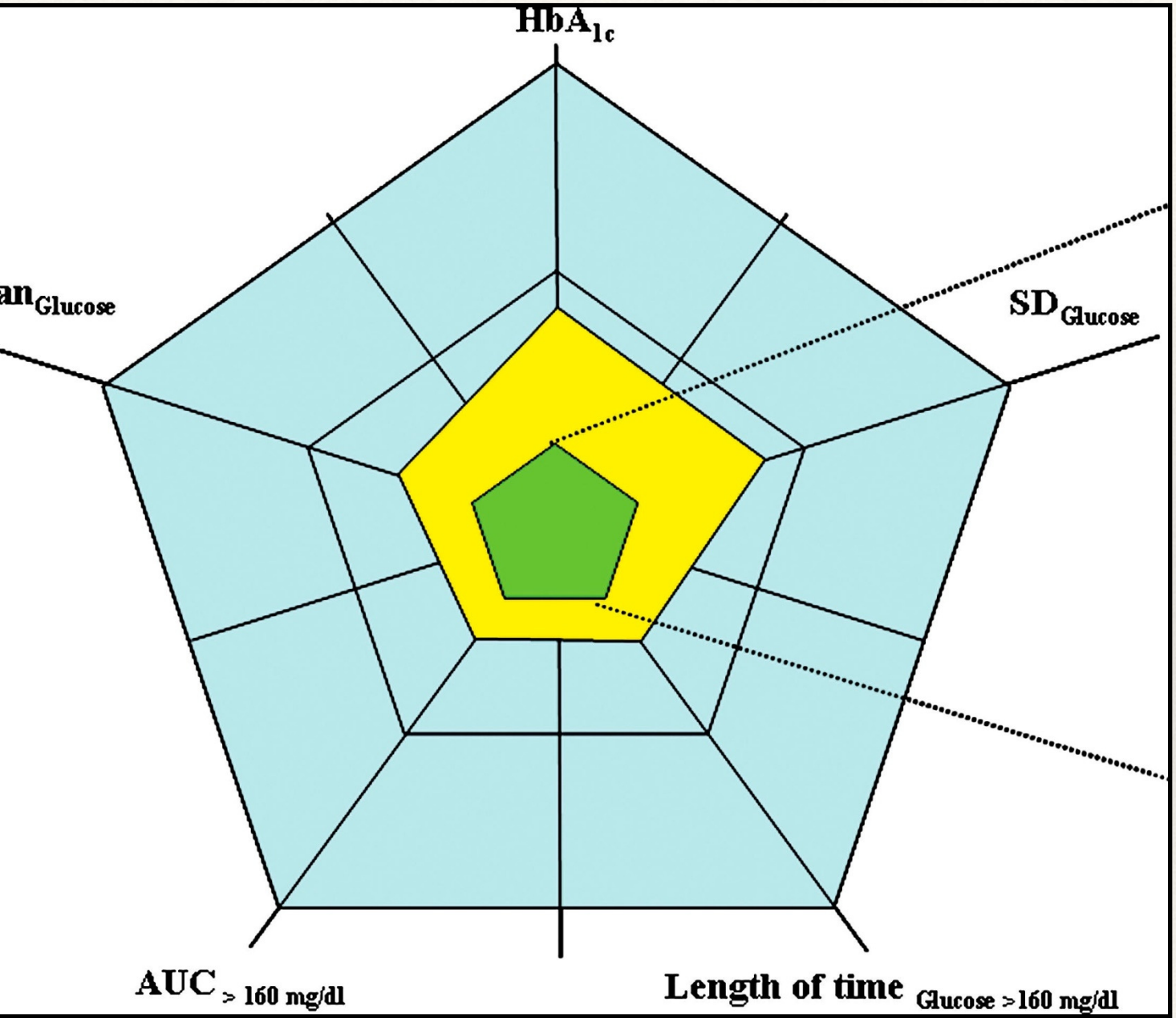


Predominio de hiperglucemia con CAD recurrentes (59%)

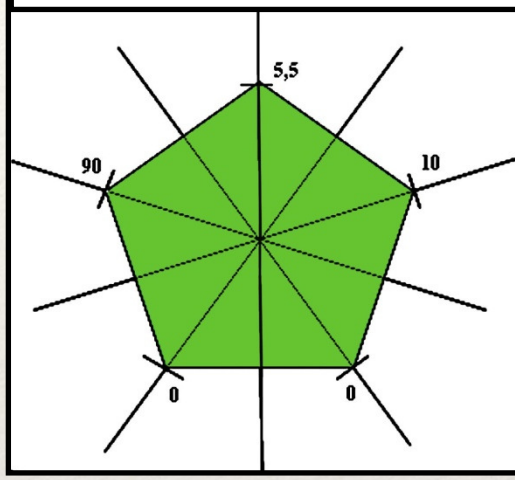
Formas de inestabilidad

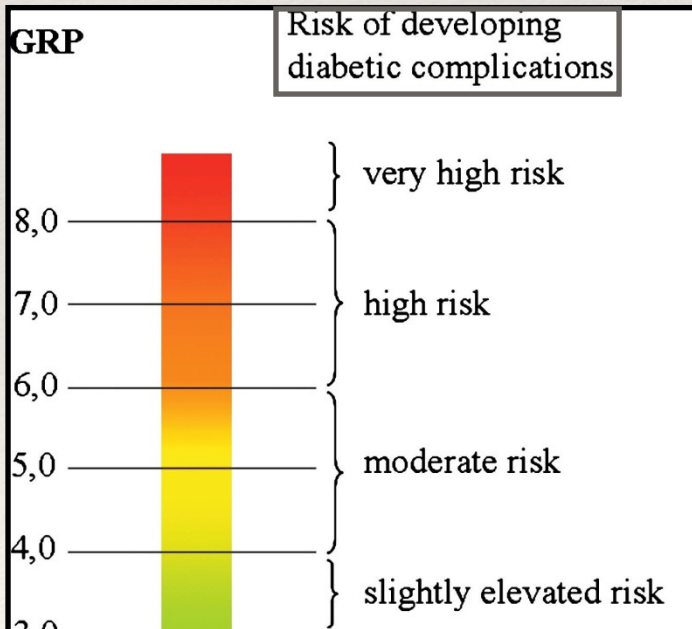
Predominio de hipoglucemia

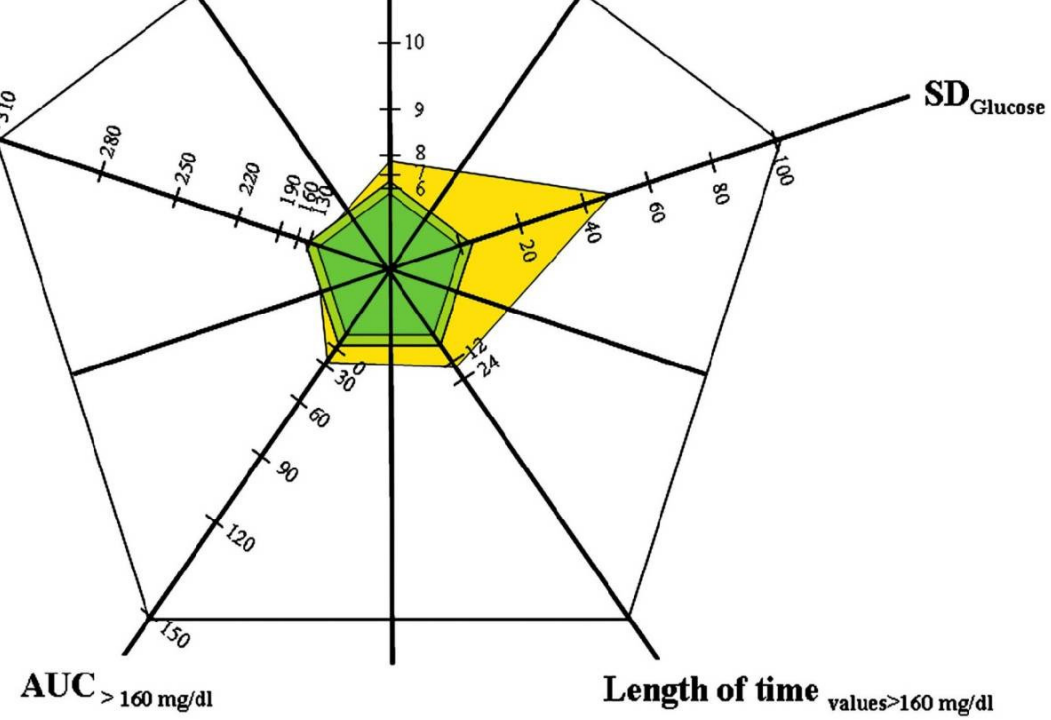
atients with Diabetes Mellitus by a Model Integra
Different Parameters from Glucose Profiles

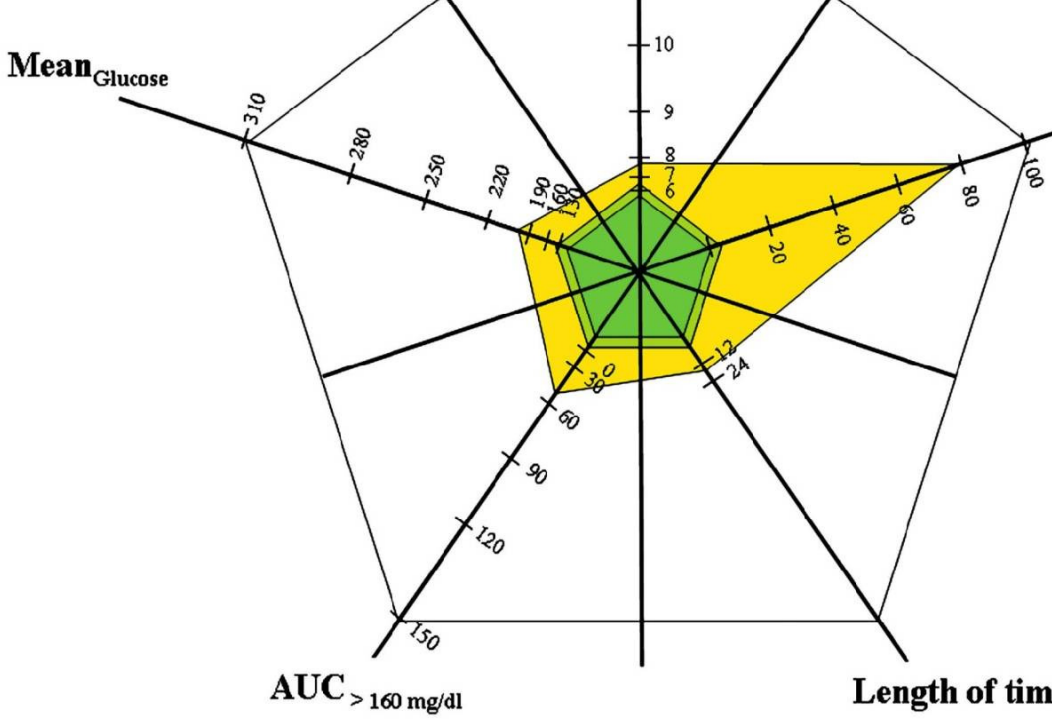


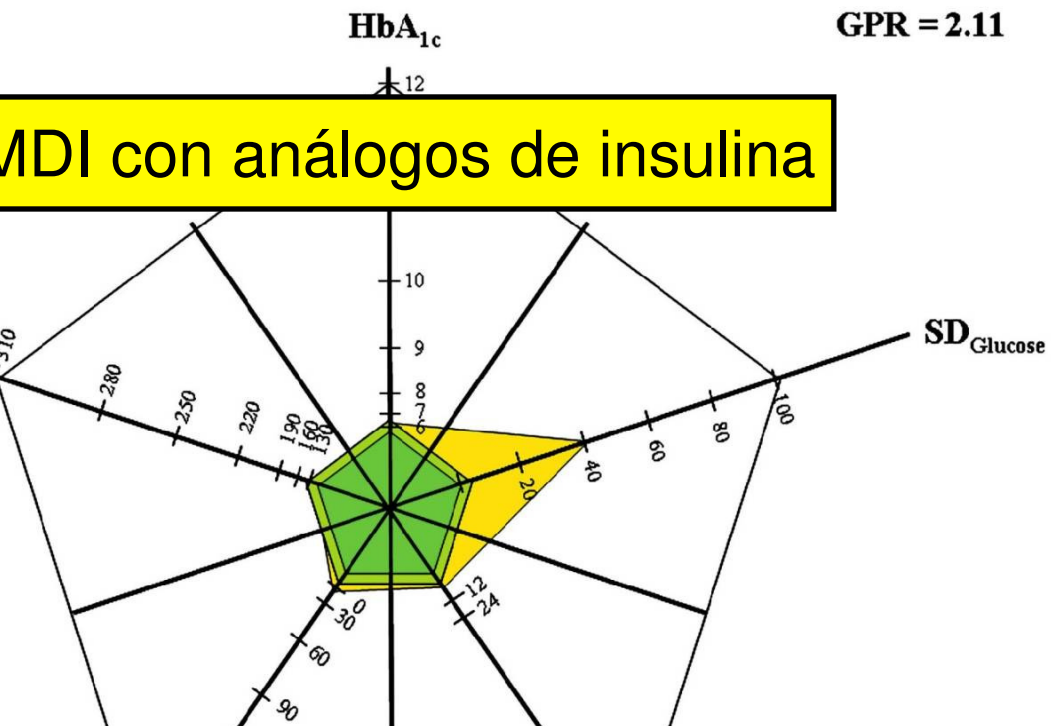
Individuos sanos

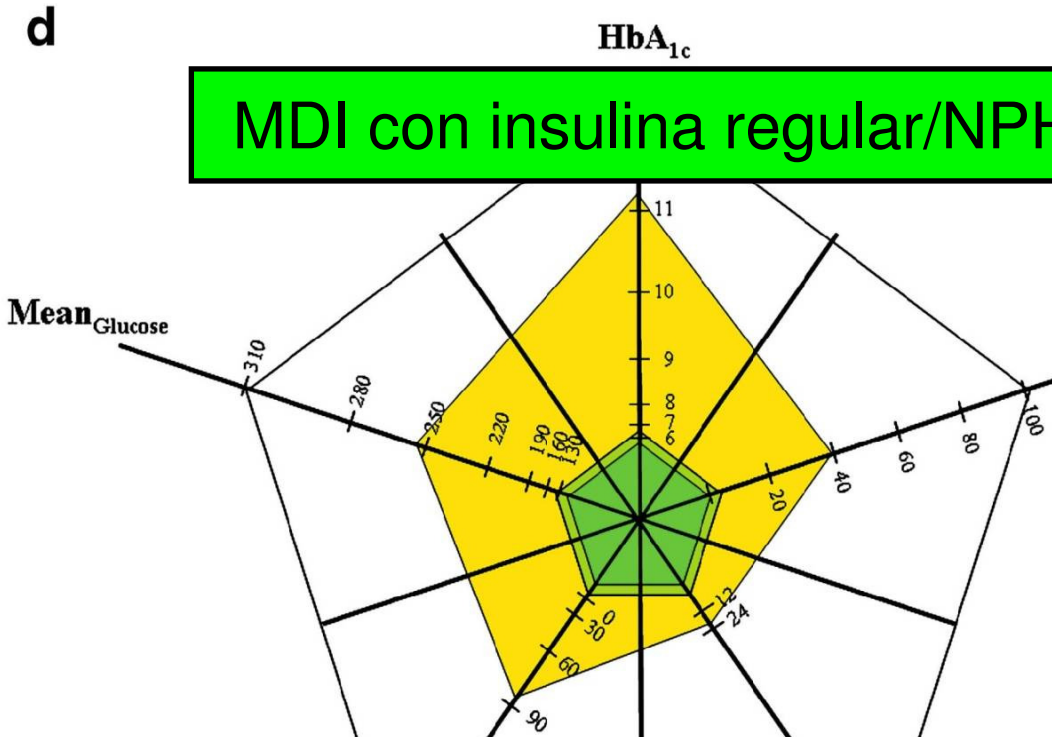





SD Glucose
AUC > 160 mg/dl
Length of time values>160 mg/dl


Mean Glucose
AUC > 160 mg/dl
Length of tim


HbA1c
GPR = 2.11
MDI con análogos de insulina
SD Glucose


d
HbA1c
MDI con insulina regular/NPH
Mean Glucose

IERRAMIENTAS PARA TRATAR LA VG

EDUCACION DIABETOLÓGICA

TERAPIA INSULINICA:

- nuevos análogos
- ICSI - MCG-RT

TERAPIA NO

TRANSPLANTE DE PANCREAS
TRANSPLANTE DE ISLOTES

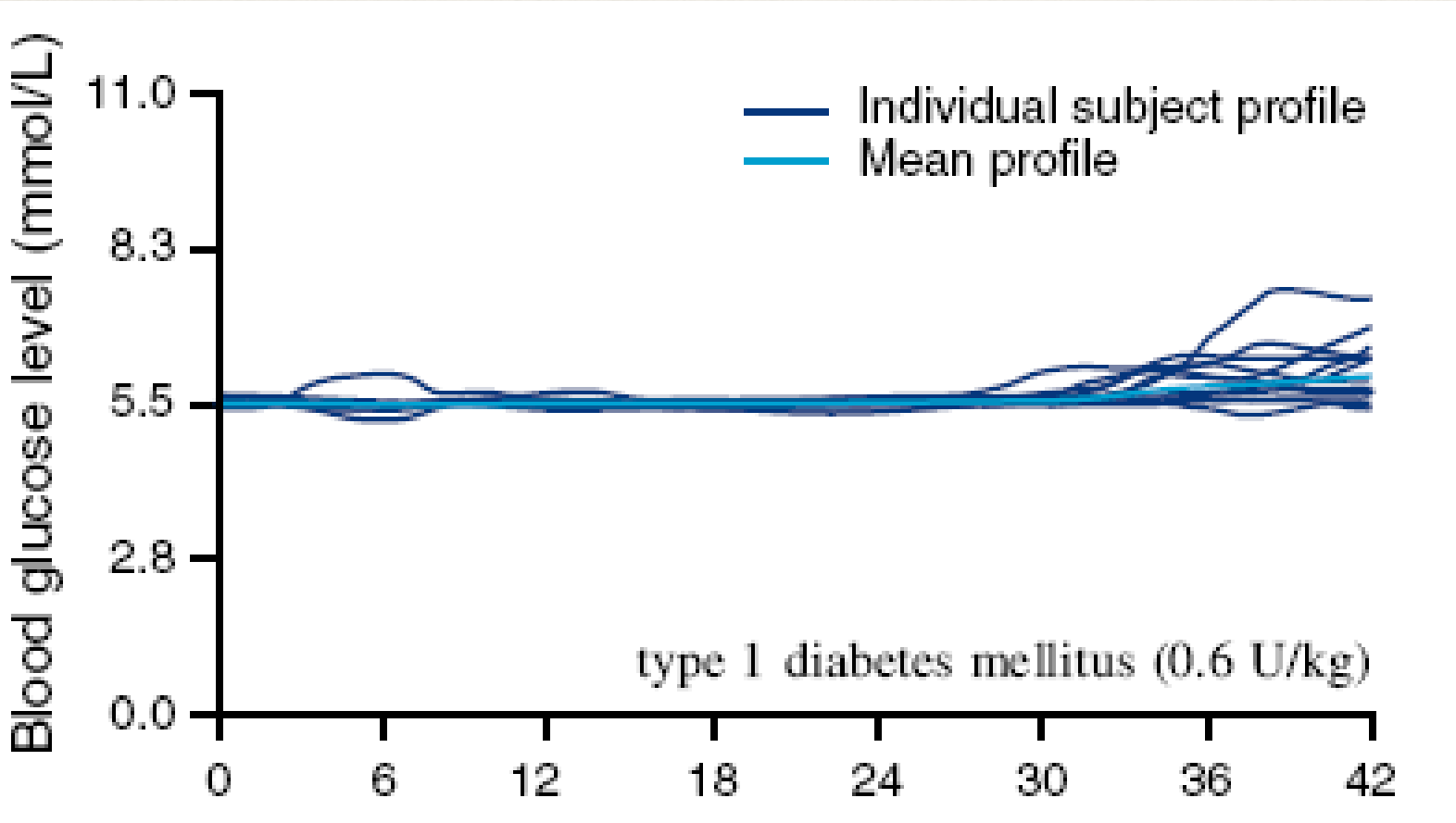
TERAPIA INSULINICA

kinet (2014) 53:787–800

Hanne Haahr · Tim Heise

ARTICLE

w of the Pharmacological Properties of Insulin Degludec
eir Clinical Relevance



TERAPIA NO INSULINICA

016 Feb;22(2):220-30. doi: 10.4158/EP15869.RA. Epub 2015 Oct 20.

RGING ROLE OF ADJUNCTIVE NONINSULIN ANTIHYPERGLYCEMIC THERAPY IN THE MANAGEMENT OF TYPE

.
g SK.

ble data on adjunctive therapies for type 1 diabetes (T1D), with a special focus on newer antihyperglycemic agents.

a on hypoglycemia, obesity, mortality, and goal attainment in T1D were reviewed to determine unmet therapeutic needs. PubMed databases and a
es meetings were searched using the term "type 1 diabetes" and the available and investigational sodium-glucose cotransporter (SGLT) inhibitors, g
P-1) receptor agonists, dipeptidyl peptidase 4 inhibitors, and metformin.

of patients with T1D do not meet glycated hemoglobin (A1C) goals established by major diabetes organizations. Hypoglycemia risks and a rising inc
etabolic syndrome featured in the T1D population limit optimal use of intensive insulin therapy. Noninsulin antihyperglycemic agents may enable T
t A1C levels using lower insulin doses, which may reduce the risk of hypoglycemia. In pilot studies, the SGLT2 inhibitor dapagliflozin and the GLP-1
tide reduced blood glucose, weight, and insulin dose in patients with T1D. Phase 2 studies with the SGLT2 inhibitor empagliflozin and the dual SGL
or sotagliflozin, which acts in the gut and the kidney, have demonstrated reductions in A1C, weight, and glucose variability without an increased inc
.
N:
perglycemic agents, particularly GLP-1 agonists, SGLT2 inhibitors, and dual SGLT1 and SGLT2 inhibitors, show promise as adjunctive treatment fo
ents achieve better glucose control without weight gain or increased hypoglycemia.

HERRAMIENTAS PARA TRATAR LA VG

EDUCACION DIABETOLÓGICA

TERAPIA INSULINICA:

- nuevos análogos
- ICSI - MCG-RT

TERAPIA NO

TRANSPLANTE DE PANCREAS
TRANSPLANTE DE ISLOTES

En general, la respuesta a la pregunta …

“**¿Cómo medir la variabilidad glucémica?**”

Aún no se ha encontrado con exactitud, pero de manera similar al enfoque científico completo sobre esta cuestión, estamos avanzando...