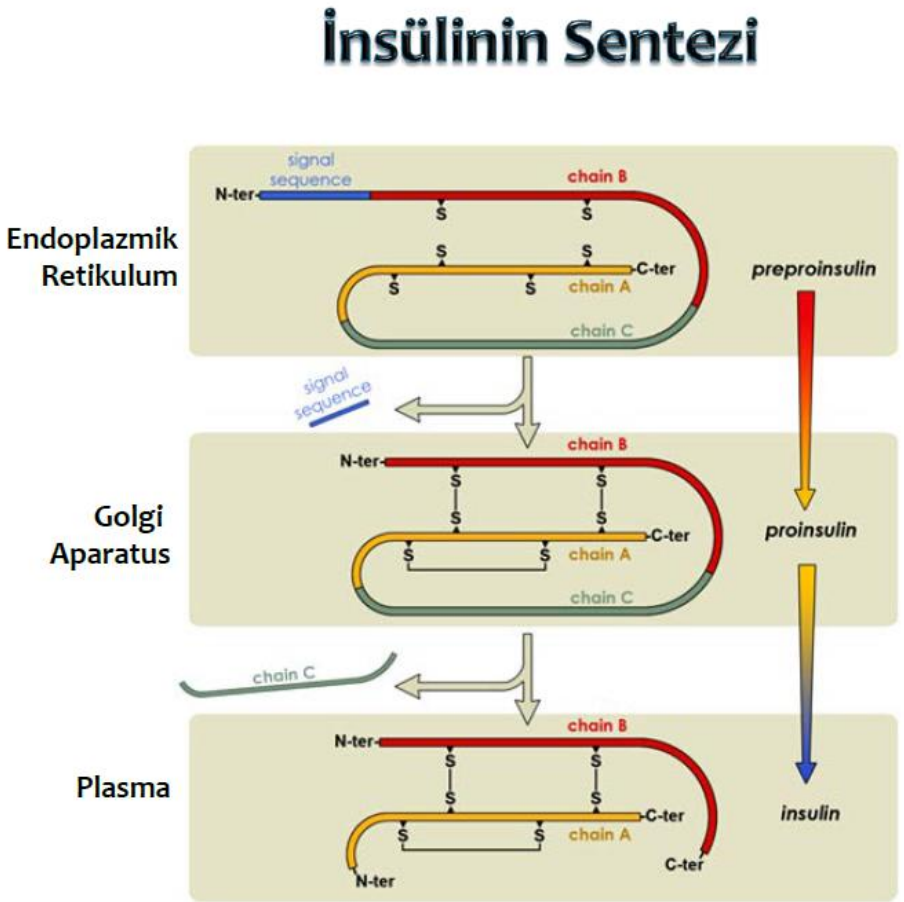
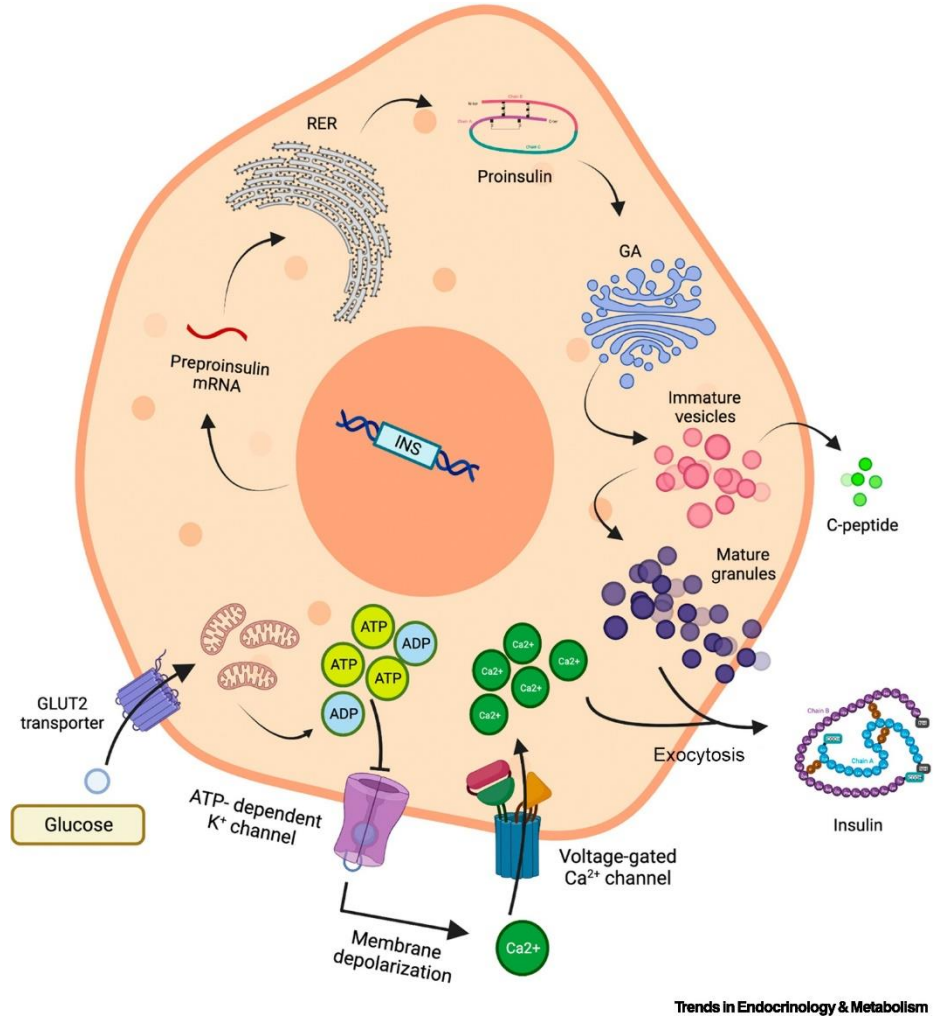
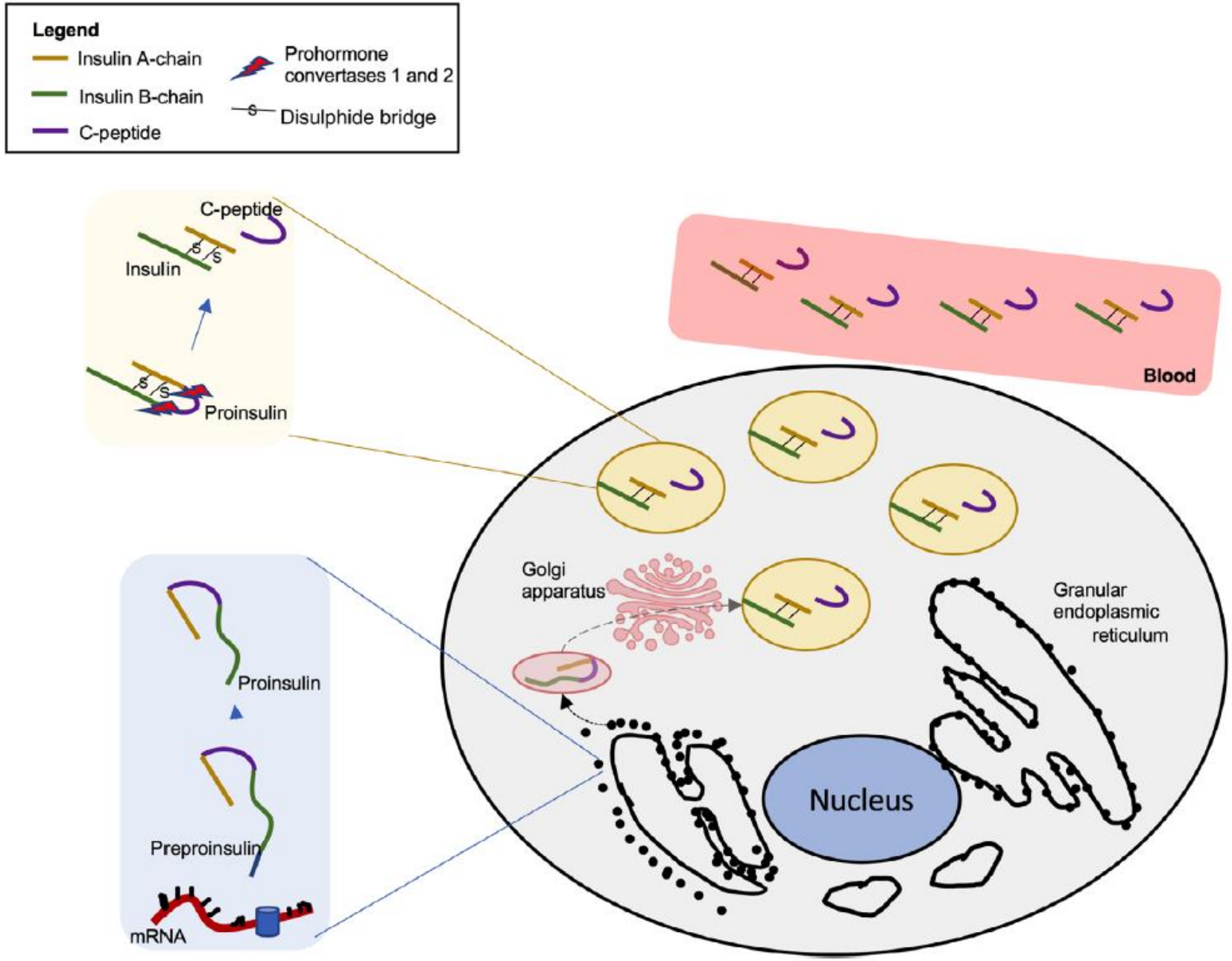
# C PEPTİD

DOÇ. DR. KAĞAN GÜNGÖR

# İnsülin sentezi

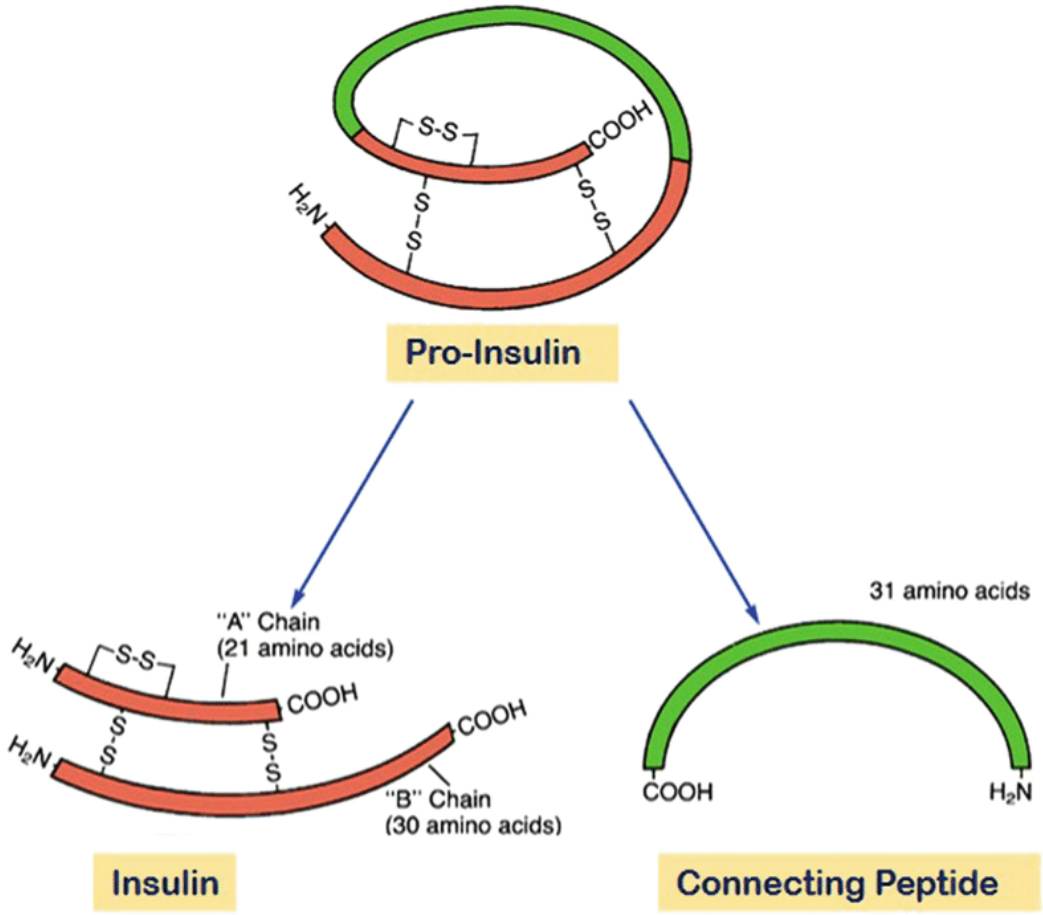



Legend
Insulin A-chain
Insulin B-chain
C-peptide
Prohormone convertases 1 and 2
Disulphide bridge
C-peptide
Insulin
Proinsulin
Blood
Golgi apparatus
Granular endoplasmic reticulum
Nucleus
Proinsulin
Preproinsulin
mRNA

# C Peptid Nedir?
## Connecting Peptid

- Proinsülinin endopeptidaz enzimleri ile parçalanması ile oluşur
- ***İnsülin*** ile ***eş miktarda C peptid*** salınır



# Neden C peptid insülin değil ?

**İNSÜLİN**

- Yarı ömrü 3-5 dakika
- Hepatik ilk geçiş etkisi ile %50 si salgılanır salgılanmaz metabolize edilir.
- Periferik klirensi değişkendir
- Eksojen ve endojen insülin cross reaksiyona girer ayırt edilemez

**C PEPTİD**

- Yarı ömrü 20-30 dakika
- Hepatik ilk geçiş etkisinden etkilenmez
- Periferik klirensi sabit hızla olur
- Eksojen ve endojen insülin etkisinden bağımsız değerlendirilir

SONUÇ; BETA HÜCRE REZERVİNİ DEĞERLENDİRMEDE C PEPTİD ALTIN STANDART TESTTİR

# C-peptid

- Sağlıklı erişkinlerde
  - plazma C-peptid düzeyleri açlıkta 0.3-0.6 nmol/L (0.91-1.82 ng/mL),
  - toklukta 1-3 nmol/L (3.03-9.09 ng/mL).
- 1 nmol/ L = 1 pmol/ml = 1000 pmol/l = 3 ng/ml

Jones AG et al. Diabet. Med. 2013;30:803-817.
Leighton E et al, Diabetes Ther, 2017

# *C peptid düzeyini etkileyen durumlar*

## Beta hücre kitlesinden bağımsız

| | |
|---|---|
| Glukoz düzeyi | ❖ Düşük glukoz düşük C peptid<br>❖ Glukoz > 140 mg/dL iken ölçülen C peptid stimule (uyarılmış) C peptid olarak değerlendirilmelidir |
| İnkretin etki | ❖ İnkretin fizyolojisinin bozulması beta hücresinin öğünlere insülin yanıtını bozar<br>❖ Öğünden sonra geçen zaman ve öğün içeriği C peptid düzeyine etki eder |
| İnsülin direnci | ❖ C peptid düzeyleri artar |
| Böbrek fonksiyonu | ❖ C peptid klirensi böbrek yetersizliğinde azalır |
| Standardizasyon | ❖ Laboratuvarlar ve kullanılan kitler arasındaki farklılıklar |

# C peptid ölçüm standardı

Dünya Sağlık Örgütünün C peptid ölçümünde getirdiği standardizasyona rağmen farklı kit ve laboratuvar ölçümleri arasında farklılık olabilmektedir. Mümkünse aynı laboratuvar ve kitlerle yapılmış test sonuçlarını karşılaştırmak (takip için art arda değerler bakılacaksa) önerilir
World Health Organization Standart (International Reference Reagent (IRR) 84/510

# C-peptid: Ölçüm Yöntemleri

- C-peptid ölçüm yöntemleri:

  - **<u>İdrar:</u>**
  - İdrar düzeyi: Borik asit ile toplandığında oda ısısında üç gün kalabilir. Böbrek fonksiyonu normal olanlarda pankreas tarafından üretilen C-peptidin %5-10'nunu yansıtır.
  - İdrar C-peptid/kreatinin: Normal glukoz toleransı olanlarda 24 saatlik idrar C-peptidi ile iyi koreledir.

  - **<u>Kan:</u>**
  - Uyarılmamış serum düzeyi: Açlık veya herhangi bir zamanda alınabilir
  - Uyarılmış serum düzeyi: Glukagon, IV/oral glukoz, tolbutamid, sülfonilüre, GLP-1, aminoasitler, miks-meal

Leighton E et al, Diabetes Ther, 2017

# C peptid ?

***Açlık C peptid***

- Denge statik durumu gösterir

***Random (Rastgele) C peptid***

- Dinamik değerlendirme
- Öğün sonrası artan glukoz düzeyi ve inkretin etkiden etkilenir

# Dinamik C peptid değerlendirme testleri

- Glukagon Stimulasyon Testi GST
- Mix Meal Tolerans Testi MMTT
- Oral Glukoz Tolerans Testi OGTT

# C peptidin tıbbi kullanım yerleri

1) Tanısal
2) Prognostik
3) Tedavi yanıtı değerlendirme öngörme

# C peptidin tanısal kullanımı

- Tip 1 Diyabet tanısı koymada
- Tip 1 ile Tip 2 Diyabeti ayırt etmede
- MODY tanısı koymada
- LADA tanısı koymada antikor testi ile birlikte
- CGMS (sürekli glukoz monitörize eden sistemlerin) kullanım endikasyonu açısından

Leighton E et al. Diabetes Ther. 2017: 8:475–487

# C peptidin prognostik anlamı

- Diyabet süresinin belirteci
- Düşük C peptid Tip 1 diyabetik hastada daha çok mikrovasküler komplikasyon öngörüsü anlamına gelir
- Düşük C peptid daha yüksek glukoz variabilitesi (değişkenliği) daha yüksek HbA1C
- Ne kadar düşük C peptid o kadar yüksek hipoglisemi riski

Leighton E et al. Diabetes Ther. 2017: 8:475–487

# C peptidin tedavi yanıtı değerlendirme ve öngörmede yeri

- Ne kadar düşük bazal C peptid o kadar fazla insülin ihtiyacı
- Ne kadar düşük bazal C peptid o kadar kısa sürede insülin gereksinimi
- Bazal C peptid düzeyi yüksek olan hastalar metformine ve sülfanilürelere iyi yanıt verir
- Bazal C peptid düzeyi yüksek olan hastalar thiazolidindionlara iyi yanıt verir
- Bazal C peptid düzeyi yüksek olan hastalar GLP-1 analoğu tedavilerine iyi yanıt verir

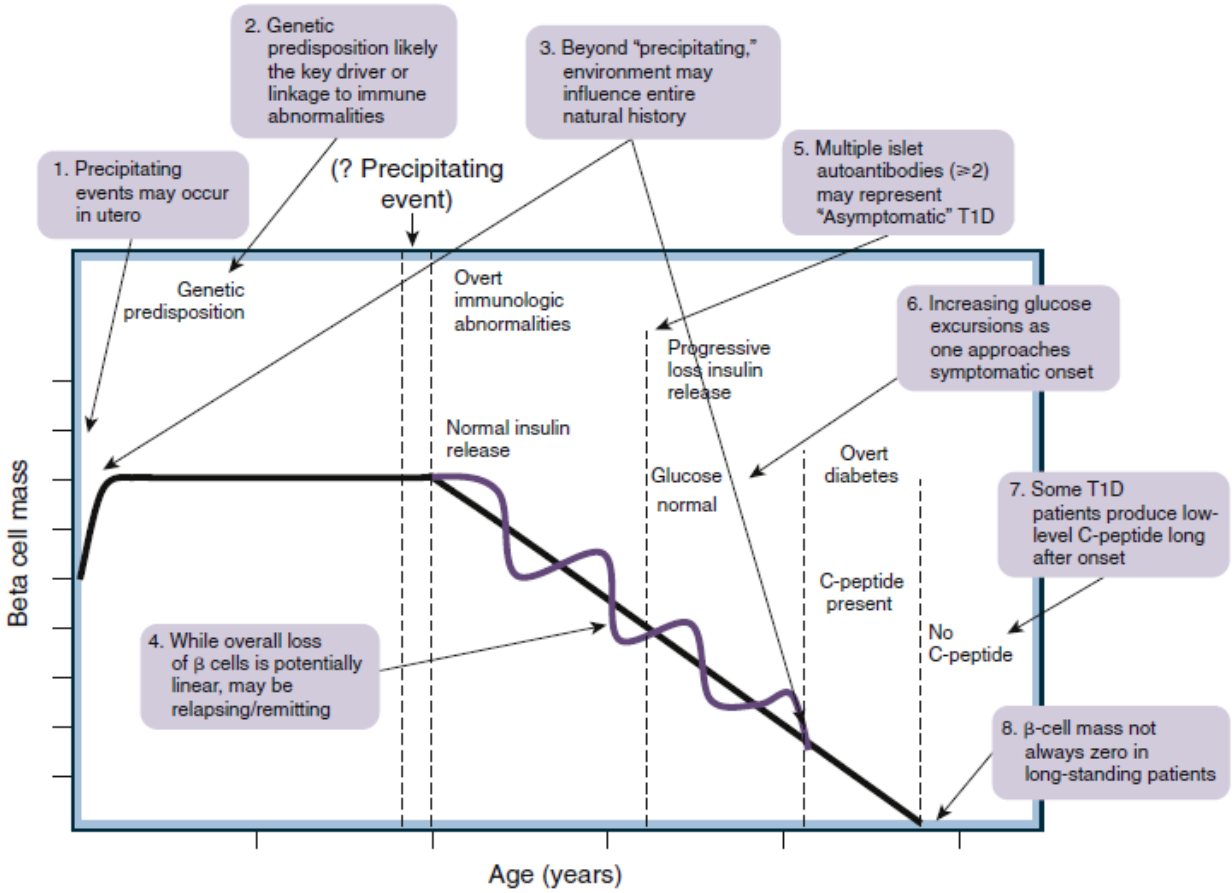
Leighton E et al. Diabetes Ther. 2017: 8:475–487

# C-peptid Diyabet dışı kullanım

- C-peptid, diyabet dışı hipoglisemilerin tanısında  önemlidir:
  - İnsülinoma
  - Faktisyöz hipoglisemi

Leighton E et al. Diabetes Ther. 2017: 8:475–487

# Tip 1 diyabet




• **Fig. 36.3** The natural history of type 1 diabetes mellitus—a 25-year-old concept revisited. A re-creation of the model as originally proposed in 1986 is tracked by the *black line*. Several additions and conjectures can be made to this model based on recent knowledge gains (*lavender line*). *T1D*, type 1 diabetes. (Redrawn from Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet*. 2014;383:69–82, used with permission.)

# C-peptid: Tip 1 ve Tip 2 diyabeti ayırt etmede tanısal değeri

| Reference | Number, population and study design | C-peptide test* | C-peptide threshold and predictive value of values below or above threshold for diabetes subtype or islet autoantibody status | Notes |
|---|---|---|---|---|
| At diagnosis of diabetes | | | | |
| Ludvigsson, 2012 [67] | 2734 children newly diagnosed with diabetes (Type 1 95%, Type 2 or MODY 3%). C-peptide alone compared with final diagnosis incorporating clinical features and knowledge of autoantibody status, C-peptide, human leukocyte antigen (HLA) status and (in some cases) MODY genetics | Non-fasting 'random' | < 0.2 nmol/l > 99.8% predictive value Type 1 diabetes ≥ 1.0 nmol/l 46% predictive value Type 2 diabetes or MODY | C-peptide at diagnosis a much stronger predictor of Type 2 diabetes or MODY than age or glycaemia |
| Thunander, 2012 [18] | 1178 adults diagnosed over 20 years (mean age 66). C-peptide at diagnosis compared with presence or absence of islet autoantibodies (GAD or ICA, 4.9% antibody positive) | Fasting | < 0.6 nmol/l 30.1% predictive value autoantibodies, > 0.6 nmol/l 97.4% predictive value absence of autoantibodies | C-peptide superior to age and BMI in discriminating autoimmune and non-autoimmune diabetes |
| Katz, 2007 [129] | 175 children with new-onset diabetes. Type 2 diabetes (15%) if obese, relative with Type 2 diabetes, ability to wean from insulin, GAD antibody negative | Fasting | < 0.28 nmol/l 98% predictive value Type 1 diabetes > 0.28 nmol/l 48% predictive value Type 2 diabetes | |
| Torn, 2001 [38] | 486 newly diagnosed aged 15–34 years, C-peptide measured in either fasting or non-fasting 'random' and compared with presence of islet autoantibodies (ICA, GAD, IA-2A, 74% antibody positive) | Fasting and non-fasting 'random' | Fasting < 0.3 nmol/l 85% predictive value autoantibodies Non-fasting < 0.3 nmol/l 94% predictive value autoantibodies Fasting > 1.0 nmol/l 75% predictive value absense of autoantibodies Non-fasting > 1.0 nmol/l 83% predictive value absense of autoantibodies | |

Jones AG et al. Diabet. Med. 2013;30:803-817

| Reference | Number, population and study design | C-peptide test* | C-peptide threshold and predictive value of values below or above threshold for diabetes subtype or islet autoantibody status | Notes |
|---|---|---|---|---|
| | | | autoantibodies | |
| Long-standing diabetes | | | | |
| Besser, 2011† [65] | Urine C-peptide:creatinine ratio measured post-home meal in 70 patients with Type 1 diabetes (diagnosis age < 30 years, insulin from diagnosis) and 69 patients with Type 2 diabetes (diagnosis ≥ 30 years, no insulin in first post-diagnosis year) | Urine C-peptide: creatinine ratio | < 0.2 nmol/mol 98.5% predictive value Type 1 diabetes > 0.2 nmol/l 95.3% predictive value Type 2 diabetes | Long duration diabetes (Type 1 diabetes median 34 years) may account for high performance of the low threshold in predicting Type 2 diabetes |
| Berger, 2000 [39] | Retrospective analysis of 1093 patients with well-defined diabetes type (34% Type 1) who had had C-peptide measured in clinical care (duration at C-peptide testing not reported). Type 2 diabetes: clinicians diagnosis and no insulin for 3 years. Type 1 diabetes: clinicians diagnosis and continuous insulin for > 3 years from diagnosis | Fasting<br>Non-fasting C-peptide with glucose > 8 mmol/l<br><br>Glucagon stimulated | Fasting < 0.42 nmol/l 81.0% predictive value Type 1 diabetes<br>Fasting > 0.42 nmol/l 91.3% predictive value Type 2 diabetes<br>Non-fasting < 0.5 nmol/l 91.5% predictive value Type 1 diabetes<br>Non-fasting > 0.5 nmol/l 95.3% predictive value Type 2 diabetes<br>Glucagon-stimulated < 0.6 nmol/l 93.9% predictive value Type 1 diabetes<br>Glucagon-stimulated > 0.6 nmol/l 77.1% | C-peptide may have influenced diagnosis. Included patients whose C-peptide was measured at or close to diagnosis |
| Service, 1997 [130] | 346 patients with diabetes (mostly long-standing) classified as insulin-dependent diabetes (24%) and non-insulin-dependent diabetes (76%) by clinical algorithm. Clinical | Fasting and increment in mixed-meal tolerance test | Fasting C-peptide < 0.17 nmol and mixed-meal tolerance test increment < 0.07 predictive value Type 1 diabetes 77%. All other C-peptide responses | Follow-up for up to 8 years showed C-peptide classification remained stable |

| Reference | Number, population and study design | C-peptide test* | C-peptide threshold and predictive value of values below or above threshold for diabetes subtype or islet autoantibody status | Notes |
|---|---|---|---|---|
| | classification compared with classification by C-peptide—fasting < 0.17 nmol/l and increment < 0.07 indicating insulin-dependent diabetes, all other responses defined as Type 2 diabetes | | predictive value Type 2 diabetes 93% | |
| Prior, 1993 [41] | 373 (Type 2 diabetes 114) adults with known retinopathy meeting study definitions of Type 1 diabetes ($n$ = 259, diagnosis < 30 years, insulin within 1 year, weight < 120% desirable) or Type 2 diabetes ($n$ = 114, diagnosis > 30 years and not on insulin or diagnosis > 40 years and weight 120% desirable) | Fasting and 90 min in mixed-meal tolerance test | Mixed-meal tolerance test C-peptide < 0.08 nmol/l = 100% predictive value Type 1 diabetes. Mixed-meal tolerance test C-peptide > 0.08 nmol/l 91% predictive value Type 2 diabetes. Fasting C-peptide < or > 0.08 nmol/l 97.4% agreement with mixed-meal tolerance test classification | Long duration of diabetes (retinopathy required for inclusion) may account for the low threshold chosen |

# LADA C peptid çalışmalar

| Study | Diabetes type | C-peptide levels (nmol/L) of clinical interest | | Interpretation |
|---|---|---|---|---|
| Buzzetti et al.[91] | LADA | <0.30 | → | Identify people requiring insulin therapy |
| | | ≥0.30 and ≤0.70 | → | Identify people who might benefit from a flexible therapeutic approach and from regular C-peptide measurements over time |
| | | >0.70 | → | Identify people who can be treated according to the T2D guidelines and who should repeat C-peptide measurement if glycaemic control deteriorates |
| Wod et al.[89] | Adult-onset newly diagnosed diabetes | 0.30 (fasting) | → | Stratify people with adult-onset diabetes for different risk metabolic profiles independently from GADA and age at onset |

Maddoloni et al. Diabetes Obes Metab.2022;24:1912-1926

# MODY
# **M**aturity **O**nset **D**iabates of **Y**oung

- Tip 1 diyabet tanısı almış bir hastada tanıdan 3-5 yıl zaman geçmiş olmasına rağmen;
  - Açlık C peptid> 0.08 nmol/L
  - Random ya da uyarılmış C peptid > 0.2 nmol/L
  - Yemek sonrası idrar C peptid/ kreatinin oranı > 0.2 nmol/mmol
- MODY/ T2DM düşün
  - Açlık C peptid> 0.2 nmol/L
  - Random ya da uyarılmış C peptid > 0.4 nmol/L
  - Yemek sonrası idrar C peptid/ kreatinin oranı > 1.1 nmol/mmol

Jones AG et al, DiabeticMedicine ,2013

# Özet

- Kanda
  - Uyarılmış C-peptid < 0.2 nmol/L
  - Açlık < 0.08 nmol/L veya
  - Yemek sonrası idrar C-peptid:kreatinin oranı < 0.2 nmol/ mmol

  mutlak insülin eksikliğini ve mutlak insülin gereksinimini doğrular.

- İnsülin kullanan bir diyabetlide;
  - Uyarılmış C-peptid < 0.6 nmol/L
  - Açlık C-peptid < 0.25 nmol/L ve/veya
  - Yemek sonrası idrar C-peptid:kreatinin oranı < 0.6 nmol/ mmol

  ise ciddi insülin eksikliği ve Tip 1 DM'a işaret eder.

- C-peptid değerleri tanıdan 3-5 yıl sonra hala bu değerler üstünde ise tanıda Tip 2 DM veya monogenik diyabet düşünülmelidir.

Jones AG et al, DiabeticMedicine ,2013

# LADA

WHO 2019: slowly evolving, immune-mediated diabetes of adults (LADA)
World Health Organization, Classification of Diabetes Mellitus, Geneva, (2019).

- Yaş >30 (ileri yaş (>60) LADA ile ilgili veri yetersiz)
- Özgeçmiş ve soygeçmişte otoimmun hastalık hikayesi
- Tip 2 diyabete göre daha az metabolik sendrom özellikleri (daha düşük BKI, daha az hipertansiyon, daha düşük HOMA ve daha normal HDL Kolesterol düzeyleri)
- C peptid düşük olur ancak C peptid zamanla düşüşü Tip 1 den yavaş
- Anti GAD en spesifik antikor (diğerleri daha az ve spesifik ICA, IA-2A, ZNT8A ve tetraspanin 7)
- Hastalık başlangıcında genelde insülin ihtiyacı göstermez

Buzzetti R,et al.Diabetes,2020

# Hangi hastada LADA taranmalı ?

1) Akut diyabet semptomları
2) BKI< 25
3) Diyabet tanı yaşı <50
4) Özgeçmişinde otoimmun hastalık
5) Soygeçmişinde otoimmun hastalık

- Beş kriterden 2 ve daha fazlası varsa LADA araştırılmalı
- ***LADA risk skoru ≥ 2***

S. Fourlanos, C. Perry, M.S. Stein, J. Stankovich, L.C. Harrison, P.G. Colman, A clinical screening tool identifies autoimmune diabetes in adults, Diabetes Care (2006), https://doi.org/10.2337/dc05-2101.

# LADA TİP 2 DİYABET AYIRICI TANISI

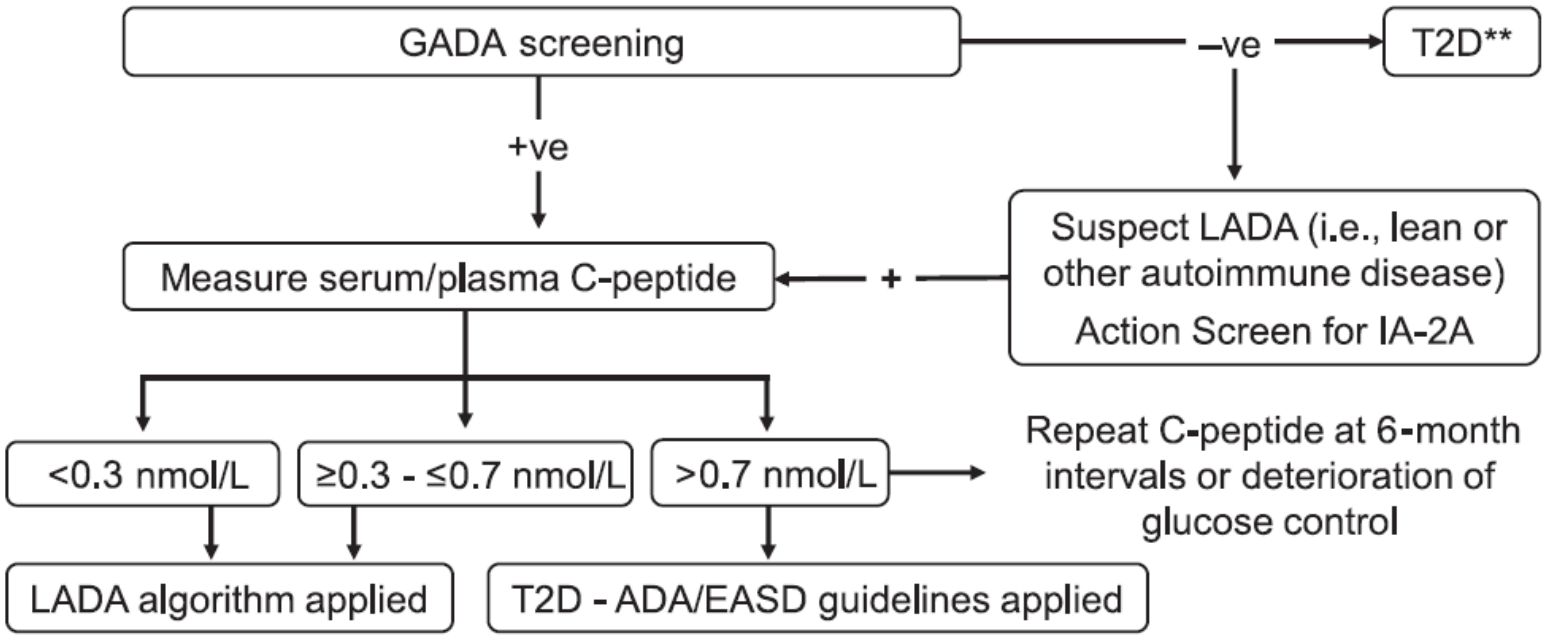



**Figure 1**—Algorithm for LADA diagnostic pathway based on autoantibody screening and C-peptide levels at diagnosis (to be used when financial restriction does not apply). **Consider also pancreatitis or monogenic diabetes.

Buzzetti R,et al.Diabetes,2020

# TEDAVİ

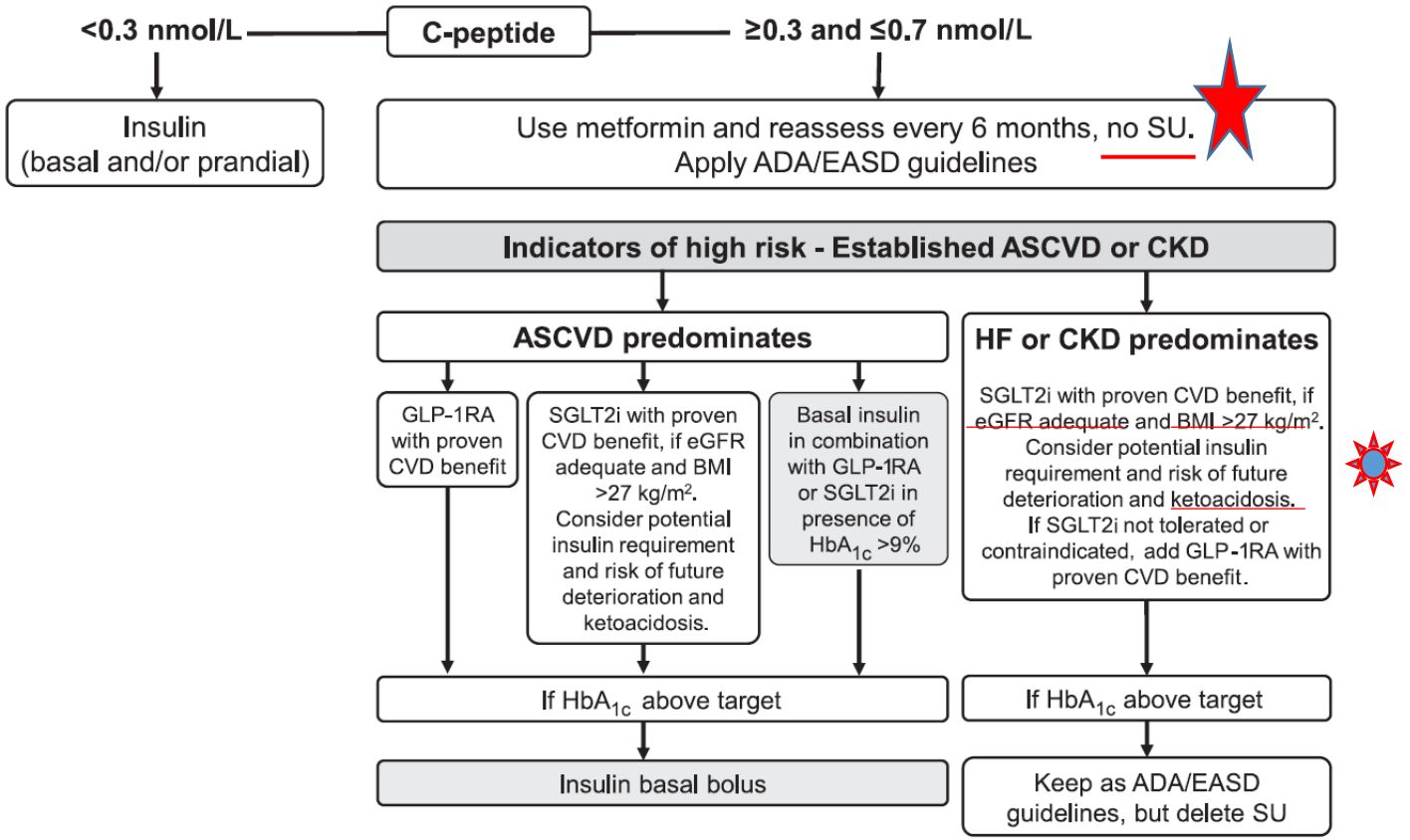



**Figure 2**—Algorithm for glucose-lowering medications in LADA patients with C-peptide <0.3 mmol/L or with C-peptide ≥0.3 and ≤0.7 nmol/L. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure.

Buzzetti R,et al.Diabetes,2020

# TEDAVİ

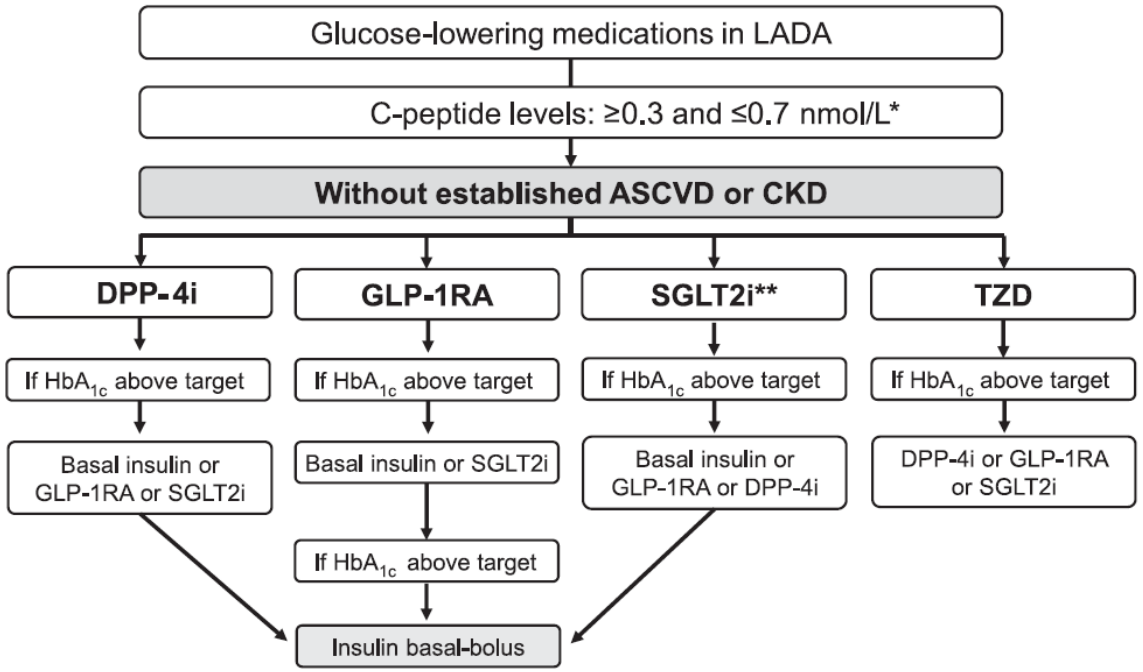



**Figure 3**—Algorithm for glucose-lowering medications in LADA patients with C-peptide levels ≥0.3 and ≤0.7 nmol/L without established ASCVD (atherosclerotic cardiovascular disease) or CKD (chronic kidney disease). *Deviation from ADA/EASD T2D algorithm. **Increased risk of diabetic ketoacidosis, especially in patients with BMI ≤27.

Buzzetti R,et al.Diabetes,2020

# C-Peptid: Yaş ve Diyabet Süresi prognostik veriler

- C-peptid düzeyleri diyabet süresi ile paralel düşüş gösterir.
  - Tip 1 DM'de miks meal sonrası C-peptid düzeyi 0.2 nmol/L (0.61 ng/ml) olanların oranı
  - 5 yılda %48
  - 5-15 yılda %8

- Hastalık ortaya çıkış yaşı küçüldükçe (10 yaş altı) daha hızlı bir kayıp olur.

- 18 yaş üstünde tanı koyulanlarda daha fazla hastada ölçülebilir C-peptid düzeyleri görülür. (18 yaş altında tanı konanlara kıyasla)

Leighton E et al, Diabetes Ther, 2017

# Tip 1 Diyabet C peptid çalışmalar prognostik veriler

| Study | Diabetes type | C-peptide levels (nmol/L) of clinical interest | | Interpretation |
|---|---|---|---|---|
| Jacobsen et al.[34] | T1D (stage 1) | Index 60* <1.0 | → | Reduced risk (77%) of T1D among children with multiple pancreatic aAb |
| Evans-Molina et al.[35] | T1D (stage 1) | N/A | | Compared with aAb negative youths, those with detectable pancreatic aAb have lower C-peptide levels already ≥5 y before T1D onset<br>Among progressors, fasting C-peptide increases and early C-peptide response to OGTT decreases as the onset of T1D approaches |
| Willemsen et al.[22] | T1D | N/A | | C-peptide measurement in dried blood spots is feasible to monitor beta-cell function slopes at home |
| Rickels et al.[43] | T1D | >0.40 (after MMTT) | → | Higher time in range |
| Zenz et al.[44] | T1D | ≥0.05 (fasting) | → | Higher glucagon and endogenous glucose production in response to hypoglycaemia |
| Gibb et al.[45] | T1D | >0.01 (random) | → | Lower time below range |
| Marren et al.[46] | T1D (>5 y) | >0.02 (after MMTT) | → | Lower rate of self-reported hypoglycaemia |
| Gubitosi-Klug et al.[47] | T1D | >0.03 (after MMTT) | → | Lower risk of severe hypoglycaemia |
| Thivolet et al.[48] | T1D | >0.03 (after MMTT) | → | No association with glucagon response to MMTT |
| Jeyam et al.[50] | T1D | >0.20 (random) | | Lower insulin requirement, HbA1c, DKA and hypoglycaemia risk. The association with hypoglycaemia episodes was linear down to C-peptide levels of 0.003 nmol/L |
| Foteinopoulou et al.[118] | T1D | ≥0.20 (random) | → | Consider further evaluations to eventually reclassify diabetes type |

Maddoloni et al. Diabetes Obes Metab.2022;24:1912-1926

# Tip 2 Diyabet C peptid Çalışmalar prognostik veriler

| Study | Diabetes type | C-peptide levels (nmol/L) of clinical interest | | Interpretation |
|---|---|---|---|---|
| Sokooti et al.[97] | T2D | N/A | | Fasting C-peptide improves the FOS risk score for the estimation of T2D risk in the general population (the higher the C-peptide, the higher the risk) Sensitivity analyses showed C-peptide was an independent predictor only among people without hypertension |
| Tuccinardi et al.[104] | T2D (insulin-treated) | 0.36 (fasting) | → | Cut-off with 45% sensitivity and 81% specificity for identifying people with T2D on basal-bolus treatment among people with T2D on insulin treatment |
| Landgraf et al.[113] | T2D | ≤0.40 (fasting) | → | Worse HbA1c values and higher rate of hypoglycaemic episodes (including severe) after starting basal insulin, despite lower insulin dose (IU/kg), compared with people with higher C-peptide values |
| Hope et al.[114] | T2D (insulin-treated) | <0.20 (random) | → | High hypoglycaemic risk, including risk of severe hypoglycaemias |

Maddoloni et al. Diabetes Obes Metab.2022;24:1912-1926

# C-Peptid: İnsülin Tedavi Kararı

- Tanıda açlık C-peptid düzeyinin < 0.25 nmol/L (0.76 ng/ml) olması daha sonraki insülin tedavisi için bağımsız bir risk faktörüdür.
- Glukagon uyarı testi sonrası pik değerin 0.6 nmol/L (1.82 ng/ml) den düşük olması insülin tedavi ihtiyacını gösterir.
- Tip 2 DM'lularda insülin tedavisine başlama süresi; miks meal testi sonrası C-peptid düzeyi en fazla 0.2 nmol/L (0.61 ng/ml) olanlarda 2.5 yıl iken; bu değerin üstünde olanlarda 6 yıldır.
- Uyarılmış C-peptid değerinin 0.2 nmol/L (0.61 ng/ml) ve altı olması; yetersiz beta hücre rezervi ve insülin tedavi ihtiyacı için bir cut-off değer olarak kullanılabilir. Bu hastalarda yoğun insülin tedavisi faydalı olur.
- Açlık C-peptid değerinin 0.25 nmol/L (0.76 ng/ml) altında olması ve/veya ICA pozitifliği insülin tedavi gerekliliği için yararlı bir göstergedir.

Leighton E et al, Diabetes Ther, 2017

Original Article
DOI: 10.25179/tjem.2017-56550
Turk J Endocrinol Metab 2017;21:68-71

# C-peptide Measurement may not be Necessary for Choosing a Treatment Modality in Type 2 Diabetes Mellitus: A Retrospective Analysis

## C-peptid Ölçümü Tip 2 Diabetes Mellitusda Tedavi Seçiminde Gerekli Olmayabilir: Retrospektif Bir Analiz

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## Özet

**Amaç:** C-peptid beta hücre fonksiyonunu gösteren özgül bir belirteçtir ve tedavi algoritmasında kullanıma sahip olabilir. Bu retrospektif değerlendirmede, daha önce tanı almış ve tedavi altındaki tip 2 diyabet mellitus (T2DM) hastalarının tedavilerinin güncel kılavuzda yer alan CP güdümlü tedavi önerileri ile uyumunun incelenmesi amaçlandı.

**Gereç ve Yöntem:** Bu retrospektif çalışmaya kliniğimize başvuran, klinik kayıtları ve eşzamanlı açlık plazma glukozu, c-peptid düzeyi ve HbA1c düzeyi ölçülmüş 179 T2DM hastası alındı. CP düzeyleri tedavi altında ölçüldü ve tedavi değiştirme veya yeni tedavi başlama amacıyla kullanılmadı. Analiz için SPSS 17.0 paket programı kullanıldı.

**Bulgular:** Ortalama CP düzeyi tüm hastalarda 2.71 ng/mL saptandı. On iki hastada (%6.7) yetersiz rezervuar (CP<0.5 ng/mL), yetmiş hastada (%39.1) sınırda rezervuar (CP: 0.5-2 ng/mL) ve 97 hastada (%54.2) yeterli rezervuar bulunmuştur. Her üç grup da yaş, cinsiyet, açlık kan glukozu ve HbA1c açısından benzerdir. Yeterli rezervuar grubunda metformin kullanımı daha sık iken, yetersiz rezervuar grubundaki tüm hastalar insulin kullanmaktadır.

**Tartışma:** CP ölçümünün literatürde diyabet tipi belirleme, tedavi yanıtını tahmin etme ve beta hücre rezervuarını gösterme gibi endikasyonları olsa da, bu çalışma sonucunca T2DM hastaları için tedavi seçiminde CP ölçümünün kullanımının kısıtlı olduğunu düşünmekteyiz.

**Anahtar kelimeler:** C-peptid; insulin; tip 2 diyabetes mellitus

# Tip 1 diyabet C peptid eksikliği ve diyabetik komplikasyonlar

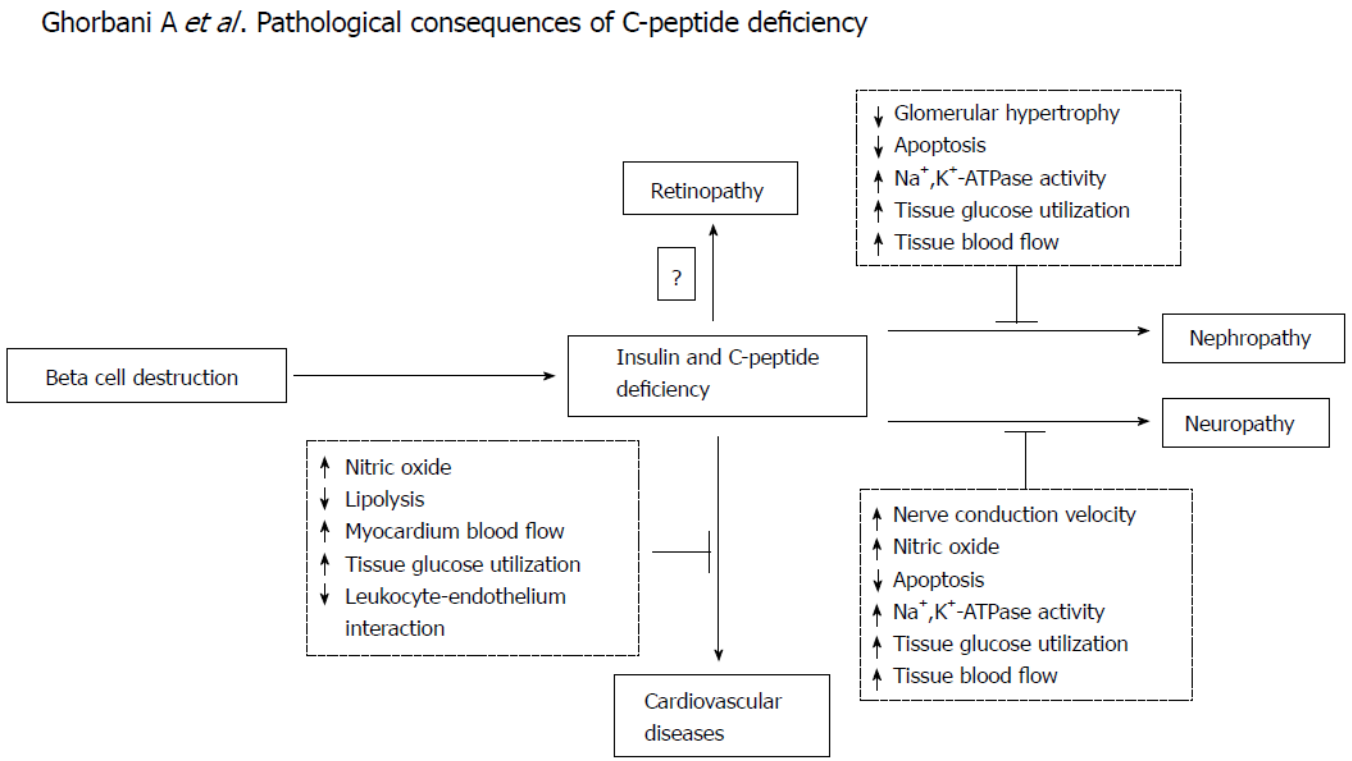
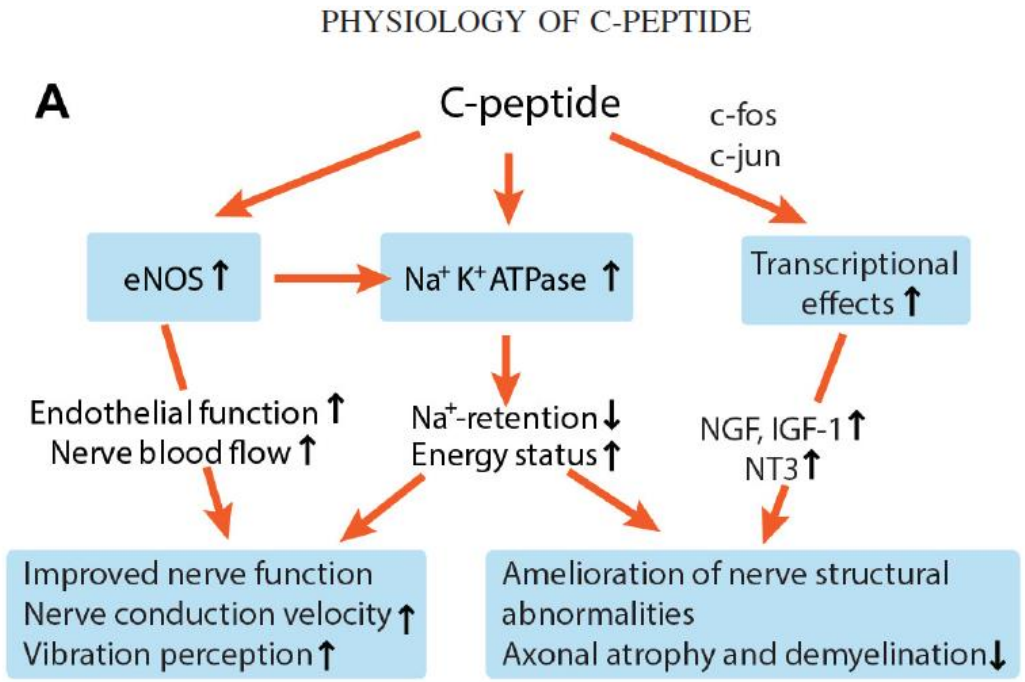



**Figure 1 Proposed mechanisms (dashed rectangles) by which C-peptide may prevent, retard, or ameliorate diabetic complications in patient with type-1 diabetes.** ↓: Decrease; ↑: Increase.

**Ghorbani A.** World J Diabetes. 2015 Feb 15;6(1):145-50. doi: 10.4239/wjd.v6.i1.145.




Yosten GLC. Am J Physiol Endocrinol Metab. 2014 Dec 1;307(11):E955-68.

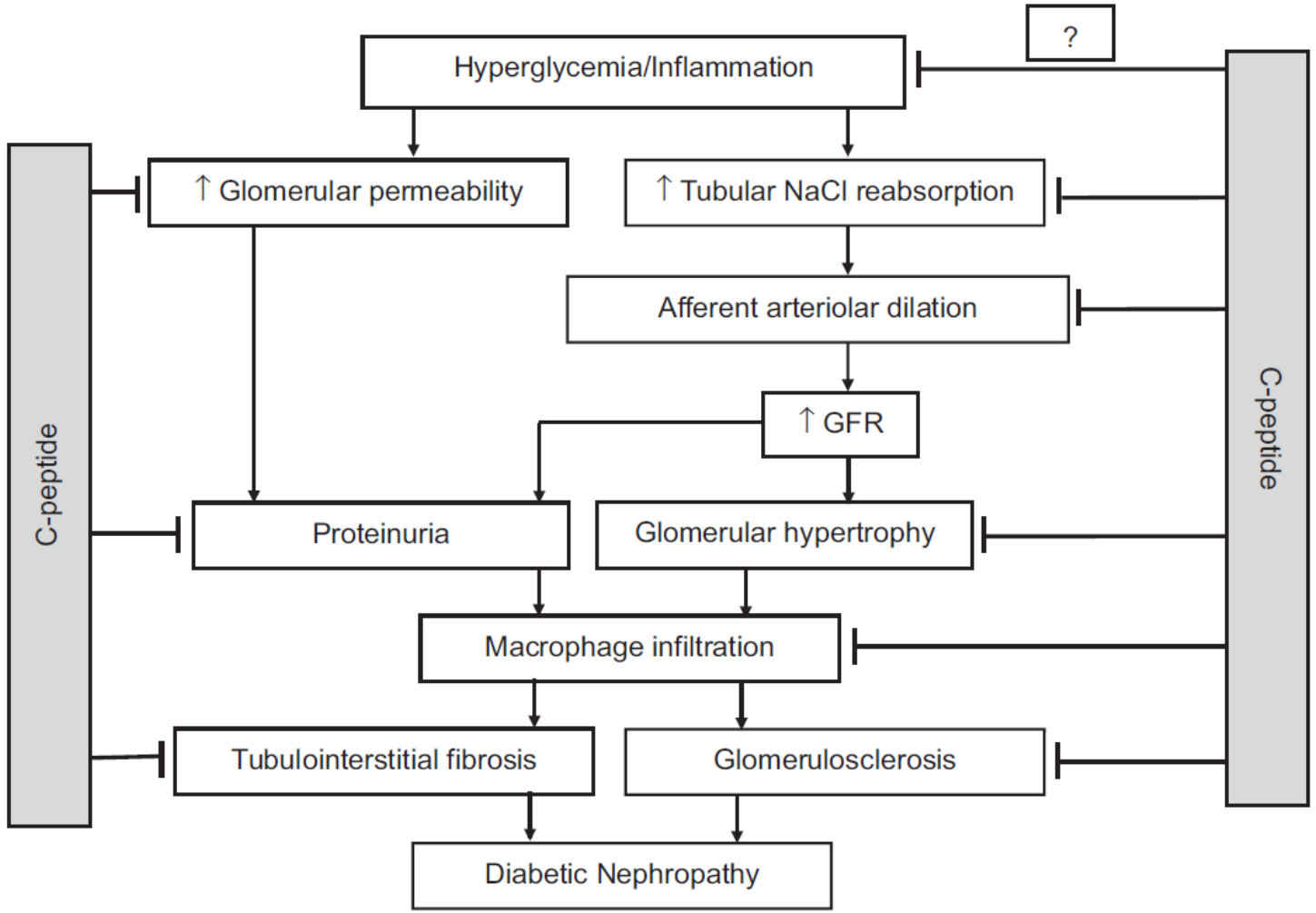
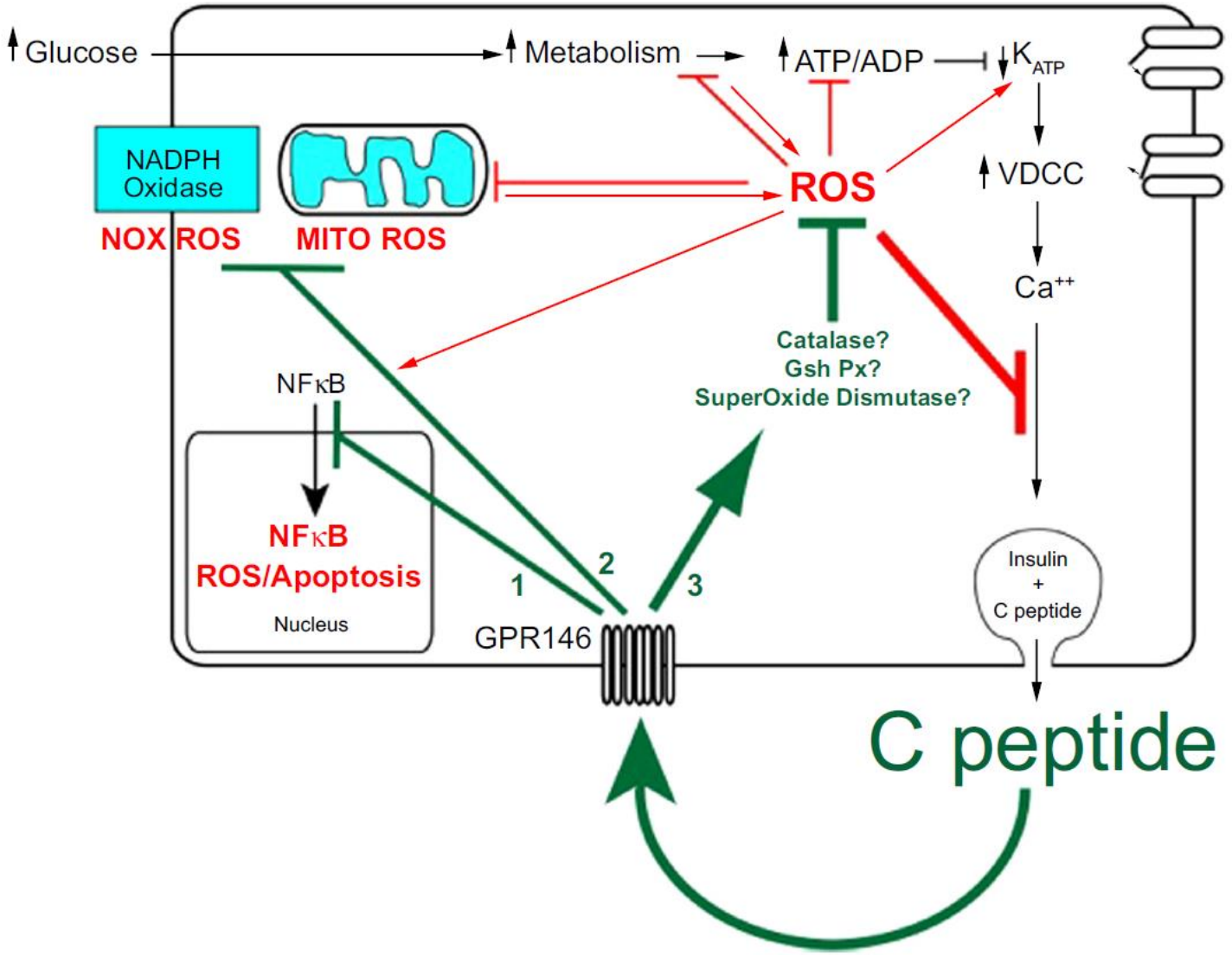



Fig. 2. Simplified model of the pathogenesis of diabetic nephropathy. C-peptide is renoprotective in type 1 diabetes via inhibiting tubular sodium reabsorption, reducing afferent arteriolar diameter and glomerular permeability, preventing and attenuating the progression of glomerular hyperfiltration, hypertrophy and microalbuminuria, renal inflammation, glomerulosclerosis, and tubulointerstitial fibrosis. GFR, glomerular filtration rate. Studies from our laboratory have also shown that C-peptide may also have blood glucose-lowering effects; however, it appears that C-peptide exerts its renoprotective effects independently of blood glucose regulation.

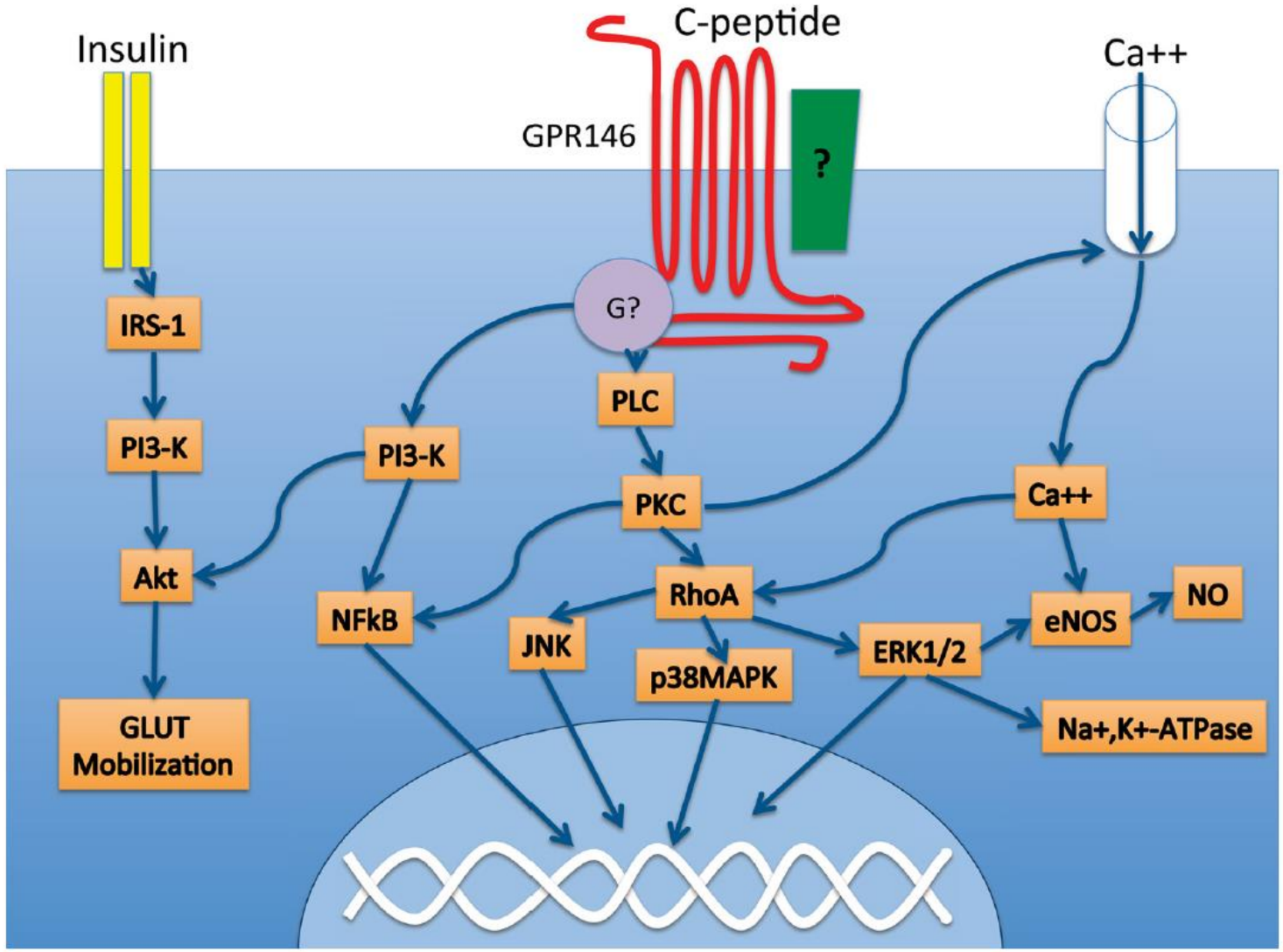
Yosten GLC. Am J Physiol Endocrinol Metab. 2014 Dec 1;307(11):E955-68.

Fig. 3. Autocrine C-peptide model underlying β-cell adaptation to oxidative stress. The centerpiece of functional β-cell mass is insulin secretion, which is cosecreted in equimolar amounts with C-peptide. Autocrine action of C-peptide, which protects functional β-cell mass, should therefore provide a buffer of protection for its own secretion as well as that of insulin. In addition to binding to its receptor GPR146 for such autocrine actions, C-peptide is predicted to regulate at least 3 distinct pathways in the β-cell: 1) deactivation of the NF-κB pathway, which protects against apoptosis; *2*) inhibition of pathways that generate ROS including the plasmalemma NADPH oxidase and the mitochondrial electron transport chain; 3) activation of pathways that catalyze the degradation of ROS by activating antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase. In the absence of these autocrine actions of C-peptide, more prolonged and higher accumulation of ROS and apoptosis would accelerate loss of β-cell functional mass. This suggests a tipping point in loss of functional β-cell mass where the loss in C-peptide secretion and its autocrine protection results in a downward spiral of both secretion and protection, ultimately leading to few if any β-cells.




Yosten GLC. Am J Physiol Endocrinol Metab. 2014 Dec 1;307(11):E955-68.

Fig. 4. C-peptide-initiated signaling cascades. C-peptide is associated with the regulation of several signaling cascades, including phospholipase C (PLC) and the NF-κB pathway. These intracellular signaling events are likely mediated by a G protein-coupled receptor such as GPR146, which has been shown to be necessary for C-peptide signaling in KATOIII cells. GPR146 interacts with an as yet unknown G protein, which could be either $G\alpha_i$ or $G\alpha_o$, since several of the cellular actions of C-peptide were shown to be pertussis toxin sensitive. GPR146 may interact physically with additional proteins on the cell membrane, such as an integrin (green box). C-peptide and insulin appear to functionally interact, particularly at the level of Akt. Akt, protein kinase B; $Ca^{++}$, calcium ion; eNOS, endothelial NO synthase; ERK1/2, extracellular signal-regulated kinase; G?, G protein; GLUT, glucose transporter; IRS-1, insulin receptor substrate 1; JNK, c-Jun $NH_2$-terminal kinase; $Na^+$,$K^+$-ATPase, sodium/potassium ATPase; NO, nitric oxide; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PKC, protein kinase C; PLC, phospholipase C; PI3-K, phosphotidylinositol 3-kinase; p38 MAPK, mitogen-activated protein kinase; RhoA, Ras homolog gene family, member A.




Yosten GLC. Am J Physiol Endocrinol Metab. 2014 Dec 1;307(11):E955-68.

# C-Peptide in Insulin Resistance and Vascular Complications:

## Teaching an Old Dog New Tricks

**Dennis Bruemmer**
*From the Division of Endocrinology and Molecular Medicine, University of Kentucky College of Medicine, Lexington.*

**Keywords**

insulin resistance; C-peptide; smooth muscle cell; proliferation

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## Clinical Evidence Linking Insulin Resistance, Hyperinsulinemia, and Cardiovascular Disease

Based on the recent evidence that patients with type 2 diabetes have the same risk of myocardial infarction as nondiabetic subjects with a history of infarction, diabetes has been designated as an atherosclerosis equivalent.[1] Insulin resistance plays a primary role in the development of type 2 diabetes and considerable evidence supports the association between insulin resistance, hyperinsulinemia, and vascular disease.[2,3] Although the molecular mechanisms are incompletely understood, this association is supported by several large clinical studies showing a direct relationship between insulin levels and cardiovascular risk. The Paris Prospective Study[4] and the Multiple Risk Factor Intervention Trial (MRFIT)[5] reported positive relationships between insulin levels and atherosclerotic events. In addition, the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT)[6] demonstrated the highest incidence of cardiovascular events in the subgroups with highest levels of insulin. Finally, the landmark Insulin Resistance Atherosclerosis Study (IRAS) provided further evidence for an inverse relationship between carotid intima-medial thickness and insulin sensitivity.[7]

## C-Peptide: The Old Dog With a New Trick

In this issue of *Circulation Research*, Walcher and colleagues extend our current knowledge on mechanisms promoting SMC proliferation under conditions of hyperinsulinemia by adding C-peptide to the list of mitogens.[18] C-peptide, the 31 amino-acid residue formed during

**Bruemmer D.**Circ Res. 2006 Nov 24;99(11):1149-51.

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

# Is C-peptide a predictor of severity of coronary artery disease in metabolic syndrome? An observational study

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*Keywords:*
C-peptide
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Coronary artery disease
Insulin resistance
SYNTAX score

ABSTRACT

*Background:* Various cardiovascular disease (CVD) risk factors have been implicated to correlate with the severity of the disease. Present study was conducted to correlate one such risk factor i.e. fasting serum C-peptide with the presence or absence and the severity of CVD in Indian population.
*Methods:* 68 patients with metabolic syndrome who underwent coronary angiogram for suspected CVD were included. Their fasting serum C-peptide levels were measured in addition to routine biochemical and cardiological tests. They were divided into 2 groups – those with a positive coronary angiography findings (Group 1) and those with normal coronary angiograms (Group 2). The former group was further divided into those with an Acute Coronary Syndrome (ACS) (Group 1a) and those with Chronic Stable Angina (CSA) (Group 1b). SYNTAX scoring was done to assess the severity of coronary artery disease in groups 1a and 1b. Levels of C-peptide were compared between the groups.
*Results:* The mean C-peptide of all patients was 1.9 (±0.8) ng/mL. Among the group 2 patients, mean serum C-peptide value was 1.6 (±0.4) ng/mL. And it was 2.7 (±0.8) ng/mL and 1.7 (±0.9) ng/mL among the ACS and the CSA groups respectively. The ACS and CSA group had statistically significant higher values of C-peptide compared to patients with normal coronary angiograms. The two-way ANOVA done to find out the variability of C-peptide among the 3 groups revealed significant differences among the groups with a p-value of <0.001. When correlated with SYNTAX scores, this yielded significant results.
*Conclusion:* C-peptide levels appear to correlate with the severity of the CVD as measured by SYNTAX score.

International Archives of Medical Research
Volume 10, No.2, pp.27-31, 2018.

ORIGINAL RESEARCH PAPER

# High c-peptide level: marker of mortality in type 2 diabetes mellitus patients

**Çiğdem BUDAK ECE[1], Zafer PEKKOLAY*[2], Alpaslan Kemal TUZCU[2]**

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*[2] Dicle University Medical Faculty, Department of Adult Endocrinology, Diyarbakır/Turkey*

## Abstract

***Objective:*** *We aimed to retrospectively investigate the effect of c-peptide level on mortality in patients with Type 2 Diabetes Mellitus.*

***Methods:*** *Patients who applied to the Dicle University Medical Faculty in 2012 were screened in the database and included a 1000 DM patient with c-peptide, after 5 years the patients were re-evaluated. The patients were then categorized. The patients were divided into two groups, dead patients and living patients. Two groups of c-peptide levels were compared.*

***Results:*** *Totally 1000 patients included in the study. 392 (39.2%) of the patients were male and 608 (60.8%) were female, the mean age was 57. Patients were divided into two groups: the patient group who died and the patient group who was living. The number of patients died was 146 (14.6%) and the number of living patients was 844 (75.4%). C-peptide levels were found to be higher in patients who died (3,5 ± 2,7 ng / ml) than those who survived (2,9 ± 1,7 ng / ml) and statistically significant ($p<0.05$).*

***Conclusion:*** *The high c-peptide levels in patients with Diabetes Mellitus, it may be an important parameter to predict mortality.*

# Tip 2 diyabet hastalarında artan C peptid KV ve tüm nedenlerden mortalite ile ilişkilidir

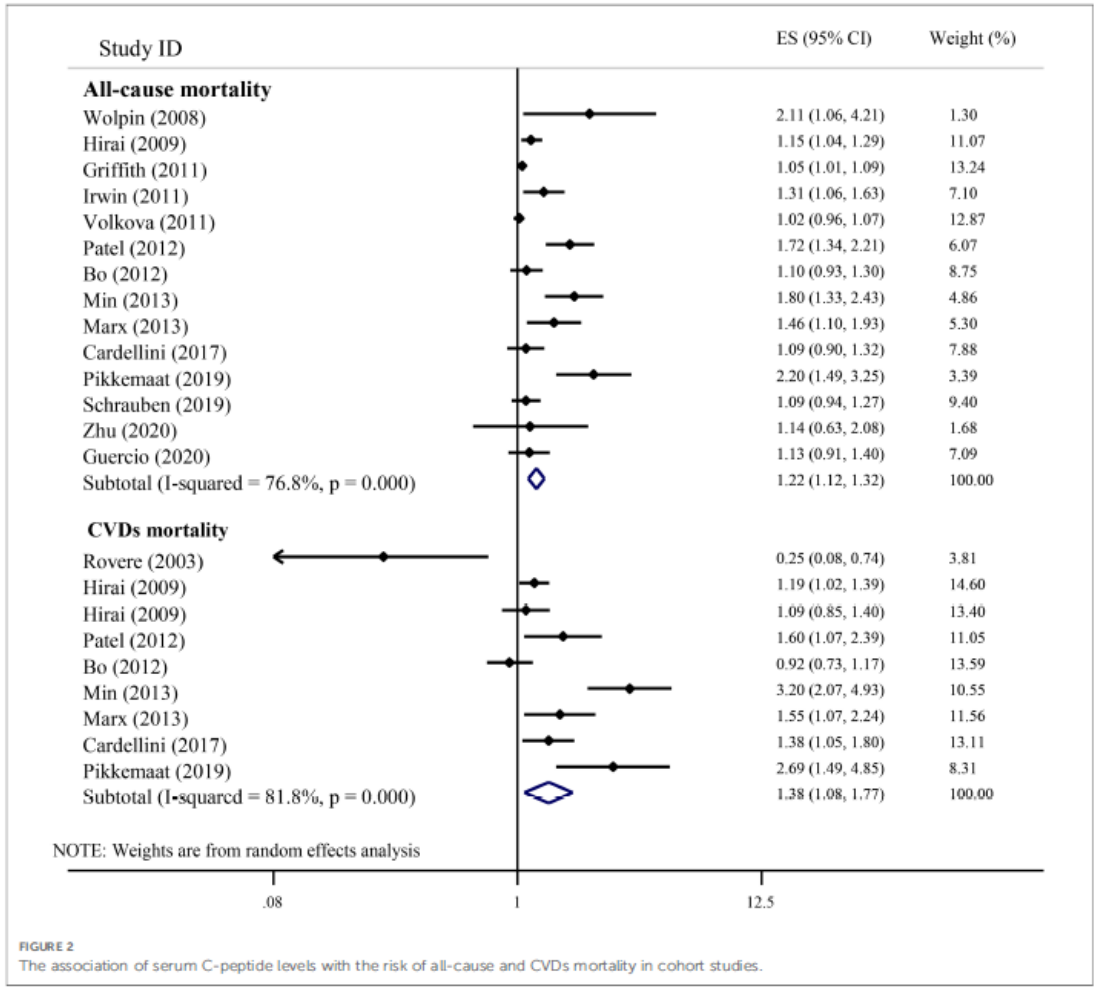


FIGURE 2
The association of serum C-peptide levels with the risk of all-cause and CVDs mortality in cohort studies.

**Ahmadirad H**,Front Cardiovasc Med. 2023 Jul 7;10:1205481.

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

# C-peptide concentrations in patients with type 2 diabetes treated with insulin

Mehmet Uzunlulu [a], Aytekin Oguz [a], Müzeyyen Arslan Bahadir [b], Ayse Naciye Erbakan [c, *], Mirac Vural Keskinler [b], Banu Alpaslan Mesci [a]

[a] Istanbul Medeniyet University, Göztepe Training and Research Hospital, Istanbul, Turkey
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Type 2 diabetes
C-peptide
Beta-cell reserve
Insulin use

ABSTRACT

*Aims:* To determine beta cell reserves of patients with type 2 diabetes who are treated with insulin by using fasting C-peptide concentrations and to investigate the clinical features related to C-peptide concentrations.

*Materials and methods:* Patients with type 2 diabetes, who were using insulin as monotherapy or in combination therapy, were divided into three groups; those with an insufficient beta cell reserve (C-peptide: <0.5 ng/mL), borderline reserve (C-peptide: 0.5–2 ng/mL) and sufficient reserve (C-peptide:> 2 ng/mL).

*Results:* In the 249 patients (mean age, 61.77 ± 9.34 years; 40.6% male), the mean duration of diabetes was 13.9 ± 8.43 years. The mean HbA1c concentrations, fasting glucose and C-peptide concentrations were 8.88 ± 1.87%, 184.29 ± 77.88 mg/dL and 1.95 ± 1.37 ng/mL, respectively. Fifty-seven percent of patients (n = 142) had a borderline beta cell reserve and 37% (n = 92) had high C-peptide concentrations. Only 6% of patients (n = 15) had an insufficient beta cell reserve. C-peptide levels were positively correlated with waist circumference (r: 0.282; p = 0.001), hip circumference (r: 0.251; p = 0.001), body mass index (r: 0.279; p = 0.001), fasting glucose concentrations (r: 0.309; p = 0.001) and triglyceride concentrations (r: 0.358; p = 0.001).

*Conclusion:* In this study, almost all patients with type 2 diabetes using insulin were found to have sufficient or borderline beta cell reserves and insulin resistance-related parameters were prominent in those with adequate beta cell reserve.

*Clinical trials no:* NCT04005261

# C peptid
# İnsülin Direnci göstergesi

+Model
DIABET-789; No. of Pages 2

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& Diabetes Metabolism

Diabetes & Metabolism xxx (2016) xxx–xxx

Letter to the editor

**Fasting serum C-peptide levels (> 1.6 ng/mL) can predict the presence of insulin resistance in Japanese patients with type 2 diabetes**

# Obezite Cerrahisi

## Preoperative Fasting Plasma C-Peptide Levels as Predictors of Remission of Type 2 Diabetes Mellitus after Bariatric Surgery: A Systematic Review and Meta-Analysis

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**ABSTRACT**

*Aims*: The study evaluated the predictive role of preoperative fasting C-peptide, hemoglobin (Hb)A1c, fasting plasma glucose (FPG), and body mass index (BMI) levels on diabetes remission in patients with type 2 diabetes following bariatric surgery. *Meth*ods: Medline, PubMed, Central, and Google Scholar databases of up to September 7, 2016 were searched using the following terms: type 2 diabetes mellitus, gastric bypass, Roux-en-Y, anastomosis, C-peptide, weight loss, HbA/HbA1c, predictive/predictor. *Results*: Meta-analysis of the pooled data indicated that fasting C-peptide was predictive of increased chance of remission of type 2 diabetes (pooled difference in means = 0.93, 95% confidence interval [CI] = 0.61 to 1.25, $p < .001$). The analysis also found that FPG (pooled standardized mean difference = −0.42, 95% CI: −0.64 to −0.20, $p < .004$) and HbA1c levels (pooled difference in means = −1.05, 95% CI: −1.48 to −0.62, $p < .001$) were associated with reduced odds of type 2 diabetes remission. BMI was not found to be associated with remission (pooled difference in means = 0.29, 95% CI: 0.30 to 0.88, $p = .343$). In general, subgroup analysis, which evaluated the pooled data from the retrospective and prospective studies separately, gave similar results. *Conclusions*: Preoperative fasting plasma C-peptide was associated with increased type 2 diabetes remission after bariatric surgery, whereas baseline HbA1c and FPG levels were associated with reduced chance of remission. These parameters may be used as a guideline in weighing the risks and benefits for surgical intervention in patients with type 2 diabetes.

**Keywords** diabetes; bariatric; surgery; C-peptide; remission; meta-analysis

# DPP4 tedavisine yanıtı öngörmede

Hindawi Publishing Corporation
Journal of Diabetes Research
Volume 2016, Article ID 4509603, 4 pages
http://dx.doi.org/10.1155/2016/4509603

Hindawi

*Research Article*

## C-Peptide Levels Predict the Effectiveness of Dipeptidyl Peptidase-4 Inhibitor Therapy

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*Background*. Our aim was to define the conditions that affect therapeutic success when dipeptidyl peptidase-4 (DPP-4) inhibitor is added to metformin monotherapy. *Materials and Methods*. We reviewed the medical records of 56 patients who had received DPP-4 inhibitor as an add-on to metformin monotherapy and evaluated their response in the first year of therapy. Fasting blood glucose (FBG), HbA1c, C-peptide, and weight of the patients were recorded at 3-month intervals during the first year of treatment. *Results*. Patients who added DPP-4 inhibitor to metformin monotherapy had significant weight loss ($P = 0.004$) and FBG and HbA1c levels were significantly lowered during the first 6 months (both $P < 0.001$). Baseline levels of C-peptide were predictive for success of the treatment ($P = 0.02$), even after correction for confounding factors, for example, age, gender, or BMI ($P = 0.03$). Duration of diabetes was not a predictor of response to treatment ($P = 0.60$). *Conclusion*. Our study demonstrates that in patients having inadequate glycemic control, the addition of a DPP-4 inhibitor as a second oral agent to metformin monotherapy provides better glycemic control, protects $\beta$-cell reserves, and does not cause weight gain. These effects depend on baseline C-peptide levels.

# GLP-1 tedavisine yanıtı öngörmede

Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

**Research Article**

J Exp Clin Med
2022; 39(3): 798-802
**doi:** 10.52142/omujecm.39.3.39

## Fasting plasma c-peptide level predicts the response of glucagon-like peptide-1 agonist (exenatide) add on to metformin monotherapy in obese type 2 diabetics

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post-treatment (r: 0.4, p: 0.01). Multivariate logistic regression analysis showed that the baseline fasting plasma C-peptide level was an independent predictor of successful glycemic control [exp.B: 6.6 (1.63-26-9) p: 0.008]. In a receiver operating characteristics (ROC) curve analysis, a baseline plasma C-peptide level of 2.56 ng/mL was the best cut-off value. Initial fasting plasma C-peptide levels can predict the treatment response of the GLP1-RA (exenatide 10 mcg, twice daily) add on to metformin monotherapy in obese type 2 diabetics.

# Obezitede kronik inflamasyonu öngörmede

doi: 10.4183/aeb.2023.31



## C-PEPTIDE AS AN INFLAMMATORY MARKER IN OBESE WOMEN

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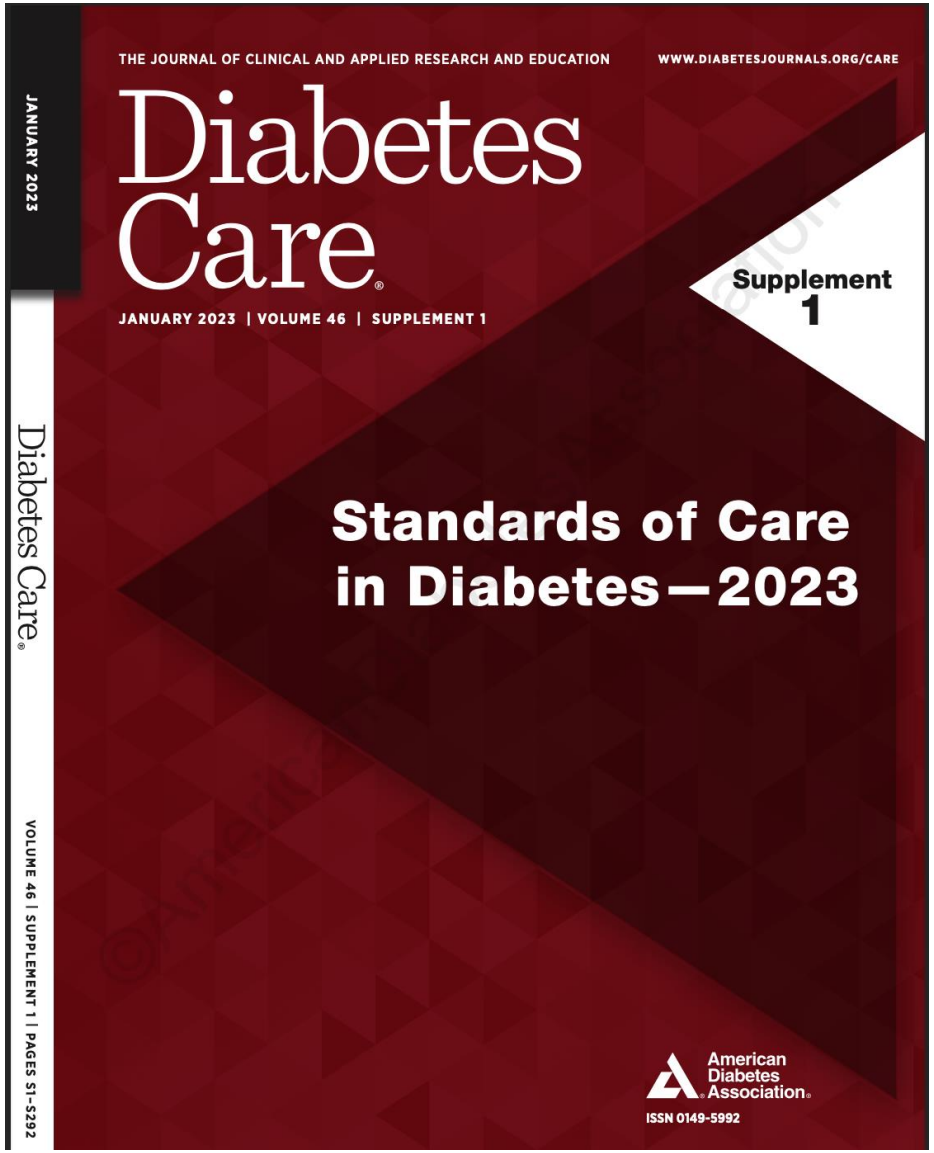
*[1]Istanbul Medeniyet University Faculty of Medicine – Department of Internal Medicine, Division of Endocrinology and Metabolism, [2]Department of Family Medicine, Istanbul, Turkey*

**Results.** The C-peptide levels of our patients showed a highly significant correlation with HOMA-IR ($p<0.001$). A significant positive correlation was found between fasting plasma C-peptide levels and NLR ($r=0.36$ and $p<0.003$) in obese women. The increase in C-peptide levels had a significant effect on the increase in NLR ($r2=0.31$, $p=0.002$), however insulin had no similar effect on NLR ($r2=0.01$, $p=0.544$).

**Conclusion.** Plasma C-peptide levels are better correlated with NLR compared to other parameters of IR. C-peptide may be used as an efficient laboratory marker with high relevance in IR and chronic inflammatory conditions in obese women.


GUIDELINES




**Diagnosis of Monogenic Diabetes**

A diagnosis of one of the three most common forms of MODY, including HFN1A-MODY, GCK-MODY, and HNF4A-MODY, allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members. Genetic screening is increasingly available and cost-effective (176,178).

A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members suspected should be referred to a specialist for further evaluation if available, and consultation can be obtained from several centers. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (186), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. A biomarker screening pathway, such as the combination of urinary C-peptide/creatinine ratio and antibody screening, may aid in determining who should get genetic testing for MODY (187). It is critical to correctly diagnose one of the monogenic forms of diabetes because these individuals may

Can J Diabetes 42 (2018) S10–S15

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage:
www.canadianjournalofdiabetes.com

2018 Clinical Practice Guidelines

# Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome

Diabetes Canada Clinical Practice Guidelines Expert Committee

Zubin Punthakee MD, MSc, FRCPC, Ronald Goldenberg MD, FRCPC, FACE, Pamela Katz MD, FRCPC

Clinical features distinguishing type 1 diabetes, type 2 diabetes and monogenic diabetes

| Clinical features | Type 1 diabetes | Type 2 diabetes | Monogenic diabetes |
|---|---|---|---|
| Age of onset (years) | Most <25 but can occur at any age (but not before the age of 6 months) | Usually >25 but incidence increasing in adolescents, paralleling increasing rate of obesity in children and adolescents | Usually <25; neonatal diabetes <6 months* |
| Weight | Usually thin, but, with obesity epidemic, can have overweight or obesity | >90% at least overweight | Similar to general population |
| Islet autoantibodies | Usually present | Absent | Absent |
| C-peptide | Undetectable/low | Normal/high | Normal |
| Insulin production | Absent | Present | Usually present |
| First-line treatment | Insulin | Noninsulin antihyperglycemic agents, gradual dependence on insulin may occur | Depends on subtype |
| Family history of diabetes | Infrequent (5%–10%) | Frequent (75%–90%) | Multigenerational, autosomal pattern of inheritance |
| DKA | Common | Rare | Rare (except for neonatal diabetes*) |


## 1.6. | SPESİFİK DİYABET TİPLERİ

Bu bölümde spesifik nedenlerle ortaya çıkan başlıca diyabet formları hakkında kısa bilgi verilmiştir.

### 1.6.1. | MONOJENİK DİYABET SENDROMLARI

Beta hücre disfonksiyonuna neden olan monojenik defektler (neonatal diyabet, MODY) diyabet hastalarının %5´ten azını oluşturmaktadır.

#### Neonatal Diyabet

Yaşamın ilk altı ayından önce ortaya çıkan ve %80-85 oranında monojenik defektlere bağlı gelişen diyabet tipidir. Geçici ya da kalıcı olabilir. Kalıcı formlar genellikle beta hücrelerinde yer alan KATP kanallarındaki Kir6.2 subunit (KCNJ11) ve SUR1 subunit (ABCC8) mutasyonları ya da Insulin gen (INS) mutasyonlarından kaynaklanmaktadır.

#### Gençlerde görülen erişkin tip diyabet (MODY)

Gençlerde görülen ve erişkin başlangıçlı diyabet gibi seyreden monogenik diyabet (maturity onset diabetes of the young; MODY) şüphesi olan hastalar genellikle genç (diyabet başlangıç yaşı <25) ve ailesinde iki veya daha fazla kuşakta diyabet olan (otozomal dominant geçişli), normal kiloda, insülin direnci olmayan ve pankreas rezervi iyi olan hastalardır. Asıl defekt, insülin sekresyon mekanizmasındadır. Bu hastalarda otoantikorlar negatif bulunur. Kan glukoz regülasyonu için insülin tedavisi gerekmez veya düşük doz insülinle regülasyon sağlanır.

MODY vakaları, adolesan çağından sonra ortaya çıkan tip 1 diyabet ya da genç yaşta başlayan tip 2 diyabet vakaları ile karışabilir. Tip 1 diyabet şüphesi varsa C-peptid düzeyi ve otoantikorlara bakılarak ayırıcı tanı yapılmalıdır.


## 1.7.5. | DİĞER TANI TESTLERİ

### C-peptid düzeyi

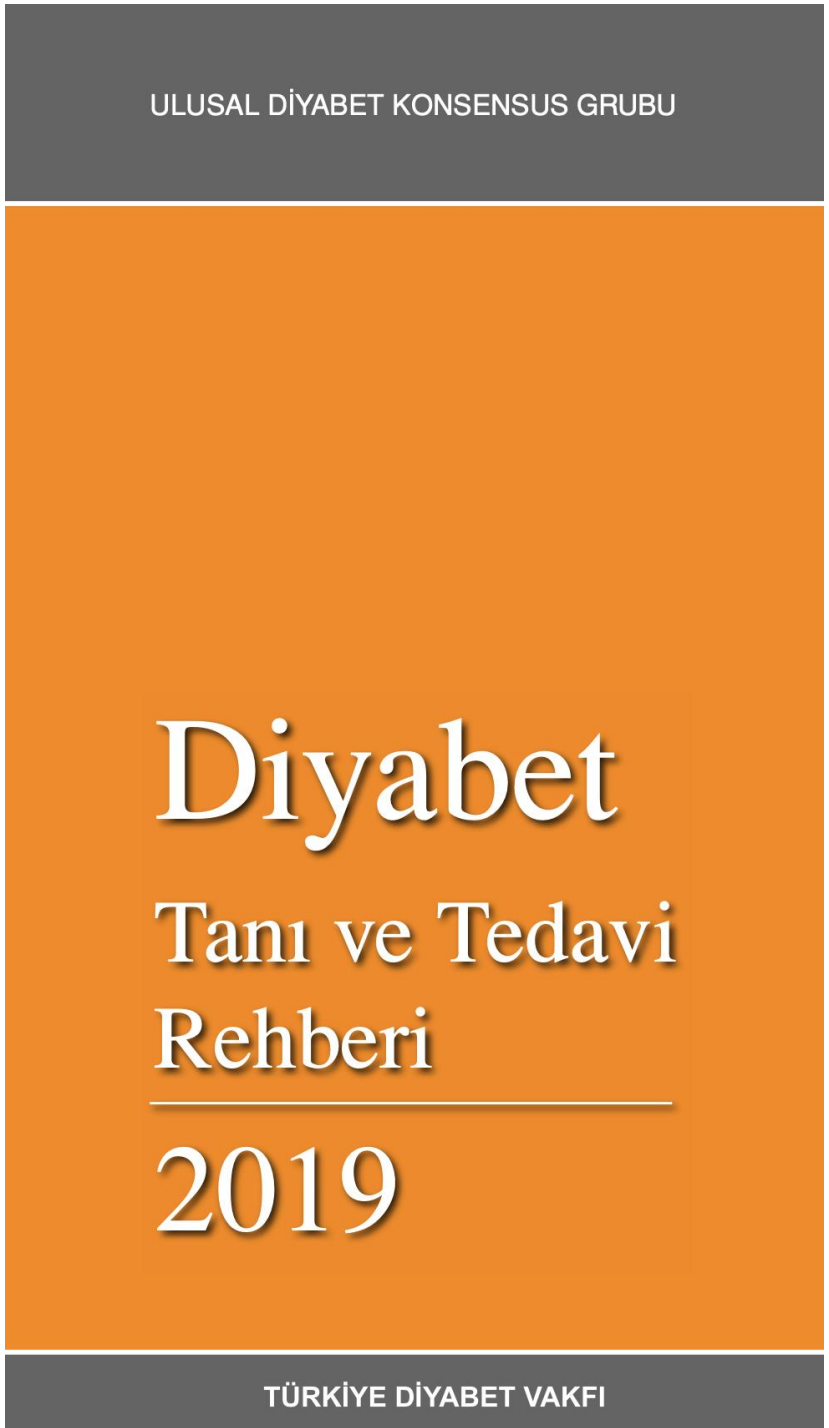
Genel olarak C-peptid bir tanı testi olarak kabul görmemekle birlikte, pankreas beta hücre (endojen insülin) rezervini anlamada faydalıdır. Ancak, aşırı hiperglisemi durumunda glukoz toksisitesinin pankreas beta hücrelerine etkisi nedeniyle, C-peptid düzeyi gerçek endojen insülin rezervini yansıtmayabilir. Böyle bir şüphe varsa glukoz toksisitesi (örneğin DKA) düzeltildikten en az 2 hafta sonra C-peptid ölçümü tekrarlanmalıdır. İnsülin veya sülfonilüre kullananlarda ölçümün son dozdan 24 saat sonra yapılması daha iyi fikir verebilir.

Tip 1 diyabette rutin olarak C-peptid ölçülmesine gerek olmamakla birlikte özellikle LADA gibi otoimmün diyabet formlarının tip 2 diyabetten ayrılmasında ve insülin tedavisine geçilecek tip 2 diyabet olgularının belirlenmesinde açlık ve uyarılmış C-peptid düzeyleri faydalıdır. C-peptid düzeyinin <0.6 ng/ml olması mutlak insülin ihtiyacı olduğunu düşündürür. Öte yandan, insülin tedavisi almakta olan hastalarda deintensifikasyon veya insülin kesilme kararı almada C-peptid ölçümü yol gösterici olabilir.


Tip 1 diyabetin önlenmesi konusunda Amerika´da Juvenile Diabetes Research Foundation (JDFR), National Institute for Diabetes, Digestive and Kidney Disease (NDDK) ve TrialNet Grupları ile onların Almanya, Avustralya, Finlandiya, İsveç ve İtalya´daki işbirliği merkezlerinde 200´den fazla çalışma yürütülmüştür. Bu çalışmalar negatif sonuçlansa da tip 1 diyabeti preklinik evrede tanımaya yönelik önemli bilgiler elde edilmiştir. Günümüzde tip 1 diyabet açısından yüksek riskli bireylerde (örneğin tip 1 diyabetlilerin birinci derece akrabalarında) pankreas adacık hücrelerine yönelik otoantikor [glutamik asit dekarboksilaz (AntiGAD-GADA), adacık ile ilişkili peptid 2 (IA2) ve endojen insüline yönelik insülin otoantikoru (IAA)] tayinleri ve β-hücre rezervini belirlemeye yönelik i.v. glukoz tolerans testi (IVGTT) ve C-peptid uyarı testleri ile tip 1 diyabeti erken evrede tanımlamak mümkündür. Şimdilik bu riskli bireylerin tip 1 diyabet önleme çalışmalarına katılımlarını teşvik etmek dışında bir müdahale yapılması mümkün olmazsa da belki de tip1 diyabeti ketoasidoz (DKA) evresinden önce tanımayı sağlayarak, endojen insülin rezervi tamamen tükenmeden tedaviye başlamak yararlı bir yaklaşım olacaktır.

## Tip 2 DM tedavisinde ilaç seçimlerinde, kombinasyonlarında dikkat edilmesi gereken ilaç ve hasta faktörleri

- Yaşam şekli değişikliği tüm basamaklarda önerilmelidir.
- Akarboz tüm basamaklarda kombinasyon olarak kullanllabilir.
- Tip 2 diyabette glisemi regülasyonu sağlandıktan sonra dinamik izlem sürdürülmeli, gerekirse tekrar bir önceki basamağa dönülerek ilaçlar ve dozları azaltılmalıdır.
- C peptid beta hücre rezervinin en önemli göstergesidir. Tip 2 diyabette C peptid düzeyleri hiperglisemik koşullardan ve glukotoksisiteden negatif olarak etkilenebilir. Ancak C peptid düzeyleri hiperglisemik koşullara rağmen yüksekse tedaviye yanıt açısından önem taşır.
- Beta hücre rezervi yetersiz (C Peptid < 0.5 ng/ml) tüm hastalar HbA1c'den bağımsız olarak insülinle tedavi edilmelidir.
- Bazal insülin ve GLP-1 agonist koformülasyonu bir seçim olabilir.
- En fazla 3 aylık tedaviye rağmen HbA1c %8'in üstünde ise bir sonraki basamağa geçmelidir.
- Etkin bir oral antidiyabetik tedavisine rağmen HbA1c %10'un üzerinde ise doğrudan insülin tedavisine geçilmelidir.
- Pioglitazon serebral ve kardiyak vasküler yeni olayları önlemektedir fakat kalp yetmezliği klinik bulguları veya ejeksiyon fraksiyonu değerlendirilerek kullanılmalıdır.
- İnsülin direnci ön planda olan hastalarda tedavi seçiminde pioglitazon düşünülmelidir.
- Saptanmış vasküler olay (kardiyak, serebral veya periferik) yeni olay geçirmeyi önlemek için SGLT2 inhibitörleri veya GLP1 reseptör agonistleri (GLP1 RA) seçilebilir.
- Kalp yetmezliği olanlarda SGLT2 seçilebilir
- Renal hastalığı (GFR azalması veya albuminürisi) olanlarda öncelik SGLT2 inhibitöründe olmak üzere GLP1 RA'de seçilebilir.
- Obez olan hastalarda kilo vermeye katkısı olacak GLP1 RA öncelikli olarak seçilmelidir.
- SGLT2 inhibitörleri azda olsa kilo verdirici etkisi nedeniyle obez hastalarda oral kombinasyonlarda tercih edilebilir.
- İlaçların kullanımlarında kardiyak, renal etkiler ve maliyet yönünden en uygun ilaçlar seçilmelidir.
- İnsülin başlanan hastalarda kontrendikasyon yok ise metformine devam edilmelidir.
- Çoklu insülin kullanan hastalarda metformin dışında en fazla bir oral antidiabetik seçilmelidir.
- İnsülin kullanan hastalarda enjeksiyon yerleri mutlaka kontrol edilmelidir.
- Bazal insülin ve GLP1 RA kombinasyonları enjeksiyon sayısını azaltması nedeniyle obez ve insülin gereken hastalarda tedavi kolaylığı sağlar.




## C-peptid düzeyi

Pankreas beta hücre rezervini gösteren en iyi testdir. Tip 1 DM'de rutin ölçülmesi gerekli değildir. LADA veya Tip 1 DM'yi TİP 2 DM den ayrımında, insülin tedavisinin gerekli olup olmadığı düşünülen bazı Tip 2 DM olgularının saptanmasında plazma açık veya uyarılmış C-peptid düzeyleri faydalı olabilir.

Yüksek hiperglisemisi olan ve kronik böbrek yetmeziği durumlarında C-peptid düzeyi gerçeği yansıtmayabilir.

ULUSAL DİYABET KONSENSUS GRUBU

# Diyabet

## Tanı ve Tedavi Rehberi

## 2019

TÜRKİYE DİYABET VAKFI

### Tip 1 Diyabet ve Tip 2 Diyabetin Ayırıcı Tanısı*

| Klinik Özellikler | T1DM | T2DM |
|---|---|---|
| Başlangıç yaşı | Genellikle ≤ 30 yaş | Genellikle ≥ 30 yaş |
| Başlangıç şekli | Genellikle akut, semptomatik | Yavaş, çoğunlukla asemptomatik |
| Ketozis | Sıklıkla var | Sıklıkla yok |
| Başlangıç kilosu | Genellikle zayıf | Genellikle fazla kilolu/obez |
| Ailede diyabet yükü | Yok veya belirgin değil | Yoğun |
| C - peptid | Düşük | Normal / Yüksek / Düşük |
| Otoantikor (ICA, AntiGAD, IA2Ab, IAA) | Genellikle pozitif | Negatif |
| Otoimmün hastalık birlikteliği | Var | Yok |

# TİP 2 DİYABETTE TEDAVİ YAKLAŞIMI

| HbA1c | BETA HÜCRE REZERVİ (C peptid: ng/ml) | TEDAVİ PLANI | TEDAVİ SEÇENEKLERİ |
|---|---|---|---|
| <8 | YETERLİ | Metformin | Yaşam Tarzı Değişikliği |
| 8 - 10 | YETERLİ | İKİLİ KOMBİNASYON Metformin | Sülfonilüre veya Glinidler; Pioglitazon; DPP4 İnhibitörleri; SGLT2 İnhibitörleri; GLP1 RA |
| >10 | YETERLİ | ÜÇLÜ KOMBİNASYON Metformin | Sülfonilüre veya Glinidler; Pioglitazon; DPP4 İnhibitörleri; SGLT2 İnhibitörleri; GLP1 RA |
| >10 | SINIRDA | BAZAL İNSÜLİN KOMBİNASYONLARI Metformin | Sülfonilüre veya Glinidler; Pioglitazon; DPP4 İnhibitörleri; SGLT2 İnhibitörleri; GLP1 RA |
| >10 | YETERSİZ | ÇOKLU DOZ İNSÜLİN KOMBİNASYONLARI Metformin | Miks insülin kombinasyonları 1'li, 2'li, 3'lü; Bazal/ Bolus, Bazal + plus Koformilasyon insülin; DPP4, SGLT2, GLP1 RA |

■ Tip 2 DM tedavisinde ilaç seçimlerinde ve kombinasyonlarında dikkat edilmesi gereken ilaç ve hasta faktörleri yan sayfadadır.

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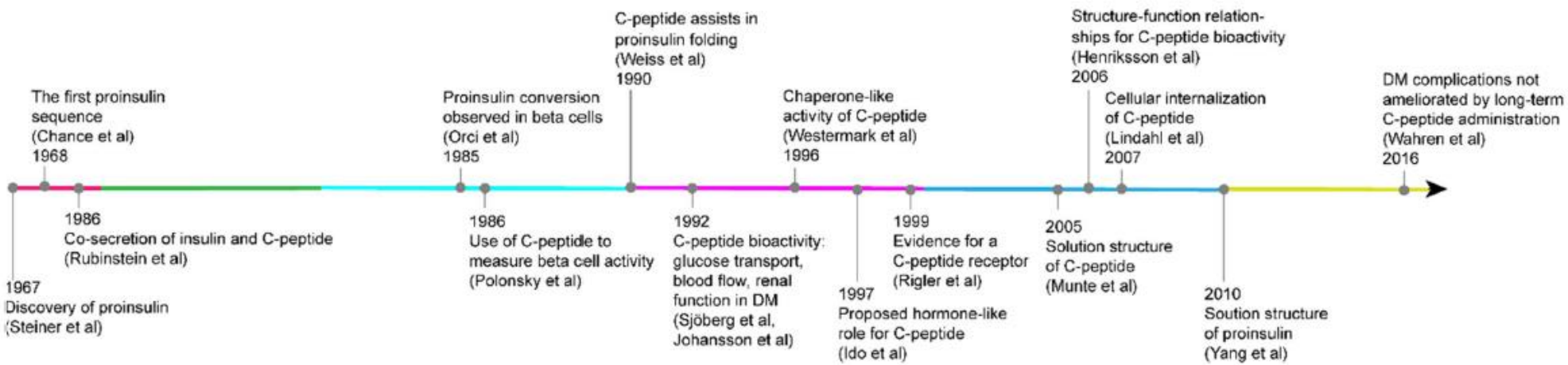
Cellular and Molecular Life Sciences

VISIONS AND REFLECTIONS

# Biological activity versus physiological function of proinsulin C-peptide

Michael Landreh[1] · Hans Jörnvall[2]



# C Peptid

- Diyabet heterojen kompleks bir hastalık
  - C peptid diyabeti değerlendirmede basit ucuz güvenilir bir klinik belirteç
  - Patofizyoloji ve hastalık progresyonu hakkında bilgilendirir
  - Komplikasyonlar ve hipoglisemiyi öngörmede yardımcı
  - Tedavinin bireyselleştirilmesi ve yönetiminde yönlendirici

*Diabetes Obes Metab.* 2022;24:1912–1926.