

# Telmisartan and irbesartan alleviate methylglyoxal-induced elevation of MG-H1 in vascular smooth muscle cells

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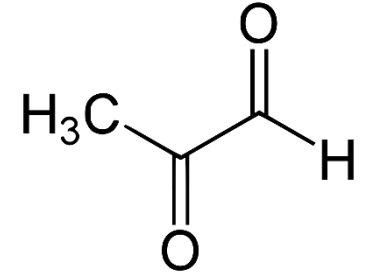
# Background

- Diabetes mellitus is a global health problem.
- Turkey will be in the top 10 countries in terms of diabetic patients numbers in 2045, according to IDF projections.
- The major complications of diabetes is related to high glucose concentration in the blood.

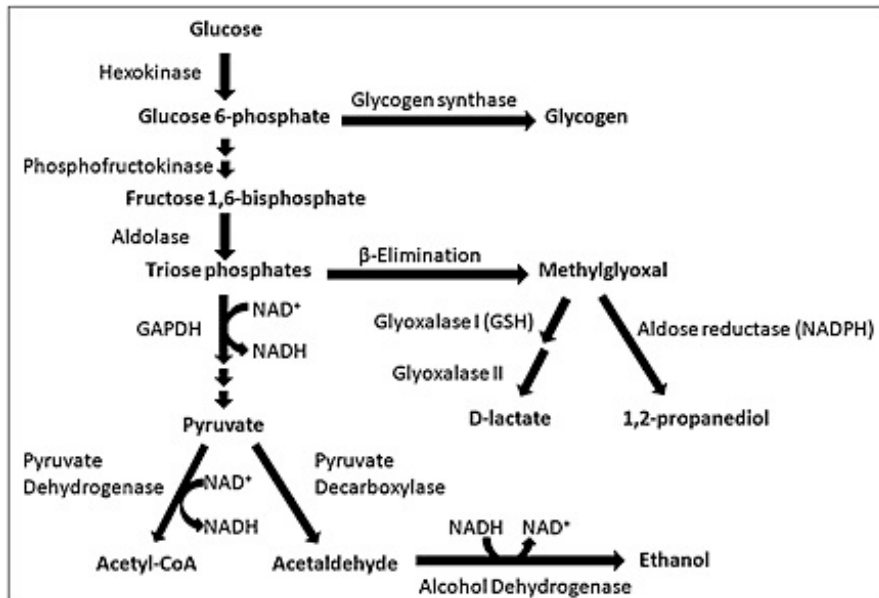
Table 3.2 Top ten countries/territories for number of people with diabetes (20-79 years), 2017 and 2045

2017			2045		
Rank	Country/territory	Number of people with diabetes	Rank	Country/territory	Number of people with diabetes
1	China	114.4 million (104.1-146.3)	1	India	134.3 million (103.4-165.2)
2	India	72.9 million (55.5-90.2)	2	China	119.8 million (86.3-149.7)
3	United States	30.2 million (28.8-31.8)	3	United States	35.6million (33.9-37.9)
4	Brazil	12.5 million (11.4-13.5)	4	Mexico	21.8 million (11.0-26.2)
5	Mexico	12.0 million (6.0-14.3)	5	Brazil	20.3 million (18.6-22.1)
6	Indonesia	10.3 million (8.9-11.1)	6	Egypt	16.7million (9.0-19.1)
7	Russian Federation	8.5 million (6.7-11.0)	7	Indonesia	16.7million (14.6-18.2)
8	Egypt	8.2million (4.4-9.4)	8	Pakistan	16.1 million (11.5-23.2)
9	Germany	7.5 million (6.1-8.3)	9	Bangladesh	13.7 million (11.3-18.6)
10	Pakistan	7.5 million (5.3-10.9)	10	Turkey	11.2 million (10.1-13.3)

# Methylglyoxal (MGO)

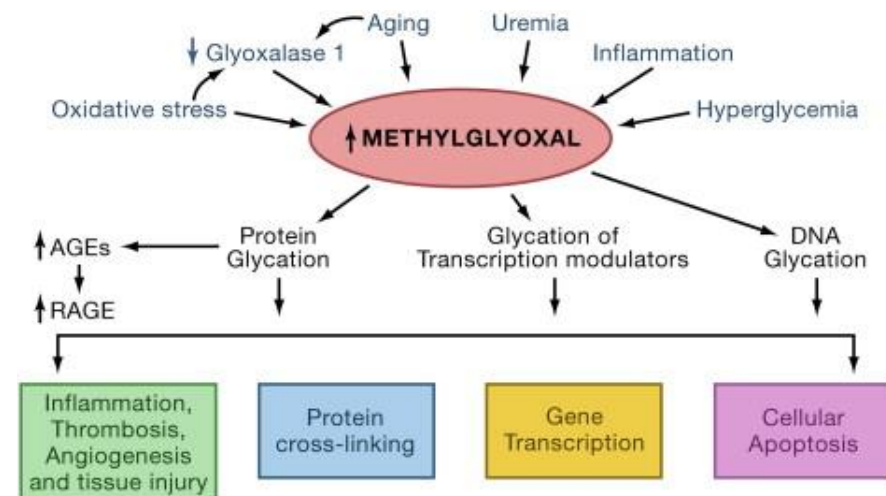
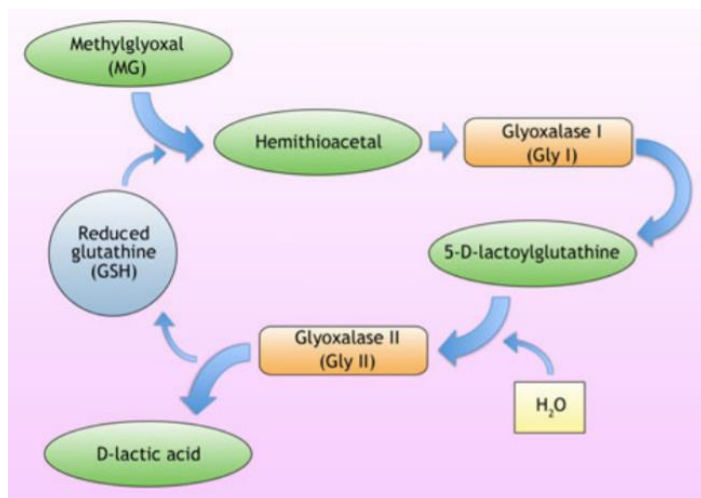


- MGO is a small, reactive dicarbonyl compound elevated in diabetic patients.
  - 5-6 fold in T1DM, and 2-3 fold in T2DM.
- Elevated MGO causes dicarbonyl stress, resulting in enhanced AGE formation.



- MGO is a glycolysis by-product and  $> \%99$  detoxified by the **glyoxalase** system in healthy humans.
- The major physiological MGO-derived AGE is hydroimidazolone 1 (**MG-H1**).

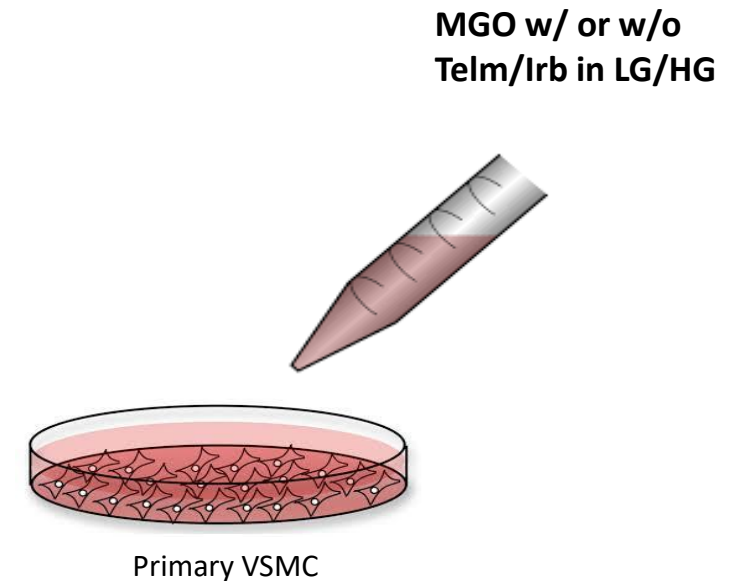
- Main component of the glyoxalase system is Glyoxalase 1 enzyme (Glo1).
  - Glo1 level is also reduced in diabetic patients in parallel to elevated MGO conc.
- Recently, MGO is associated with most of diabetic complications.
  - These include vascular diseases, atherosclerosis, hypertension, and restenosis.
- Telmisartan (Telm) and irbesartan (Irb) were suggested to be protective against MGO.



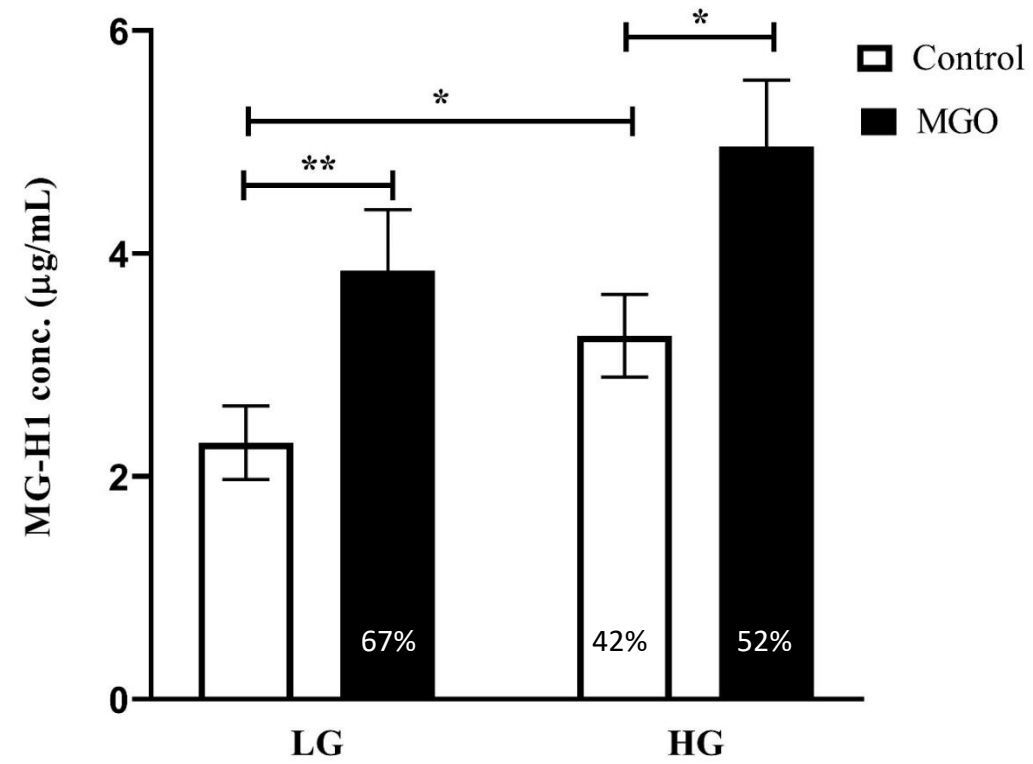
- Vascular smooth muscle cells (VSMCs) are one of the main cell types found in vasculature.
- VSMCs play a prominent role in vascular pathophysiology, such as atherosclerosis, hypertension and restenosis.
- The aim of this study was to explore whether MGO affects MG-H1 conc. in VSMCs under low glucose (LG) or high glucose (HG) media (an *in vitro* model of diabetic hyperglycemia), and
- To determine the potential protective roles of Telm and Irb.

# Materials and Methods

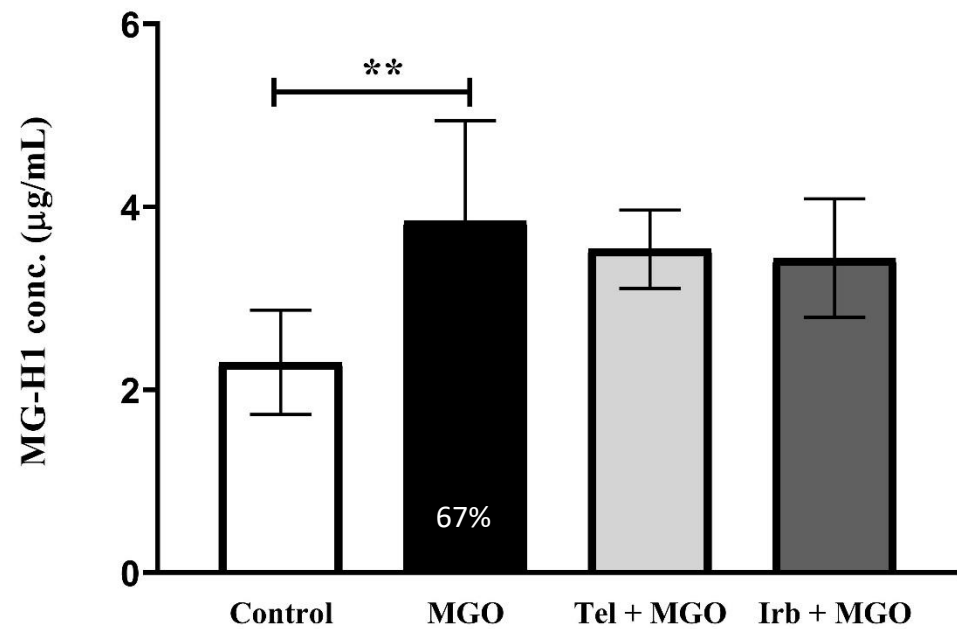
- VSMCs were isolated from SD rat aorta and primarily cultured.
  - Passages 3-5 were used.
- Cells were induced by 200  $\mu$ M MGO in LG (5,5 mM) or HG (25 mM) media for 48 h, after 24 h serum starvation.
  - Telm or Irb (both 10  $\mu$ M) were applied at least 30 m before MGO treatment.
- MG-H1 was measured by ELISA technique as triplicates.
- Statistical analysis was done by ANOVA, the post-hoc test was Tukey's method.



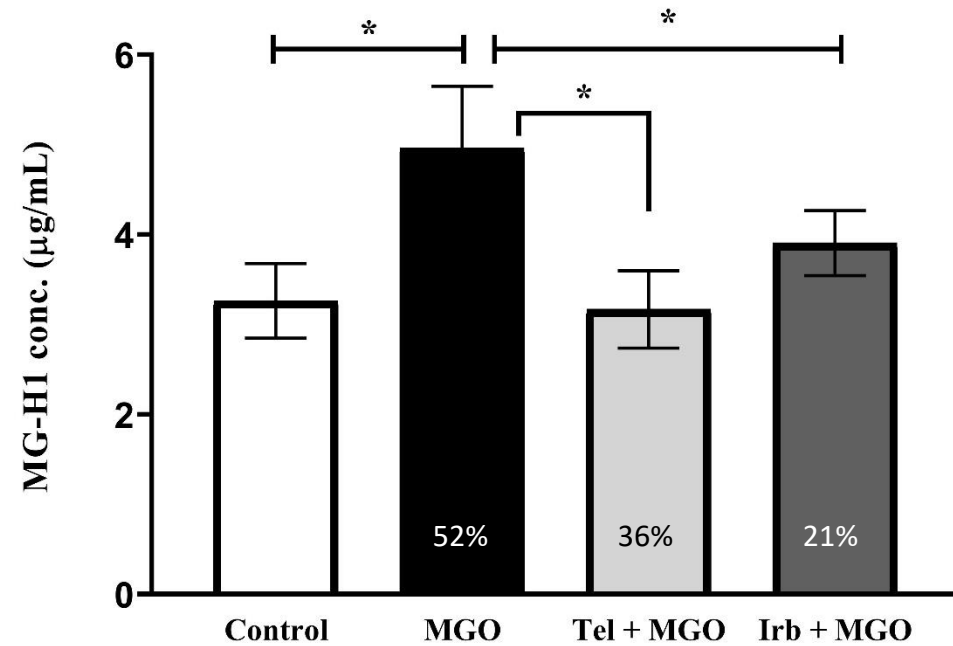
# Results



\* =  $p < 0,05$ ; \*\* =  $p < 0,001$



**LG**



**HG**

\* =  $p < 0,05$



# Discussion and Conclusion

- MGO ↑ MG-H1 conc. in LG and HG media, HG alone displayed a similar effect.
- Telm and Irb were not found effective to lower MG-H1 level in LG milieu.
- In contrast, they showed significant MG-H1 reduction in HG media.
- Rabbani et. al. reported that irbesartan treatment in hypertensive T2DM patients resulted in diminished MG-H1 conc. in urine.
- However, Miller et al. showed that candesartan was not effective against MGO-AGEs, but the measurement was not specific to MG-H1.

- MGO may be responsible for some of effects of HG. Thus, MGO scavenging could be a therapeutic target to prevent diabetic complications.
- Cruciferous vegetables rich diets may be beneficial for diabetics as these contain sulforaphane (activator of Glo1).
- Antihypertensive drugs Telm and Irb might be protective against MGO toxicity and dicarbonyl stress in diabetic hypertensive patients.
- As HG increases metabolic flux to the glycolysis, effect of MGO in HG background is more detrimental.
- Why Telm and Irb perform in HG but not in LG might be attributable to ↑ synthesis of Ang II in response to HG (actually AGE, Lavrentyev et. al.),
- As Miller et. al. have shown that Ang II inhibits Glo1 in the diabetic retina.
- Telm and Irb action on MG-H1 level in HG environment needs to be further studied.

# Limitations

- One dose and one incubation time
- Number of measurements (n=3)
- Only protein expression was quantitated
- An *in vitro* study
- Only one method-based observation

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# References

- McLellan AC.; Thornalley PJ.; Benn J.; Sonksen PH. *Clin Sci (Lond)*. 1994, 87(1):21-9.
- Rabbani N, Adaikalakoteswari A, Rossing K, Rossing P, Tarnow L, Parving HH, Thornalley PJ. *Amino Acids*. 2012, 42(5):1627-39.
- Rabbani, N., Thornalley, P. J. *Nature Protocols*. 2014, 9,1969-1979.
- Miller AG, Tan G, Binger KJ, et al. *Diabetes*. 2010, 59(12):3208–3215.
- Rabbani N.; Thornalley PJ. *Antioxid Redox Signal*. 2019, 20;30(3):354-374.
- Lavrentyev EN, Estes AM, Malik KU. *Circ Res*. 2007 31;101(5):455-64.
- Hanssen, N. M. J.; Scheijen, J.; Jorsal, A.; Parving, H. H.; Tarnow, L.; Rossing, P.; Schalkwijk, C. G. *Diabetes*. 2017, 66(8), 2278.
- Rabbani, N.; Thornalley, P. J. *Biochem Soc Trans*. 2014, 42(2), 425.
- Yao D.; Brownlee M. *Diabetes*. 2010, 59(1):249-55.
- Marsboom, G.; Archer, S. L. *Circ Res*. 2008, 103(10), 1047.
- Duan, W.; Shen, X.; Lei, J.; Xu, Q.; Yu, Y.; Li, R.; Ma, Q. *BioMed Res Int*. 2014, 461917.