GLUKOMETRELERİN ULUSAL STANDARDİZASYONU

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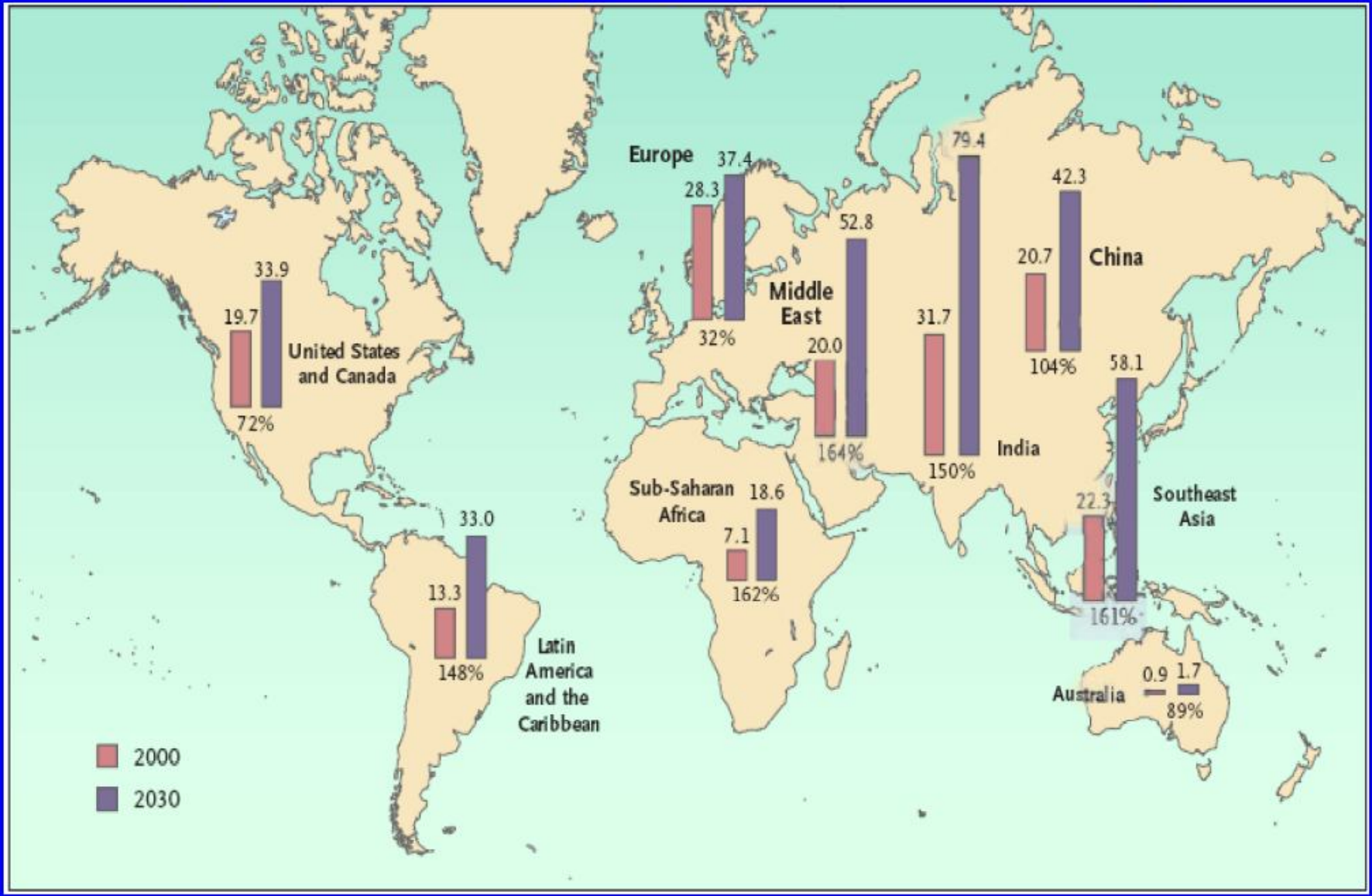
Millions of Cases of Diabetes (in 2000 and projections for 2030)



NEJM 2007; 356:213

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  - 1. Glukometrelerin tarihçesi
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  - 4. CLSI
  - 5. Ülkemizdeki çalışmalar
  - 6. Öneriler

GLUKOMETRELERİN TARİHÇESİ

A 'bright' start: the first blood glucose meters:1970–1980

Boehringer Mannheim introduced the Reflomat in 1974 and the Reflolux in 1984.

Meeting the challenge: 1981–1990

-enzim elektrod stripler

- daha az kan hacmi, daha küçük strip ve cihaz

- 1987: İlk glukoz biyosensor sistemi Medisense tarafından piyasaya sunuldu

Emergence of smaller meters: 1991–2000

Table 2. Summary of developments in the evolution of blood glucose systems for self-monitoring.

Year	Development	Example	Company
1957	First reagent strip using glucose oxidase reaction	Clinistix	Ames
1964	Modified reagent strip for blood glucose	Dextrostix	Ames
1970	Reflectance photometry with Dextrostix	Ames Reflectance Meter	Ames
1973	Mains-powered, single analogue scale	Eyetone	Ames
1974	Reduced blood volume, strip wiping	Reflomat	Boehringer Mannheim
1980	Digital display, whole blood standard	Dextrometer	Ames
1980	Automatic timing	Glucochek/Glucoscan	Lifescan
1981	Improved countdown timer with audio alarm	Glucometer I	Ames
1981	Stored calibration, low/high result alarms	Glucometer I	Ames
1986	Data storage of results	Glucometer M	Ames
1987	Non-wipe, automatic timing, 45-second measurement time test strip	OneTouch	Lifescan
1987	First biosensor enzyme electrode sensors	Exactech	Medisense
1991	Capillary-fill sampling with 5 µL blood	HemoCue	
1997	Downloading results to personal computers	Glucometer Esprit	Bayer
2001	Plasma calibration	OneTouch Ultra	Johnson & Johnson
2002	Catering for visually impaired persons	AccuChek Voicemate	Roche
2003	Biosensor using coulometry, alternative site testing	Freestyle Freedom	Abbott
2003	Autodisc of 10 strips replaced reagent strips	Ascensia Breeze	Bayer
2005	17-test strip barrel	AccuCheck Compact	Roche
2008	Talking blood glucose meter	SensoCard Plus	BBI

2007 reduce interference by Htc and nongluc. Reactive subst. Statstri NovaBiomedical

Lab on a chip:

- managing operator certification and device lockout
- reporting on operator performance
- reporting on both liquid and equivalent quality control
- reporting on reagent usage
- laboratory Information System interfacing

KAN ŞEKERİNİZİ İPHONE İLE TEST EDİN

NewsFlash: FDA Approves the iBGStar Meter for iPhone/iPod Touch!

By AmyT on December 7, 2011

It is quite possibly a new era in blood glucose monitoring! This morning, the FDA approved Sanofi-Aventis' groundbreaking iBGStar product, the first and only BG meter that connects directly to your Apple iPhone or iPod touch. No cables are necessary, as this little meter sports an Apple-compatible plug built right in!

MEDGADGET EXCLUSIVE / MEDICINE / PEDIATRICS

Non-Invasive Measurement of Blood Glucose Levels Using GlucoTrack: Interview with CEO Avner Gal

by GAURAV KRISHNAMURTHY on Oct 15, 2013 • 12:30 pm

Integrity Applications, an Israeli company, has developed a non-invasive method to measure glucose levels in the blood and received the European CE Mark for it. The device is yet to make it to market, but we had the opportunity to speak with Avner Gal, CEO of Integrity Applications, regarding their latest technology and what makes their product unique.

Gaurav Krishnamurthy, *Medgadget*: What does Integrity Applications do/what is your ma offering?

Avner Gal: Integrity Applications has developed the GlucoTrack non-invasive glucose monitoring device. People with diabetes have to keep close tabs on their blood sugar (i.e., glucose) levels, monitoring it several times a day. GlucoTrack is designed to help people with diabetes obtain these blood glucose level measurements without the pain,

- It uses three independent technologies: **ultrasonic, electromagnetic and thermal**, to painlessly obtain blood glucose levels.
- Additionally, the results can be downloaded from the device via USB cable for future reference and further analysis

GLUKOMETRE CİHAZLARININ ÖLÇÜM TEKNOLOJİLERİ

1. REFLEKTANS FOTOMETRİ

- Daha eski bir teknoloji
- Numunedeki glukoz konsantrasyonuyla orantılı olarak renk değişimi
- Stripe kan damlatıldığı zaman plazma fraksiyonu reaktifin olduğu tabakaya yürür
- Plazma fraksiyonundaki glukoz enzimle reaksiyona girer, reaksiyon alanındaki indikatör boya foto diodlarla ölçülebilen bir renk değişimine yol açar

$$\beta\text{-D-glucose} + H_2O + O_2 \xrightarrow{\textit{glucose oxidase}} \text{D-gluconic acid} + H_2O_2$$

$$H_2O_2 \longrightarrow 2H^+ + O_2 + 2e^-$$

2. ELEKTROKİMYASAL (BİOSENSOR) TEKNOLOJİSİ

GLUKOMETRE CİHAZLARININ ÖLÇÜM TEKNOLOJİLERİ

1. **REFLEKTANS FOTOMETRİ**

2. **ELEKTROKİMYASAL (BİOSENSOR) TEKNOLOJİSİ**

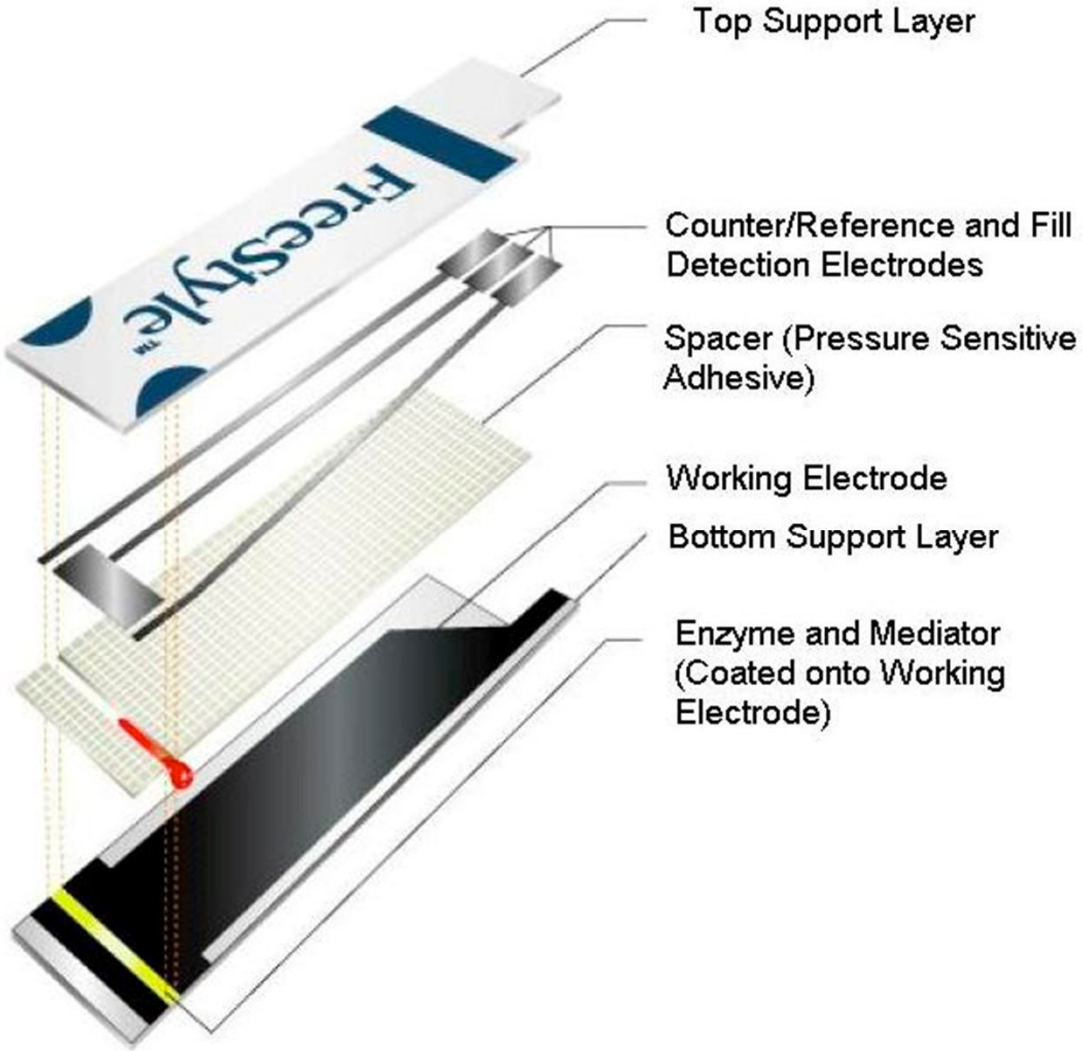
- Test bölgesindeki elektrodlarda glukoz, enzim ve spesifik bir mediatör arasında iyon değişimleriyle açığa çıkan elektriksel yük elektrokimyasal reaksiyonlarla ölçülür
- Amperometrik veya koulometrik ölçüm prensibi
- Açığa çıkan yük glukoz konsantrasyonuyla orantılıdır
- Bisensor teknolojisinde askorbik asit, paracetamol (acetaminophen) gibi elektro-aktif maddeler interferans verebilir
- Isı değişikliklerine duyarlı

Test Stripleri

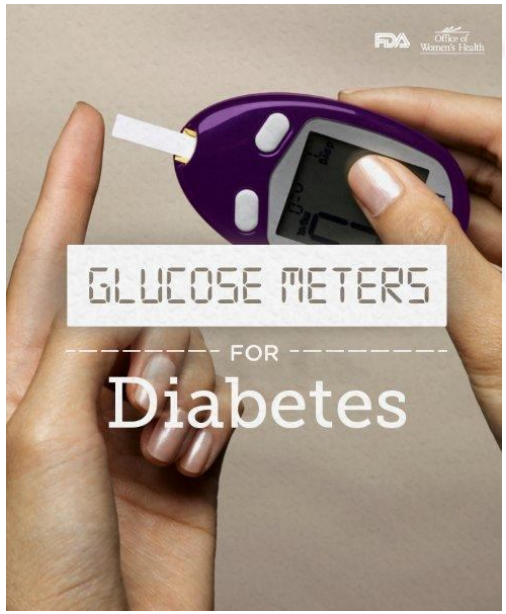
- Kan eklendiği zaman glukoz çalışma elektrodundaki enzim tarafından okside olur

- Çalışma ve referans elektrod arasında voltaj uygulanır

- Çalışma ve referans elektrod arasındaki akım ölçülür



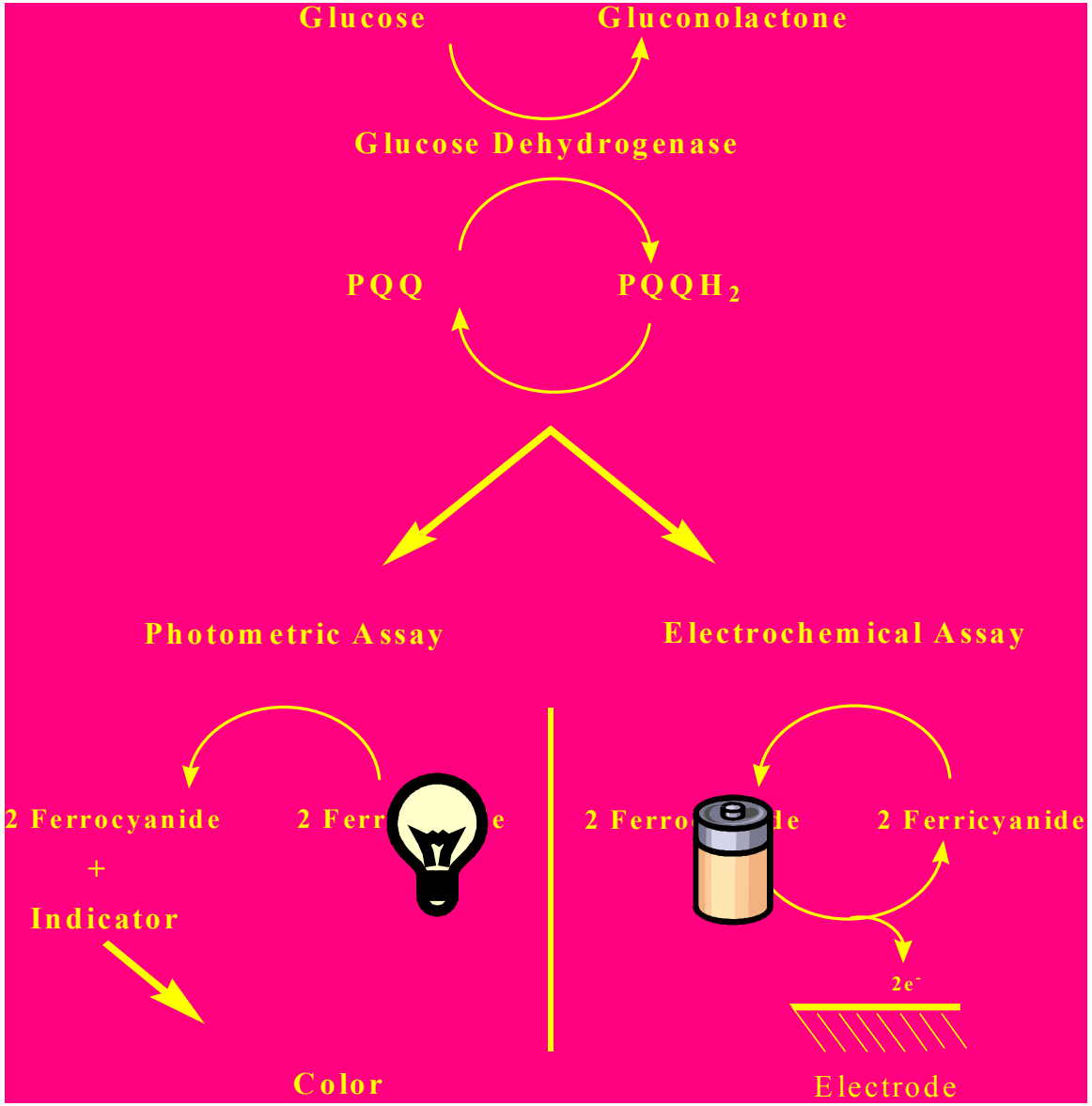
STRİPLERDE KULLANILAN ENZİMLER



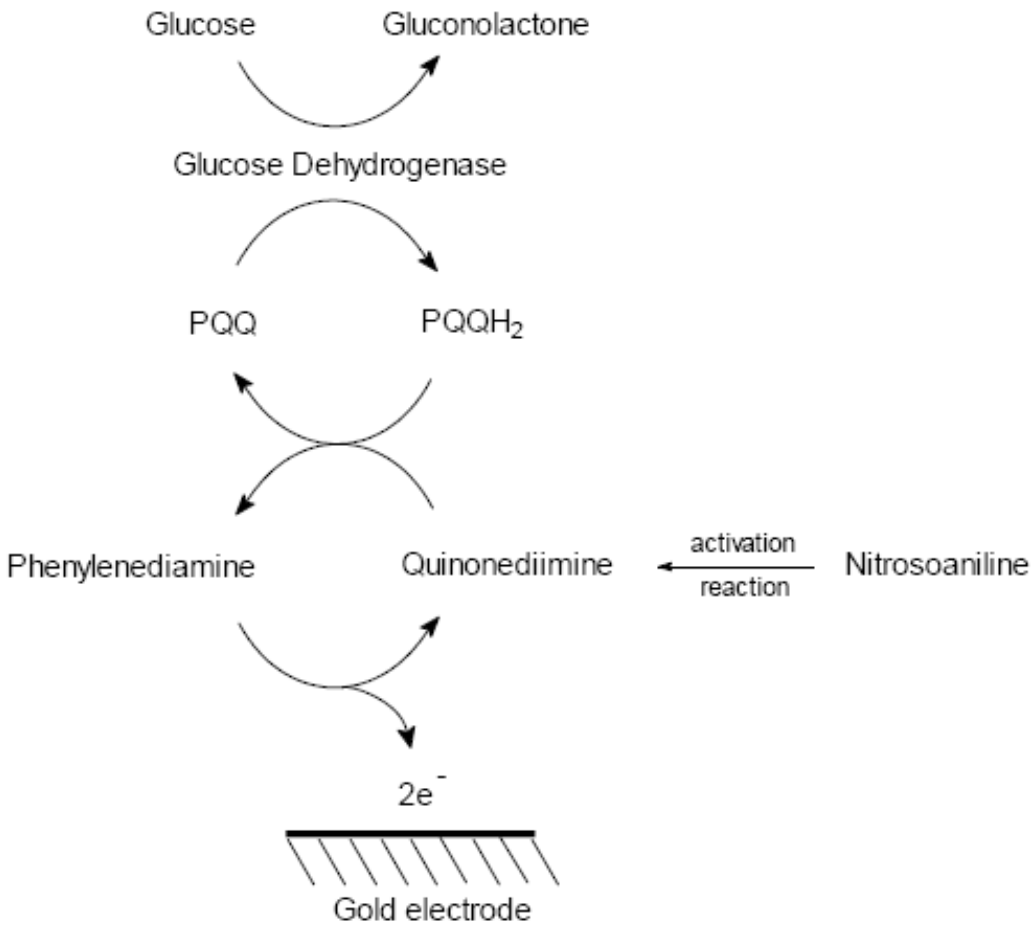
- Glukoz oksidaz
- Glukoz dye oksidoreduktaz
- Glukoz dehidrogenaz (kofaktör: NAD)
- Glukoz dehidrogenaz (kofaktör : FAD)
- Glukoz dehidrogenaz PQQ
- Mutant Glukoz dehidrogenaz PQQ

Mut Q-GDH = glucose dehydrogenase with pyrrolo quinoline quinone modified to eliminate maltose interference

GDH-PQQ ÖLÇÜM PRENSİBİ



Glukoz Dehidrogenaz- PQQ Prensibi



The PQQ-dependent enzyme, glucose dioxidoreductase (EC 1.1.99.17), oxidizes D-glucose to gluconolactone. The coenzyme PQQ (pyrroloquinoline) is reduced to $PQQH_2$.

After the activation of nitrosoaniline to form quinonediimine, the reduced coenzyme reduces quinonediimine to phenylenediamine.

When voltage is applied, phenylenediamine is reoxidized to quinonediimine, producing two electrons. Thus, the number of electrons produced is twice the glucose concentration of the sample and is measured by the ACCU-CHEK Aviva meter.

POTANSİYEL HATA KAYNAKLARI

Table 1. Summary of potential sources of variation and error.

Source of error	Blood glucose result error
Pre-analytical	
Incomplete deposition of reagents on test strip	↓ ↑
Test, calibration, control strip surface damaged	↓ ↑
Test strip exposure to high temperature during storage	↑
Test strip is date expired	↓ ↑*
Testing at high altitude	↑ – glucose oxidase
Operator	
Diet or medication containing excessive galactose	↑ – GDH-PQQ
Diet or medication containing, maltose or xylose	↑ – GDH-PQQ
Diet containing excessive ascorbic acid (vitamin C)	↓ or ↑ – GDH biosensor only
Acetaminophen (paracetamol)	↓ – glucose oxidase biosensor
L-Dopa	↓ or ↑ – glucose oxidase biosensor
High haematocrit	↓
Low haematocrit	↑
High blood triglycerides	↓ – Glucose oxidase
Low blood oxygen	↑ – Glucose oxidase
High blood uric acid	↓ – Glucose oxidase
Analytical errors	
Miscoding test, calibration, control strip to meter	↑ or ↓
Contamination to sampling site (e.g., with fruit juice)	↑
Insufficient blood applied to test zone	↓
Reagent strip not fully inserted into meter	↓
Overloaded test strip	↑
Post-analytical	
Misreading of result display	↑ or ↓

GDH: glucose dehydrogenase, PQQ: pyrroloquinoline quinone. *Varies according to blood glucose monitoring system.

Interference between Extraneal Peritoneal Dialysis Solution and Advantage II Blood Glucose test strips for Accu-Chek and Accu-Trend blood glucose monitors

Top of page

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Problem

The TGA has received a small number of adverse event reports, including one death, associated with the use of certain types of blood glucose test strips by patients who are also on peritoneal dialysis.

In the case of the reported death, the peritoneal dialysis fluid being used was Extraneal or Icodextrin, manufactured by Baxter Healthcare. The patient and the hospital appear to have been using an Accu-Chek blood glucose monitor with Advantage II test strips, manufactured by Roche to monitor blood glucose levels. The patient died of undetected severe hypoglycaemia.

Extraneal contains maltose which interferes with the blood glucose readings obtained when using Accu-Chek and Accu-Trend blood glucose monitors with Advantage II Blood Glucose test strips. The blood glucose readings in these cases are falsely high, causing the patient to overdose on insulin, leading to serious consequences.

The use of Advantage II test strips for patients on Extraneal is contraindicated by both Baxter and Roche. Maltose in the Extraneal reacts with the glucose dehydrogenase on the test strips and gives a false high level of blood glucose. The patient then gives themselves another injection of insulin or a higher dose of insulin. The patient is then hypoglycaemic and they can swiftly fall into a coma. The physician who reported the problem indicated that he knew that this false positive reaction does exist in the literature but is not commonly known by physicians.

The TGA investigated a similar (non-fatal) event in 2003 which led to both Baxter and Roche issuing Safety Alerts to all diabetes educators. Contraindications about the use of the two products in combination appear in the instructions for use of both Extraneal and the Advantage II test strips.

Recommendation

If a patient is prescribed Extraneal check if they are a diabetic and if so, what blood glucose monitor and test strips they are using. If there are doubts about the information received, contact a diabetic educator and the manufacturer(s) of the monitor and test strips to make sure that they are not using a glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) method for testing.

To ensure that this does not occur, the test method chosen (for both monitor and test strips) must use a glucose-specific enzyme such as glucose oxidase or hexokinase. GDH-PQQ BASED METHODS MUST NOT BE USED.

Table 1. Blood Glucose Monitoring Systems

The following Blood Glucose Monitoring Systems should NOT be used in patients receiving products containing icodextrin, maltose, galactose or xylose.

Manufacturer and Glucometer	Test Strips	Enzyme Utilized in Test Strips
Abbott Diabetes Care, Inc. (Alameda, CA)		
FreeStyle blood glucose monitoring system	FreeStyle test Strips	Glucose dehydrogenase-PQQ
FreeStyle Flash® blood glucose monitoring system	FreeStyle test Strips	Glucose dehydrogenase-PQQ
FreeStyle Freedom blood glucose monitoring system	FreeStyle test Strips	Glucose dehydrogenase-PQQ
FreeStyle Freedom Lite blood glucose monitoring system	FreeStyle Lite test strips	Glucose dehydrogenase-PQQ
FreeStyle Lite blood glucose monitoring system	FreeStyle Lite test Strips	Glucose dehydrogenase-PQQ
Bayer HealthCare Diabetes Care (Tarrytown, NY)		
Ascensia CONTOUR blood glucose monitoring system[a]	Ascensia CONTOUR test strips	Glucose dehydrogenase-PQQ
Roche Diagnostics (Basel, Switzerland)		
Accu-Chek Active meter	Accu-Chek Active test strips	Glucose dehydrogenase-PQQ
Accu-Chek Advantage meter	Accu-Chek Comfort Curve test strips	Glucose dehydrogenase-PQQ
Accu-Chek Aviva system	Accu-Chek Aviva test strips	Glucose dehydrogenase-PQQ
Accu-Chek Complete meter	Accu-Chek Comfort Curve test strips	Glucose dehydrogenase-PQQ
Accu-Chek Inform system	Accu-Chek Comfort Curve test strips	Glucose dehydrogenase-PQQ
Accu-Chek Performa system	Accu-Chek Performa test strips	Glucose dehydrogenase-PQQ
Accu-Chek Voicemate meter	Accu-Chek Comfort Curve test strips	Glucose dehydrogenase-PQQ
Accu-Chek Compact meter	Accu-Chek Compact test strips (drum)	Glucose-dye-oxidoreductase
Accu-Chek Compact Plus system	Accu-Chek Compact test strips (drum)	Glucose-dye-oxidoreductase
Accu-Chek Go system	Accu-Chek Go test strips	Glucose-dye-oxidoreductase
Accu-Chek Integra system	Accu-Chek Integra test strips	Glucose-dye-oxidoreductase

Hematokritin Etkisi

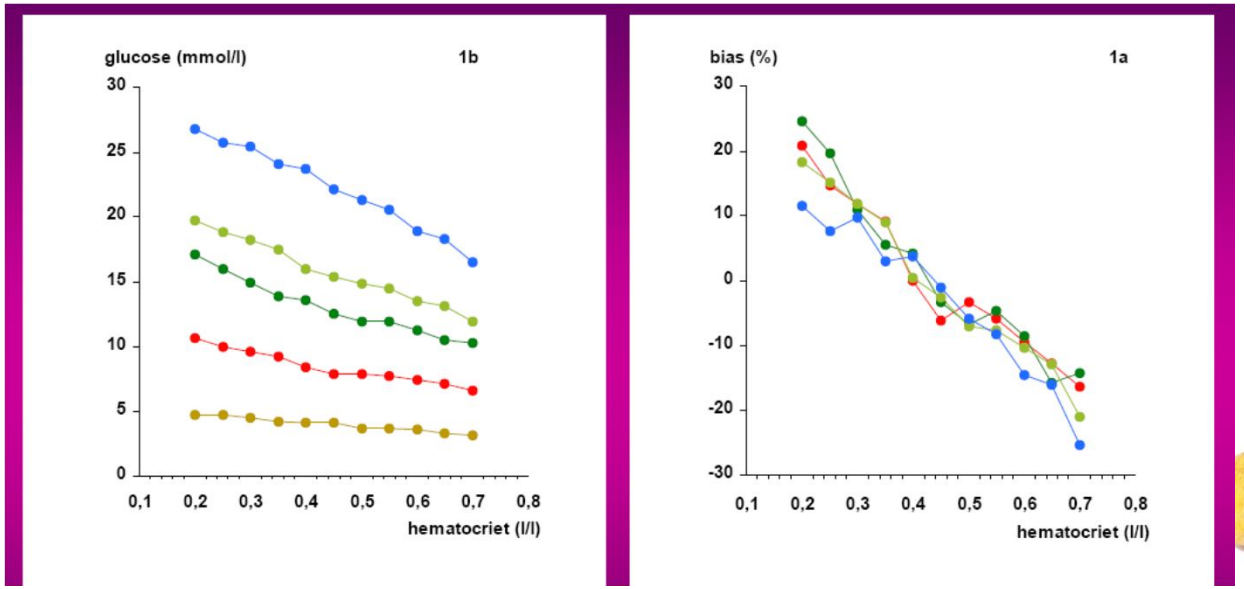
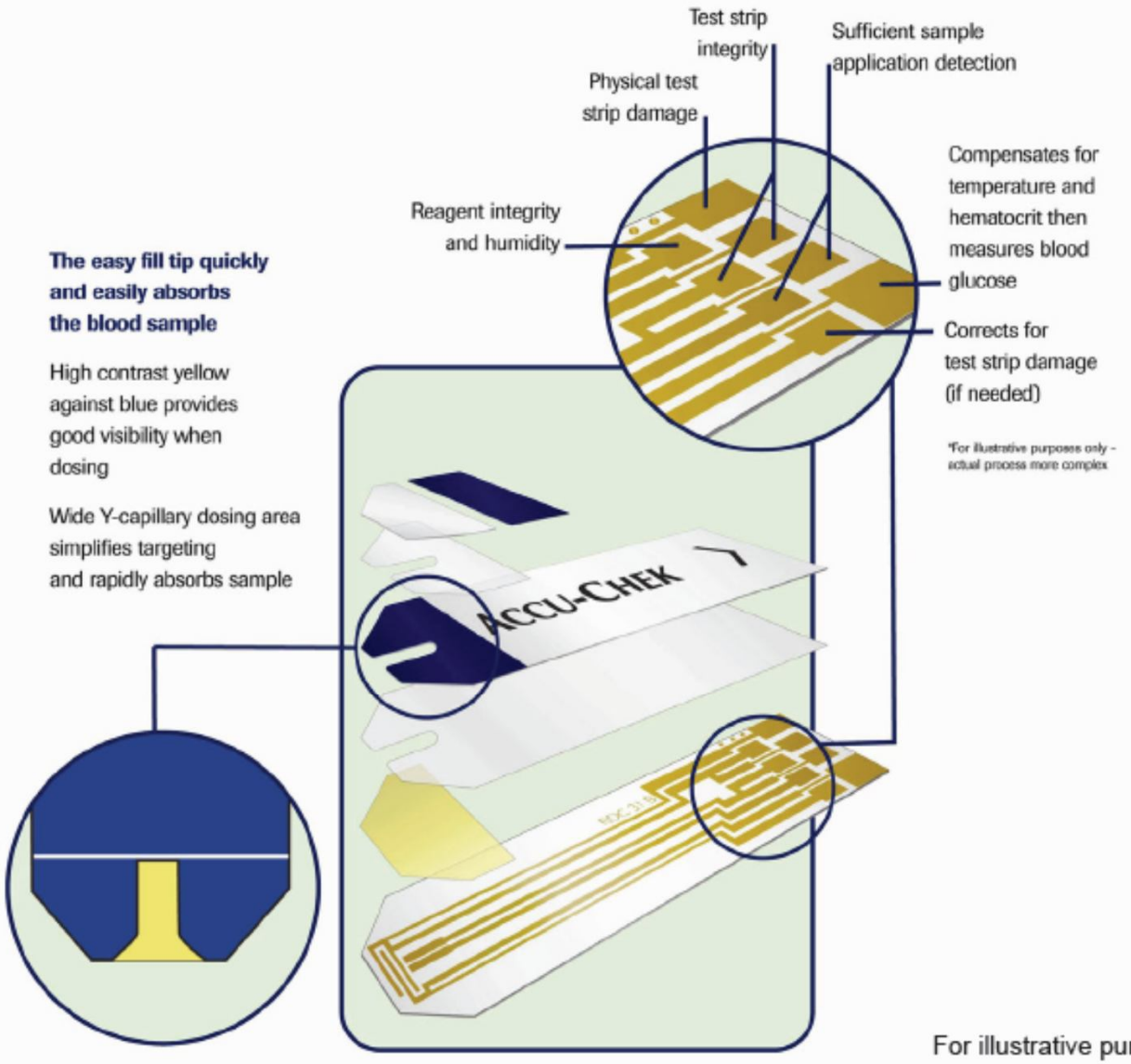
- **Artmış hematokrit düzeyleri glukoz ölçümünü azaltırken, azalmış hematokrit düzeyleri glukozun yüksek okunmasına neden olur**
- Kapiller kanda artmış RBC **mekanik** etkiyle plazmanın reaktif tabakalarına geçişini engeller.
- Ayrıca Htc kanın yüzey gerilimini ve viskositesini değiştirerek reaktif tabakasına sıvı geçirgenliğini de azaltır
- Yeni cihazların bazılarında Htc düzeylerini ölçerek, otomatik düzeltme fonksiyonu bulunmaktadır
- 

Figure 2.

8 laser engraved gold contacts enable the meter to quality check for*:



The easy fill tip quickly and easily absorbs the blood sample

High contrast yellow against blue provides good visibility when dosing

Wide Y-capillary dosing area simplifies targeting and rapidly absorbs sample

*For illustrative purposes only - actual process more complex

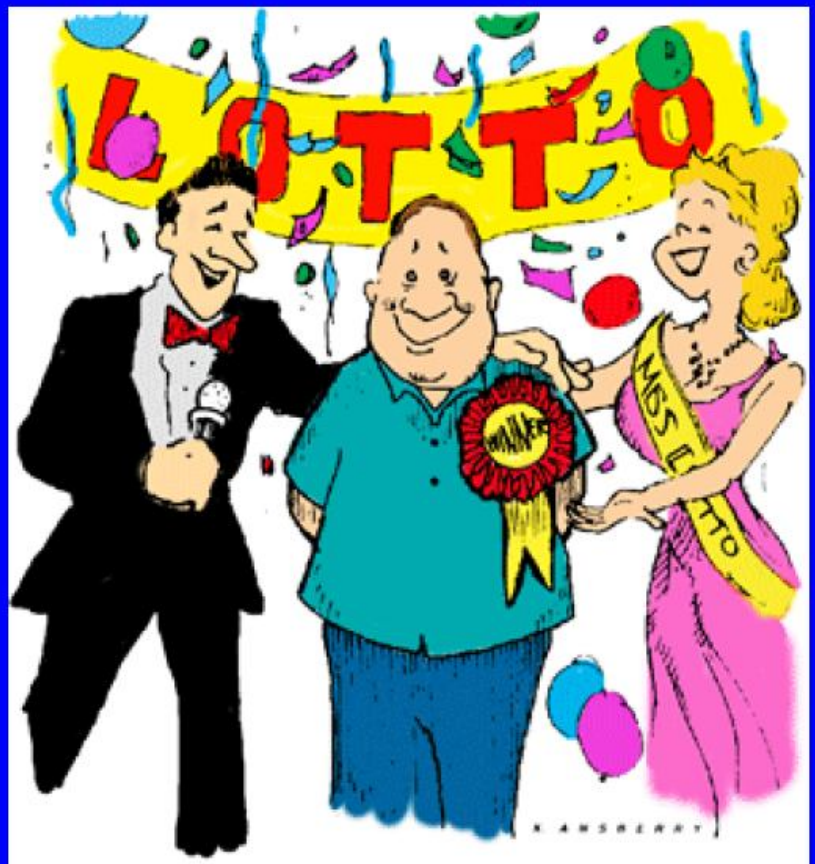
For illustrative purp

Contra-indications/interferences

The instructions for use for all glucose meters/strips detail a number of situations/conditions where the test result may be affected and when the meter/strips should not be used. Staff must be aware of the need to perform a laboratory measurement of glucose using a venous sample in cases where contra-indications are observed or suspected and when abnormal or unexpected results are obtained.

Contra-indications	Examples
Dialysis treatments	CAPD fluids may contain maltose which can interfere with some test strip methodology
Peripheral circulatory failure	Severe dehydration, hyperglycaemic-hyperosmolar state with or without ketosis. Hypotension, shock, peripheral vascular disease
Severe dehydration	Vomiting or diarrhoea, prescription drugs (diuretics), sustained uncontrolled diabetes
Variations in blood oxygen tension	Patients receiving intensive oxygen therapy
High concentrations of non-glucose reducing substances in the blood	Intravenous infusion of ascorbic acid
High bilirubin values	Jaundice
Extremes of haematocrit	Neonatal blood samples, pregnancy
Hyperlipidaemia	Total parenteral nutrition, hyperlipidaemia

Glukometrelerin Doğruluk Değerlendirmeleri



"...and our lucky super lotto winner has just told us his winning five numbers '75-83-89-80-90' were the results of his last five blood glucose tests..."

International Organization for Standardization

- ISO 15197 :2003

- **ISO 15197 :2013**

In vitro **diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus**

ISO 15197

- Uzman olmayan kişiler (laypersons) tarafından kullanılan kan glukozu izleme sistemleri için geliştirilmiştir

- *Performans kriterleri*: **aküresi**-doğruluğa (presizyon-kesinlik ve trueness-gerçeklik) dayanarak belirlenmiştir

- *Kapsamı:* Bu uluslararası standart, bu tür sistemlerin üreticileri ve sistemlerin performansını değerlendiren diğer kuruluşlar (örn. ruhsatlandırma yetkilileri ve uygunluğu değerlendiren kuruluşlar) için geçerlidir.

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DRAFT 2011

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#

7. Kesinlik (precision) değerlendirmesi

7.2.2 Tekrarlanabilirlik(Repeatibility) çalışması

10 cihaz, Her bir cihazla 5 farklı konsantrasyondaki kan örneklerinde 10'ar ölçüm yapılır

Bu sırada başlangıç ve bitiş ölçümleri arasındaki fark >100 mg/dL'de <%4; <100 mg/dL'de <4 mg/dL olmalıdır (referans yöntemle çift çalışma)

Her düzey ve her bir cihaz için ortalama ve standart sapma, %CV hesaplanır

Table 1 — Glucose concentration intervals for measurement repeatability evaluation

Interval	Glucose concentration mmol/L (mg/dL)
1	1,7 to 2,8 (30 to 50)
2	2,9 to 6,1 (51 to 110)
3	6,2 to 8,3 (111 to 150)
4	8,4 to 13,9 (151 to 250)
5	14,0 to 22,2 (251 to 400)

7. Kesinlik değerlendirmesi

7.2.3. Ara Kesinlik (Intermediate Precision)

- 10 gün boyunca 10 cihazın her birine 3 seviye kontrol solusyonu okutulur

Table 2 — Glucose concentration intervals for intermediate measurement precision evaluation

Interval	Glucose concentration mmol/L (mg/dL)
1	1,7 to 2.8 (30 to 50)
2	5,3 to 8.0 (96 to 144)
3	15.5 to 23.3 (280 to 420)

7.3. Sistem Doğruluğu: Yöntem Karşılaştırma

10 cihaz, 10 gün boyunca, min 100 hasta

Table 3 — Glucose concentrations of samples for system accuracy evaluation

Bin #	Percentage of samples %	Glucose concentration mmol/L (mg/dL)
1	5	≤ 2,77 (≤ 50)
2	15	> 2,77 – 4,44 (> 50 – 80)
3	20	> 4,44 – 6,66 (> 80 – 120)
4	30	> 6,66 – 11,10 (> 120 – 200)
5	15	> 11,10 – 16,65 (> 200 – 300)
6	10	> 16,65 – 22,20 (> 300 – 400)
7	5	> 22,20 (> 400)

7.3. Sistem Doğruluğu: Yöntem Karşılaştırma

- ISO 15197-2013

Table 3 — Glucose concentrations of samples for system accuracy evaluation

Bin #	Percentage of samples %	Glucose concentration mmol/L (mg/dL)
1	5	≤ 2,77 (≤ 50)
2	15	> 2,77 – 4,44 (> 50 – 80)
3	20	> 4,44 – 6,66 (> 80 – 120)
4	30	> 6,66 – 11,10 (> 120 – 200)
5	15	> 11,10 – 16,65 (> 200 – 300)
6	10	> 16,65 – 22,20 (> 300 – 400)
7	5	> 22,20 (> 400)

Only unaltered capillary blood samples shall be used for glucose concentrations in Bins #3 through #5.

In Bin #2, at least 8 of the samples shall be unaltered.

In Bin #6, at least 5 of the sample shall be unaltered.

If necessary to obtain sufficient samples in Bins #1, 2, 6, and 7, glucose concentrations may be adjusted

Kabul edilebilir minimum sistem doğruluğu

ISO 15197-2003

Bireysel glukoz sonuçlarının yüzde doksan beşi (%95), üreticinin < 4.2 mmol/L **(< 75 mg/dL**) glukoz konsantrasyonlarında gerçekleştirilen ölçüm prosedüründen alınan sonuçların ± 0.83 mmol/L (**15 mg/dL**) dahilinde ve ≥ 4.2 mmol/L (≥ **75 mg/dL**) glukoz konsantrasyonlarında alınan sonuçların **± %20'si** dahilinde olmalıdır.

- ISO 15197-2013

7.4.1 System accuracy requirement

The minimum acceptable accuracy for results produced by a glucose monitoring system shall be as follows:

a) Ninety-five percent (95 %) of the individual glucose results shall fall within ± 0,83 mmol/L (15 mg/dL) of the results of the manufacturer's measurement procedure at glucose concentrations < 5,55 mmol/L (< 100 mg/dL) and within ± 15 % at glucose concentrations ≥ 5,55 mmol/L (≥100 mg/dL).

ISO 15197-2013

Table 4 — System accuracy results for glucose concentration < 5,55 mmol/L (100 mg/dL)

Within ± 0,28 mmol/L (Within ± 5 mg/dL)	Within ± 0,56 mmol/L (Within ± 10 mg/dL)	Within ± 0,83 mmol/L (Within ± 15 mg/dL)
68/150 (45 %)	105/150 (70 %)	143/150 (95 %)

Table 5 — System accuracy results for glucose concentration ≥ 5,55 mmol/L (100 mg/dL)

Within ± 5 %	Within ± 10 %	Within ± 15 %
221/450 (49 %)	383/450 (85 %)	439/450 (97.6 %)

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System Accuracy Evaluation of 27 Blood Glucose Monitoring Systems According to DIN EN ISO 15197

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Serge Kocher, Ph.D.,[2] Jacques Tshiananga, M.P.H.,[2] Frank Heister, Ph.D.,[2] and Cornelia Haug, M.D.[1]

Abstract

Background: Blood glucose (BG) monitoring systems enable diabetes patients to effectively control and adjust their therapy. BG monitoring systems with a Conformité Européenne (CE) label should meet the standard DIN EN ISO 15197:2003: ≥95% of the BG results shall fall within ±15 mg/dL of the reference method at BG concentrations <75 mg/dL and within ±20% at BG concentrations ≥75 mg/dL. We intended to verify if BG monitoring systems with a CE label fulfill these minimum accuracy requirements.

Methods: We evaluated 27 BG monitoring systems from 18 manufacturers for system accuracy according to DIN EN ISO 15197:2003. Twenty-four systems were compared with the glucose oxidase reaction (YSI 2300 glucose analyzer [YSI Life Sciences, Yellow Springs, OH]) and three systems with the hexokinase reaction (Hitachi 917 [Roche Diagnostics GmbH, Mannheim, Germany]). Duplicate measurements of 100 blood samples with a defined distribution of BG concentrations from 20 mg/dL to 600 mg/dL from ≥100 subjects were included in the evaluation.

Results: Sixteen of the 27 BG monitoring systems fulfilled the minimum accuracy requirements of the standard, i.e., ≥95% of their results showed the minimum acceptable accuracy. Overall, the mean percentage of results showing the minimum acceptable accuracy was 95.2 ± 5.2%, ranging from 80.0% to 100.0%.

Conclusions: More than 40% of the evaluated BG monitoring systems did not fulfill the minimum accuracy requirements of DIN EN ISO 15197:2003. As inaccurate BG monitoring systems bear the risk of false treatment decisions by the diabetes patient and subsequent possible severe health injury, manufacturers should regularly and effectively check the quality of BG meters and BG test strips.

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SEARCH

U.S. Food and Drug Administration
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Medical Devices

Home › Medical Devices › News & Events (Medical Devices) › Workshops & Conferences (Medical Devices)

News & Events (Medical Devices)

- Workshops & Conferences (Medical Devices)
- 2013 Medical Device Meetings and Workshops

FDA/CDRH Public Meeting: Blood Glucose Meters - March 16-17, 2010

POST MEETING INFORMATION:

Slides are available on the Diabetes Technology society website.

Copies of the transcripts from this meeting are posted below under the section marked "Transcripts".

Journal of Diabetes Science and Technology
Volume 4, Issue 3, May 2010
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EDITORIAL

The Food and Drug Administration Is Now Preparing to Establish Tighter Performance Requirements for Blood Glucose Monitors

David C. Klonoff, M.D., FACP

Abstract

On March 16 and 17, 2010, the Food and Drug Administration (FDA) presented a public meeting about blood glucose monitoring at the Gaithersberg Hilton Hotel. The meeting was intended to present expert opinions and solicit input from the public about whether to develop new regulatory policies for blood glucose monitors. The meeting was divided into three sections: (1) Clinical Accuracy Requirements for Blood Glucose Monitors, (2) Interferences and Limitations of Blood Glucose Monitors, and (3) Tight Glycemic Control. Many officials from the Center for Devices and Radiologic Health and the Office of *In Vitro* Diagnostic Devices, which are the parts of FDA that regulate approval of blood glucose mon the audience. Approximately 300 people attended; they were pediatric endocrinologists, internists, clinical chemists, intensi industry officials from companies involved in glucose mon regulatory consulting.

J Diabetes Sci Technol 2010;4(3):499-504

Conclusions

Comments of participants at the FDA Blood Glucose Monitor Meeting generated five conclusions:

1. Better analytical performance is needed.
2. Better clinical performance is needed.
3. Better adherence to human factor behaviors that can affect the accuracy of blood glucose monitoring, in addition to inherent monitor accuracy, is needed.
4. Better labeling of interfering substances is needed.
5. Better agreement on glycemic targets of hospitalized patients is needed.

SKUP

- Bağımsız bir İskandinav kuruluş
- Birinci basamak sağlık hizmetlerinde kullanılan lab. cihazlarının İskandinav ülkelerindeki değerlendirmesini yapıyor

SKUP Scandinavian evaluation of laboratory equipment for primary health care

SKUP

Accu-Chek Mobile

Meter and test cassettes
designed for glucose self-measurement
Manufactured by Roche Diagnostics GmbH

Report from the evaluation SKUP/2013/99*

organised by SKUP at the request of Roche Diagnostics Scandinavia AB

892 Bergen. Phone +47 55 97 95 02. www.SKUP.no

Recent SKUP evaluations

Evaluation no.	Component	Instrument/testkit	Producer
SKUP/2013/99*	Glucose	Accu-Chek Mobile	Roche Diagnostics
SKUP/2013/98*	Glucose	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/96	Haemoglobin	DiaSpect Hemoglobin T	DiaSpect Medical GmbH
SKUP/2012/95	Glucose[1]	Mendor Discreet	Mendor Oy
SKUP/2012/94	Glucose[1]	Contour XT	Bayer HealthCare
SKUP/2011/93*	Glucose	Accu-Chek Performa	Roche Diagnostics
SKUP/2012/91	HbA1c	Quo-Test A1c	Quoient Diagnostics Ltd
SKUP/2011/90	CRP	*i*-Chroma	BodiTech Med. Inc.
SKUP/2010/89*	Glucose	FreeStyle Lite	Abbott Laboratories
SKUP/2010/88*	HbA1c	*Confidential*	
SKUP/2011/86	Glucose[1]	OneTouch Verio	LifeScan, Johnson & Johnson
SKUP/2013/85	Glucose	StatStrip	Nova Biomedical
SKUP/2011/84*	PT-INR	Simple Simon PT and MixxoCap	Zafena AB
SKUP/2010/83*	Glucose	*Confidential*	
SKUP/2010/82*	Glucose, protein, blood, leukocytes, nitrite	Medi-Test URYXXON Stick 10 urine test strip and URYXXON Relax urine analyser	Macherey-Nagel GmbH & Co. KG
SKUP/2010/81*	Glucose	mylife PURA	Bionime Corporation
SKUP/2010/80	PT (INR)	INRatio2	Alere Inc.
SKUP/2010/79*	Glucose, protein, blood, leukocytes, nitrite	CombiScreen 5SYS Plus urine test strip and CombiScan 100 urine analyser	Analyticon Biotechnologies AG
SKUP/2010/78	HbA1c	In2it	Bio-Rad
SKUP/2011/77	CRP	*Confidential*	
SKUP/2009/76*	HbA1c	*Confidential*	
SKUP/2009/75	Glucose	Contour	Bayer HealthCare
SKUP/2009/74	Glucose[1]	Accu-Chek Mobile	Roche Diagnostics
SKUP/2010/73	Leukocytes	HemoCue WBC	HemoCue AB
SKUP/2008/72	Glucose[1]	*Confidential*	
SKUP/2009/71	Glucose[1]	GlucoMen LX	A. Menarini Diagnostics
SKUP/2011/70*	CRP	smartCRP system	Eurolyser Diagnostica GmbH
SKUP/2008/69*	Strep A	Diaquick Strep A test	Dialab GmbH
SKUP/2013/68	Allergens	ImmunoCap Rapid	Phadia AB
SKUP/2010/67	Allergens	*Confidential*	
SKUP/2008/66	Glucose[1]	DANA DiabeCare IISG	SOOIL Developement co. Ltd
SKUP/2008/65	HbA1c	Afinion HbA1c	Axis-Shield PoC AS
SKUP/2007/64	Glucose[1]	FreeStyle Lite	Abbott Laboratories
SKUP/2007/63	Glucose[1]	*Confidential*	
SKUP/2007/62*	Strep A	QuikRead	Orion Diagnostica Oy
SKUP/2008/61	CRP	i-CHROMA	BodiTech Med. Inc.
SKUP/2007/60	Glucose[1]	*Confidential*	
SKUP/2007/59	Glucose[1]	Ascensia BREEZE2	Bayer HealthCare

*A report code followed by an asterisk indicates evaluations at special request from the supplier, or evaluations that are not

SKUP GLUKOMETRE DEĞERLENDİRMELERİ

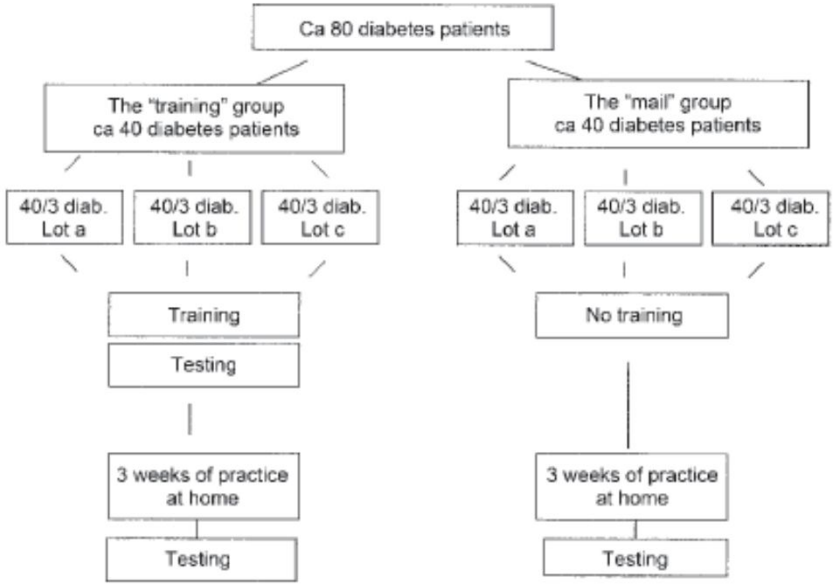
- Temel prosedür genelde sabit olmakla birlikte, modifikasyonlar yapabiliyor (cihaz sayısı, hasta sayısı vb..)

- Karşılaştırma yöntemi: Biyokimya analizörü (hekzokinaz yöntemi) (izlenebilirlik!)

- Truness - kapiller tam kan (karşılaştırma cihazı için plazması ayrılıyor)

- Presizyon- her hastadan bir glukometre için yapılan çift ölçümden hesaplanır

- 2 aşamalı
  - Deneyimli laboratuvar teknisyeninin kontrol altındaki optimum koşullarda yaptığı değerlendirmeler
  - Diyabet hastalarının değerlendirmeleri



SKUP- Sonuçların değerlendirilmesi

- **Akküresi hedefi:** ISO 15197-2003
- **Presizyon hedefi:** CV < %5 (ref ADA)

American Diabetes Association. *Self-monitoring of blood glucose*. Diabetes Care 1996;**19** (suppl 1):62– 66.

Agreement between a Glucose Meter and Results from a Comparative Laboratory Method

Organization or society	Glucose range	Performance criteria
ADA 1987	All levels	±15%
ADA 1994	All levels	±5%
CSA	<45 mg/dl (2.5 mmol/liter)	±25% (CV < 12.5%)
	≥90 mg/dl (5.0 mmol/liter)	±15% (CV < 7.5%)
FDA (95% of data)	<100 mg/dl (5.6 mmol/liter)	±20 mg/dl (1.1 mmol/liter)
	≥100 mg/dl (5.6 mmol/liter)	±20%
ISO (95% of data)	<100 mg/dl (5.6 mmol/liter)	±10 mg/dl (1.1 mmol/liter)
	≥100 mg/dl (5.6 mmol/liter)	±20%
IMSS	<60 mg/dl (3.3 mmol/liter)	±25%
	≥60 mg/dl (3.3 mmol/liter)	±20%
CLSI (C30A)	<100 mg/dl (5.6 mmol/liter)	<15 mg/dl (0.83 mmol/liter)
	≥100 mg/dl (5.6 mmol/liter)	±20%
TNO	<117 mg/dl (6.5 mmol/liter)	±20 mg/dl (1.11 mmol/liter)
	≥117 mg/dl (6.5 mmol/liter)	±15 mg/dl (0.83 mmol/liter) (CV < 10%)

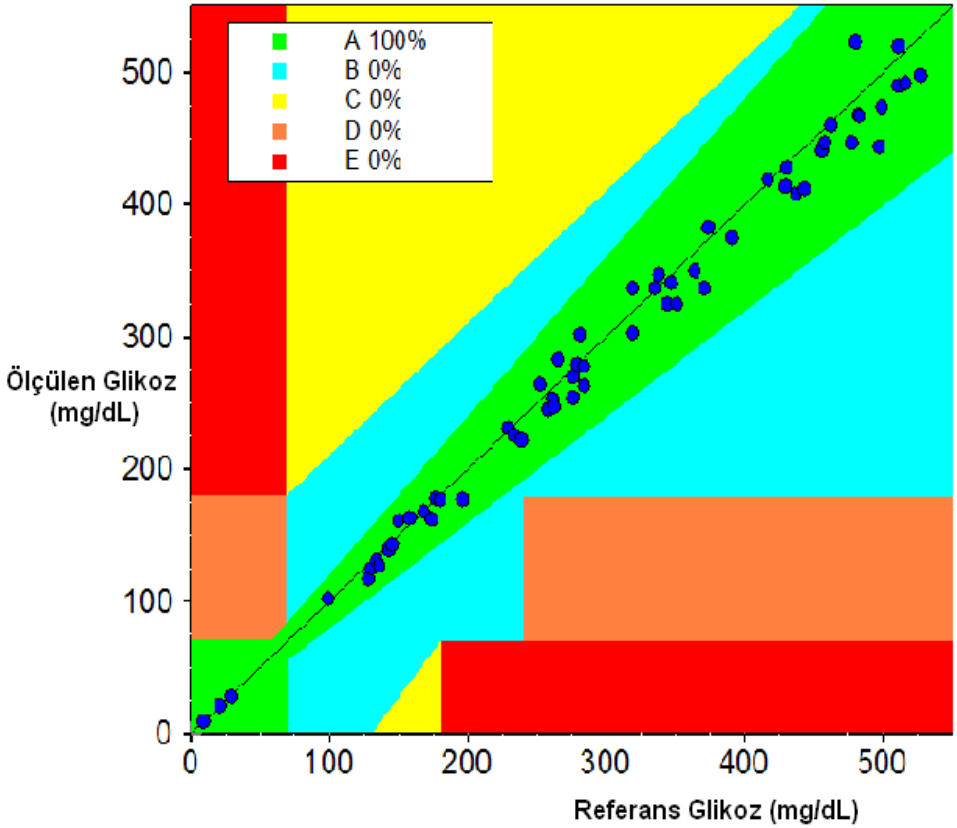
CV, coefficient of variation; CSA, Canadian Standards Association; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization; IMSS, Instituto Mexicano del Seguro Social; CLSI, Clinical and Laboratory Standards Institute; TNO, Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek

J Diabetes Sci Technol Vol 3, Issue 4, July 2009

Clarke Error Grid Analizi

- Hatanın yol açacağı tıbbi riske göre:

- A ve B: Tedavi değişikliği yok
- C: Tedavi değişikliği klinik durumu etkileyebilir (overcorrection)
- D: Önemli tıbbi risk (hipo/hiperglisemi)
- E: Tehlikeli sonuçlar ortaya çıkabilir



CLINICAL AND LABORATORY STANDARDS INSTITUTE®

January 2013

POCT12-A3

Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline—Third Edition

This document contains guidelines for performance of point-of-care blood glucose meter systems that stress quality control, training, and administrative responsibility.

CLSI POCT12-A3

- Eğitimli hastane personelince yapılır
- Performans kriterleri: İmpresizyon, trueness, linearite, ölçüm aralığı
- Hedef subgrupda çalışılmalı (örn. Neonatal, ICU)
- Numune türü:

  1. **Glukoz konsantrasyonu değiştirilmemiş, taze, antikoagulanlı arteryal veya venöz kan**

  (min. 40- ölçüm aralığını kapsayan numune)

  2. **Değiştirilmiş kan örnekleri**

  - Üreticinin önerisi varsa ve <50 mg/dl ve > 400 mg/dl değerleri için yeterli sayıya ulaşılmak amacıyla
- Aynı örnekten 2 şer ölçüm hem glukometre cihazı ile hem de lab. Karşılaştırma cihazı ile (tam kan veya 5 dk içinde santrifuj edilmiş kandan hazırlanan serum/plazma)
- Karşılaştırma cihazının doğruluğu sertifiye referans materyalle veya trueness kontrol materyali ile doğrulanmalıdır

CLSI POCT12-A3

Glukometre performans değerlendirme kriterleri:

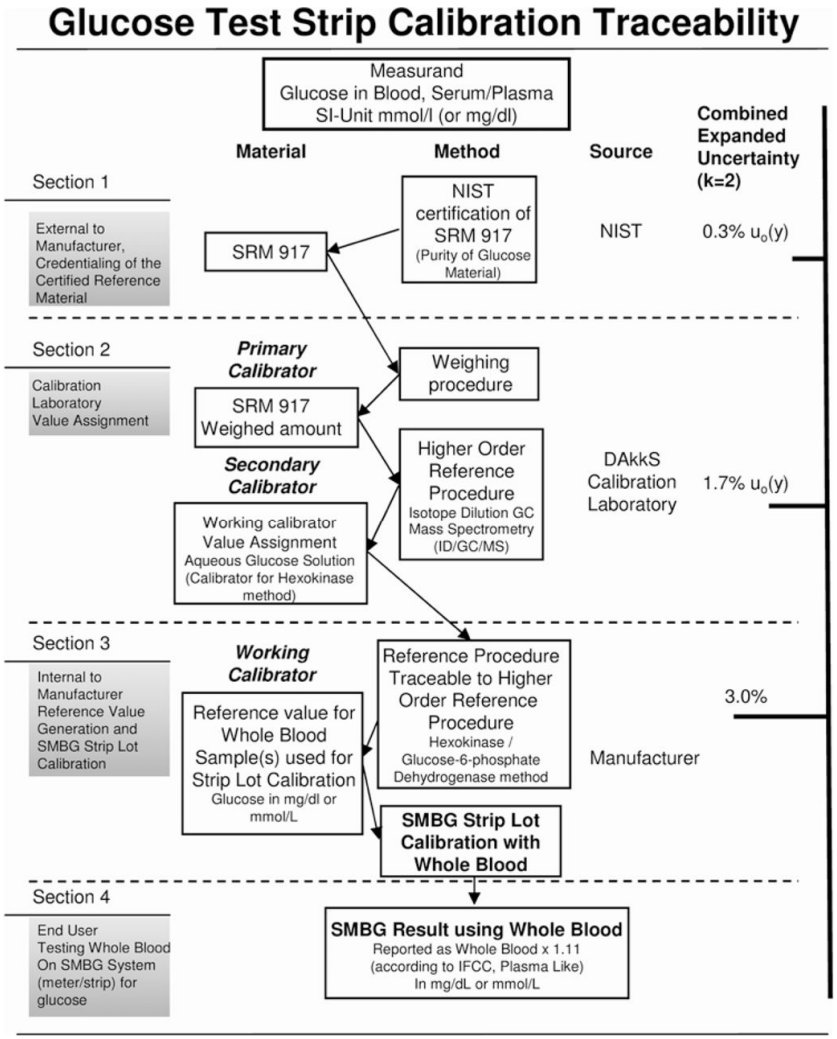
- Sonuçların %95'i <100 mg/dl glukoz konsantrasyonlarında ±**12 mg/dl**, ≥ 100 mg/dl konsantrasyonlarında ±**%12.5** aralığında olmalıdır.

- <75 mg/dl glukoz değerlerinde 15 mg/dl'den fazla sapan sonuçların sayısı ve ≥75 mg/dl glukoz konsantrasyonlarında %20 den fazla sapan örneklerin sayısı tüm sonuçların %2'sinden fazla olmamalıdır.

GLUKOMETRE CİHAZLARININ KALİBRASYONU

- Glukometre cihazlarının tamamının kalibrasyonu için ortak bir referans metod yok
- Üreticiler NIST standartlarıyla kalibre ettikleri "in house" metodlar kullanıyorlar
- Bu durum farklı cihazlar arasında sistematik farklara yol açıyor

Outline of the complete traceability chain of the ID/GC/MS reference method using a multistep calibration procedure.



Andreis E et al. J Diabetes Sci Technol 2014;1932296814523886

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- TÜRKİYEDE GLUKOMETRE CİHAZLARININ PERFORMANS DEĞERLENDİRMELERİ

GLİKOMETRE SİSTEMLERİNİN PERFORMANS RAPORLARI

RSHM Başkanlığınca 15 Şubat 2011 tarihinde analitik performans niteliklerinin değerlendirilmesi amacıyla laboratuarımıza teslim edilen, aşağıda marka ve modelleri verilen *41 adet glikometre cihazı ve stripleri, çalışma grubumuz tarafından değerlendirilerek, teknik kanaat raporları ekte ayrı ayrı verilmiştir.

TÜRKİYE DİYABET ÖNLEME VE KONTROL PROGRAMI

HbA1c Tayin Yöntemleri ve Glukometrelerin Standardizasyonu Çalıştay Raporu

11 Aralık 2012
ANKARA

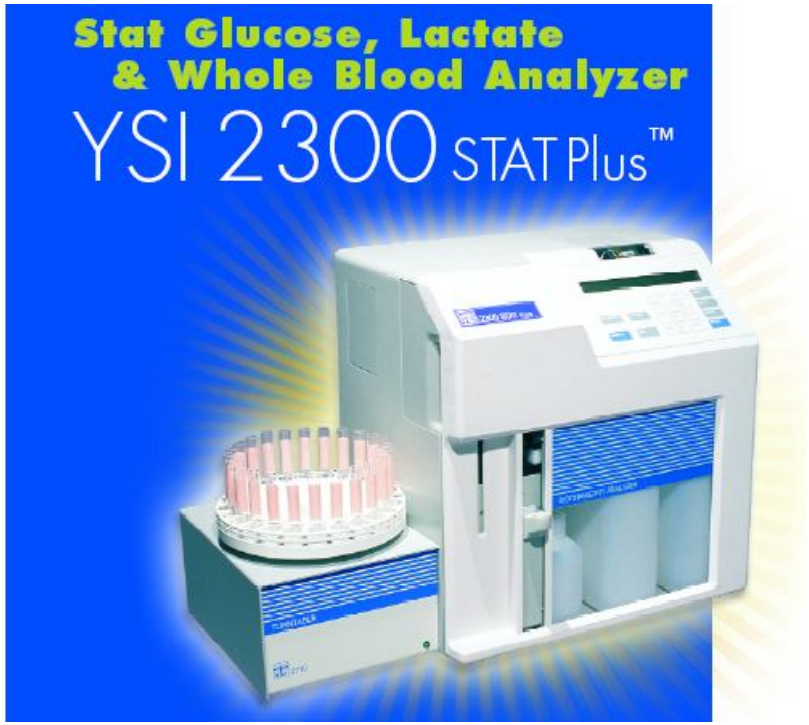
Sağlık Bakanlığı
Türkiye Halk Sağlığı Kurumu
Obezite, Diyabet ve Metabolik Hastalıklar Daire Başkanlığı

UYGULAMAKTA OLDUĞUMUZ DOĞRULUK ÇALIŞMASI PROTOKOLÜ

- 10 glukometre cihazı içinden random seçilen 2 cihaz
- Karşılaştırma yöntemi: Yellow spring Inst. (YSI)
- Doğruluk çalışması: taze kapiller tam kan
- Gün-içi tekrarlanabilirlik çalışması: venöz tam kan
- Günler arası tekrarlanabilirlik çalışması: kontrol solüsyonu

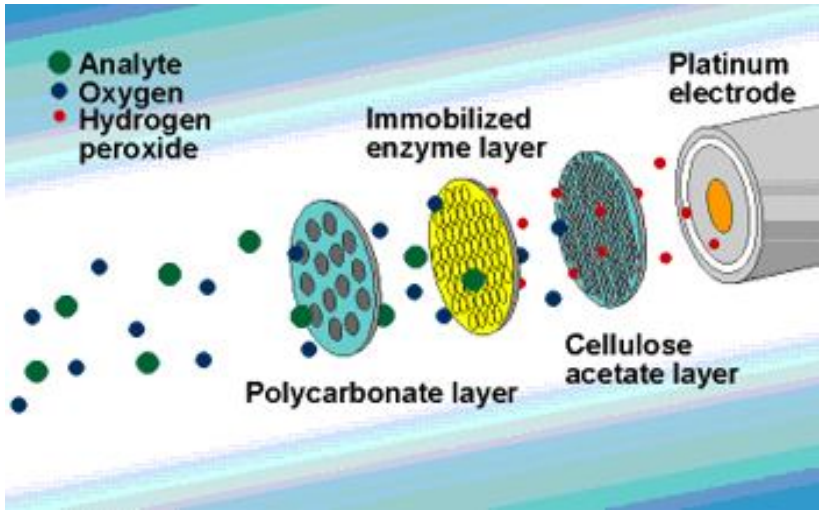
Karşılaştırma Cihazımız: YSI

- Numune miktarı: 25 µl (aspire miktarı)
- Ölçüm aralığı: -900 mg/dl
- Ölçüm süresi: 65 sn
- Ölçüm prensibi: GO
- -O2 duyarlı elektrod yerine H2O2 duyarlı elektrod kullanır
- Enzim: immobilize glukoz oksidaz



YSI Çalışma Prensibi

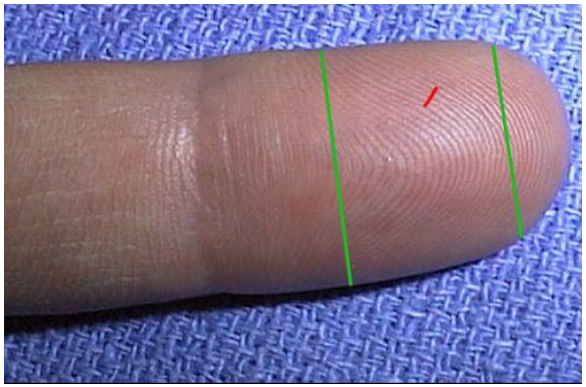
- Substrat iki membran tabakası arasında immobilize olmuş enzim tabakasına ulaştığında okside olur.
-
- Hidrojen peroksit üretir, oluşan H2O2 selüloz asetatı geçerek platinyum elektroda ulaşır. Burada okside olur.

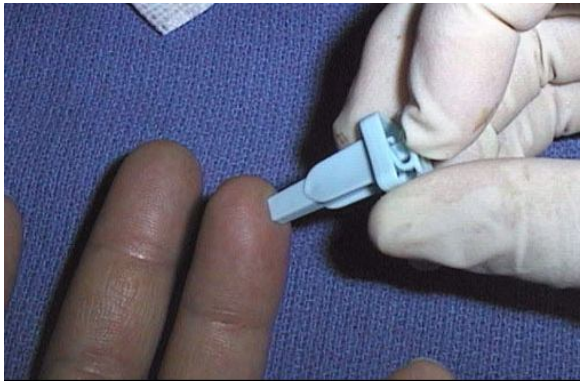


- Oluşan akım substrat konsantrasyonlu ile doğru orantılıdır.

1) D-Glucose + oxygen $\xrightarrow[\text{oxidase}]{\text{glucose}}$ gluconolactone + H_2O_2
2) The H_2O_2 sensitive electrode oxidizes a constant portion of the H_2O_2 at the platinum anode: $H_2O_2 \rightarrow 2H^+ + 2e^- + O_2$.
3) The circuit is completed by a silver cathode at which oxygen is reduced to water: $4H + O_2 \rightarrow 2H_2O + 4e^-$

Kapiller Kan Alımı





Presizyon (Tekrarlanabilirlik) Çalışması

- Antikoagulanlı (üretici aksi yönde bilgi vermediyse heparinli) venöz tam kan
- Her bir cihazda 5 seviyede 10 ar ölçüm

Tablo1. Gün içi tekrarlanabilirlik çalışması için glukoz konsantrasyon aralıkları

Aralık	Glukoz konsantrasyonu mg/dL
1	30 - 50
2	51 - 110
3	111 - 150
4	151 - 250
5	251 - 400

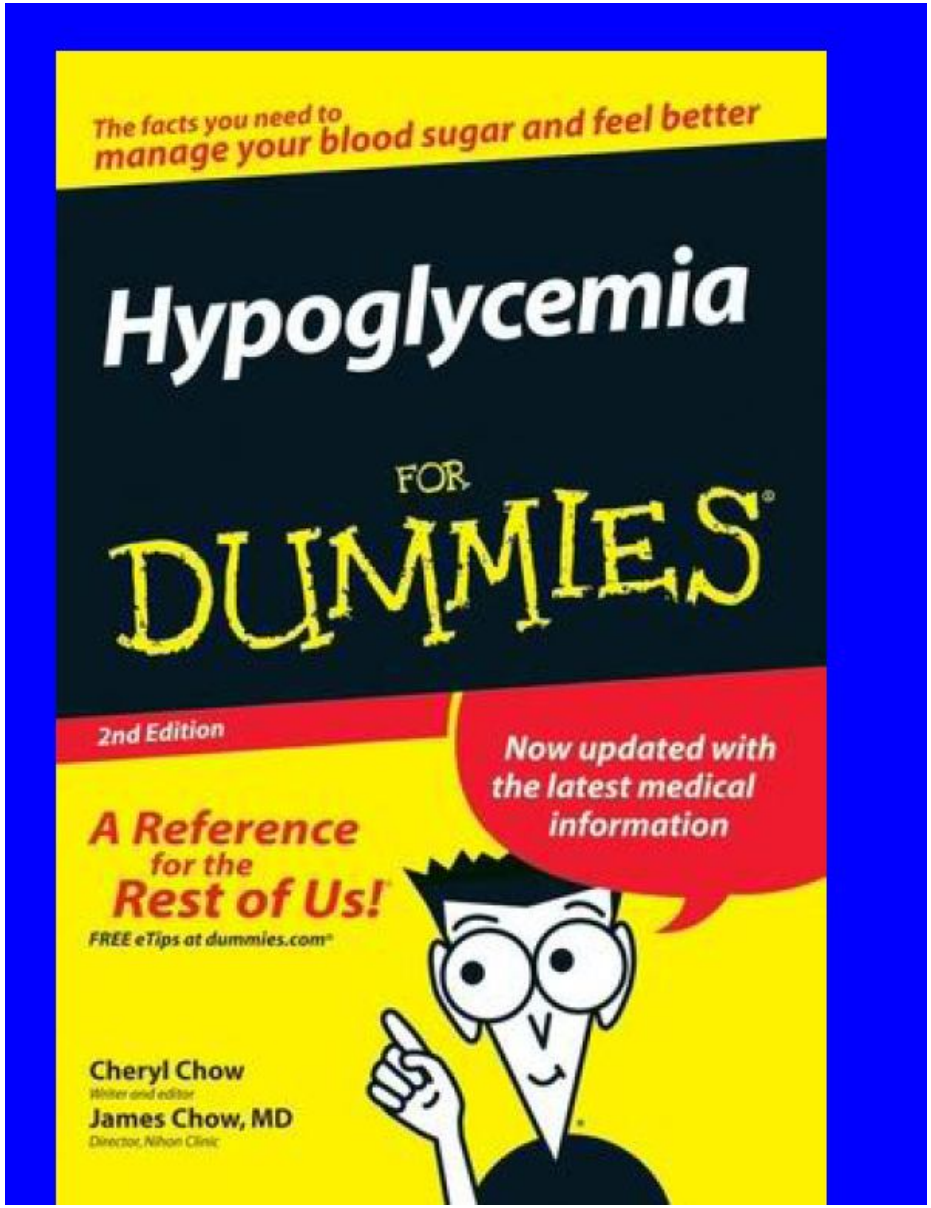
Doğruluk Çalışması

- Taze kapiller tam kan (~100)
- Hastalar SKUP protokolü örnek alınarak üç gruba ayrılır;
  - <125 mg/dl
  - 125-180 mg/dl
  - >180 mg/dl
- Çalışma başında ve sonunda karşılaştırma cihazı için heparinli tüpe kan alınır
- Her hastada iki cihazla ikişer ölçüm

Sonuçların Değerlendirilmesi

- **Doğruluk Değerlendirmesi:**
- ISO 15197-2003 aküresi kriterlerine göre imalatçının cihazıyla ölçüm işlemlerindeki sonuçlara göre, bütün glukoz sonuçlarının yüzde doksan beşi (%95), <75 mg/dL glukoz konsantrasyonlarında ±15 mg/dL içinde ve ≥75 mg/dL glukoz konsantrasyonlarında ± % 20 içinde olmalıdır.

- **Tekrarlanabilirlik Değerlendirmesi:**
- American Diabetes Association (ADA) kriterlerine göre % CV< 5 olan tekrarlanabilirlik sonuçları uygun kabul edilecektir.



FDA Pushes for Higher Standards on Blood Glucose Meters

Agency Outlines Separate Tracks for Lay and Professional Use Devices

For the first time, FDA is proposing two separate standards for lay-use blood glucose meters and for those used in the hospital. The latter has been under the most scrutiny by laboratorians, many of whom feel that FDA has overreached.

The draft guidance for professional-use meters would require manufacturers to demonstrate that 99% of all values are within ±10% of the reference method for glucose concentrations >70 mg/dL. The current FDA standard is 95% of results within ±20%.

This guidance aims higher than the bar set in two existing standards for blood glucose meters. The Clinical and Laboratory Standards Institute (CLSI) POCT12-A3 consensus standard recommends 95% of values within 12.5%. However, this standard is intended for use by clinical labs, not for manufacturers. Similarly, the most recent standard from the International Organization for Standardization, ISO 15197, recommends 95% of values within ±15%. This standard is intended for manufacturers, but specifically for lay-use devices and not hospital instruments.

Abbott, which manufactures blood glucose meters and other point-of-care instruments, said it would like to see FDA conform to the guidelines set by ISO and CLSI. "Adopting and uniformly enforcing these standards would bring immediate and substantial improvements in blood glucose monitoring accuracy to patients and promises the most impact for patient health and safety," the company said in a statement.

In addition to new performance requirements, the guidance would require more extensive clinical studies of at least 350 patients for a meter intended for the hospital. At least 50 samples each from the surgical and medical intensive care units have to be included.

Separately, a new guidance for meters intended for lay users also bumps up the standard. Manufacturers of new over-the-counter meters would need to demonstrate that 95% of all results fall within ±15% of the reference measurement across the entire claimed

Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: January 7, 2014

You should submit comments and suggestions regarding this draft document within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Patricia Bernhardt at patricia.bernhardt@fda.hhs.gov, or at 301-796-6136.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Radiological Health
Division of Chemistry and Toxicology Devices

- **Reducing the Risk of Bloodborne Pathogen Transmission**
- **Performance Evaluation for Prescription-Use BGMS Devices**
  - Precision Evaluation Study (both repeatability and intermediate precision)

Table 1. Glucose Concentrations for Repeatability Evaluation

Interval	Glucose Concentration Range (mg/dL)
1	30-50
2	51-110
3	111-150
4	151-250
5	251-400

Venöz kan

10 cihaz, 10 vial , 3 lot

10ar ölçüm

  - Linearity Evaluation Study
  - Method Comparison/User Evaluation
    - İddia edilen her örnek türünden (arteriyel, kapiller, veniö) min. 350şer hasta
    - <80 mg/dl ve >300 mg/dl den en az 10 ar değiştirilmemiş kan
    - Tüm sonuçların %99'u >70 mg/dL için ref. Metoddan ± 10% , <70 mg/dL için ± 7 mg/dL olmalıdır.
    - Ayrıca sonuçların hiç biri >70 mg/dL de ± 20% , <70 mg/dL de ± 15 mg/dL den fazla sapamaz

"Sorry. It's just my glucose monitor."

SİZLER HASTANENİZDE GLUKOMETRE CİHAZLARINIZI NASIL DEĞERLENDİREBİLİRSİNİZ?

POCT KOMİSYON ÜYELERİ İÇİN ÖNERİLER

- Teknik direktör/ Laboratuvar uzmanı
- Tıbbi direktör/ Klinisyen
- Hemşire Sorumlusu
- Eğitim koordinatörlüğü
- Kalite kontrol birimi
- Laboratuvar sorumlusu
- Büyük kurumlarda özel bir POC Süpervizörü/ Kooordinatörü
- Satın alma ve Bilgi İşlemden temsilcilere konsultan olarak danışılabilir
-

POCT KOMİTESİNİNİ POLİTİKALARI

- Yazılı bir POCT programı/Politikası belirlenir
- Program/Politika şunları içermelidir:
- 1. Programın kısımlarındaki kilit isimlerin belirlenmesi, kim programın hangi kısmından sorumlu
- 2. Test nerede ve kim tarafından yapılacak
- 3. POCT sistemlerinin her birinin kullanım amacını belirlemek (tarama, tanı,tedavi..)
- 4. Metodu kim seçecek? Laboratuvar mı POCT komisyonu mu?
- 5. Başlangıçta hangi metod validasyon çalışmaları yapılacak , kim yapacak?
- 6. Raporlama prosedürü nasıl olacak
- 7. Personel eğitimi, kompetans programlarına devamlılık, end-userlarla iletişim, geri bildirimler
- 8. Kalite kontrol protokolleri
- 9. Bütçe

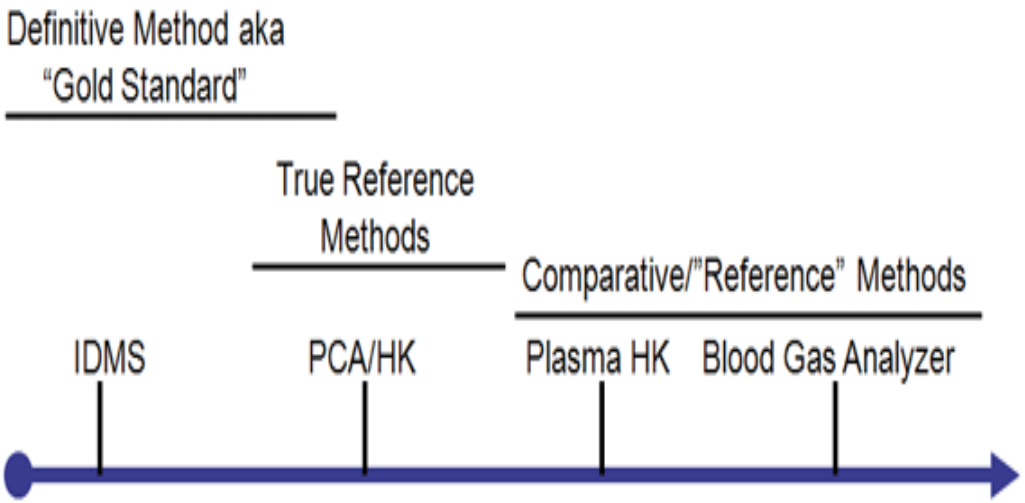
- 1. Programın kısımlarındaki kilit isimlerin belirlenmesi, kim programın hangi kısmından sorumlu
- **Laboratuvar POC Koordinatörü.** Testi yapan personelin listesinin tutrulması, personele verilecek eğitimin koordinasyonu, test metodlarının seçimi, kalite kontrolun takibi, teknik konularda konsultasyonluk
- **Hemşire Sorumlusu:** Politikaların uygulanmasınınn sağlamak, yeni eğitimlerin planlanması, yıllık POC kompetansın planlanması
- **Eğitim Koordinatörlüğü.** Testi yapan personelin yıllık sertifikasyonu, yeni işe alınanların eğitimi, eğitim toplantıların organizasyonuna yardımcı olmak
- **Laboratuvar personeli.** Cihazların düzgün çalıştığını ve bakımlarını verifiye etmek, yeni elemanların eğitimi, testi yapan personelin yıllık sertifikasyonuna yardımcı olmak, kalite kontrol datalarının takibini yapmak

Staff involved in training and advising people with diabetes should ensure that they inform them of potential sources of error and give advice on how to interpret results.

Training should include:

- basic principles of measurement
- expected results in normal and pathological states
- demonstration of the proper use of the equipment in accordance with the manufacturer's specification
- demonstration of the consequences of improper use
- knowledge of operator dependent steps
- instruction in the collection of appropriate blood samples
- health and safety aspects
- instruction in the importance of complete documentation of all data produced
- appropriate calibration and quality control techniques
- practical experience of the procedures, including a series of analyses to satisfy the instructor that the trainee is competent
- information regarding contra-indications
- information on basic troubleshooting, error messages and potential sources of error.

GLUKOMETRELERİN DEĞERLENDİRİLMESİNDE LABORATUVAR UZMANLARINA ÖNERİLER



- Glukometrelerin aküresini belirlemek için ideal olan <u>aynı örnekten</u> alınan numunelerin hem glukometre hem de referans/karşılaştırma yöntemiyle çalışılmasıdır

- Referans/karşılaştırma yöntemi dökümante edilmiş aküresi ve yüksek presizyona sahip olmalıdır. İnterferanslardan minimum etkilenmelidir.

#

Farklı Yayınlar Farklı Yaklaşımlar

- Kapiller tam kan, karşılaştırma cihazı için venöz kan plazma örneği
- Taze venöz tam kan, karşılaştırma cihazı için aynı örnekten plazma
- Kapiller tam kan, karşılaştırma cihazı için kapiller kandan plazma hazırlanması

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System Accuracy Evaluation of 27 Blood Glucose Monitoring Systems According to DIN EN ISO 15197

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Abstract

Background: Blood glucose (BG) monitoring systems enable diabetes patients to effectively control and adjust their therapy. BG monitoring systems with a Conformité Européenne (CE) label should meet the standard DIN EN ISO 15197:2003: ≥95% of the BG results shall fall within ±15 mg/dL of the reference method at BG concentrations <75 mg/dL and within ±20% at BG concentrations ≥75 mg/dL. We intended to verify if BG monitoring systems with a CE label fulfill these minimum accuracy requirements.

Methods: We evaluated 27 BG monitoring systems from 18 manufacturers for system accuracy according to DIN EN ISO 15197:2003. Twenty-four systems were compared with the glucose oxidase reaction (YSI 2300 glucose analyzer [YSI Life Sciences, Yellow Springs, OH]) and three systems with the hexokinase reaction (Hitachi 917 [Roche Diagnostics GmbH, Mannheim, Germany]). Duplicate measurements of 100 blood samples with a defined distribution of BG concentrations from 20 mg/dL to 600 mg/dL from ≥100 subjects were included in the evaluation.

Results: Sixteen of the 27 BG monitoring systems fulfilled the minimum accuracy requirements of the standard, i.e., ≥95% of their results showed the minimum acceptable accuracy. Overall, the mean percentage of results showing the minimum acceptable accuracy was 95.2 ± 5.2%, ranging from 80.0% to 100.0%.

Conclusions: More than 40% of the evaluated BG monitoring systems did not fulfill the minimum accuracy requirements of DIN EN ISO 15197:2003. As inaccurate BG monitoring systems bear the risk of false treatment decisions by the diabetes patient and subsequent possible severe health injury, manufacturers should regularly and effectively check the quality of BG meters and BG test strips.

- 100 taze kapiler kan örneği (hematokrit değerleri %30 ile %55 arasında)

- referans ölçüm işlemi (biyokimya otoanalizörü HK yöntemi) için:

GOx yöntemi için: Li-heparinli tüp

HK yöntemi için: 20 µL tam kan 400 µL 0.33 mmol/litre perklorik asit içeren tüplerde hemoliz ve deproteinizasyondan sonra santrifüj edilir. Süpernatanlar -20 ° C'de saklanır

Değerlendirme: ISO 15197-2003

–plazma eşdeğeri KG değeri (mg/dL) =tam kan glukoz değeri (mg/dL olarak) / [1 – (0.0024 x hematokrit değeri [%]

Tablo 2.
Hafif Modifikasyonlarla DIN EN ISO 15197'ye göre Glukoz Konsantrasyonu Dağılımı

Örnek yüzdesi	Glukoz konsantrasyonu mmol/litre (mg/dL)
5	<2.8 (≈ <50)
15	≥2.8–<4.35 (≈ ≥50–<80)
20	≥4.35–<6.7(≈ ≥80–<120)
30	≥6.7–<11.15 (≈ ≥120–<200)
15	≥11.15–<16.65 (≈ ≥200–<300)
10	≥16.65–<22.2 (≈ ≥300–<400)
5	≥22.2 (≈ ≥400)

TEŞEKKÜRLER !!