KALP CERRAHİSİNDE ŞEKER KONTROLÜ: SIKI KONTROL MÜ? LİBERAL REJİM Mİ?

Doç Dr Ayten BİLİR

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi
Anesteziyoloji ve Reanimasyon ABD
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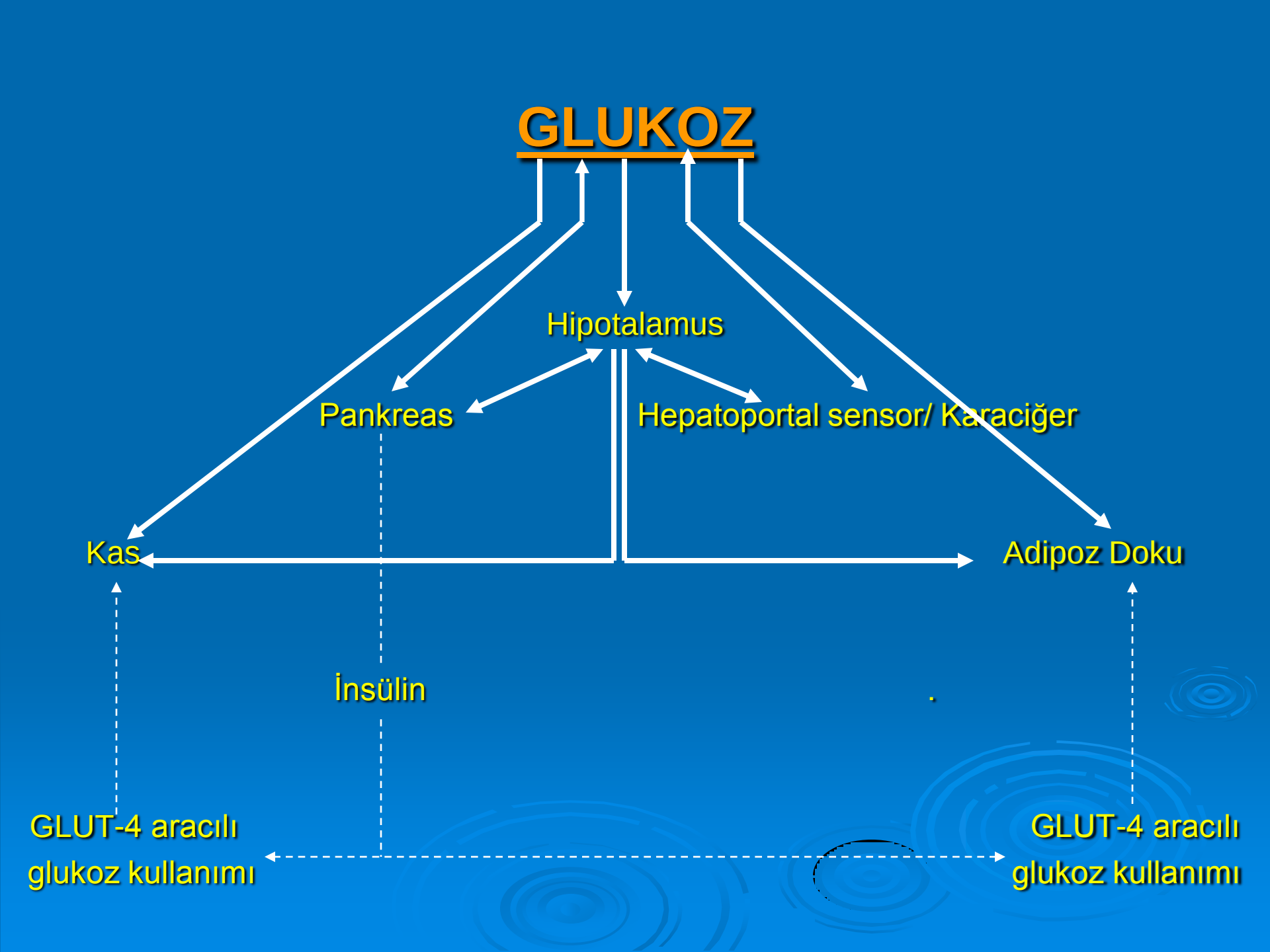
Açlık Kan Şekeri (mg/dL)	75 g glukoz yüklemesinden 2 saat sonraki kan şekeri (mg/dL)		
	<140	140- <200	≥200
<110	NORMAL	BOZULMUŞ GLUKOZ TOLERANSI	DİYABET
≥110 – <126	BOZULMUŞ AÇLIK GLUKOZU		
<126			
≥126			

Diabetes mellitus operatif komplikasyon insidansını arttırır.

- *Hertzer NR, Bena JF, Karafa MT. A personal experience with the influence of diabetes and other factors on the outcome of infrainguinal bypass grafts for occlusive disease. J Vasc Surg 2007;46:271–9*
- *Bagry HS, Raghavendran S, Carli F. Metabolic syndrome and insulin resistance: perioperative considerations. Anesthesiology 2008;108:506–23*

Perioperatif gelişen hiperglisemi gelişebilecek istenmeyen sonuçların habercisidir.

- *Puskas F, Grocott HP, White WD, Mathew JP, Newman MF, Bar-Yosef S. Intraoperative hyperglycemia and cognitive decline after CABG. Ann Thorac Surg 2007;84:1467–73*
- *Bochicchio GV, Sung J, Joshi M, Bochicchio K, Johnson SB, Meyer W, Scalea TM. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005;58: 921–4*
- *Bochicchio GV, Salzano L, Joshi M, Bochicchio K, Scalea TM. Admission preoperative glucose is predictive of morbidity and mortality in trauma patients who require immediate operative intervention. Am Surg 2005;71:171–4*


GLUKOZ
Hipotalamus
Pankreas
Hepatoportal sensor/ Karaciğer
Kas
Adipoz Doku
İnsülin
GLUT-4 aracılı glukoz kullanımı
GLUT-4 aracılı glukoz kullanımı

Glukozun hücre içine girişi

- **Kolaylaştırılmış difüzyon**

  Glukoz taşıyıcıları; *GLUT 1-12,*

  H+/myoinositol transporter,
  Sodyum-bağımlı glukoz kotransporter 1-6

- **Aktif transport**

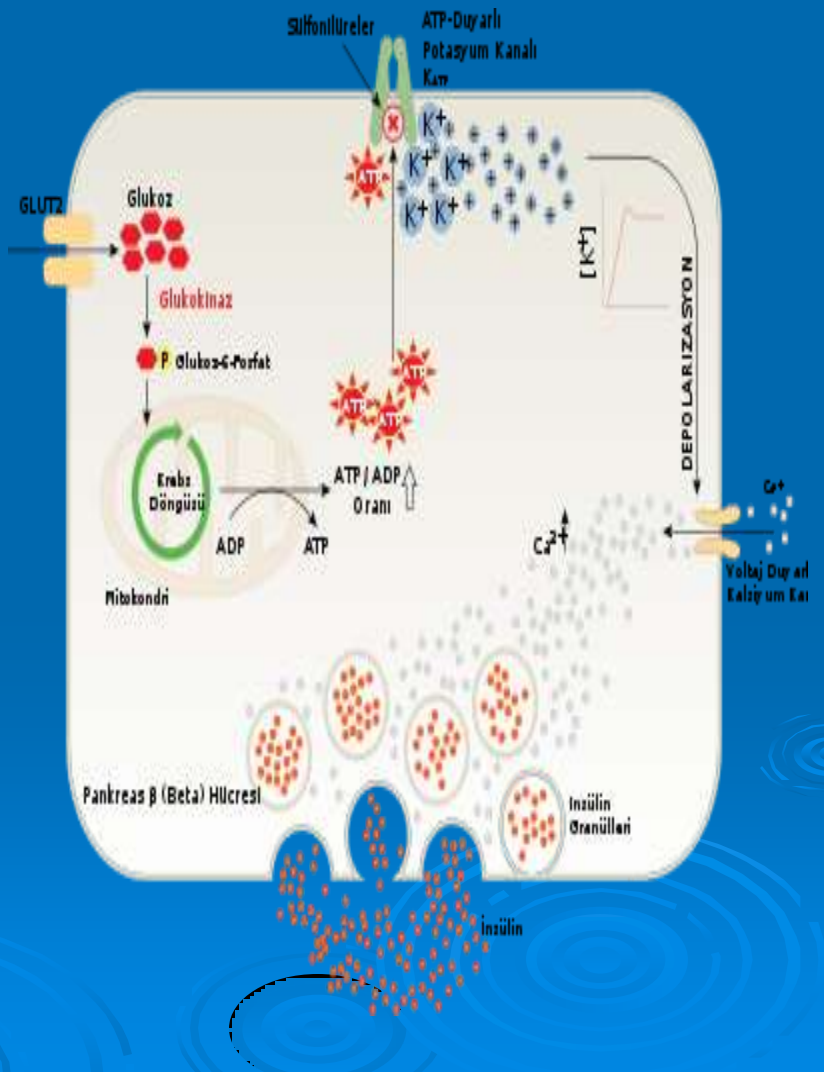
Glukoz transportunda insülinin yeri

- **Glukoz transportu insüline bağımlı olmayan dokular;**
  - *Pankreas*
  - *Beyin*
  - *İmmün ve endoteliyal hücreler*

- **Glukoz transportu insüline bağımlı olan dokular;**
  - *İskelet ve kardiyak kaslar*
  - *Adipoz doku (GLUT-4 aracılığı ile)*
  - *Karaciğer (GLUT-2 aracılığı ile, insüline bağımlı glukoz alımında hız kısıtlayıcı basamak)*

İnsülin sekresyonunu etkileyen faktörler

- Pankreatik hormonlar
- İntestinal hormonlar
- Plazma glukozu konsantrasyonunun artışı
- Nitrik oksit
- Arginin
- Lösin
- Beta-ketoasitler
- Sitozolik C-AMP artışı
- Vagal stimülasyon
- Sempatik stimülasyon
- Hücre içi potasyum artışı
- İnhalasyon ajanları



İnhalasyon ajanları ve insülin

- İsofluran, Desfluran;
  - Glukoz ile indüklenen insülin sekresyonu ↓
- Desfluran/Remifentanil anestezisi;
  - İnsülin seviyesi etkilenmez
  - İnsülin sensitivitesi ↓ → Kan glukoz seviyesi hafif ↑
- İntravenöz anestezikler;

Nöroendokrin cevap ↓

↓

İnsülin sekresyonu değişmez

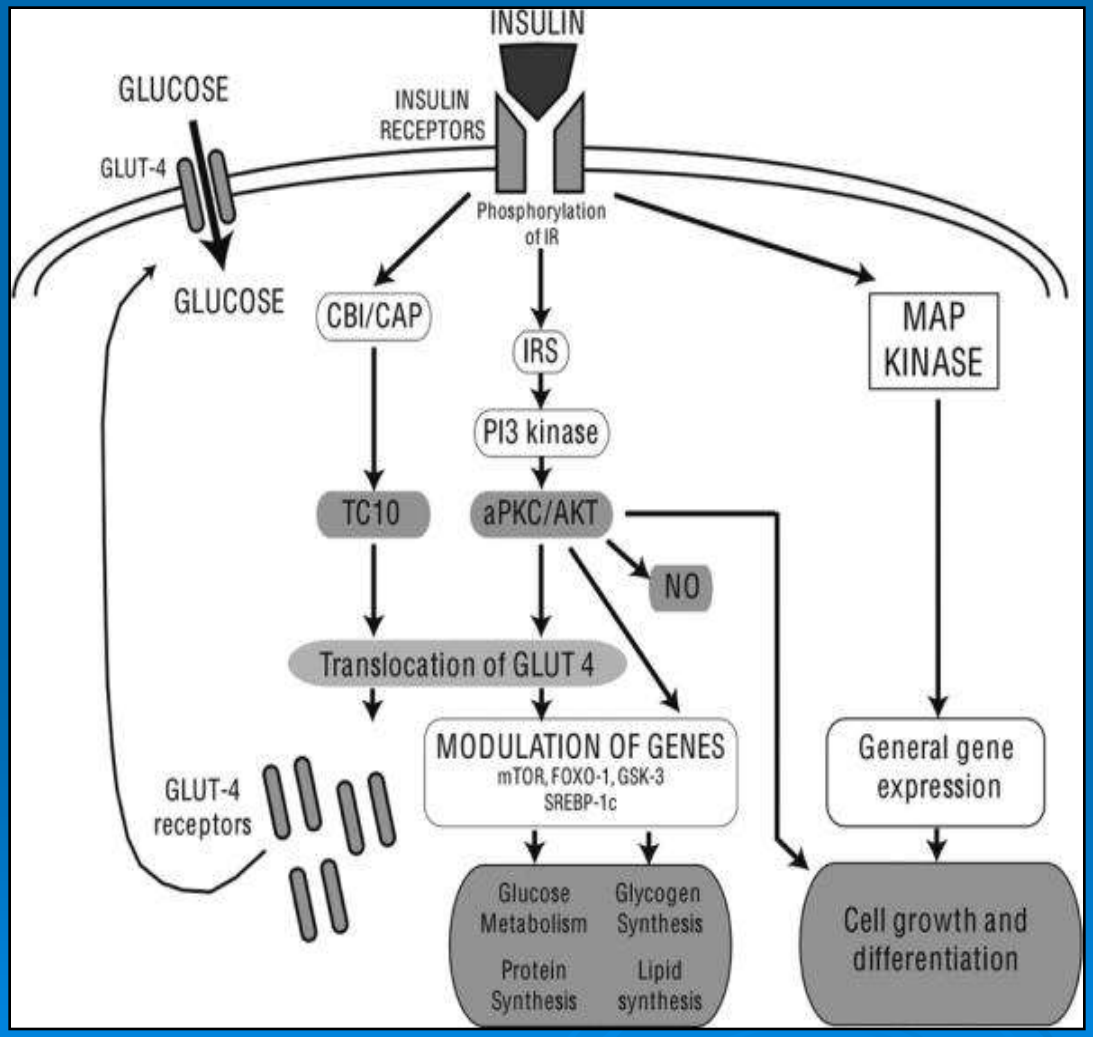
↓

İnsülin sensitivitesi ↓

↓

Kan glukoz seviyesi hafifçe ↑

İnsülinin metabolik etkileri



1. İnsüline hassas hücrelerde glukoz transporterlarının aktivasyonu ile glukoz alımının arttırılması
2. Glikojen sentezinin arttırılması
3. Glukoneogenez, glikoliz, lipojenik ve sterol sentezi yollarının düzenlenmesi

İnsülinin non-metabolik etkileri

- Proinflamatuar transkripsiyon faktörü ↓
  - Nükleer faktör-κβ
  - Early growth response-1
  - Aktive edici protein-1
- Endotoksin aracılı inflamatuar mediatörler
  - IL-1β
  - IL-6
  - TNF-α

İnsülinin non-metabolik etkileri

- İnsülin;
  - Plateletlerde ve endotelde nitrik oksit yapımını ↑

↓

  - Platelet aggregasyonu inhibisyonu, selektif vazodilatatör etki

- İnsülin;

Doku faktörü↓
Plazminojen aktivatör inhibitör-1 ↓
Reaktif oksijen ürünleri ↓
Hücre içi adezyon molekülü-1 ↓

↓

ANTİOKSİDAN, ANTİTROMBOTİK, ANTİFİBRİNOLİTİK

Diabetik veya nondiyabetik hastalarda özellikle kardiyovasküler cerrahi sırasında hiperglisemi sıktır.

- *Carvalho G, Moore A, Qizilbash B, Lachapelle K, Schricker T. Maintenance of normoglycemia during cardiac surgery. Anesth Analg. 2004;99:319-24.*


Akut İnsülin Rezistansı
Nöroendokrin Stres Cevap
Kardiyak cerrahi
Cerrahi süresi
Cerrahinin yeri
Cerrahi teknik
PERİOPERATİF HİPERGLİSEMİ
İntraoperatif Yönetim
Anestezikler
Dextroz içeren ilaçlar
Steroidler
Adrenerjik agonistler
Alfa-2 agonistler
Hipotermi
Preoperatif metabolik durum
Dibetes mellitus
Sepsis/İnflamasyon
Obezite

PEROPERATİF HASAR

Artmış Hormonal Stres
Epinefrin↑, Kortizol ↑, İnflamatuar mediatörler ↑
İnhalasyon Anestezikleri
Aktivitenin Düşmesi
Glukokortikoid tedavi
Enteral veya Parenteral Nutrisyon

HİPERGLİSEMİ

İmmün Fonksiyon↓
Oksidatif Stres ↑
Endotelyal Disfonksiyon
İnflamatuar Mediatörler ↑
Prokoagülan durum
Mitogen seviyesi ↑
Sıvı şiftleri
Elektrolit değişiklikleri

Yara iyileşmesinde gecikme
Enfeksiyonlarda ↑
Derlenmede gecikme
Potansiyel son-organ disfonksiyonu
Miyokardial hasar
Serebral Hasar
Renal Hasar

- Preoperatif metabolik hast.
  (Diabetes mellitus)
- Nöroendokrin cevap ↑
  (Glukagon, epinefrin, kortizol aracılığı ile)
- Metabolik sendrom
- Varolan insülin rezistansı
- Altta yatan β-hücre disfonksiyonu

Perioperatif hiperglisemi riski ↑

Akut hiperglisemininin etkileri

- İmmün fonksiyon baskılanır
  - Kemotaksis
  - Fagositoz
  - ROS yapımında değişiklik
  - İnrasellüler bakteriyolizis

  } ↓

- Dolaşımdaki inflamatuar sitokin konsantrasyonu ↑

- NO yapımı ↓
  Angiotensin II↑
  ↑ SVR

  } Vasküler reaktivite değişiklikleri

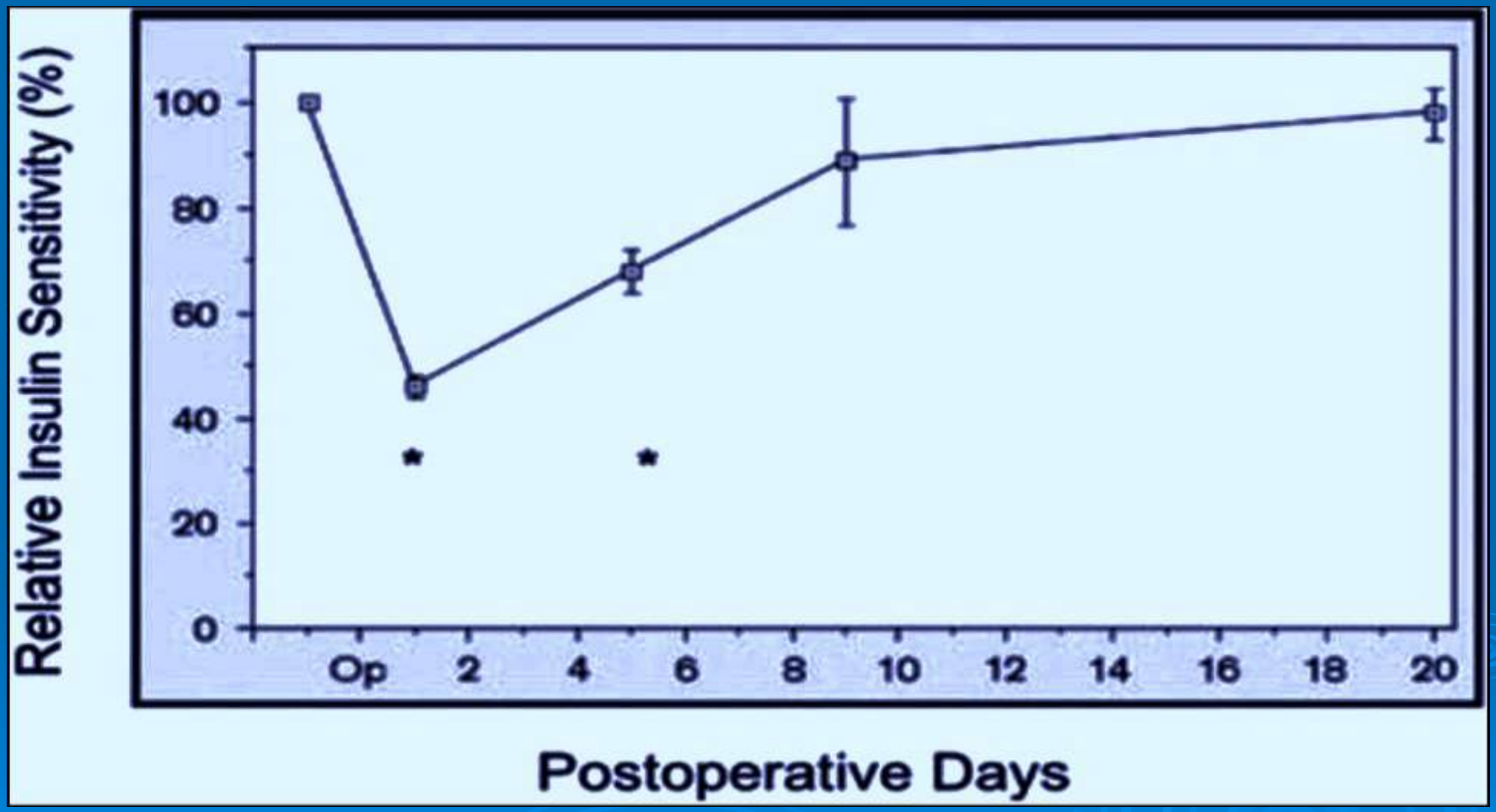
- Renal eşik geçildiğinde → Ozmotik diürez → Dehidratasyon → Elektrolit , asit-baz dengesizliği

- Hiperozmolarite → SSS disfonksiyonu → Serebral ödem

İnsülin rezistansı

- Etkili faktörler;
  - Yaş
  - Genetik predispozisyon
  - Etnik köken
  - Fiziksel aktivite seviyesi
  - Vücut ağırlığı
  - Perioperatif ↓ kalori
  - Negatif nitrojen dengesi
  - Proinflamatuar hücreler
  - Serbest yağ asitleri
  - Kontraregülatuar hormonlar(glukagon, epinefrin, kortizol)
- Esas etkili olduğu yer;
  - Adipoz doku
  - Karaciğer
  - Kalp ve iskelet kasları

Postoperatif insülin rezistansı



Scientific principles and clinical implications of perioperative glucose regulation and control.
Akhtar S; Barash PG; Inzucchi SE

Anesthesia & Analgesia. 110(2):478-97, 2010 Feb.

İntraoperatif dönemde glisemik kontrol?.....

Kardiyak cerrahi hastalarında optimal intraoperatif hiperglisemi tedavisinde fikirbirliği sağlanamamıştır.

Postoperatif glukoz konsantrasyonları düzenlendiği takdirde intraoperatif hiperglisemi ölüm dahil perioperatif bağımsız risk faktörlerinden birini oluşturmaktadır.

Glukoz konsanrasyonu > 100 mg/dL ⇒ Her 20 mg/dL

Postoperatif komplikasyon oranında % 34 artış

Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA,et al. ***Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients.*** *Mayo Clin Proc. 2005;80:862-6.*

Kardiyak cerrahi geçiren yoğun bakım hastalarında sıkı kan şekeri kontrolü morbidite ve mortaliteyi düşürür.

Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. ***Intensive insulin therapy in the critically ill patients.*** *N Engl J Med. 2001;345:1359-67.*

Kardiyak cerrahi geçiren hastalarda çok sıkı glisemik takip ve kontrol rutin uygulama haline gelmelidir.

Garber AJ, Moghissi ES, Bransome ED Jr, Clark NG, Clement S, CobinRH, et al. ***American College of Endocrinology position statement on inpatient diabetes and metabolic control.*** *Endocr Pract. 2004;10 Suppl 2:4-9.*

Diğer taraftan….

İntraoperatif hiperglisemi sadece altta yatan ***stres*** nedeni ile olabilir

Hipergliseminin kontrolü perioperatif komplikasyonları ve riskleri azaltmaz

Yoğun insülin tedavisi nedeni ile maliyet artar, ***kar-zarar ilişkisi*** bozulur…….

- Hiperglisemi kötü sonuçlara ***sebep olan faktör*** mü?.....

- Hiperglisemi kötü sonuçlara ***eşlik eden faktör*** mü?.....

- 400 kardiyak cerrahi hastası
  - ***Sıkı glisemik kontrol grubu***;
    - Kan glukoz seviyesi **80-100 mg/dL**
  - ***Konvansiyonel grup***;
    - Kan glukoz seviyesi **< 200 mg/dL**
    - ≥200 mg/dL ➡ 4 Ü insülin
    - >250 mg/dL ➡ İv insülin ile <150 mg/dL

Gunjan Y. Gandhi, Gregory A. Nuttall, Martin D. Abel, Charles J. Mullany, Hartzell V. Schaff,et al. ***Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery*** *Annals of Internal Medicine. 2007; 16:233-243*

Appendix Table 1. Insulin Infusion Protocol*

Column 1†		Column 2‡		Column 3§	
Serum Glucose Level, *mg/dL*	Insulin Infusion Rate, *U/h*	Serum Glucose Level, *mg/dL*	Insulin Infusion Rate, *U/h*	Serum Glucose Level, *mg/dL*	Insulin Infusion Rate, *U/h*
>400	18	>400	25	>400	30
351–400	16	351–400	22	351–400	27
301–350	14	301–350	20	301–350	24
251–300	12	251–300	18	251–300	21
201–250	10	201–250	15	201–250	18
176–200	8	176–200	12	176–200	15
151–175	6	151–175	9	151–175	12
121–150	4	121–150	7	121–150	9
101–120	2	101–120	4	101–120	6
80–100	1	80–100	2	80–100	3
<80	Off	<80	Off	<80	Off

Gunjan Y. Gandhi, Gregory A. Nuttall, Martin D. Abel, Charles J. Mullany, Hartzell V. Schaff,et al. ***Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery*** *Annals of Internal Medicine. 2007; 16:233-243*

Table 2. **Glycemic Control in Study Patients***

Characteristic	Intensive Treatment Group	Conventional Treatment Group	Mean Difference (95% CI)	*P* Value†
Intraoperative				
Baseline glucose level				
Patients, *n*‡	185	186		
Mean level (SD)				
mmol/L	6.2 (1.2)	6.2 (1.7)	0 (−0.3 to 0.3)	0.98
mg/dL	111 (22)	111 (31)	0 (−5 to 6)	
Post-CPB glucose level				
Patients, *n*‡	184	184		
Mean level (SD)				
mmol/L	6.8 (1.3)	8.2 (1.9)	−1.4 (−1.8 to −1.1)	<0.001
mg/dL	123 (24)	148 (35)	−25 (−32 to −19)	
Mean total amount of insulin, *U*	19 (16)	2 (5)	17 (15 to 20)	<0.001
ICU				
Baseline glucose level				
Patients, *n*‡	185	186		
Mean level (SD)				
mmol/L	6.3 (1.6)	8.7 (2.3)	−2.4 (−2.8 to −1.9)	<0.001
mg/dL	114 (29)	157 (42)	−43 (−50 to −35)	
24-h glucose level				
Patients, *n*‡	126	129		
Mean level (SD)				
mmol/L	5.7 (0.9)	5.8 (1.2)	−0.1 (−0.3 to 0.2)	0.72
mg/dL	103 (17)	104 (22)	−1 (−6 to 4)	
Mean total amount of insulin (SD), *U*	72 (41)	73 (37)	−1 (−9 to 7)	0.83

* Variables are compared across treatment groups using *t*-test or Wilcoxon rank-sum test. CPB = cardiopulmonary bypass; ICU = intensive care unit.
† *P* values are unadjusted.
‡ Number of patients with data available. The 8 patients (3 in the intensive treatment group and 5 in the conventional treatment group) who were randomly assigned but were lost to follow-up are not included in the analyses.

Gunjan Y. Gandhi, Gregory A. Nuttall, Martin D. Abel, Charles J. Mullany, Hartzell V. Schaff,et al. ***Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery*** *Annals of Internal Medicine. 2007; 16:233-243*

Appendix Table 3. **Glycemic Control in Patients with Diabetes***

Variable	Intensive Treatment Group	Conventional Treatment Group	Mean Difference (95% CI)	*P* Value†
Intraoperative				
Baseline glucose level				
Patients, *n*‡	37	36		
Mean level (SD)				
mmol/L	7.7 (1.7)	7.8 (3)	−0.1 (−1.2 to 1)	0.83
mg/dL	139 (31)	141 (53)	−2 (−22 to 18)	
Post-CPB glucose level				
Patients, *n*‡	37	35		
Mean level (SD)				
mmol/L	7.3 (1.6)	9.4 (2.7)	−2.1 (−3.1 to −1)	<0.001
mg/dL	132 (29)	169 (49)	−37 (−56 to −18)	
Mean total amount of insulin, *U*	26 (19)	4 (8)	22 (15 to 29)	<0.001
Intensive care unit				
Baseline glucose level				
Patients, *n*‡	37	36		
Mean level (SD)				
mmol/L	7.2 (1.6)	10 (2.8)	−2.8 (−3.8 to −1.7)	<0.001
mg/dL	130 (29)	180 (50)	−50 (−69 to −30)	
24-h glucose level				
Patients, *n*‡	28	28		
Mean level (SD)				
mmol/L	5.9 (1)	5.8 (1.4)	0.1 (−0.6 to 0.7)	0.84
mg/dL	106 (18)	105 (25)	1 (−10 to 13)	
Mean total amount of insulin (SD), *U*	99 (42)	82 (46)	17 (−4 to 38)	0.104

* Variables are compared across treatment groups using *t*-test or Wilcoxon rank-sum test. CPB = cardiopulmonary bypass.
† *P* values are unadjusted.
‡ Number of patients with data available.

Appendix Table 4. **Glycemic Control in Patients without Diabetes***

Variable	Intensive Treatment Group	Conventional Treatment Group	Mean Difference (95% CI)	*P* Value†
Intraoperative				
Baseline glucose level				
Patients, *n*‡	148	150		
Mean level (SD)				
mmol/L	5.8 (0.7)	5.8 (0.9)	0 (−0.2 to 0.2)	0.83
mg/dL	105 (13)	104 (16)	1 (−3 to 4)	
Post-CPB glucose level				
Patients, *n*‡	147	149		
Mean level (SD)				
mmol/L	6.7 (1.3)	7.9 (1.6)	−1.2 (−1.6 to −0.9)	<0.001
mg/dL	120 (23)	143 (29)	−23 (−29 to −17)	
Mean total amount of insulin, *U*	18 (16)	1 (3)	17 (14 to 19)	<0.001
Intensive care unit				
Baseline glucose level				
Patients, *n*‡	148	150		
Mean level (SD)				
mmol/L	6.1 (1.5)	8.4 (2.1)	−2.3 (−2.7 to −1.9)	<0.001
mg/dL	110 (27)	151 (38)	−41 (−49 to −34)	
24-h glucose level				
Patients, *n*‡	98	101		
Mean level (SD)				
mmol/L	5.7 (0.9)	5.8 (1.2)	−0.1 (−0.4 to 0.2)	0.59
mg/dL	102 (17)	104 (22)	−2 (−7 to 4)	
Mean total amount of insulin (SD), *U*	65 (38)	70 (34)	−5 (−14 to 3)	0.196

* Variables are compared across treatment groups using *t*-test or Wilcoxon rank-sum test. CPB = cardiopulmonary bypass.
† *P* values are unadjusted.
‡ Number of patients with data available.

Gunjan Y. Gandhi, Gregory A. Nuttall, Martin D. Abel, Charles J. Mullany, Hartzell V. Schaff,et al. ***Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery*** *Annals of Internal Medicine. 2007; 16:233-243*

Appendix Table 5. Comparison of Primary and Secondary Outcomes for Patients with Diabetes*

Outcome	Intensive Treatment Group (n = 37), n (%)	Conventional Treatment Group (n = 36), n (%)	P Value†
Any event‡	19 (51)	22 (61)	0.40
In hospital	19 (51)	21 (58)	
Postdischarge (up to 30 days after surgery)	2 (5)	2 (6)	
Death	2 (5)	0 (0)	0.49
In hospital	2 (5)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Stroke	2 (5)	0 (0)	0.49
In hospital	1 (3)	0 (0)	
Postdischarge (up to 30 days after surgery)	1 (3)	0 (0)	
Deep sternal infection	3 (8)	1 (3)	0.61
In hospital	2 (5)	1 (3)	
Postdischarge (up to 30 days after surgery)	1 (3)	0 (0)	
Cardiac arrest	0 (0)	0 (0)	1.00
In hospital	0 (0)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Heart block requiring pacemaker	2 (5)	0 (0)	0.49
In hospital	2 (5)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
New-onset atrial fibrillation	13 (35)	16 (44)	0.42
In hospital	13 (35)	15 (42)	
Postdischarge (up to 30 days after surgery)	0 (0)	1 (3)	
Acute renal failure	3 (8)	2 (6)	1.00
In hospital	3 (8)	1 (3)	
Postdischarge (up to 30 days after surgery)	0 (0)	1 (3)	
Prolonged (>24 h) intubation	7 (19)	9 (25)	0.53
In hospital	7 (19)	9 (25)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	

* Variables are compared across treatment groups by using chi-square or Fisher exact test.
† *P* values are unadjusted.
‡ Numbers for "any event" correspond to the number of patients who experienced ≥1 individual event.

Appendix Table 6. Comparison of Primary and Secondary Outcomes for Patients without Diabetes*

Outcome	Intensive Treatment Group (n = 148), n (%)	Conventional Treatment Group (n = 150), n (%)	P Value†
Any event‡	63 (43)	64 (43)	0.99
In hospital	59 (40)	61 (41)	
Postdischarge (up to 30 days after surgery)	6 (4)	7 (5)	
Death	2 (1)	0 (0)	0.25
In hospital	2 (1)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Stroke	6 (4)	1 (1)	0.066
In hospital	6 (4)	1 (1)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Deep sternal infection	3 (2)	6 (4)	0.50
In hospital	1 (1)	0 (0)	
Postdischarge (up to 30 days after surgery)	2 (1)	6 (4)	
Cardiac arrest	1 (1)	0 (0)	0.50
In hospital	1 (1)	0 (0)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Heart block requiring pacemaker	3 (2)	1 (1)	0.37
In hospital	3 (2)	1 (1)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
New-onset atrial fibrillation	41 (28)	43 (29)	0.85
In hospital	37 (25)	42 (28)	
Postdischarge (up to 30 days after surgery)	4 (3)	1 (1)	
Acute renal failure	3 (2)	2 (1)	0.68
In hospital	3 (2)	2 (1)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	
Prolonged (>24 h) intubation	29 (20)	29 (19)	0.95
In hospital	29 (20)	29 (19)	
Postdischarge (up to 30 days after surgery)	0 (0)	0 (0)	

* Variables are compared across treatment groups by using chi-square or Fisher exact test.
† *P* values are unadjusted.
‡ Numbers for "any event" correspond to the number of patients who experienced ≥1 individual event.

Gunjan Y. Gandhi, Gregory A. Nuttall, Martin D. Abel, Charles J. Mullany, Hartzell V. Schaff,et al. ***Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery*** *Annals of Internal Medicine. 2007; 16:233-243*

Appendix Table 7. **Comparison of Glycemic Control and Length of Stay for Patients with Diabetes***

Outcome	Intensive Treatment Group (n = 37)	Conventional Treatment Group (n = 36)	P Value†
Intraoperative hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), *n* (%)‡	0 (0)	1 (3)	0.49
Intraoperative hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), *n* (%)‡	0 (0)	5 (14)	0.025
ICU hypoglycemia (glucose <3.3 mmol/L [<60 mg/dL]), *n* (%)‡	1 (3)	5 (14)	0.214
ICU hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), *n* (%)‡	0 (0)	6 (17)	0.011
Mean length of stay in hospital (SD), *d*	8 (6)	8 (3)	0.63
Median length of stay in hospital (interquartile range), *d*	7 (5–10)	7 (6–9)	
Mean length of stay in ICU (SD), *d*	2 (2)	2 (2)	0.95
Median length of stay in ICU (interquartile range), *d*	1 (1–3)	2 (1–3)	

* Variables are compared across treatment groups using chi-square or Fisher exact test for dichotomous variables and *t*-test or Wilcoxon rank-sum test for continuous variables. ICU = intensive care unit.
† *P* values are unadjusted.
‡ Refers to number of patients who had ≥1 episode.

Appendix Table 8. **Comparison of Glycemic Control and Length of Stay for Patients without Diabetes***

Outcome	Intensive Treatment Group (n = 148)	Conventional Treatment Group (n = 150)	P Value†
Intraoperative hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), *n* (%)‡	1 (1)	0 (0)	0.50
Intraoperative hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), *n* (%)‡	0 (0)	2 (1)	0.50
ICU hypoglycemia (glucose level <3.3 mmol/L [<60 mg/dL]), *n* (%)‡	7 (5)	9 (6)	0.63
ICU hyperglycemia (glucose level >13.9 mmol/L [>250 mg/dL]), *n* (%)‡	0 (0)	5 (3)	0.060
Mean length of stay in hospital (SD), *d*	7 (4)	8 (6)	0.49
Median length of stay in hospital (interquartile range), *d*	6 (5–9)	6 (5–8)	
Mean length of stay in ICU (SD), *d*	2 (2)	2 (3)	0.35
Median length of stay in ICU (interquartile range), *d*	1 (1–2)	1 (1–2)	

* Variables are compared across treatment groups using chi-square or Fisher exact test for dichotomous variables and *t*-test or Wilcoxon rank-sum test for continuous variables. ICU = intensive care unit.
† *P* values are unadjusted.
‡ Refers to number of patients who had ≥1 episode.

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Sonuç olarak;

- İntravenöz infüzyon ile kan glukoz seviyesi normal sınırlarda tutulabilir.

- Yoğun intraoperatif insülin tedavisi konvansiyonel yöntemle kıyaslandığında ölüm veya morbidite üzerine belirgin etki oluşturamamıştır.

- Yoğun insülin tedavisi ile hastaya ölüm inme gibi zararların verilebileceği gözardı edilmemelidir.

Gunjan Y. Gandhi, Gregory A. Nuttall, Martin D. Abel, Charles J. Mullany, Hartzell V. Schaff,et al. ***Intensive Intraoperative Insulin Therapy versus Conventional Glucose Management during Cardiac Surgery*** *Annals of Internal Medicine. 2007; 16:233-243*

Table 1. Retrospective Studies

Study	Study type	Number and type of patients	Design	Glycemic goal or range	Salient findings
Preoperative					
Aristedis and Serafim[81]	Retrospective case-control	267 patients, head trauma	Nonstandardized protocol	None	Severity of head injury correlated with admission and postoperative glucose levels. Only postoperative glucose levels >200 mg/dL were predictors of poor outcomes
Yendamuri et al.[82]	Retrospective	738 patients, trauma	Nonstandardized protocol	None	Admission glucose >200 mg/dL was associated with increased mortality, increased hospital and ICU LOS, and increased rate of infection
Laird et al.[83]	Retrospective	516 patients, trauma	Nonstandardized protocol	None	Hyperglycemia (glucose >200 mg/dL) was associated with higher rate of infection and mortality
Sung et al.[84]	Prospective observational	1003 patients, trauma	Nonstandardized protocol	None	Hyperglycemia (glucose >200 mg/dL) had higher incidence of infection and hospital LOS
McGirt et al.[85]	Retrospective	1201 patients, carotid endarterectomy	Nonstandardized protocol	<200 mg/dL	Preoperative glucose >250 mg/dL was associated with increased incidence of stroke, TIA, MI, and death. Mild hyperglycemia (150–199 mg/dL) was not associated with difference in the incidence of stroke, TIA, MI, and death
Dronge et al.[86]	Retrospective	647 patients, noncardiac surgery	Nonstandardized protocol	HbA_{1c}	A HbA_{1c} < 7% associated with decreased incidence of infectious complications
Noordzij et al.[80]	Retrospective, case-control	904 patients, noncardiac, nonvascular surgery	Nonstandardized protocol	None	In patients with prediabetes 3-fold increase while in patients with diabetes 4-fold increase in cardiovascular mortality
Intraoperative					
Hill et al.[87]	Retrospective	2862 patients, CABG	Nonstandardized glucose management	None	No association between maximum blood glucose concentration and mortality (univariate analysis)
Guvener et al.[88]	Retrospective	1090 patients, CABG	Nonstandardized glucose management	150–200 mg/dL	Patients with diabetes were more prone to infectious complications. Preoperative hyperglycemia was an independent predictor of short-term infectious complications and the total hospital LOS
Estrada et al.[89]	Retrospective	1574 patients, CABG	Nonstandardized glucose management		Hyperglycemia did not predict increased mortality
Furnary et al.[90]	Prospective observational	3554 patients, CABG	SQ insulin versus continuous IV insulin	150–200 mg/dL, 125–175 mg/dL, and 100–150 mg/dL	Continuous IV insulin therapy (prebypass to 3 d postoperative) improved survival (2.5% vs 5.3%)
Doenst et al.[79]	Retrospective	6280 patients, cardiac surgery	Insulin by bolus during CPB	>270 mg/dL	Peak glucose >360 mg/dL was associated with adverse events and mortality
Gandhi et al.[78]	Retrospective	409 patients, cardiac surgery	Nonstandardized glucose management	N/A	Maximal and mean intraoperative glucose predicted increased morbidity and mortality (multivariate analysis). Increase in mean intraoperative glucose level (20 mg/dL) associated with an increase occurrence (30%) of an adverse event
D'Alessandro et al.[91]	Prospective observational	600 patients, CABG	Insulin by standardized protocol pre, intra, and postoperatively	150–200 mg/dL	No difference in cardiac, pulmonary, neurological, renal, and infectious complications. Decreased mortality in treatment group (1.3% vs 4.0%)
Puskas et al.[7]	Retrospective	525 patients, CABG	Nonstandardized glucose management	N/A	At 6 wk, nondiabetics patients, glucose >200 mg/dL was associated with decreased cognitive dysfunction. In patients with diabetes, hyperglycemia had no effect on cognitive dysfunction

(Continued)

Table 1. Continued

Study	Study type	Number and type of patients	Design	Glycemic goal or range	Salient findings
Postoperative					
Finney et al.[92]	Prospective observational	523 patients, medical (12%), surgical (88%) ICU	Insulin by nonstandardized protocol	90–145 mg/dL	Patients divided into 6 groups. Best outcomes noted in patients with glucose levels between 145 and 180 mg/dL. In all glucose groups, insulin administration was associated with increased risk of death
McAlister et al.[93]	Retrospective	291 patients, CABG	92% received IV insulin by protocol	164–209 mg/dL	Hyperglycemia on POD-1 was an independent predictor of adverse outcomes
Vriesendorp et al.[94]	Retrospective	275 patients, vascular surgery	Nonstandardized protocol	None	Postoperative infection rate correlated with hyperglycemia
Krinsley[95]	Retrospective observational	1600 patients, medical (65%)/ surgical (35%) ICU	Insulin by standardized protocol	<140 mg/dL	Lower incidence of mortality (20.9% vs 14.8%), renal dysfunction (3% vs 12%), and PRBC transfusion (20.5% vs 25.5%). No difference in infection and LOS. No benefit of hyperglycemic control if APACHE score >35
Bochicchio et al.[8]	Prospective observational	942 patients, trauma	Nonstandardized protocol	None	High (glucose > 220 mg/dL), worsening, or highly variable glucose levels associated with increased risk of infection, ICU-LOS, H-LOS, and mortality
Gale et al.[96]	Retrospective	103 patients, trauma ICU	SQ insulin by standardized protocol	<140 mg/dL	Blood glucose level >140 mg/dL was associated with increased morbidity and mortality
Schmeltz et al.[97]	Retrospective	614 patients, cardiothoracic surgery	Insulin by standardized protocol	80–110 mg/dL	Blood glucose level >200 mg/dL on admission to the ICU was associated with increased morbidity and mortality
Reed et al.[98]	Retrospective	7261 patients, trauma	Progressively stringent insulin protocol	Mean glucose decreased from 141 to 129	Decreased incidence of intraabdominal abscesses. Decreased number of days on the ventilator
Wahl et al.[99]	Prospective observational	513 patients, trauma	Insulin by standardized protocol	<140 mg/dL	Mean blood glucose levels >140 mg/dL were strongly associated with mortality but not with infection rate
Asclone et al.[100]	Retrospective	8727 patients, cardiac surgery	Insulin by standardized protocol	90–144 mg/dL	Glucose level >200 mg/dL anytime during the first 5 d was associated with increased in-hospital morbidity and mortality
Treggiari et al.[101]	Retrospective	10,456 patients, medical/ surgical	Progressively stringent insulin protocol	None 80–130 mg/dL 80–110 mg/dL	No difference in hospital mortality with glycemic control. 4X higher incidence of hypoglycemia with glycemic control
Meier et al.[102]	Retrospective	228 patients, neurotrauma	Insulin by standardized protocol	70–130 mg/dL	No difference in outcome during the first week. Decreased ICP and infection rate in the second week
Ramos et al.[103]	Retrospective	995 patients, general/ vascular surgery	Nonstandardized protocol	None	Postoperative infection rate was associated postoperative hyperglycemia
Thiele et al.[104]	Retrospective	834 neurosurgical points with SAH	Insulin by standardized protocol	<120 mg/dL	No difference in inhospital mortality

ICU = intensive care unit; LOS = length of stay; TIA = transient ischemic attack; MI = myocardial infarction; HbA1c = hemoglobin A1c; PRBC = packed red blood cells; CABG = coronary artery bypass surgery; ICU-LOS = intensive care length of stay; H-LOS = hospital length of stay; ICP = intracranial pressure; SAH = subarachnoid hemorrhage; POD = postoperative day.

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Table 2. Prospective Studies

Study	Study type	Number of patients	Study design	Glycemic goal or range	Salient findings
Intraoperative					
Rassias et al.[110]	RCT	30 patients, CABG	Insulin by standardized protocol	75–125 mg/dL	Increased total neutrophil phagocytic capacity in insulin treatment group
Rao et al.[111]	RCT	1127 patients, CABG	Insulin during cardioplegia	None	No difference in myocardial injury and/or low cardiac output syndromes between treatment and control groups
Butterworth et al.[112]	Prospective	381 patients, CABG	Insulin by standardized protocol	<100 mg/dL	No difference in short- and long-term neurological complications between the groups
Koskenkari et al.[113]	RCT	40 patients, CABG + AVR	Insulin by standardized protocol	108–180 mg/dL	Improved myocardial contractile function and decreased inotropic support. No difference in clinical outcomes
Gandhi et al.[107]	RCT	400 patients, CABG	Intraoperative insulin by standardized protocol	80–100 mg/dL	No difference in composite outcomes. Increased number of deaths (4 vs 0) and stroke (8 vs 1) in the intensive insulin group
Postoperative					
van den Berghe et al.[114]	RCT	1548 patients, surgical ICU	Intensive insulin by standardized protocol	<110 mg/dL	Significant difference in morbidity and mortality, in patients who stayed >5 d. No difference in mortality in patients who stayed <5 d (1.7% vs 1.8%)
Grey and Perdrizet[115]	RCT	61 patients, general surgery	Intensive insulin by standardized protocol	80–120 mg/dL	Decrease in nosocomial infection rate
Hoedemaekers et al.[116]	RCT	20 patients, postcardiac surgery	Insulin by standardized protocol	80–110 mg/dL	No difference in outcomes between treatment groups (PRBC transfusion, time on ventilator, ICU-LOS, or renal dysfunction). No difference in IL-10, and IL-6 levels between treatment groups
Bilotta et al.[117]	RCT	78 patients, aneurysm clipping/neurosurgery	Insulin by standardized protocol	80–120 mg/dL	Infection rate was lower in treatment group. No difference in postoperative vasospasm, neurologic outcome, and mortality rates
Bilotta et al.[118]	RCT	97 patients, traumatic brain injury requiring surgery	Insulin by standardized protocol	80–120 mg/dL	Decreased length of ICU stay. No difference in infection rate and mortality
Bilotta et al.[119]	RCT	483 patients, neurosurgery	Insulin by standardized protocol	80–110 mg/dL	Decreased length of ICU stay and infection rate. No difference in mortality and Glasgow outcome scale at 6 mo
Finfer et al.[11]	RCT	6104 patients, medical/surgical ICU	Insulin by standardized protocol	81–108 mg/dL	Increased mortality in IGC group. No difference in number of days in the ICU, hospital, on mechanical ventilation, or renal replacement therapy
Subramaniam et al.[120]	RCT (unblinded)	236 patients, vascular surgery	Continuous insulin infusion versus SQ, started intraoperatively and continued 48 h	100–150 mg/dL	Decreased major cardiovascular events in patients who received continuous insulin infusion

ICU = intensive care unit; LOS = length of stay; PRBC = packed red blood cells; CABG = coronary artery bypass surgery; AVR = aortic valve replacement; ICU-LOS = intensive care length of stay; H-LOS = hospital length of stay; IL-6 = interleukin 6; IL-10 = interleukin 10; IGC = intensive glucose control; RCT = randomized controlled trial.

İntraoperatif ve postoperatif dönem değerlendirildiğinde sonuç olarak;

- *Perioperatif hiperglisemi ve kötü sonuçlar arasında güçlü ilişki mevcuttur.*
- *İntraoperatif ve postoperatif dönemdeki sıkı glukoz kontrolunun değeri prospektif olarak kanıtlanamamıştır.*
- *Bu durumda intravenöz infüzyonla sıkı glukoz kontrolünün perioperatif dönemde etkinliği savunulamaz.*

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Hipoglisemi

- Glukoz seviyesi↓ ⟶ kompansatuar stres cevap
- Glukoz seviyesi↓ ⟶ iskemik beyine laktat sağlanması ↓ ⟶ beyin hasarı↑
- İntravenöz infüzyonla sıkı glukoz kontrolünün yapıldığı hastalarda hipoglisemi insidansı %3-13 oranında↑
- ↑İnsülin infüzyonu sempatik deşarj, sodyum retansiyonu çeşitli mitojenik aktivasyonlar nedeni ile mortalite ve hipoglisemi insidansında artışa neden olabilir.

Hipoglisemiye yatkınlık;

- Dişi cinsiyet
- Sepsis
- Diabetes mellitus öyküsü
- İnsülin dozu ayarlanmamış hastada nutrisyonel desteğin azaltılması veya kesilmesi
- Sürekli venövenöz hemofiltrasyon
- Bikarbonat bazlı sıvılar
- İnotropik destek ihtiyacının olması
- Hepatik, renal, adrenal yetmezlik

Perioperatif hiperglisemide pratik yönetim

- Hipoperfüze, hipotermik, anemik hastada kapiller glukoz ölçümü doğru sonuç vermez.
- Glukometre ile konvansiyonel laboratuar ölçümleri arasında glukoz konsantrasyonu <100mg/dL olduğunda %15, >100mg/dL olduğunda %20 fark oluşabilir.
- Plazma glukoz konsantrasyonu tam kan glukoz konsantrasyonundan %11 daha yüksektir.
- Arteriyel kandaki glukoz konsantrasyonu venöz ve kapiller kandaki glukozdan yüksektir.
- Hastanın hemodinamik durumu glukoz ölçümlerinin doğruluğunu etkiler.
- L-Dopa, dopamine, mannitol, asetaminofen, unkonjuge bilirübin artışı, şiddetli hiperlipidemi ürik asit artışı gibi medikasyonlar ve durumlar glukoz ölçümünü etkileyebilir.

Perioperatif hiperglisemide pratik yönetim

- Preoperatif değerlendirmede diabete yatkınlık değerlendirilmelidir;
  - 45 yaşın üzerinde
  - Vücut kitle indeksi >25 kg/m2
  - 1. derece akrabalarda DM varlığı
  - Gestasyonel diabet öyküsü veya >4.1 kg doğum öyküsü olan kadınlar
  - HDL<35 mg/dL
  - Trigliseritler>250mg/dL
  - Polikistik over sendromu olan kadınlar
  - Fiziksel inaktivite
- HbA1c ölçümü geçmiş dönemdeki uzun süreli hiperglisemi hakkında bilgi verir.
- Ketoasidoz veya hiperglisemik hiperozmolar durum varlığında elektif cerrahi ertelenmelidir.

Perioperatif glisemik kontrol önerileri

	American College of Endocrinology	Canadian Diabetes Association	American Diabetes Association	American Heart Association/ American College of Cardiology	Society of Thoracic Surgeons (Kardiak cerrahi için)
Yoğun Bakım	140 - 180 mg/dL; Genellikle > 180 mg/dL	110mg/dL	140 - 180 mg/dL; Genellikle >180 mg/dL	110-180 mg/dL	Genellikle > 180 mg/dL Yoğun bakımda ventilatöre bağlı >3 gün; < 150 mg/dL
İntraoperatif	< 150 mg/dL	90 - 180 mg/dL	< 150 mg/dL		< 180 mg/dL
Perioperatif	Yemek öncesi < 140 mg/dL veya < 180 mg/dL (rastgele ölçüm)	90 - 180 mg/dL	Yemek öncesi < 140 mg/dL veya < 180 mg/dL (rastgele ölçüm)	NA	< 180 mg/dL

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Sonuç

- Hastanın;
  - perioperatif metabolik durumu
  - intraoperatif anestezi yönetimi
  - ekzojen glukoz uygulamaları
  - nöroendokrin cevap
  - akut insülin rezistansı gelişimi
  - endojen insülin sekresyonundaki değişiklikler

  } perioperatif glukoz düzeyini belirler

- Hiperglisemi, sebebinden bağımsız olarak kötü sonuçlar ile yakından ilişkilidir.
- Hipergliseminin düzeltilmesinin cerrahi morbidite ve mortaliteyi azalttığı kesinlik kazanamamıştır.

Sonuç

- Evrensel terapatik glisemik hedef ve perioperatif glisemik kontrolün gerçek etkinliği tanımlanamamıştır.
- Sıkı kan glukozu takibinin (<110 mg/dL) etkinliğinin kanıtlanamamasının yanında hipoglisemi riskini 3-6 kat arttırabildiğini gösteren yayınlar mevcuttur.
- Kan glukoz takibinin tamamen terkedilmesi kesinlikle önerilmemektedir.
- Perioperatif dönemde kan glukoz seviyesinin <180mg/dL olması konusunda dikkat edilmelidir.
- Perioperatif dönemde insülin tedavisi intravenöz yoldan yakın glukoz monitorizasyonu ile uygulanmalıdır.