Casual Friday Series

Functional Blood Chemistry Series
Pt. VI: Glucose (3)

A Biogenetix Clinical Presentation

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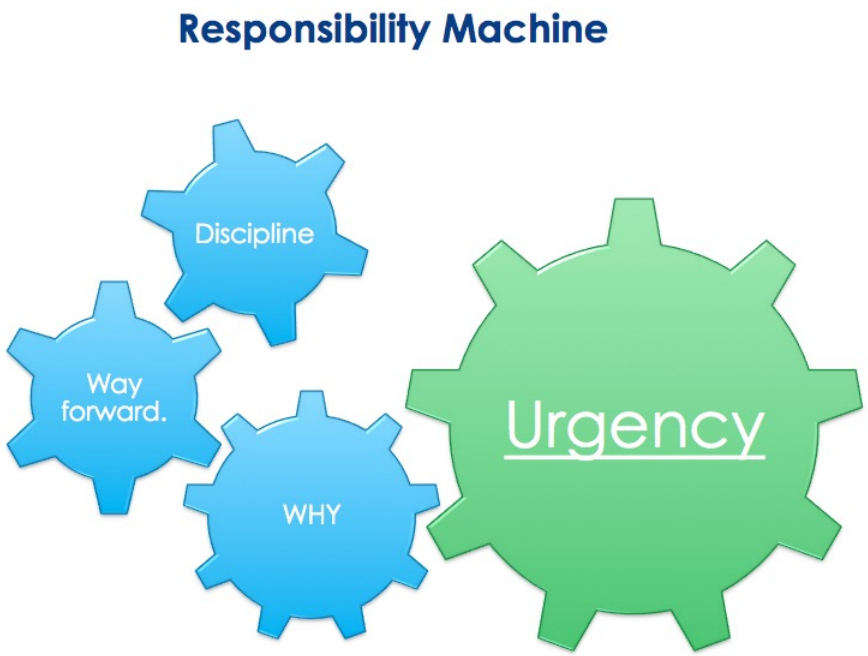
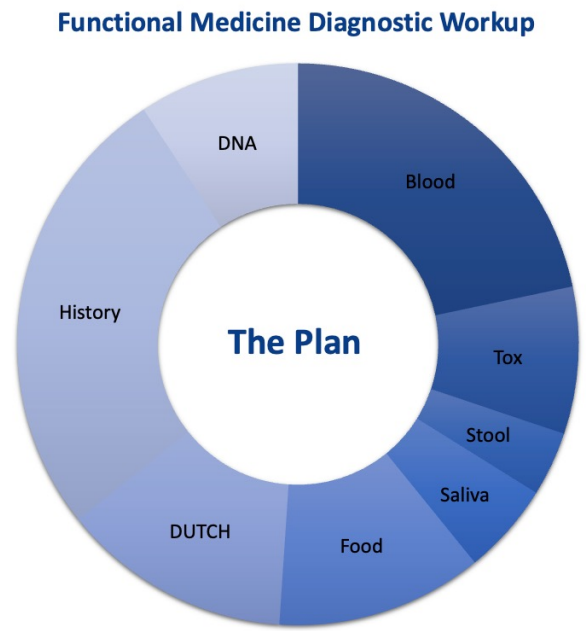
Applied FM





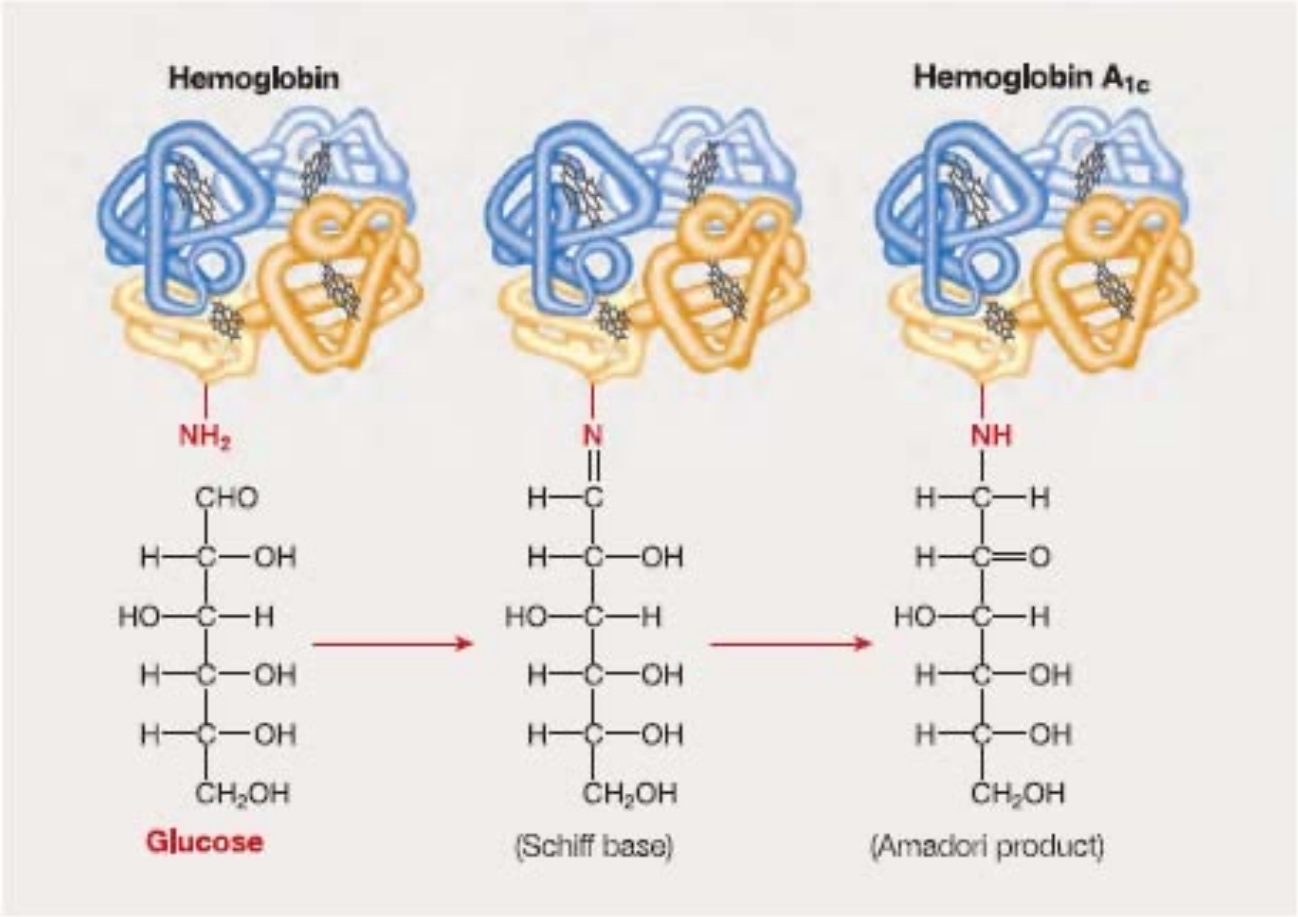
Progress.

Reactive Hypolycemia – The Short Version

- Hyperinsulinemia
- Excess GLP-1 production
- Low counter regulatory hormones
- Glucagon resistance
- Carnitine deficiency

Hemoglobin A1C

- Glycated hemoglobin is formed at a rate proportional to the average glucose concentration by a slow, non-enzymatic process within red blood cells during their 120-day lifespan.
- Glycated hemoglobin levels reflect blood sugar during a 2-3 month time period prior to the test.



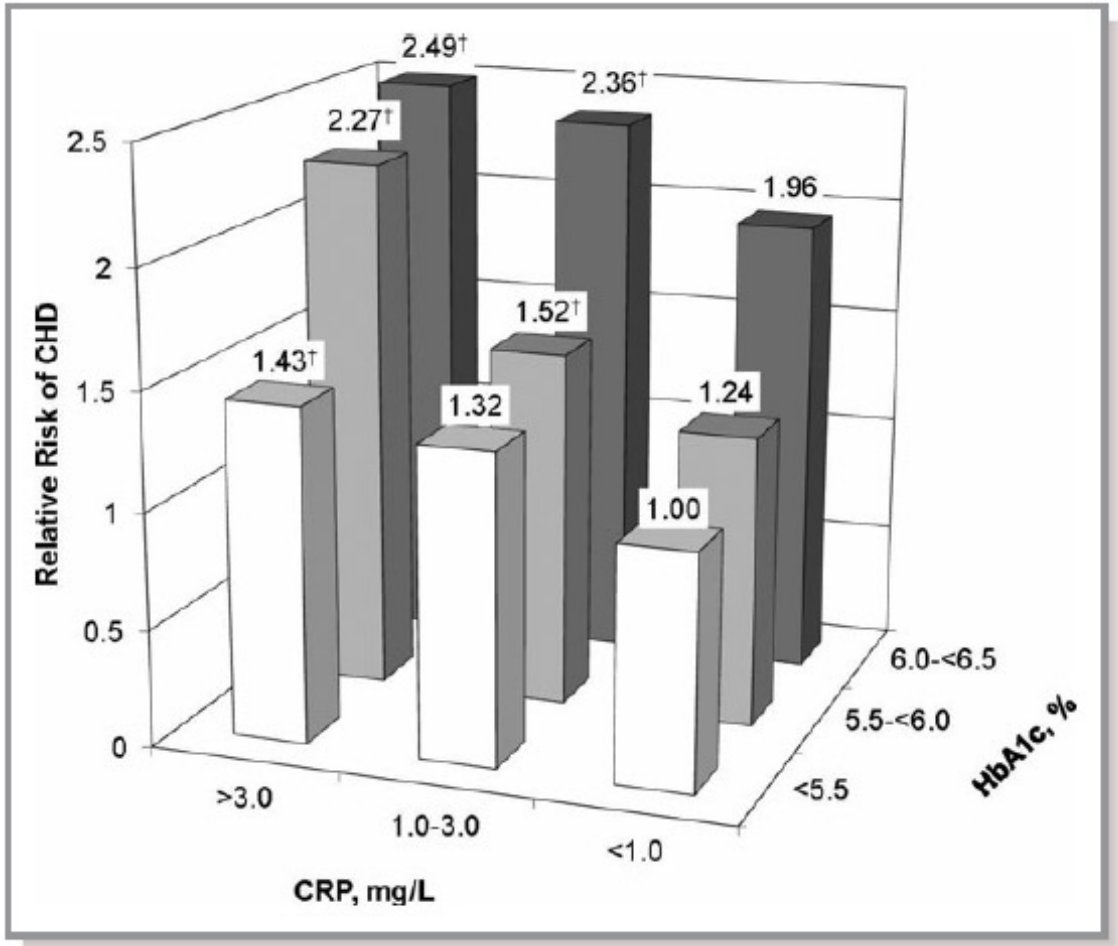
Hemoglobin A1C

Non-diabetic conditions	
Elevated	Decreased
Iron-deficiency anemia	Hemolytic anemia
Lead toxicity	Chronic blood loss
Long-lived RBC	Short-lived RBC

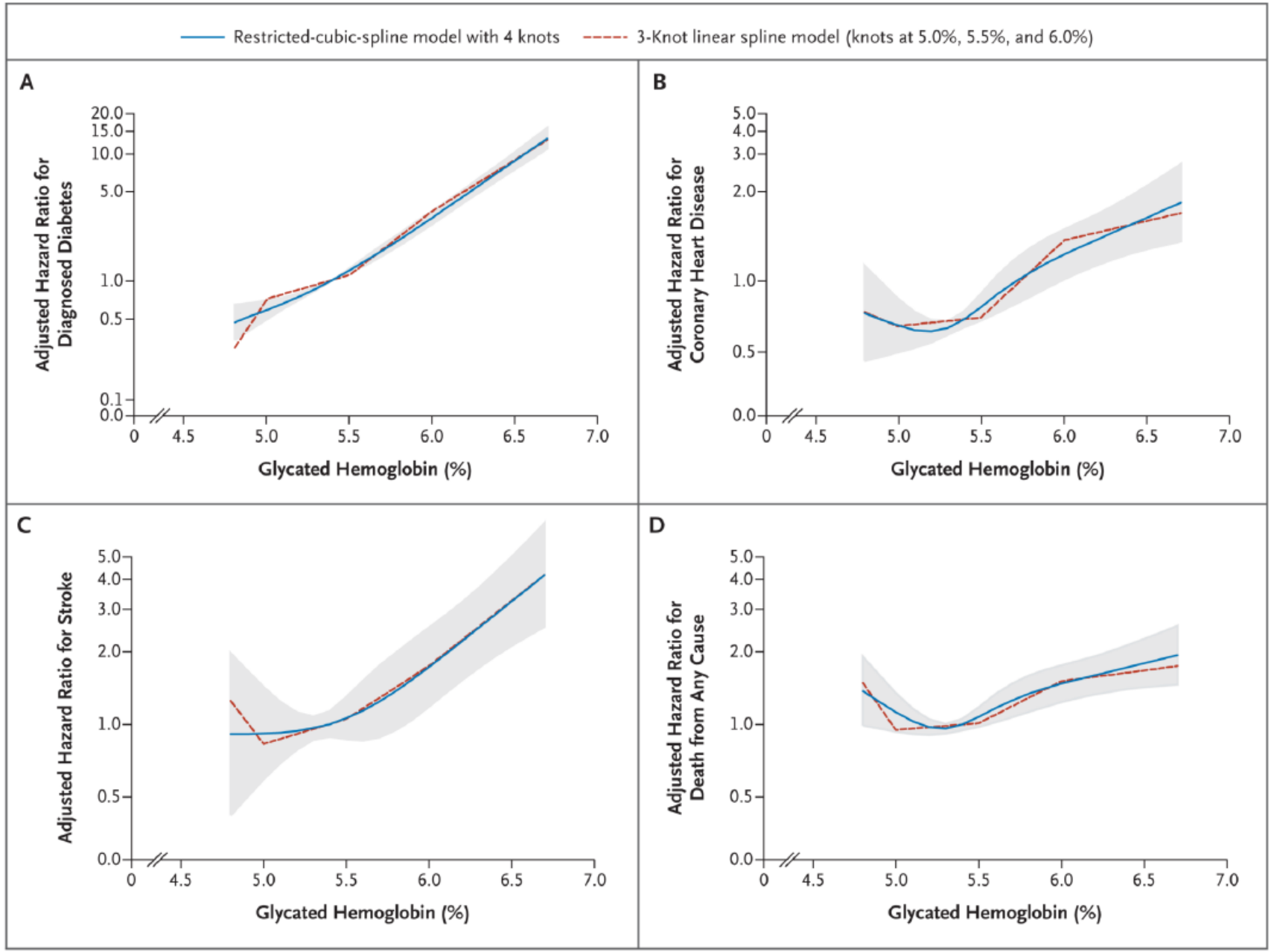
ORIGINAL RESEARCH

Hemoglobin A_{1c} Is Associated With Increased Risk of Incident Coronary Heart Disease Among Apparently Healthy, Nondiabetic Men and Women

Jennifer K. Pai, ScD, MHS; Leah E. Cahill, PhD; Frank B. Hu, MD, PhD; Kathryn M. Rexrode, MD, MPH; JoAnn E. Manson, MD, DrPH; Eric B. Rimm, ScD



hyperinsulinemia, or other metabolic pathways. In the present



HbA1C and Its Correlations

- A number of studies suggest that an A1C above 5.6% is predictive of CAD and impaired glucose tolerance, even with normal fasting glucose.

Hemoglobin A1C

- Optimal Reference Range:
  - 5.1-5.3%*

- *If lower, likely not hyperglycemia or glucose dysregulation, but according to studies, does not seem optimal

HbA1C Limitations

- Red blood cell life span
- Unexplained variations between mean glucose and A1C among patients with diabetes (more pronounced at lower levels of A1C)
- Does not discriminate between the patient with excessive fluctuations and chronically elevated glucose

Calculating RBC Lifespan

- Red Blood Cell Survival (days) = 100/[reticulocytes (percent)/reticulocyte life span (days)]

- Helpful in determining accuracy of hemoglobin A1C
  - Longer-lived RBC, leads to more hemoglobin, and thus a falsely elevated HbA1C (false positive)
  - Shorter-lived RBC, leads to less hemoglobin, and thus a falsely decreased HbA1C (false negative)

Calculating RBC Lifespan

Reticulocyte count: 0.8%
Hematocrit: 45

Correction of Reticulocyte Count	
Hematocrit (%)	Reticulocyte Life Span (RLS)
36-45	1.0
26-35	1.5
16-25	2.0
<15	2.5

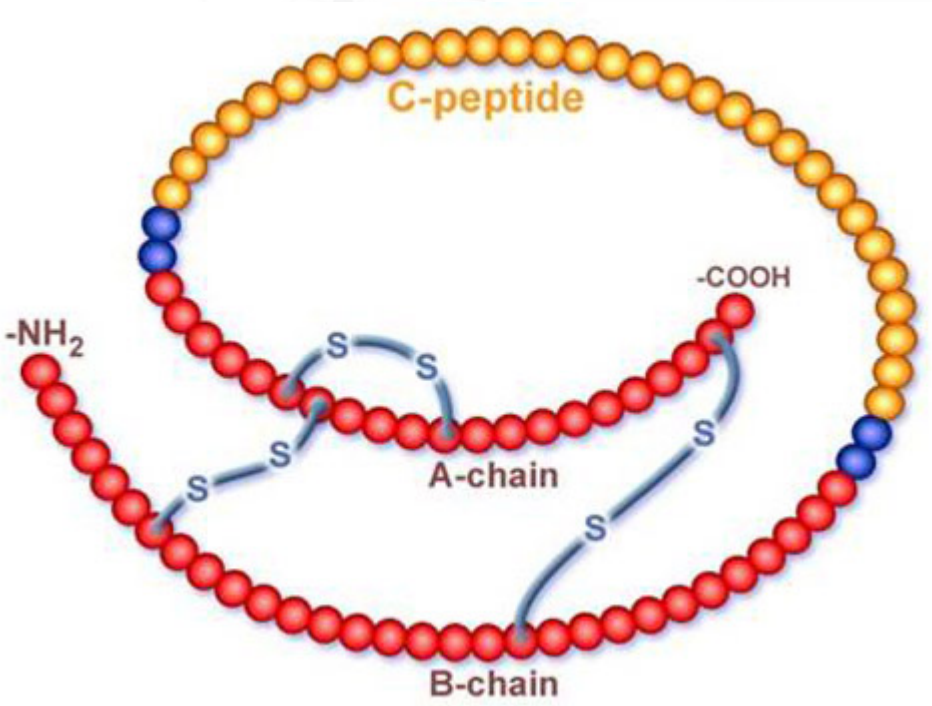
Adapted from Harrisons Principles of Internal Medicine, 18th edition.

Thus, the equation would look like this:

100/[0.8/1] = 125 days

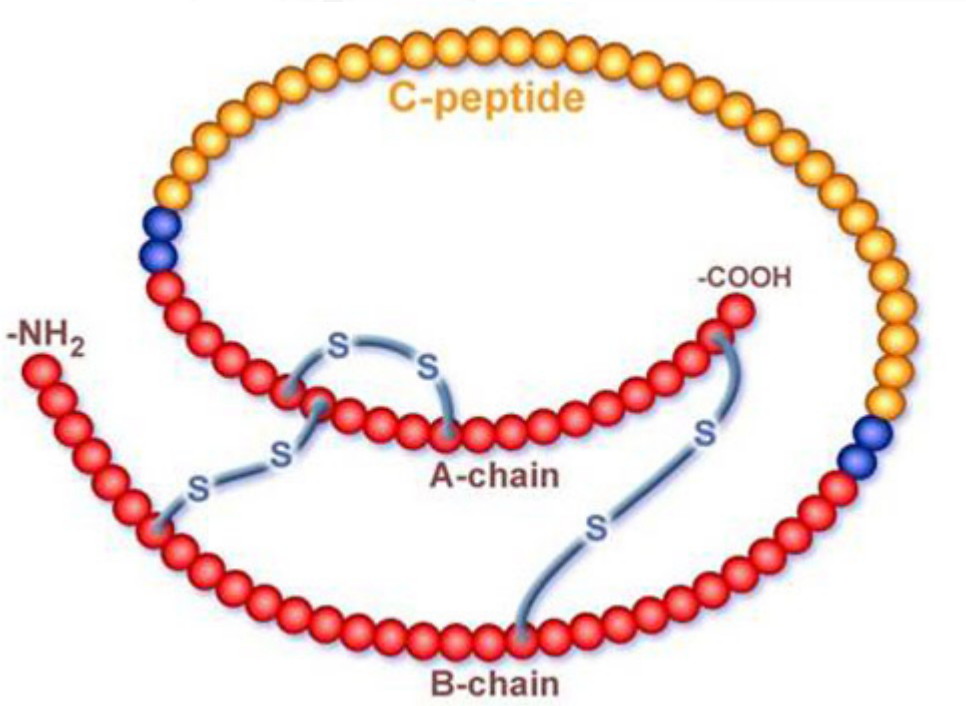
C-peptide

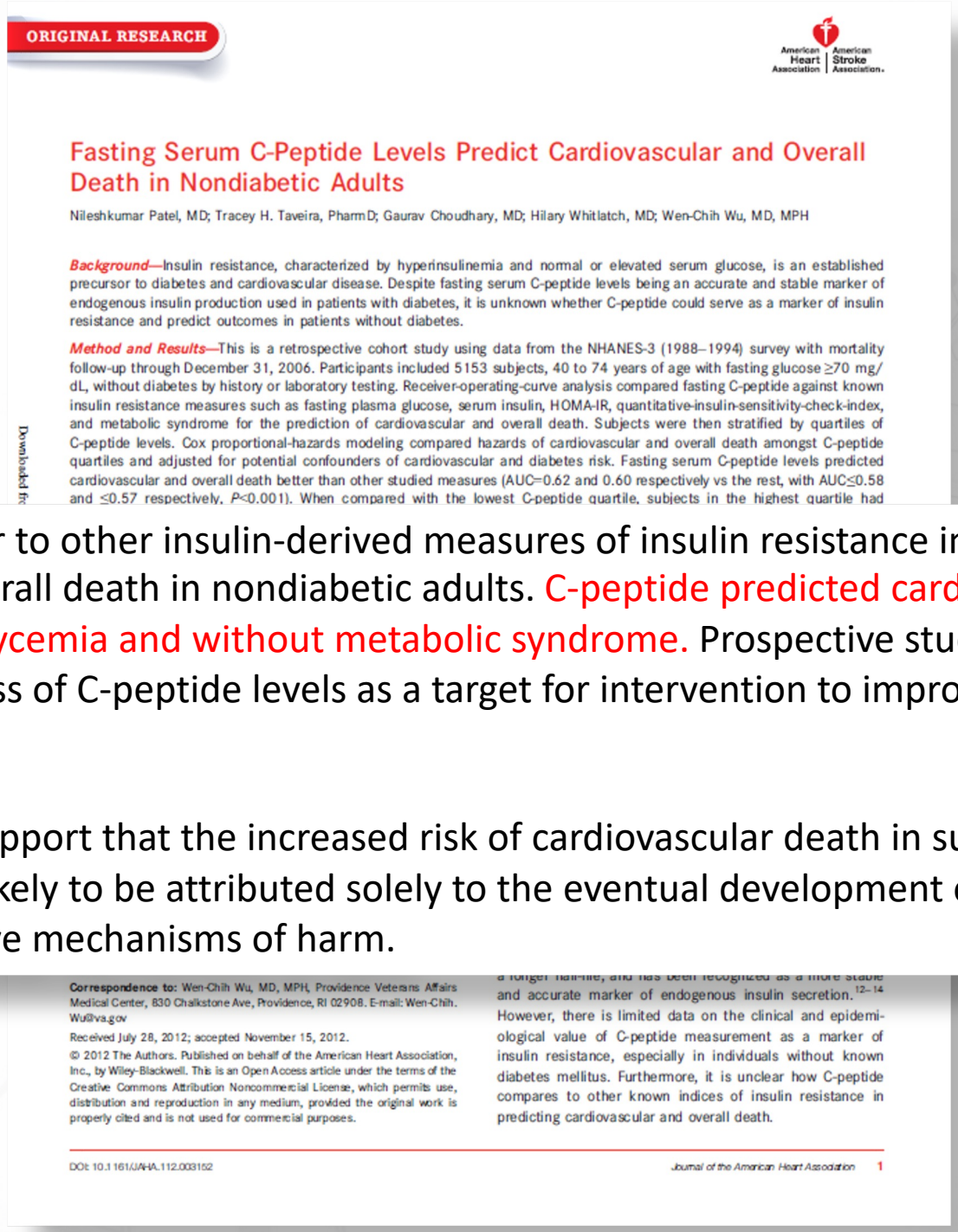
- C-peptide is formed when proinsulin is converted to insulin.
- C-peptide is released at the same time and in the same quantities as insulin but has a longer half-life and is thus a more stable and reliable measurement than insulin.
- May have its own metabolic activity, but more studies are needed



C-peptide

- C-peptide is a more reliable indicator of insulin secretion
  - Not cleared by the liver
  - Has a longer half-life than insulin (30 minutes compared to 4 minutes for insulin)
  - The pharmacokinetics of C-peptide have been well established in research studies.





ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Fasting Serum C-Peptide Levels Predict Cardiovascular and Overall Death in Nondiabetic Adults

Nileshkumar Patel, MD; Tracey H. Taveira, PharmD; Gaurav Choudhary, MD; Hilary Whitlatch, MD; Wen-Chih Wu, MD, MPH

Background—Insulin resistance, characterized by hyperinsulinemia and normal or elevated serum glucose, is an established precursor to diabetes and cardiovascular disease. Despite fasting serum C-peptide levels being an accurate and stable marker of endogenous insulin production used in patients with diabetes, it is unknown whether C-peptide could serve as a marker of insulin resistance and predict outcomes in patients without diabetes.

Method and Results—This is a retrospective cohort study using data from the NHANES-3 (1988–1994) survey with mortality follow-up through December 31, 2006. Participants included 5153 subjects, 40 to 74 years of age with fasting glucose ≥70 mg/dL, without diabetes by history or laboratory testing. Receiver-operating-curve analysis compared fasting C-peptide against known insulin resistance measures such as fasting plasma glucose, serum insulin, HOMA-IR, quantitative-insulin-sensitivity-check-index, and metabolic syndrome for the prediction of cardiovascular and overall death. Subjects were then stratified by quartiles of C-peptide levels. Cox proportional-hazards modeling compared hazards of cardiovascular and overall death amongst C-peptide quartiles and adjusted for potential confounders of cardiovascular and diabetes risk. Fasting serum C-peptide levels predicted cardiovascular and overall death better than other studied measures (AUC=0.62 and 0.60 respectively vs the rest, with AUC≤0.58 and ≤0.57 respectively, $P<0.001$). When compared with the lowest C-peptide quartile, subjects in the highest quartile had

C-peptide was superior to other insulin-derived measures of insulin resistance in predicting cardiovascular and overall death in nondiabetic adults. C-peptide predicted cardiovascular death even in subjects with normoglycemia and without metabolic syndrome. Prospective studies are needed to elucidate the usefulness of C-peptide levels as a target for intervention to improve cardiovascular outcomes.

These results would support that the increased risk of cardiovascular death in subjects with high C-peptide levels is unlikely to be attributed solely to the eventual development of diabetes, and suggest additional or alternative mechanisms of harm.

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and accurate marker of endogenous insulin secretion.[12–14] However, there is limited data on the clinical and epidemiological value of C-peptide measurement as a marker of insulin resistance, especially in individuals without known diabetes mellitus. Furthermore, it is unclear how C-peptide compares to other known indices of insulin resistance in predicting cardiovascular and overall death.

RESEARCH CMAJ

Serum C-peptide levels and risk of death among adults without diabetes mellitus

Jin-young Min PhD, Kyoung-bok Min MD PhD

Competing interests: None declared.

This article has been peer reviewed.

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CMAJ 2013. DOI:10.1503/cmaj.121950

Abstract

Background: Connecting peptide (C-peptide) plays a role in early atherogenesis in patients with diabetes mellitus and may be a marker for cardiovascular morbidity and mortality in patients without diabetes. We investigated whether serum C-peptide levels are associated with all-cause, cardiovascular-related and coronary artery disease–related mortality in adults without diabetes.

Methods: We used data from the Third Nutrition and Health Examination Survey (NHANES

cular-related and coronary artery disease–related mortality.

Results: The mean serum C-peptide level in the study sample was 0.78 (± standard deviation 0.47) nmol/L. The adjusted hazards ratio comparing the highest quartile with the lowest quartile was 1.80 (95% confidence interval [CI] 1.33–2.43) for all-cause mortality, 3.20 (95% CI 2.07–4.93) for cardiovascular-related mortality, and 2.73 (95% CI 1.55–4.82) for coronary artery disease–related mortality. Higher C-peptide levels were associ-

We found an association between serum C-peptide levels and all-cause and cause-specific mortality among adults without diabetes at baseline. Our finding suggests that elevated C-peptide levels may be a predictor of death.

Connecting peptide (C-peptide), a cleavage product of proinsulin, is secreted by pancreatic β cells in equimolar amounts along with insulin.[1] Although a considerable amount of insulin is extracted by the liver, C-peptide is subjected to negligible first-pass metabolism by the liver, thereby serving as a surrogate marker for endogenous insulin secretion.[2] C-peptide has been considered an inert by-product of insulin synthesis and has also been of great value in the understanding of the pathophysiology of type 1 and type 2 diabetes mellitus.[2,3] However, C-peptide has recently been re-evaluated as a bioactive peptide in its own right. The administration of C-peptide to patients and animals with type 1 diabetes has been reported to have a beneficial effect on diabetes-induced abnormalities of the peripheral nerves and renal and microvascular function.[4,5] C-peptide deposition occurs in the atherosclerotic lesions of patients with diabetes.[6] Recent studies have suggested that C-peptide may be a valuable predictor of cardiovascular events and mortality (all-cause and cardiovascular-related mortality).[6–12]

In this study, we investigated the association between serum C-peptide level and all-cause, cardiovascular-related and coronary artery disease–related mortality among patients without diabetes. We also estimated mortality as C-peptide increased across glycated hemoglobin and fasting blood glucose quartiles.

Methods

Study population

We used data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–94) database[13] and the NHANES III Linked Mortality Public-use File from the United States. The latter was a follow-up study of mortality that matched records from NHANES III with data in the National Death Index as of Dec. 31, 2006. NHANES III included 39 695 participants aged 2 months and older, with a weighted response rate of 82% for household interviews and 73% for examinations.[14] The date and cause of death in the National Death Index were derived from death certificates.[15]

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Plasma c-peptide levels and rates of cognitive decline in older, community-dwelling women without diabetes

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Higher c-peptide levels were associated with faster decline in global cognition and verbal memory. We found that each year of age was associated with a greater annual rate of decline by −0.01 units on the global score; thus, our finding of greater annual decline of −0.03 units comparing the highest to lowest c-peptide quartile would indicate that higher levels of c-peptide are cognitively equivalent to 3 years of aging.

Q1 = 1.08
Q2 = 1.56
Q3 = 2.07
Q4 = 3.3

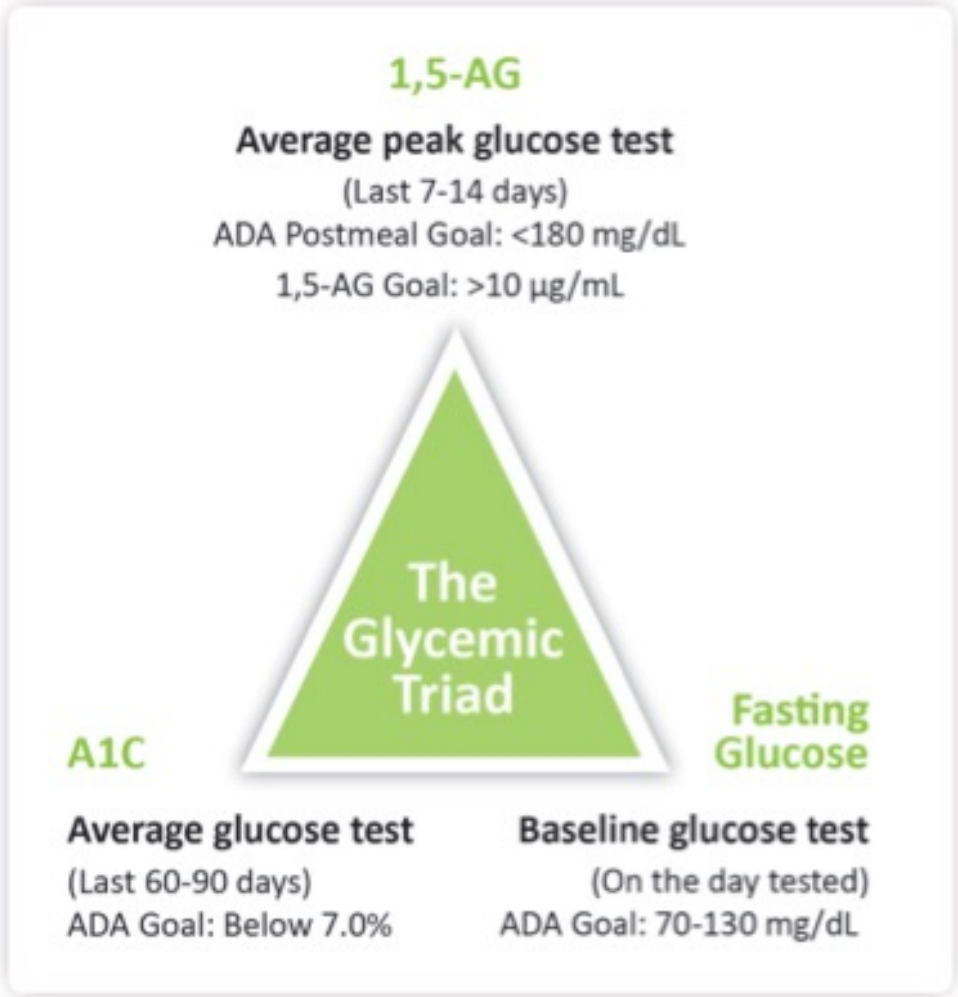
525-2008.
The authors have reported no conflicts of interest.

C-peptide

Traditional Range: 1.1 - 4.4 ng/mL

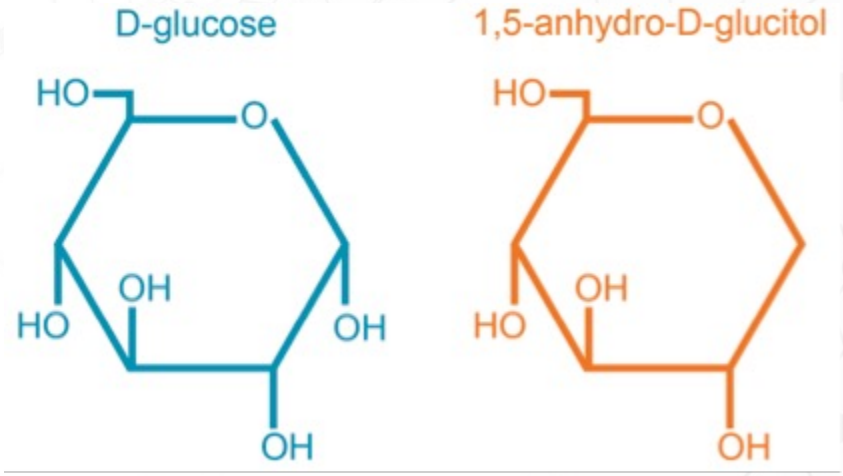
Optimal Range: 1.1 - 2.3 ng/mL (1.1-1.9?)

Glycomark


1,5-AG
Average peak glucose test
(Last 7-14 days)
ADA Postmeal Goal: <180 mg/dL
1,5-AG Goal: >10 µg/mL
The Glycemic Triad
A1C
Fasting Glucose
Average glucose test
(Last 60-90 days)
ADA Goal: Below 7.0%
Baseline glucose test
(On the day tested)
ADA Goal: 70-130 mg/dL

GlycoMark

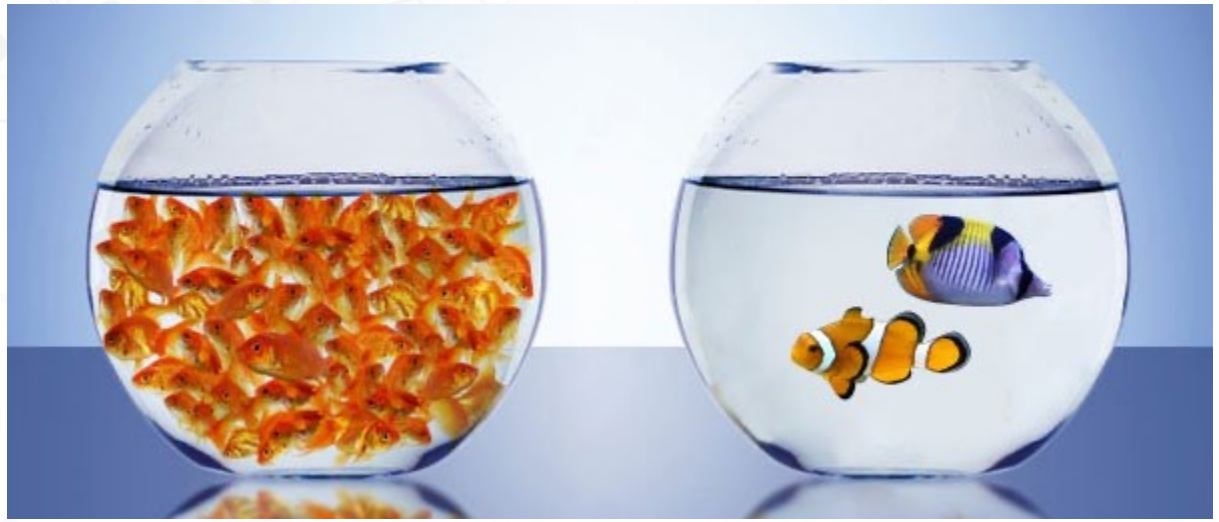
- 1,5-Anhydroglucitol (1,5-AG)
  - Naturally occurring monosaccharide in food
  - Not metabolized or used for biochemical processes
  - Normally filtered and re-absorbed in by the kidneys under normoglycemic conditions
  - However, when glucose levels are elevated, glucose and 1,5-AG compete for re-absorption in the kidneys and ultimately 1,5-AG loses and is excreted in urine *leading to lower serum levels*
    - Occurs when serum glucose levels are above 180 mg/dL.
- Thus, 1,5-AG evaluates hyperglycemic periods above 180 mg/dL for the previous two week period

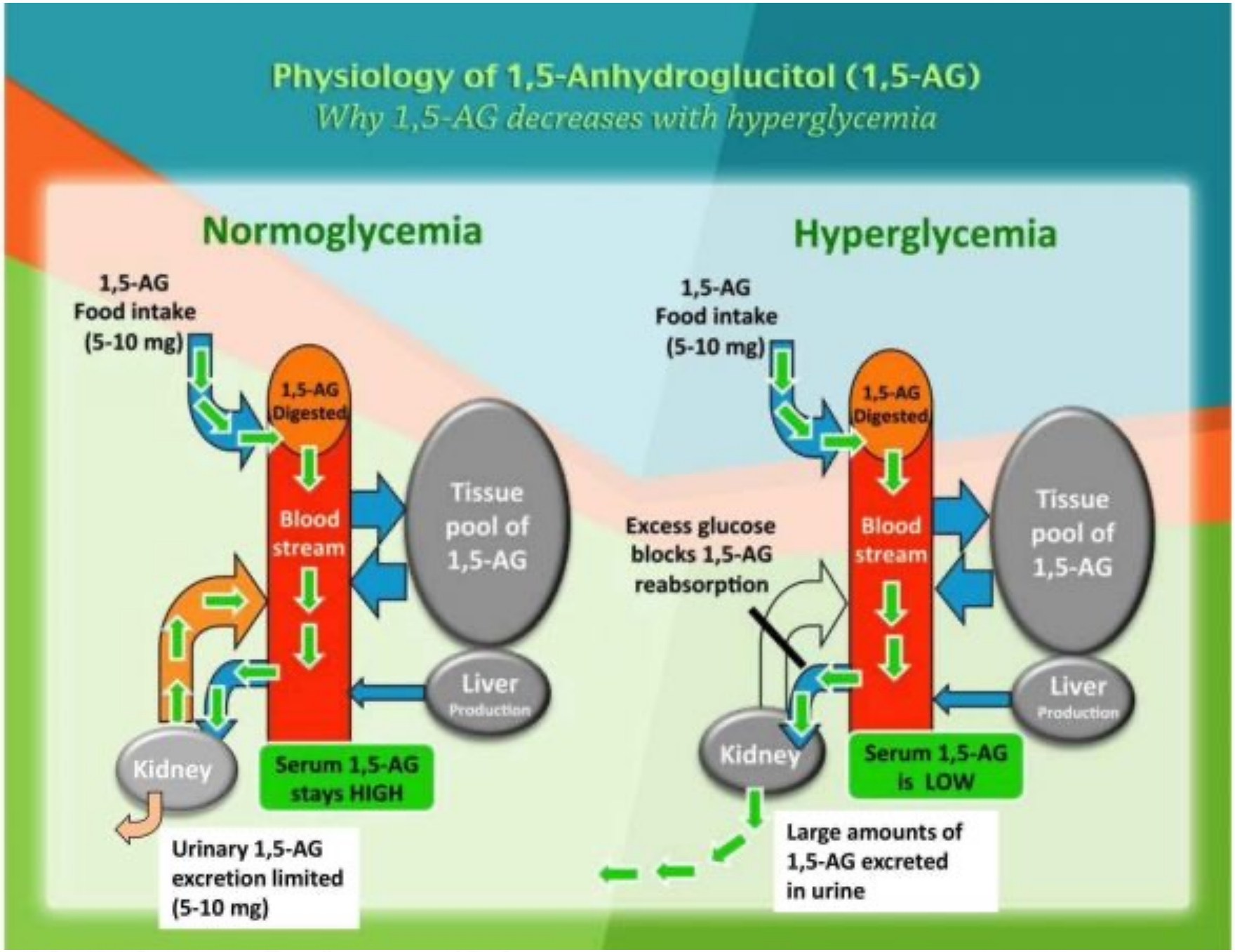


GlycoMark

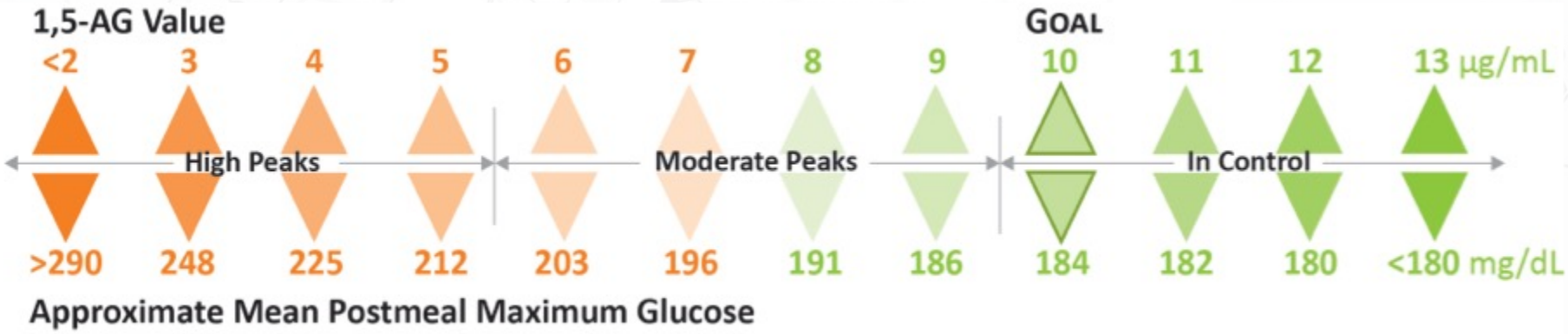
Compared to HbA1C

- A1C = quantity of glucose control
- 1,5 Anhydroglucitol = quality of glucose control



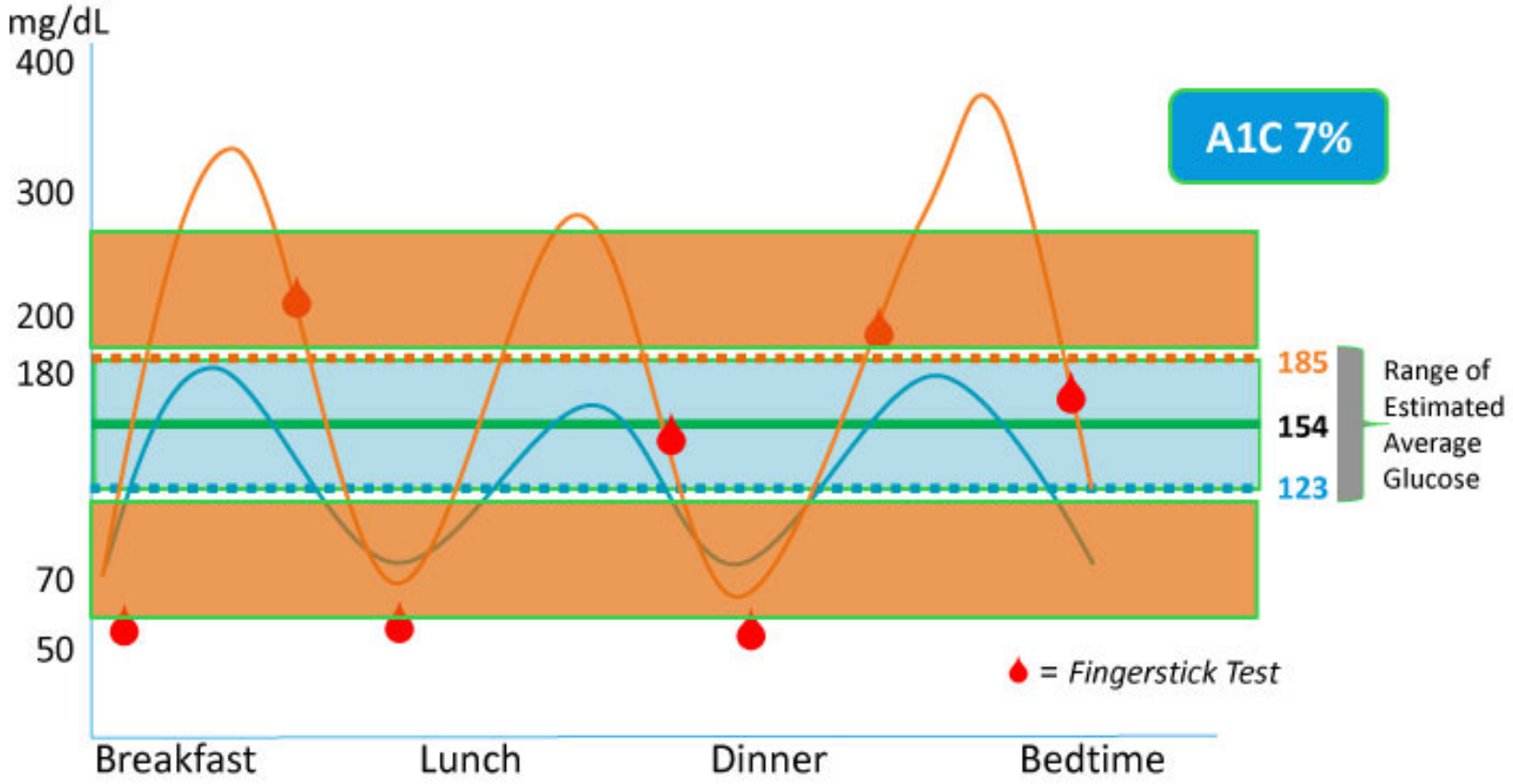

Physiology of 1,5-Anhydroglucitol (1,5-AG)
Why 1,5-AG decreases with hyperglycemia
Normoglycemia
1,5-AG
Food intake
(5-10 mg)
1,5-AG
Digested
Blood
stream
Tissue
pool of
1,5-AG
Liver
Production
Kidney
Serum 1,5-AG
stays HIGH
Urinary 1,5-AG
excretion limited
(5-10 mg)
Hyperglycemia
1,5-AG
Food intake
(5-10 mg)
1,5-AG
Digested
Excess glucose
blocks 1,5-AG
reabsorption
Blood
stream
Tissue
pool of
1,5-AG
Liver
Production
Kidney
Serum 1,5-AG
is LOW
Large amounts of
1,5-AG excreted
in urine

GlycoMark (µg/mL)	Approximate Mean Postmeal Maximum Glucose (mg/dL)
> 12	< 180
10	185
8	190
6	200
4	225
< 2	> 290



GlycoMark Tells You More

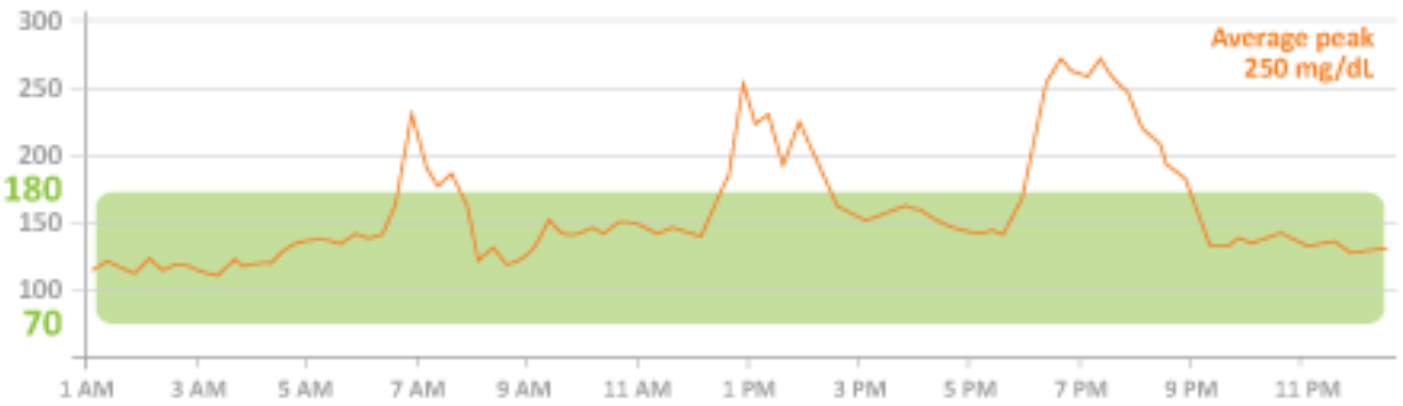
***A1C** is a three-month average. Fingersticks are data points at the moment taken.*
Only GlycoMark identifies maximum glucose spikes over the past two weeks.



D Nathan et al, Translating the A1C Assay into Average Glucose Values,
Diabetes Care, Vol. 31, No. 8, August 2008

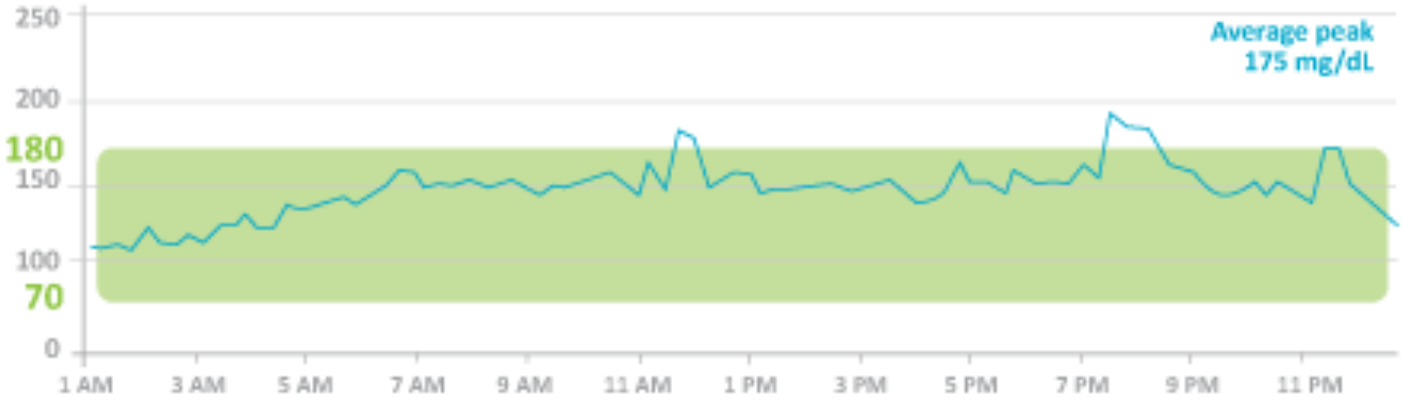
Glycemic Variability

GlycoMark Value 3.0 µg/mL | **A1C 7.4%** | **Mary**

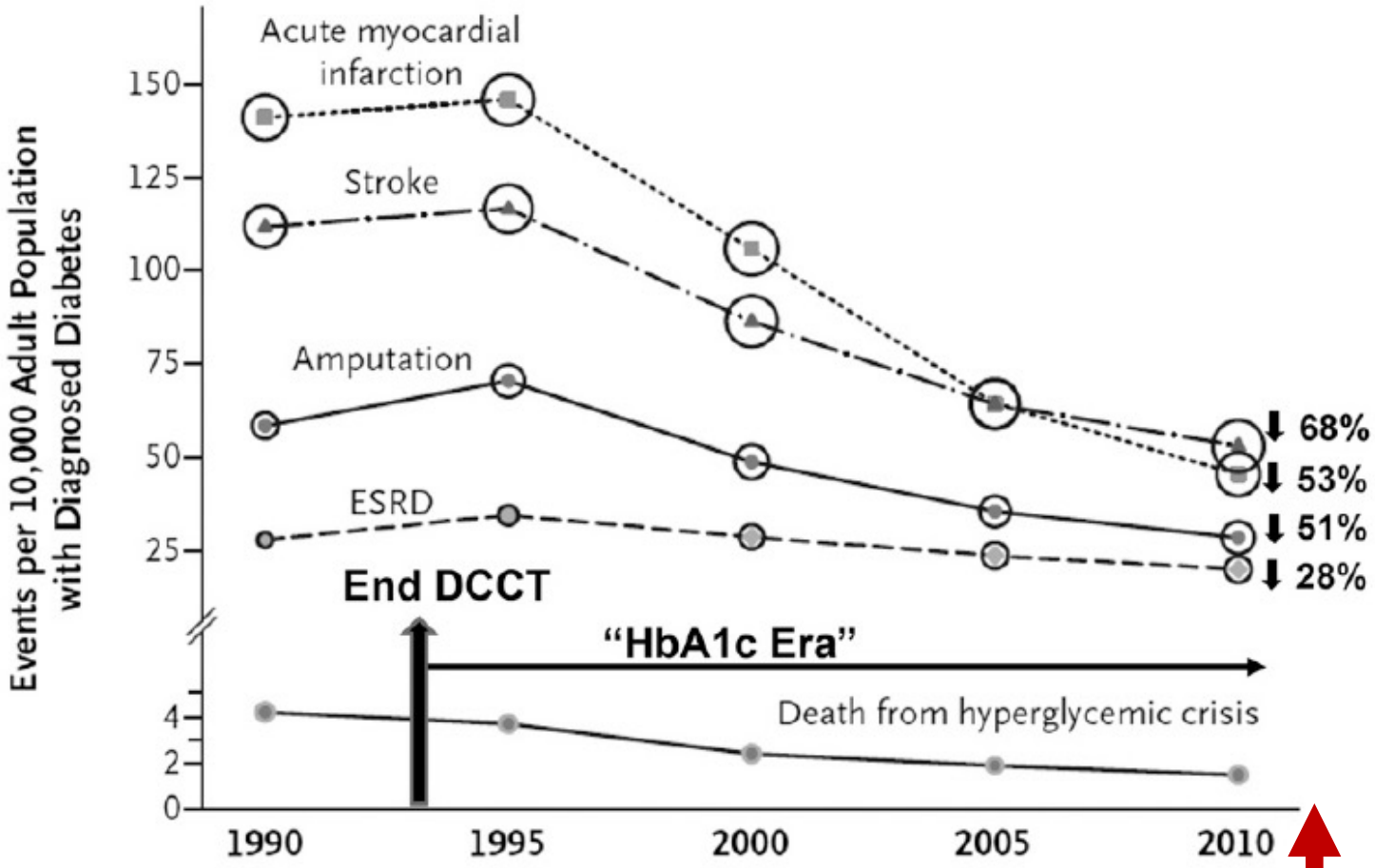


Extreme frequent glucose peaks

GlycoMark Value 15.1 µg/mL | **A1C 7.4%** | **William**



High baseline glucose overall



GlycoMark Era?

Glycemic Variability

- Increased oxidative stress
- Increases oxidative stress in adipocytes leading to less adiponectin and more resistin (highly pro-inflammatory)
- Hypoglycemic tendencies
  - Inflammation
- Decreased brown adipocyte thermogenesis
- Association between obesity and glycemic variability
- Decreased HRV (women)
- Micro- and macrovascular complications
- Mood, depression, and poor quality of life

ORIGINAL ARTICLE

Oscillating Glucose Is More Deleterious to Endothelial Function and Oxidative Stress Than Mean Glucose in Normal and Type 2 Diabetic Patients

Antonio Ceriello,[1] Katherine Esposito,[2] Ludovica Piconi,[3] Michael A. Ihnat,[4] Jessica E. Thorpe,[4] Roberto Testa,[5] Massimo Boemi,[5] and Dario Giugliano[2]

OBJECTIVE—To explore the possibility that oscillating glucose may outweigh A1C levels in determining the risk for cardiovascular diabetes complications.

RESEARCH DESIGN AND METHODS—A euinsulinemic hyperglycemic clamp at 5, 10, and 15 mmol/l glucose was given in increasing steps as a single "spike" or oscillating between basal and high levels over 24 h in normal subjects and type 2 diabetic patients. Flow-mediated dilatation, a marker of endothelial function, and plasma 3-nitrotyrosine and 24-h urinary excretion rates of free 8-iso PGF2α, two markers of oxidative stress, were measured over 48 h postclamp.

In this study, we have been able to show that oscillating glucose, over a period of 24 h, is more damaging to endothelial function than stable constant high glucose. This is true not only when a subject is exposed to the same total amount of glucose for 24 h (i.e., 10 mmol/l clamp) but even when the total amount is higher (i.e., 15 mmol/l clamp). Finally, data suggest that oxidative stress plays a key role in all of these phenomena.

value alone. It is therefore unknown whether two individuals with the same mean blood glucose but extremes of glucose variability might have the same or different level of risk for complications.

In a 1995 report of the Diabetes Control and Complications Trial, the risk of retinopathy progression associated with a given level of mean A1C differed significantly between intensively and conventionally treated patients (4). It was suggested that this may be a consequence of larger glycemic excursions in the conventional group (4). However, with regard to cardiovascular complications, it has been reported that fasting plasma glucose instability is

A strong relationship between the mean levels of glycemia, measured as A1C, and diabetes complications (1–2), including cardiovascular complications (3), has been demonstrated. However, what is still unclear is whether glycemic instability may confer additional risk to the development of complications over that predicted by the mean glucose

From the [1]Centre of Excellence in Diabetes and Endocrinology, University Hospital of Coventry and Warwickshire, Warwick Medical School, University of Warwick, Coventry, U.K.; the [2]Division of Metabolic Diseases, Center of Excellence for Cardiovascular Diseases, 2nd University of Naples SUN, Naples, Italy; the [3]Morpurgo-Hofman Research Laboratory on Aging, Udine, Italy; the [4]Department of Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; and the [5]Diabetology Unit, INRCA, Ancona, Italy.

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FMD, flow-mediated dilatation; PGF2α, prostaglandin F2α.

RESEARCH DESIGN AND METHODS

Twenty-seven type 2 diabetic patients and 22 healthy subjects were recruited (Table 1). The diabetic patients had newly diagnosed (within 6 months) type 2 diabetes, were on diet alone, and had no evidence of any cardiovascular complications. The protocol of the study was approved by the ethics committee of our institution. All subjects gave informed consent before being tested. The subjects of this study underwent periods of hyperglycemia and periods of normoglycemia. Below, the techniques used to attain these conditions are described.

To maintain euinsulinemia, endogenous insulin secretion was inhibited during all the experiments using somatostatin (Sandostatin; Novartis Pharma, Basel, Switzerland) (10). Somatostatin was infused in two phases: *1*) as a bolus dose of 25 μg over 1 min given 5 min before the start of the experiment and *2*) as a continuous maintenance dose of 1.0 μg/min (10). The hyperglycemic-euinsulinemic clamp metholody was a modification of the method used by Del Prato et al. (10).

Normalization of glycemia. Insulin and/or 5% glucose to keep blood glucose levels between 4 and 6 mmol/l were started (11). Blood glucose levels were determined every 5 min with adjustment of the intravenous insulin infusion until steady-state glucose levels were between 4 and 6 mmol/l. At the steady state, venous glucose samples were drawn every 30 min.

Control study with somatostastin. Five normal subjects and five diabetic patients underwent a control study with 3 h somatostatin infusion alone, and endothelial function and nitrotyrosine plasma levels were evaluated. No change in these parameters was found.

Protocols. Two different clamp protocols were planned, and the diabetic patients and the normal subjects participating in each protocol were matched for age, sex, and BMI and for fasting glycemia and A1C in the case of diabetes.

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Serum 1,5-anhydro-D-glucitol levels predict first-ever cardiovascular disease: An 11-year population-based Cohort study in Japan, the Suita study

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ABSTRACT

Objective: Serum 1,5-anhydro-D-glucitol (1,5-AG) is well-known to be a useful clinical marker of both short-term glycemic status and postprandial hyperglycemia. In addition, previous epidemiological studies have shown that an increased postload glucose level in an oral glucose tolerance test is a risk factor

Our results suggest that measurement of serum 1,5-AG levels is useful to detect individuals, especially men, at higher risk for CVD, regardless of the presence or absence of diabetes.

The HR in the category with serum 1,5-AG levels of 14.0 µg/mL or less was 2.22 compared to the reference category (24.5 µg/mL or greater). Similar results were also shown with a sensitivity analysis in non-diabetic men. Conversely, no significant relationship between serum 1,5-AG levels and CVD risks was observed in women.

also reported that acarbose, an α-glycosidase inhibitor that suppresses the elevation of postprandial glucose levels, reduced the incidence of CVD as well as type 2 diabetes [6]. These findings suggest that detection and improvement of postprandial hyperglycemia is important for CVD prevention.

An OGTT is useful for the detection of postprandial hyperglycemia, however, it requires overnight fasting, long time,

2. Methods

2.1. Study design and samples

The details of the Suita study have been described elsewhere [7–9]. Briefly, the Suita study is a prospective population-based cohort study of an urban area in Japan. In 1989, 6485 Suita city residents (age, 30–79 years) were randomly sampled and enrolled as study participants. They underwent medical examinations every 2 years. Among these participants, 2406 participants underwent medical examinations between April 1994 and February 1995, and their serum samples were collected and stored at −80 °C. In this

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EXPERT REVIEWS

1,5-anhydroglucitol (GlycoMark™) as a marker of short-term glycemic control and glycemic excursions

Table 1. Comparison of glycemic markers.

Parameter	Hemoglobin A1C	Fructosamine	1,5-anhydroglucitol
Time required for significant change	1–3 months	1–2 weeks	1–3 days
Reflection of mean glucose	++	++	+
Reflection of glucose excursions/postprandial glucose	+	+	++
Association with complications	++	NA	NA
Variance	Small	Small	Large
Greatest degree of change is found during	Moderate-to-severe hyperglycemia	Moderate-to-severe hyperglycemia	Mild-to-moderate hyperglycemia

fewer than 30% were able to maintain that target over time [4]. In routine clinical practice, glycemic control may be even more difficult to achieve, and despite recent advances in therapy, only 50% of patients with diabetes reach recommended A1C targets [5]. Further complicating the matter are the more recent calls that advocate for normoglycemia (A1C <6.0%) where it can be done safely [3]. Quality improvement initiatives may benefit patients with the worst glycemic control [6], but patients with more modest control (A1C >8%) pose a tremendous challenge to clinicians [7].

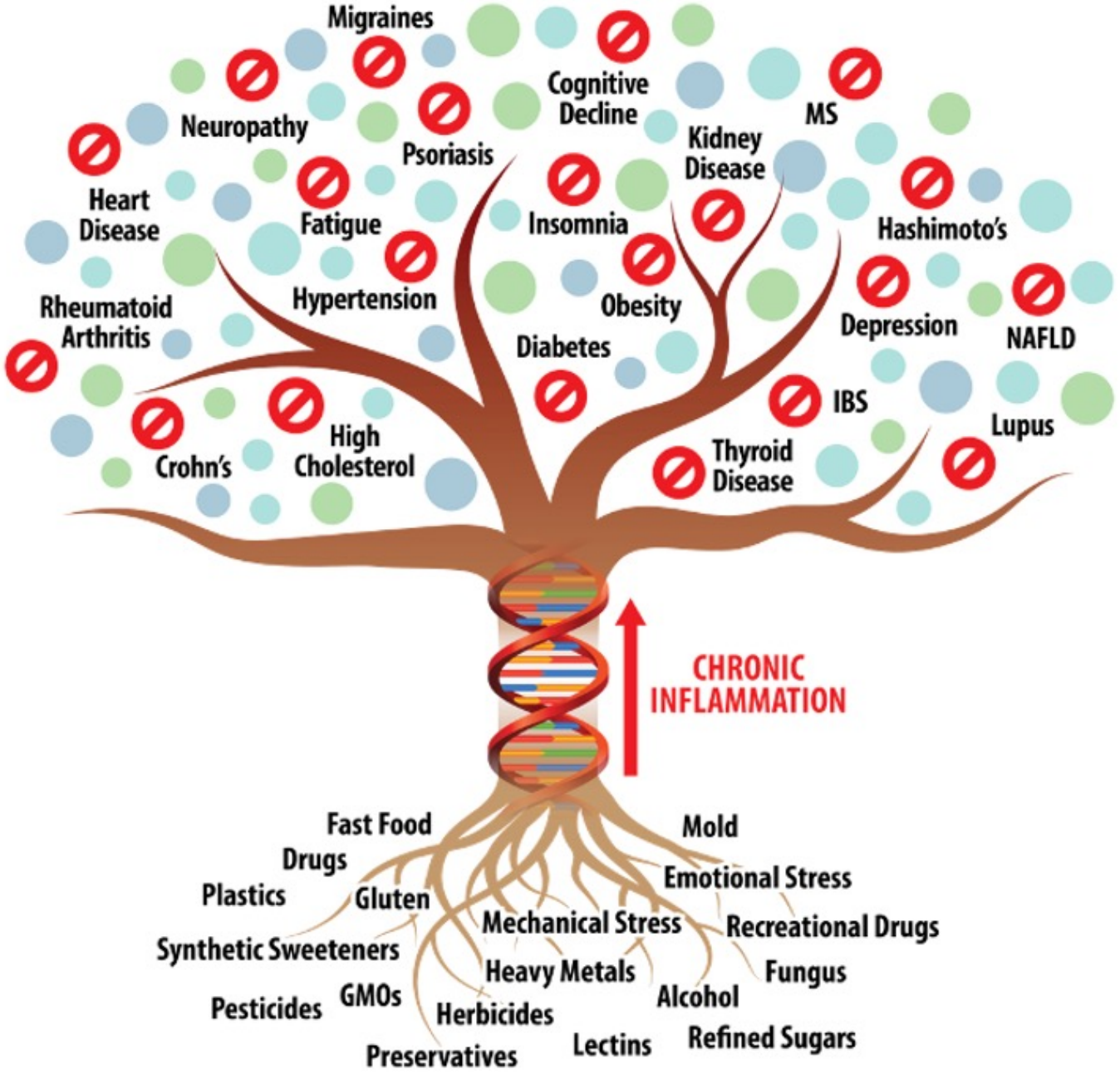
Glycemic monitoring is of paramount importance for adjusting various treatment modalities. Conventional methods of assessing glycemic mortality than fasting glucose measurements [9,10]. Therefore, quantification of glycemic fluctuations (e.g., glycemic variability, PPG or glucose excursions) might predict macrovascular disease better than mean glucose. *In vitro* data suggest that intermittent glycemic excursions may be more harmful to endothelial cells than chronic hyperglycemia, as the latter may induce relative conditioning of cellular inflammatory responses [11–13]. Oxidative stress, an important mediator of hyperglycemia-mediated cellular damage, is also associated with glycemic variability in patients with diabetes, independent of mean glucose [14]. A prospective randomized controlled study demonstrated that repaglinide,

Glycomark

- Hyperglycemia and glycemic variability have been linked to diabetes-related health complications including:
- vascular damage (reduced flow-mediated dilation and coronary lumen diameter; increased carotid artery stiffness and carotid intima-media thickness)
- oxidative stress (plasma 3-nitrotyrosine and 24-h urinary excretion rates of free 8-iso PGF2)
- increased inflammatory markers (C-Reactive Protein, Interleukin 6)
- poor cardiovascular outcomes (repeat MI, acute heart failure)
- stroke
- dementia
- increased risk of death from cardiovascular causes

Glycomark

- 1,5-anhydroglucitol in the blood and yielding a precise one- to two-week profile of average daily maximum blood glucose, thus:
- identify patients with A1Cs at 8% or less who have had more frequent and extreme hyperglycemic excursions in the past one to two weeks
- recognize recent glycemic deterioration before changes are visible with A1C
- record improvements in therapy changes within two to four weeks
- measure and positively reinforce adherence to dietary and lifestyle changes


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Preservatives
Lectins
Refined Sugars

The Wedge Protocol