



INSULIN  
100



# 57. ULUSAL DİYABET METABOLİZMA ve BESLENME HASTALIKLARI KONGRESİ

*YENİ NESİL STRES 'DİKARBONİL STRES':*

TİP 2 DİYABETİN ve KOMPLİKASYONLARININ  
GELİŞİMİNDE ROLÜ VAR MI?

DR. MUSTAFA KOÇAK

KARADENİZ TEKNİK ÜNİVERSİTESİ TIP FAKÜLTESİ

ENDOKRİNOLOJİ VE METABOLİZMA HASTALIKLARI BİLİM DALI

04/06/2021

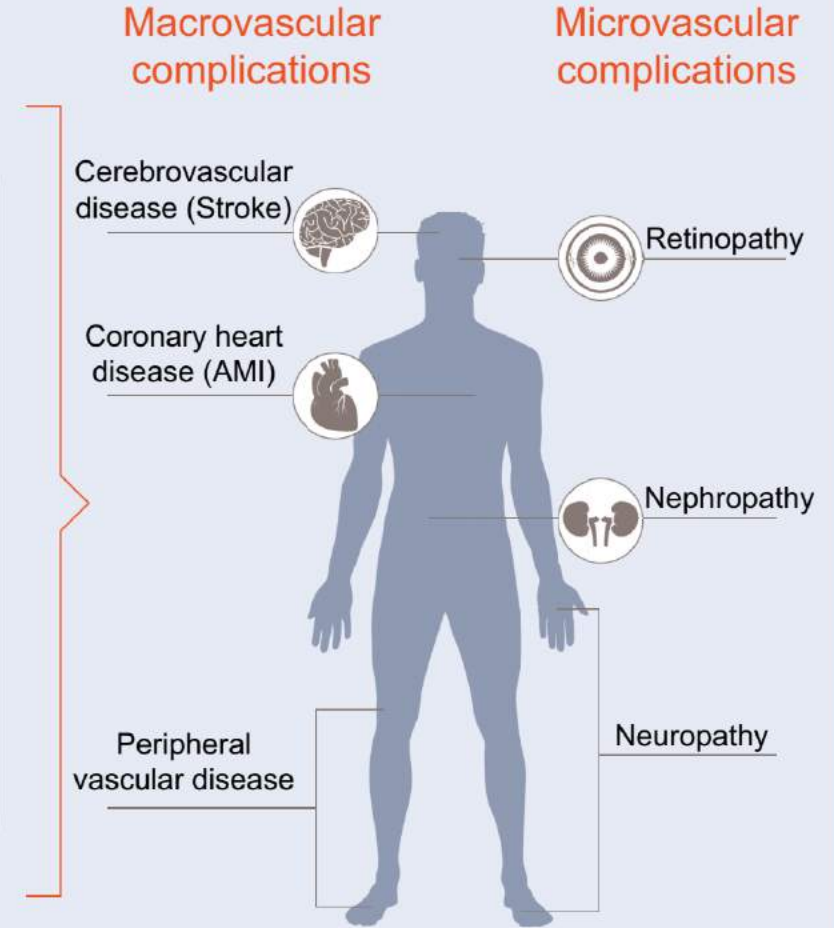
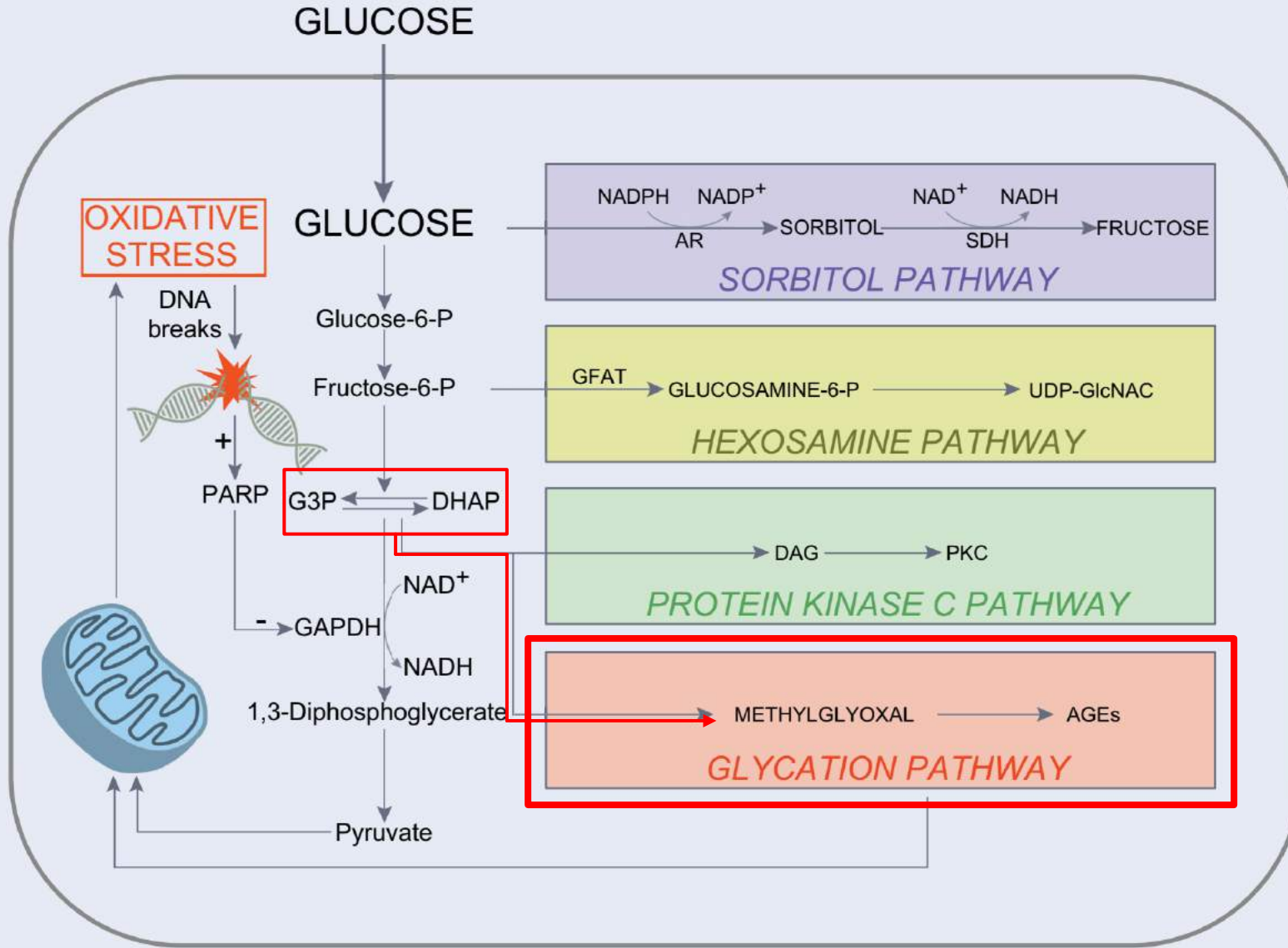
# *DİKARBONİL STRES*

## TANIM

- Yaşlanma ve hastalıkta hücre ve doku disfonksiyonuna katkıda bulunan protein ve DNA modifikasyonunun artmasına yol açan anormal  $\alpha$ -oksoaldehit metabolitlerinin birikmesi
- Hücre içi proteinlere zarar veren, hücre dışı matriks proteinlerini ve plazma proteinlerini değiştiren dikarbonil metabolitlerinin (**metilglioksal, glioksal ve 3-deoksiglukozon**) birikmesi

# Olası 4 potansiyel mekanizma

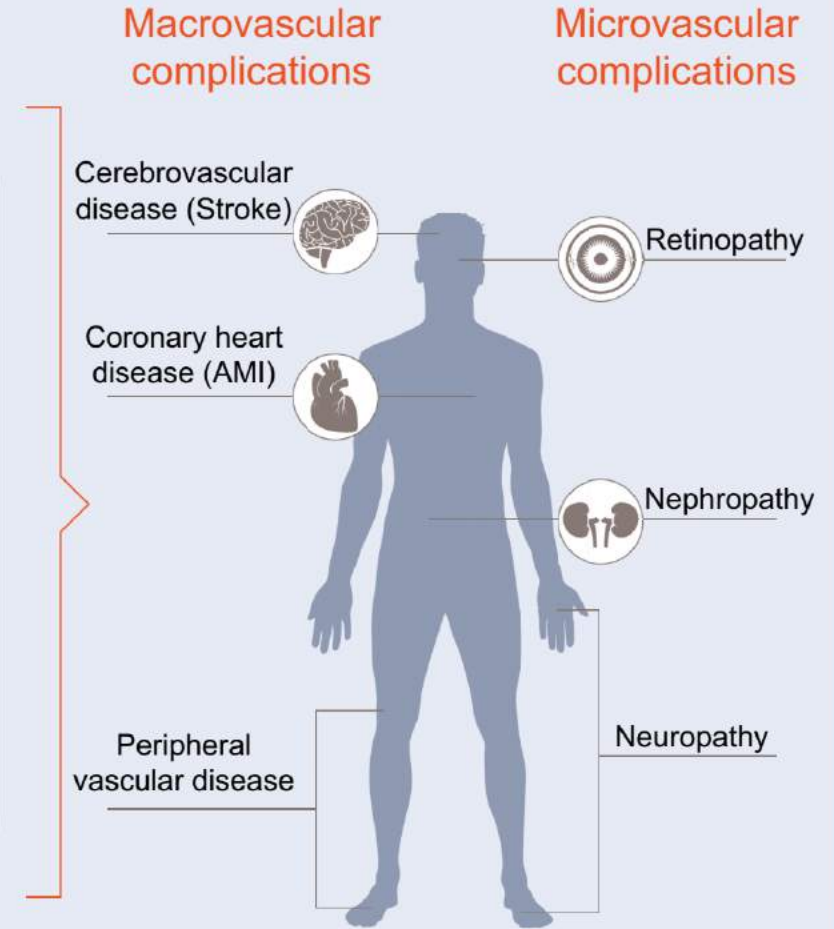
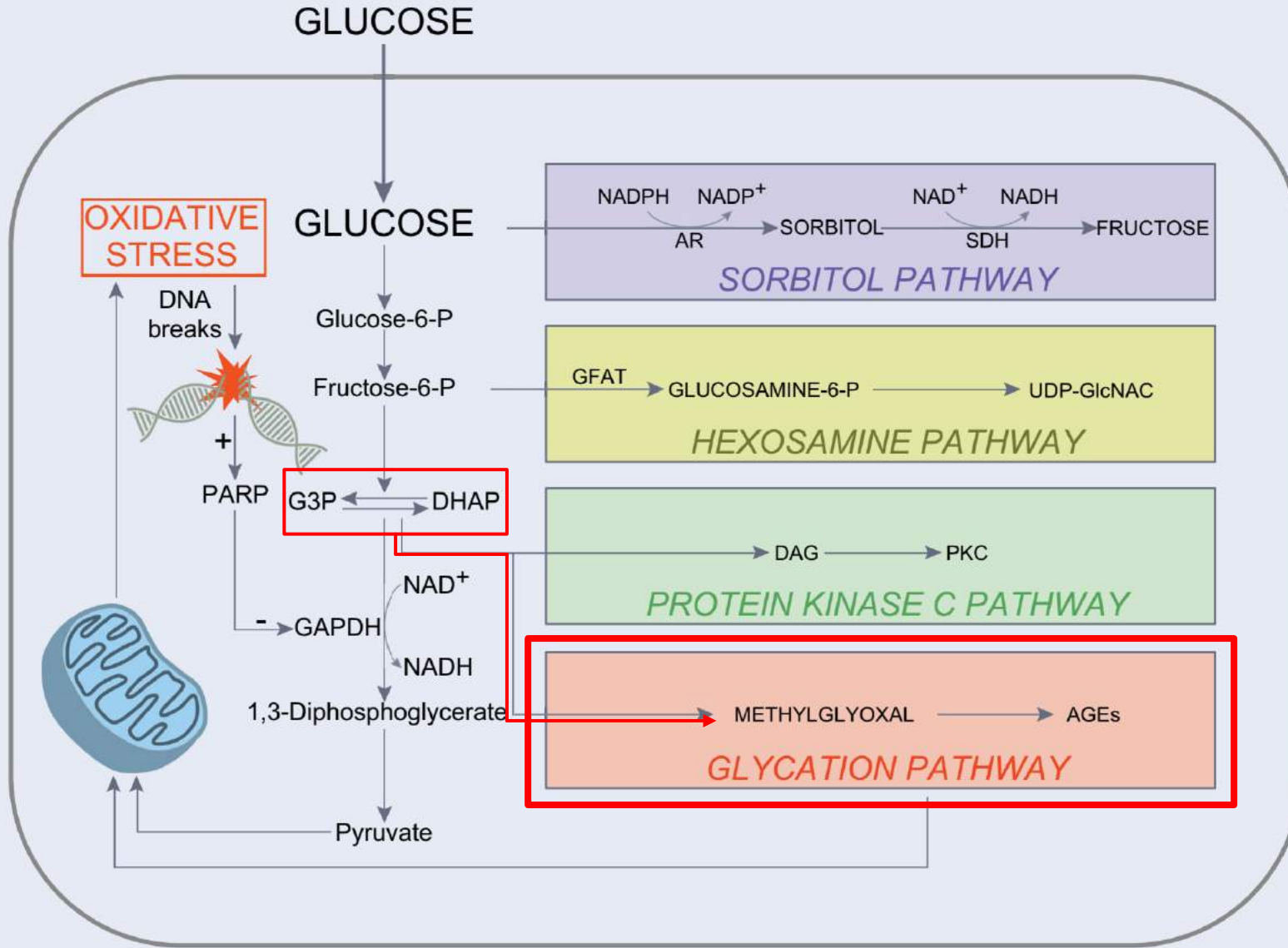
HRC. G. Schalkwijk and C. D. A. Stehouwer, *Physiol Rev* 100: 407–461. September 20, 2019; The American Physiological Society



Bu 4 biyokimyasal ve metabolik yol, mitokondride hipergliseminin neden olduğu aşırı oksidatif stres üretimi ile daha da arttırılır ve birbiriyle ilişkilidir ve birbirini güçlendirir.

# Olası 4 potansiyel mekanizma

HRC. G. Schalkwijk and C. D. A. Stehouwer, *Physiol Rev* 100: 407–461. September 20, 2019; The American Physiological Society

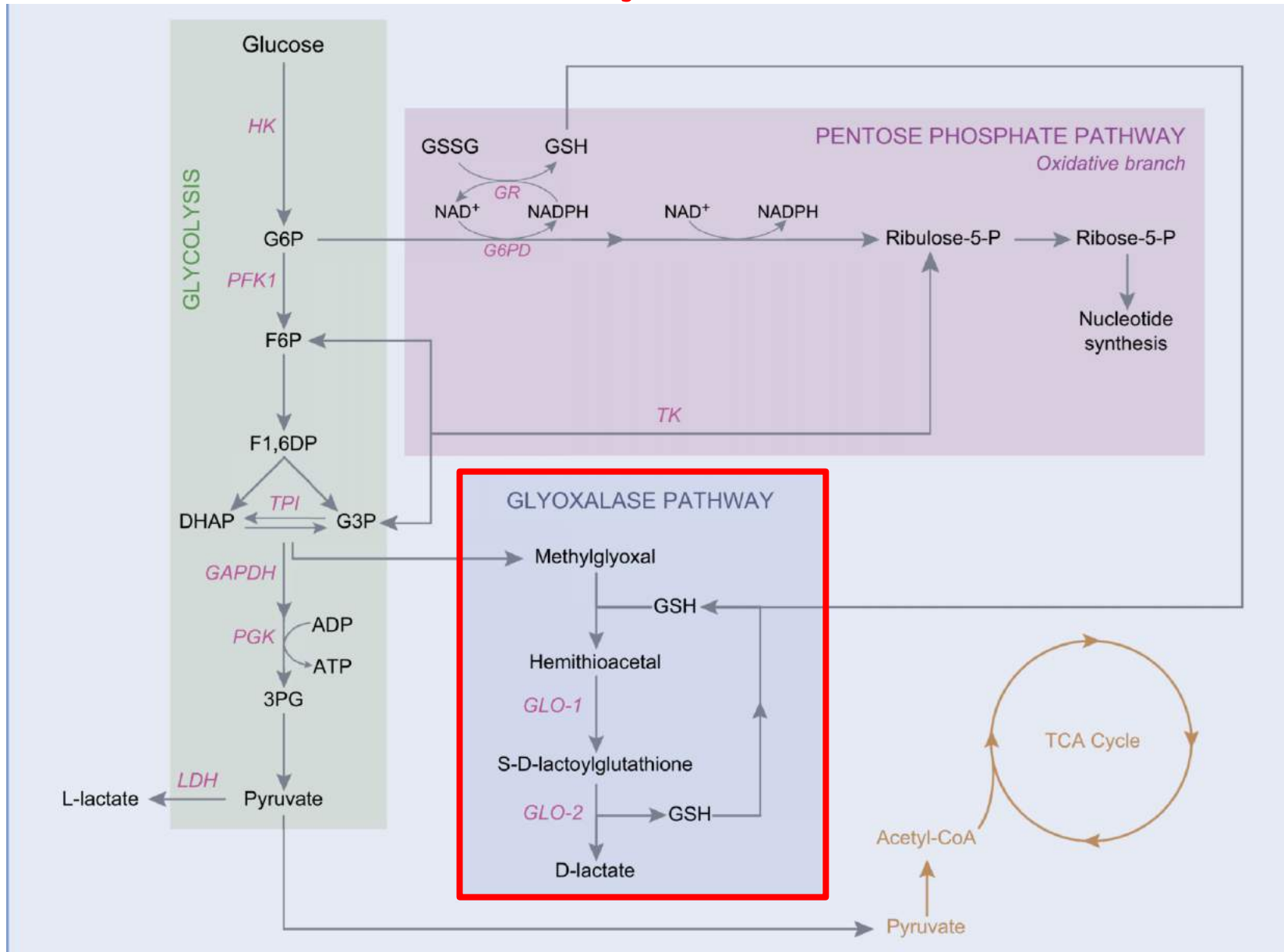


Mitokondriyal aşırı üretim ile reaktif oksijen türlerinin oluşumu, bu dört ana “pieces of the puzzle” harekete geçirir

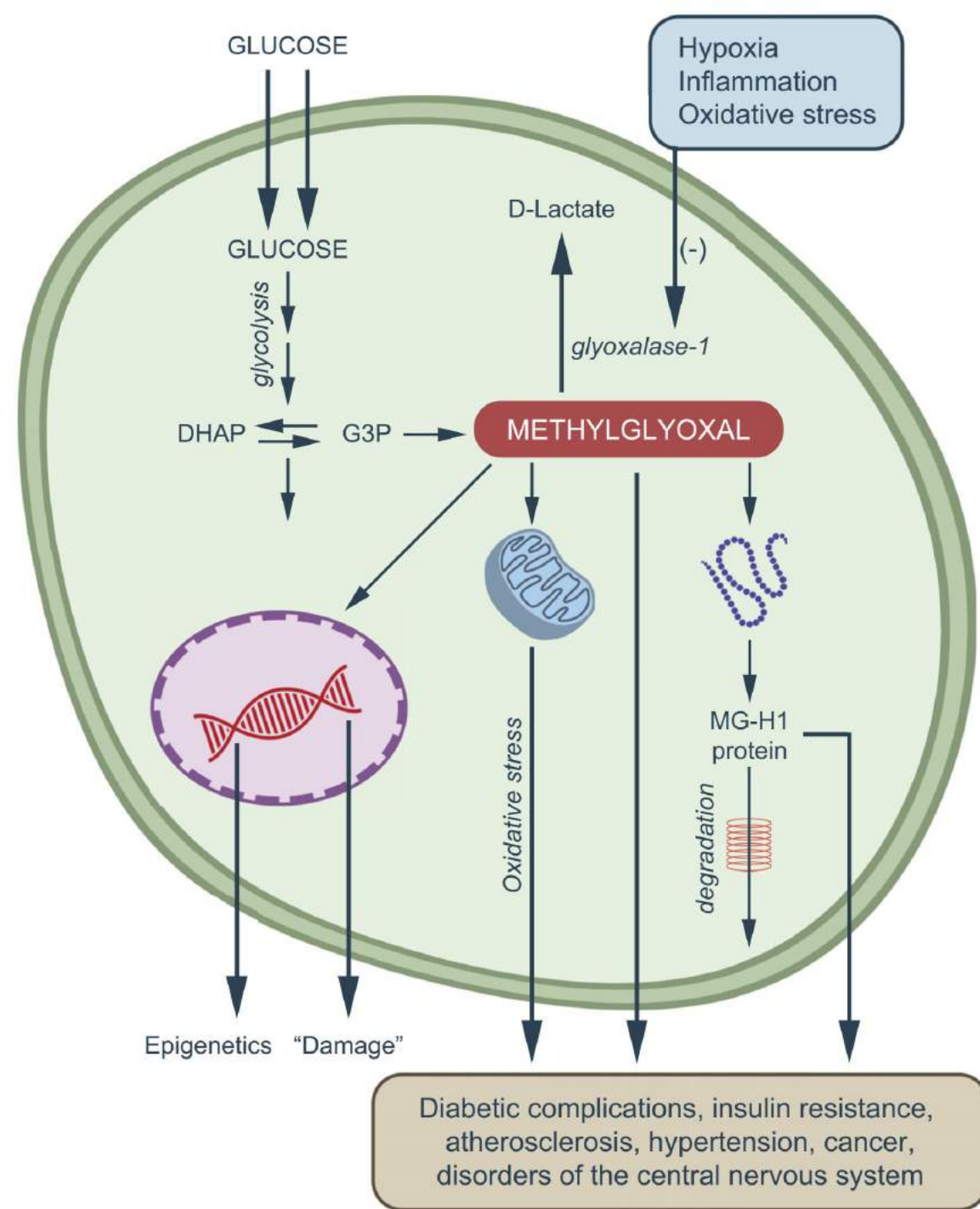
# DİKARBONİL METABOLİTLERİ

- Gliksal, MGO ve 3-Deoksiglukozan konsantrasyonları
  - İnsan plazmasında 50-150 nM,
  - Bitki ve memeli hücrelerinde 1-4  $\mu$ M
- Dikarbonil konsantrasyonları bu değerleri geçtiğinde, bozulmuş sağlık ve hastalığa yol açan protein ve hücre disfonksiyonu potansiyeli var
- MGO esas olarak glikolizin bir yan ürünü olarak oluşturulur ve fizyolojik koşullar altında gliksalaz sistemi tarafından detoksifiye edilir

# METİLGİOKSAL OLUŞUMU VE DEGRADASYONU







# DİKARBONİL METABOLİTLERİNİN ARTTIĞI DURUMLAR

- Yaşlanan bitkilerde artmış MGO,
- Yaşlanan insan lensinde artan MGO-protein modifikasyonu,
- Diyabette MGO'nin artan plazma ve doku konsantrasyonu
- Renal yetmezlikte artmış MGO, glioksal, 3-deoksiglukozan (DG) ve diğer karbonillerin artmış konsantrasyonları
- **Metilglioksal en reaktif dikarbonil ve en yüksek endojen akışa sahip**





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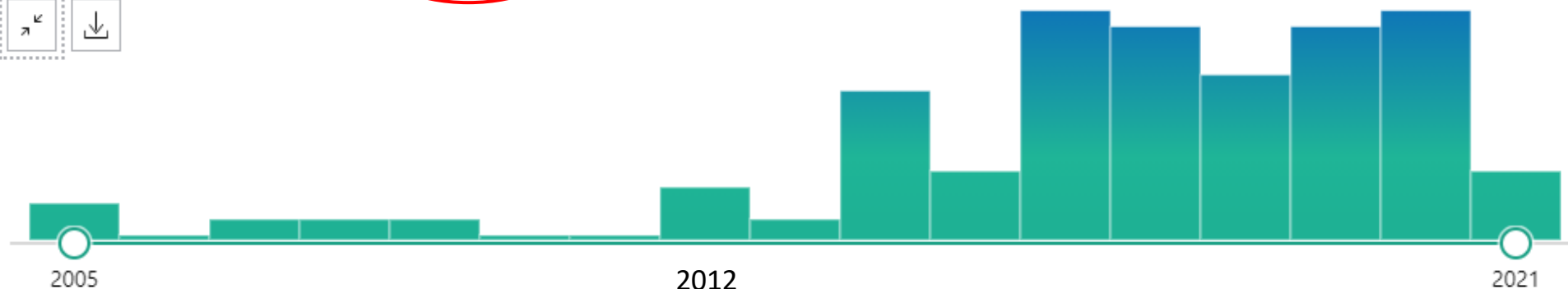
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1 [Diet-induced weight loss reduces postprandial \*\*dicarbonyl stress\*\* in abdominally obese men: Secondary analysis of a randomized controlled trial.](#)  
Cite Van den Eynde MDG, Kusters YHAM, Houben AJHM, Scheijen LJJM, van Duynhoven J, Fazelzadeh P, Joris PJ, Plat J, Mensink RP, Hanssen NMJ, Stehouwer CDA, Schalkwijk CG.  
Share Clin Nutr. 2021 Apr 15;40(5):2654-2662. doi: 10.1016/j.clnu.2021.03.042. Online ahead of print.  
PMID: 33933731 [Free article.](#)  
**Dicarbonyl stress** may already be detrimental in obesity. We evaluated whether diet-induced weight



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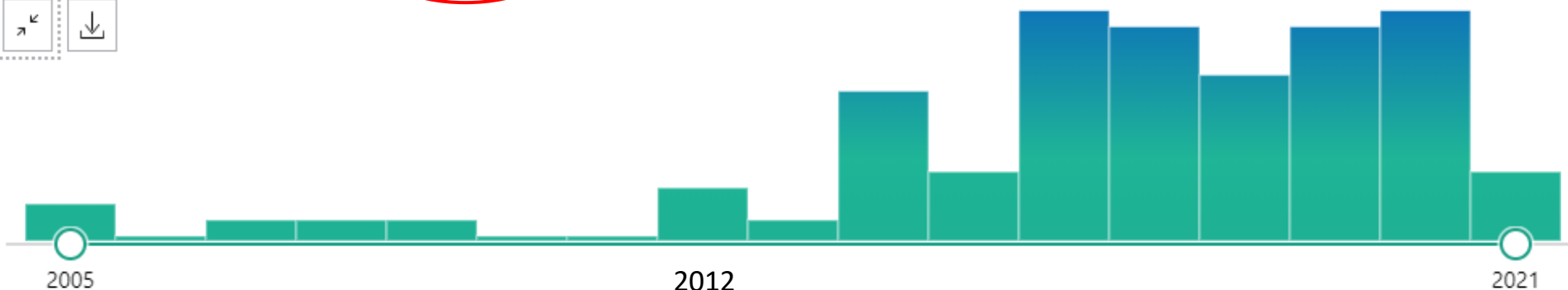
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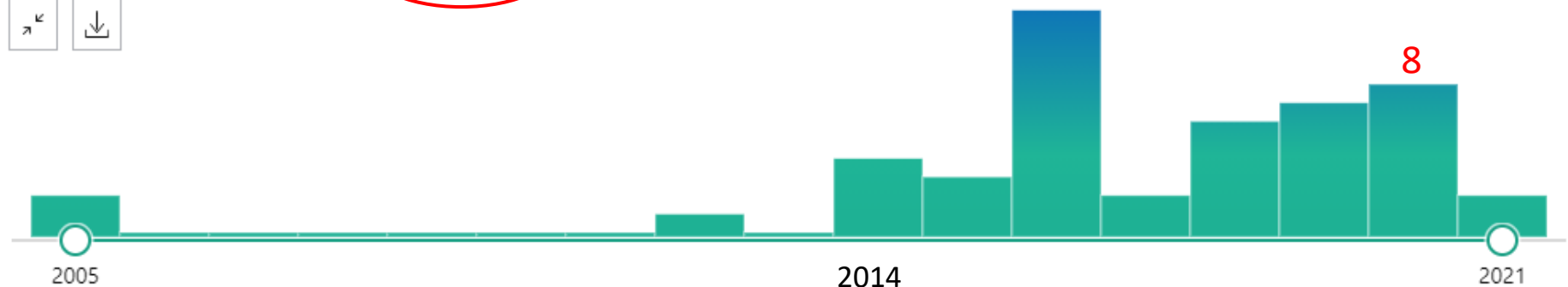
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TEXT AVAILABILITY

- Dicarbonyl stress**, protein glycation and the unfolded protein response.  
1 Rabbani N, Xue M, Thornalley PJ.  
Glycoconj J. 2021 Jun;38(3):331-340. doi: 10.1007/s10719-021-09980-0. Epub 2021 Mar 1.  
PMID: 33644826 **Free PMC article.** Review.  
Share The reactive **dicarbonyl** metabolite, methylglyoxal (MG), is increased in obesity and **diabetes** and is implicated in the development of insulin resistance, type 2 **diabetes mellitus** and vascular complications of **diabetes**. **Dicarbonyl stress** ...
- N-acetylcysteine inhibits atherosclerosis by correcting glutathione-dependent

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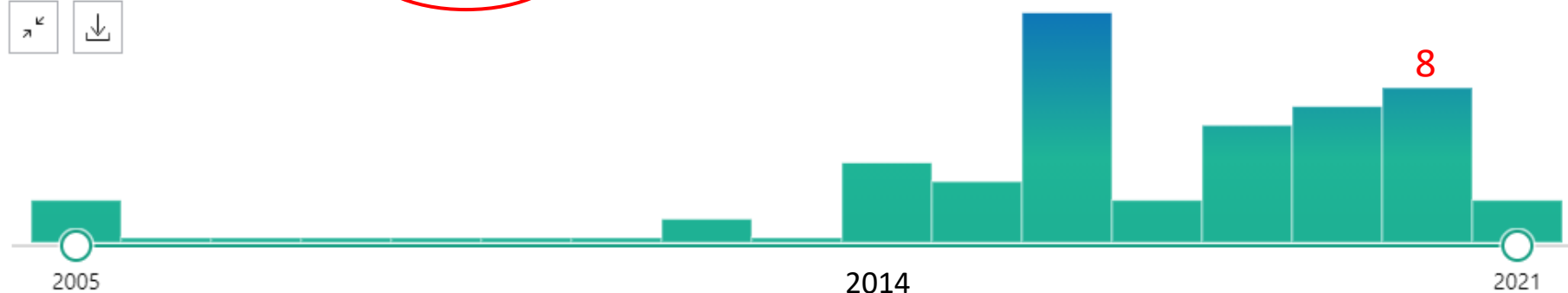
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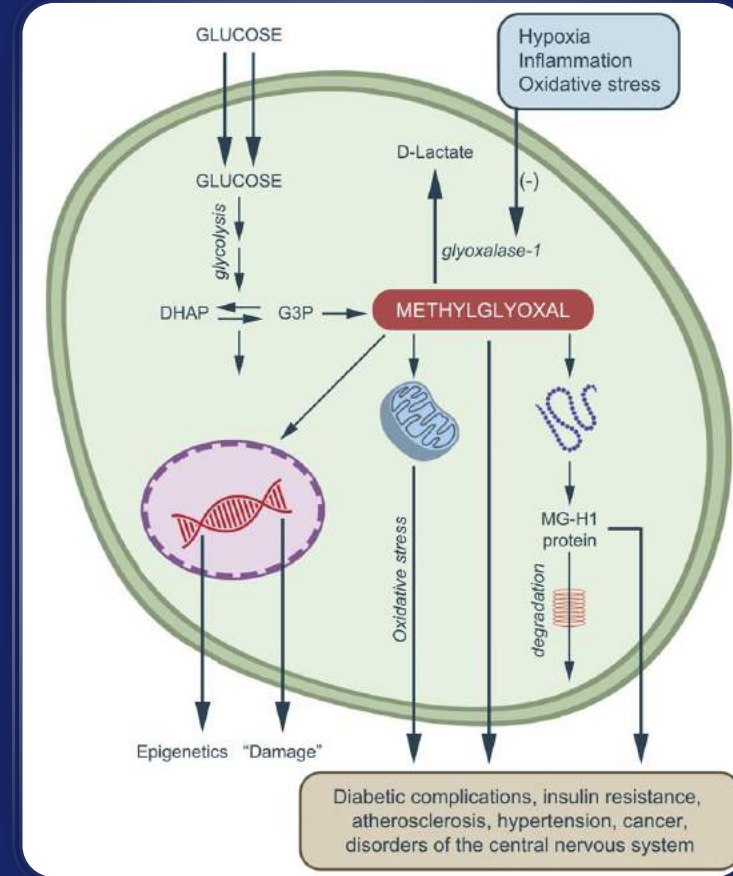
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- N-acetylcysteine inhibits atherosclerosis by correcting glutathione-dependent

# HASTALIKLARDA DİKARBONİL STRES

- Diyabette, protein modifikasyonlarına neden olan artan dikarbonil stres mekanizması, glikasyon yolu olarak bilinir
- Hiperglisemi, aşırı süperoksit üretimine neden olur ve glikolitik enzim gliseraldehit-3-fosfat dehidrojenazı kısmen inhibe ederek hücre içi dikarbonil oluşumunu tetikleyen artmış bir glukoz akışına yol açar.
- Dikarboniller, gelişmiş glikasyon son ürünleri adı verilen protein değişikliklerine neden olur.



# DİKARBONİL METABOLİTLERİ

- Hipergliseminin neden olduğu reaktif ajan metilglioksal oluşumunun vasküler komplikasyonların gelişimini artırdığına dair deneysel ve prelinik araştırmalardan elde edilen önemli bilimsel kanıtlar bulunmakta
- MGO, diyabette hipertansiyon, dislipidemi ve obezite gibi vasküler komplikasyonlar için diğer risk faktörleri ile birlikte.
- MGO'nun diyabette vasküler komplikasyonların gelişiminde kilit bir oyuncu olduğu anlamına gelebilir.



Epub 2016 May 11.

# Improved Glycemic Control and Vascular Function in Overweight and Obese Subjects by Glyoxalase 1 Inducer Formulation

Mingzhan Xue<sup>1</sup>, Martin O Weickert<sup>2</sup>, Sheharyar Qureshi<sup>2</sup>, Ngianga-Bakwin Kandala<sup>3</sup>, Attia Anwar<sup>1</sup>, Molly Waldron<sup>1</sup>, Alaa Shafie<sup>1</sup>, David Messenger<sup>4</sup>, Mark Fowler<sup>4</sup>, Gail Jenkins<sup>4</sup>, Naila Rabbani<sup>5</sup>, Paul J Thornalley<sup>6</sup>

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PMID: 27207552 DOI: 10.2337/db16-0153

Free article

## Abstract

Risk of insulin resistance, impaired glycemic control, and cardiovascular disease is excessive in overweight and obese populations. We hypothesized that increasing expression of glyoxalase 1 (Glo1)-an enzyme that catalyzes the metabolism of reactive metabolite and glycating agent methylglyoxal-may improve metabolic and vascular health. Dietary bioactive compounds were screened for Glo1 inducer activity in a functional reporter assay, hits were confirmed in cell culture, and an optimized Glo1 inducer formulation was evaluated in a randomized, placebo-controlled crossover clinical trial in 29 overweight and obese subjects. We found trans-resveratrol (tRES) and hesperetin (HESP), at concentrations achieved clinically, synergized to increase Glo1 expression. In highly overweight subjects (BMI >27.5 kg/m(2)), tRES-HESP coformulation increased expression and activity of Glo1 (27%, P < 0.05) and decreased plasma methylglyoxal (-37%, P < 0.05) and total body methylglyoxal-protein glycation (-14%, P < 0.01). It decreased fasting and postprandial plasma glucose (-5%, P < 0.01, and -8%, P < 0.03, respectively), increased oral glucose insulin sensitivity index (42 mL · min(-1) · m(-2), P < 0.02), and improved arterial dilatation Δbrachial artery flow-mediated dilatation/Δdilatation response to glyceryl nitrate (95% CI 0.13-2.11). In all subjects, it decreased vascular inflammation marker soluble intercellular adhesion molecule-1 (-10%, P < 0.01). In previous clinical evaluations, tRES and HESP individually were ineffective. tRES-HESP coformulation could be a suitable treatment for improved metabolic and vascular health in overweight and obese populations.

**Trial registration:** ClinicalTrials.gov NCT02095873.

- Önceki klinik değerlendirmelerde, tRES ve HESP ayrı ayrı etkisizdi.
- Trans-resveratrol ve Hesperetin koformülasyonu, fazla kilolu ve obez bireylerde metabolik ve vasküler sağlık için uygun tedavi olabilir.

# Post-Glucose Load Plasma $\alpha$ -Dicarbonyl Concentrations Are Increased in Individuals With Impaired Glucose Metabolism and Type 2 Diabetes: The CODAM Study

Dionne E Maessen<sup>1</sup>, Nordin M Hanssen<sup>1</sup>, Jean L Scheijen<sup>1</sup>, Carla J van der Kallen<sup>1</sup>, Marleen M van Greevenbroek<sup>1</sup>, Coen D Stehouwer<sup>1</sup>, Casper G Schalkwijk<sup>2</sup>

Affiliations + expand

PMID: 25710921 DOI: 10.2337/dc14-2605

## Abstract

**Objective:** There is **increasing** evidence that postprandial **glucose** excursions play an important role in the development of vascular complications. The underlying mechanism is unknown, but **glucose**-derived formation of reactive  **$\alpha$ -dicarbonyl** compounds may explain why acute hyperglycemia leads to **increased** risk for **diabetes** complications. In the current study, we investigated whether  $\alpha$ -dicarbonyls are **increased** after a **glucose load** in **individuals** without or with **impaired glucose metabolism** (IGM) and **type 2 diabetes**.

**Research design and methods:** Cross-sectional, linear analyses were performed in the Cohort on **Diabetes** and Atherosclerosis Maastricht (CODAM [n = 574, 61% men, 60 years old]) study.

**Individuals** with normal **glucose metabolism** (n = 279), IGM (n = 120), and **type 2 diabetes** (n = 92) who had complete data on an oral **glucose** tolerance test (OGTT) and were not on insulin treatment were included in the study population. Plasma  $\alpha$ -dicarbonyl (methylglyoxal [MGO], glyoxal [GO], and 3-deoxyglucosone [3-DG]) levels were measured in the fasting state and in samples of the OGTT by ultra-performance liquid chromatography-tandem mass spectrometry.

**Results:** The presence of both IGM and **type 2 diabetes** was significantly associated with higher  **$\alpha$ -dicarbonyl** incremental areas under the curve (iAUCs), as calculated from the OGTT (for IGM, MGO  $\beta$  = 0.190 [95% CI 0.106-0.274], GO  $\beta$  = 0.287 [95% CI 0.172-0.401], and 3-DG  $\beta$  = 0.285 [95% CI 0.221-0.349]; for **type 2 diabetes**, MGO  $\beta$  = 0.293 [95% CI 0.180-0.405], GO  $\beta$  = 0.536 [95% CI 0.382-0.689], and 3-DG  $\beta$  = 0.542 [95% CI 0.456-0.628]). Adjustment for **glucose** iAUC attenuated these associations. iAUCs of the  $\alpha$ -dicarbonyls correlated highly with **glucose** iAUC but not with fasting **glucose** levels or HbA1c.

**Conclusions:** The **increased** levels of  $\alpha$ -dicarbonyls during an OGTT in **individuals** with IGM and **type 2 diabetes** underline the potential importance of  **$\alpha$ -dicarbonyl** stress as a candidate to explain the **increased** risk of **diabetes** complications in **individuals** with postprandial hyperglycemia.

- BGT ve Tip 2 diyabetli bireylerde OGTT sırasında artan  $\alpha$ -dikarbonil seviyeleri, postprandiyal hiperglisemili bireylerde diyabet komplikasyon riskinin artmasını açıklamaya aday olarak  $\alpha$ -dikarbonil stresinin potansiyel öneminin altını çizmektedir.



*Hypothesis*

# Increased Dicarbonyl Stress as a Novel Mechanism of Multi-Organ Failure in Critical Illness

Bas C. T. van Bussel <sup>1,\*</sup>, Marcel C. G. van de Poll <sup>1,2</sup>, Casper G. Schalkwijk <sup>3</sup>  
and Dennis C. J. J. Bergmans <sup>1</sup>

- Sepsis ve majör travma gibi kritik hastalıklarda artan dikarbonil stresinin, çoklu organ yetmezliğinin gelişmesine katkıda bulunduğunu varsayılmış
- Bu mekanizma, yoğun bakımda yeni terapötik müdahale potansiyeline sahiptir.

Epub 2016 Jun 16.

## Energy restriction and Roux-en-Y gastric bypass reduce postprandial $\alpha$ -dicarbonyl stress in obese women with type 2 diabetes

Dionne E Maessen<sup>1</sup>, Nordin M Hanssen<sup>1</sup>, Mirjam A Lips<sup>2</sup>, Jean L Scheijen<sup>1</sup>, Ko Willems van Dijk<sup>2 3 4</sup>, Hanno Pijl<sup>2 4</sup>, Coen D Stehouwer<sup>1</sup>, Casper G Schalkwijk<sup>5</sup>

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PMID: 27312699 PMCID: PMC4969347 DOI: 10.1007/s00125-016-4009-1

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- Enerji kısıtlaması ve Roux-en-Y gastrik bypass, tip 2 diyabetli obez kadınlarda postprandiyal  $\alpha$ -dikarbonil stresini azaltır.

# DİKARBONİL STRESİNİN ÖNLENMESİ İÇİN TERAPÖTİK STRATEJİLER

- MGO ve MGO Modifiye Proteinleri Temizleme
  - Guanidin ailesinin ilaçlarının MG temizleyicileri olarak işlev gördüğü ve yüksek oranda reaktif MG'ye bağlanarak plazma ve dokularda MG-H1 gibi MG'nin neden olduğu protein modifikasyonlarını önlediği bilinmekte
  - Farmakolojik ajan **Aminoguanidin**, diyabetik komplikasyonları öngören laboratuvar ölçümlerini geliştirerek çok umut vaat etti
  - Bununla birlikte, klinik sonuçların olmaması ve ciddi yan etkiler, diyabette terapötik uygulamasını sınırlamakta
  - **Metformin**, T2DM için en sık reçete edilen ilaçtır ve biguanidin yapısı nedeniyle bir MG temizleyicisi olarak işlev görebilir



## Improved glycemic control induced by both metformin and repaglinide is associated with a reduction in blood levels of 3-deoxyglucosone in nonobese patients with type 2 diabetes

Lian Engelen<sup>1</sup>, Søren S Lund, Isabel Ferreira, Lise Tarnow, Hans-Henrik Parving, Jørgen Gram, Kaj Winther, Oluf Pedersen, Tom Teerlink, Rob Barto, Coen D A Stehouwer, Allan A Vaag, Casper G Schalkwijk

Affiliations + expand

PMID: 21205874 DOI: 10.1530/EJE-10-0851

### Abstract

**Objective:** Metformin has been reported to reduce  $\alpha$ -dicarbonyls, which are known to contribute to diabetic complications. It is unclear whether this is due to direct quenching of  $\alpha$ -dicarbonyls or to an improvement in glycemic control. We therefore compared the effects of metformin versus repaglinide, an antihyperglycemic agent with an insulin-secreting mechanism, on the levels of the  $\alpha$ -dicarbonyl 3-deoxyglucosone (3DG).

**Methods:** We conducted a single-center, double-masked, double-dummy, crossover study involving 96 nonobese patients with type 2 diabetes. After a 1-month run-in on diet-only treatment, patients were randomized to either repaglinide (6 mg daily) followed by metformin (2 g daily) or vice versa each during 4 months with a 1-month washout between interventions.

**Results:** 3DG levels decreased after both metformin (-19.3% (95% confidence interval (CI): -23.5, -14.8)) and repaglinide (-20.8% (95% CI: -24.9, -16.3)) treatments, but no difference was found between treatments (1.8% (95% CI: -3.8, 7.8)). Regardless of the treatment, changes in glycemic variables were associated with changes in 3DG. Specifically, 3DG decreased by 22.7% (95% CI: 19.0, 26.5) per s.d. decrease in fasting plasma glucose (PG), by 20.0% (95% CI: 16.2, 23.9) per s.d. decrease in seven-point mean plasma glucose, by 22.5% (95% CI: 18.6, 26.6) per s.d. decrease in area under the curve for PG, by 17.2% (95% CI: 13.8, 20.6) per s.d. decrease in HbA1c, and by 10.9% (95% CI: 6.4, 15.5) per s.d. decrease in Amadori albumin. In addition, decreases in 3DG were associated with decreases in advanced glycation endproducts and endothelial markers.

**Conclusion:** Improved glycemic control induced by both metformin and repaglinide is associated with a reduction in 3DG levels in nonobese individuals with type 2 diabetes. This may constitute a shared metabolic pathway through which both treatments have a beneficial impact on the cardiovascular risk.

- Non-obez 96 Tip 2 DM hastası
- Metformin ve repaglinid ile 4 aylık tedavi sonrası 3-deoksiglukozanda azalma tespit ediliyor



# DİKARBONİL STRESİNİN ÖNLENMESİ İÇİN TERAPÖTİK STRATEJİLER

## GLO1 İndükleyici Tedavi

- Nuclear factor-erythroid 2 p45 subunit-related factor 2 (NRF2) uyararak GLO1 protein ekspresyonunu arttırır
- NRF2, GLO1'in bazal ve indüklenebilir ekspresyonunu destekleyen bir transkripsiyon faktörüdür
- İnsan deneyleri, trans-resveratrol ve hesperetin (tRES/HESP) GLO1 protein ekspresyonunu ve aktivitesini arttırmada, plazma MG ve MG-yönelimli protein modifikasyonlarında NRF2 sinyalizasyonu ile azalmalar ile birlikte etkinliğini göstermiş

*(Xue M, Weickert MO, Qureshi S, Kandala NB, Anwar A, Waldron M, Shafie A, Messenger D, Fowler M, Jenkins G, Rabbani N, Thornalley PJ. Improved Glycemic Control and Vascular Function in Overweight and Obese Subjects by Glyoxalase 1 Inducer Formulation. Diabetes. 2016 Aug;65(8):2282-94. doi: 10.2337/db16-0153. Epub 2016 May 11.*

- Gelecekteki araştırmalar, tRES/HESP tedavisinin dokuya özgü NRF2-GLO1-MG eksenini üzerindeki karaciğer ve iskelet kası etkilerini araştırmalı

# SONUÇ

- **Metil glioksal;**
  - Diyabet gelişimi, diyabetin vasküler komplikasyonları ve diğer yaşa bağlı hastalıklar ile ilişkili
  - MGO ile ilişkili komplikasyonları tedavi etmeye yönelik müdahaleler henüz klinik ortamda mevcut değildir
  - Yıllar içinde MGO'yu düşürmek için çeşitli stratejiler geliştirilmeli
- **MGO'ı hedeflemek, ilgili hastalıkları hafifletmek için yeni terapötik uygulamalar sağlayabilir**

# TEŐEKKÜRLER



HIDIRNEBİ YAYLASI/AKÇAABAT/TRABZON