Methylglyoxal-induced glycation of apolipoprotein B100 reduces hepatic catabolism of low-density lipoproteins

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❶ Introduction

- Cardiovascular diseases (CVD) are a major burden in patients with type 2 diabetes (T2D).[1]
- Glycation is an irreversible and non-enzymatic post-translational modification increased in T2D.
- Methylglyoxal (MGO) is the major dicarbonyl-derived advanced glycation end-product compounds.[2]

❷ Aim

To evaluate the functional impact of MGO glycation of apoB100 in LDL metabolism.

❸ Patients & Methods

- A peptide biomarker of MGO-glycated apoB100 (MGO-apoB100) was quantified by LC-MS/MS in biological samples.
- LDL were obtained by ultracentrifugation from patients with or without T2D. LDLs were incubated with different concentrations of MGO for *in vitro* and mouse assays. Individual LDLs were used for *ex vivo* assays.
- LDL were labelled with DIL and incubated with Immortalized Human Hepatocytes. LDL binding and uptake were measured by flow cytometry.
- MGO-glycated LDL were injected in mice to assess their plasma clearance over time. LDL residence times were calculated in humans (12 controls *vs.* 18 patients with T2D) from a stable isotope kinetic study.

❹ Results

Figure 1. MGO-glycated apoB100 (MGO-apoB100) reduces LDL uptake and LDL-R binding *in vitro*

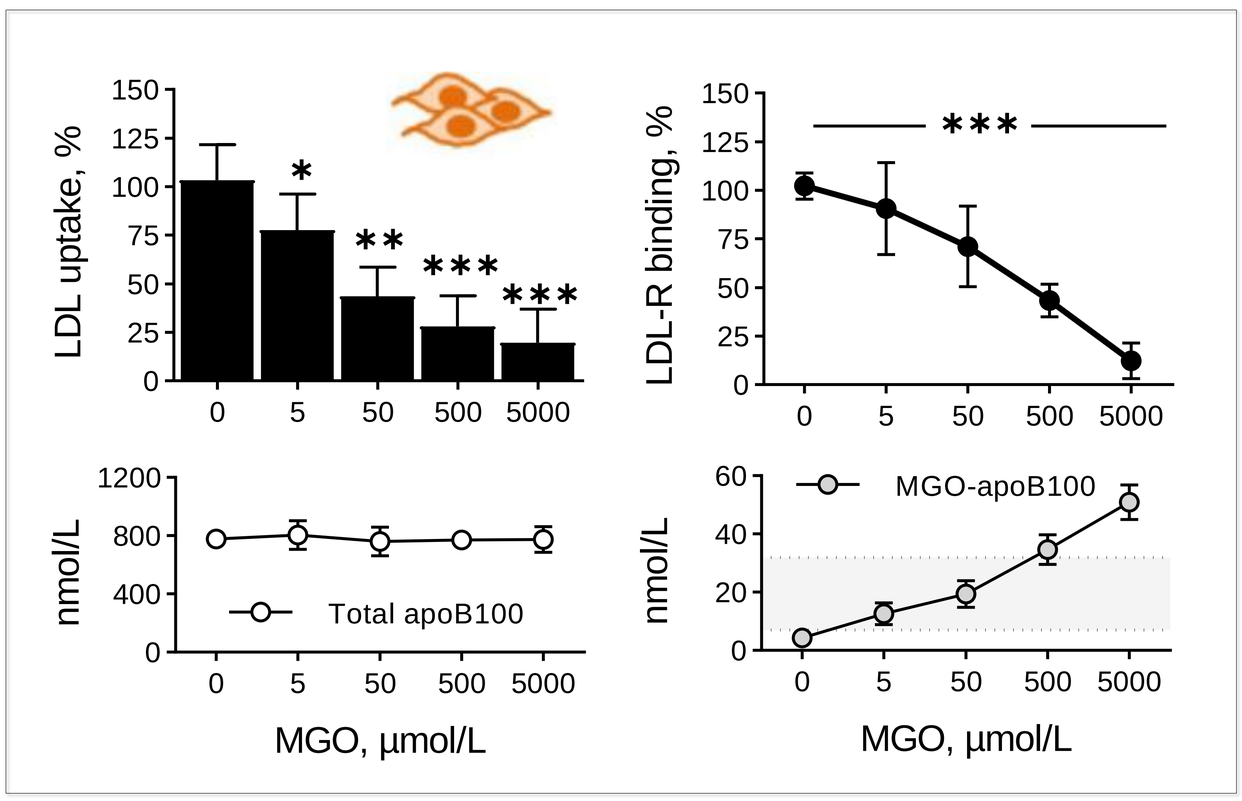


Figure 2. MGO-glycated apoB100 (MGO-apoB100) reduces LDL uptake and binding ***ex vivo***

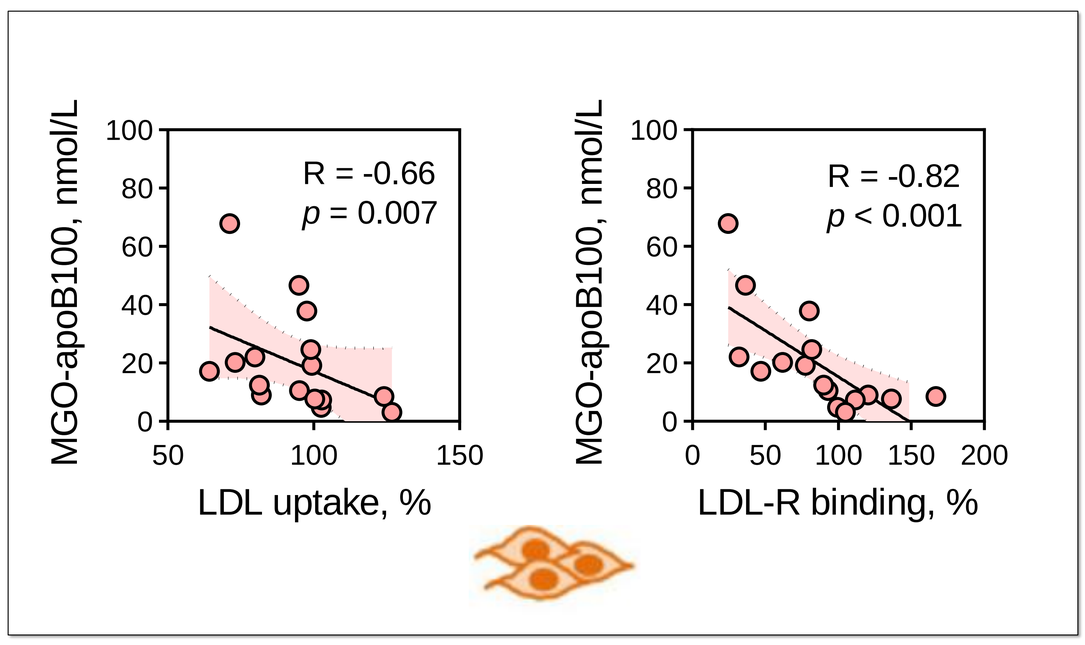


Figure 3. MGO-glycated apoB100 (MGO-apoB100) reduces LDL plasma clearance in mice (***in vivo***)

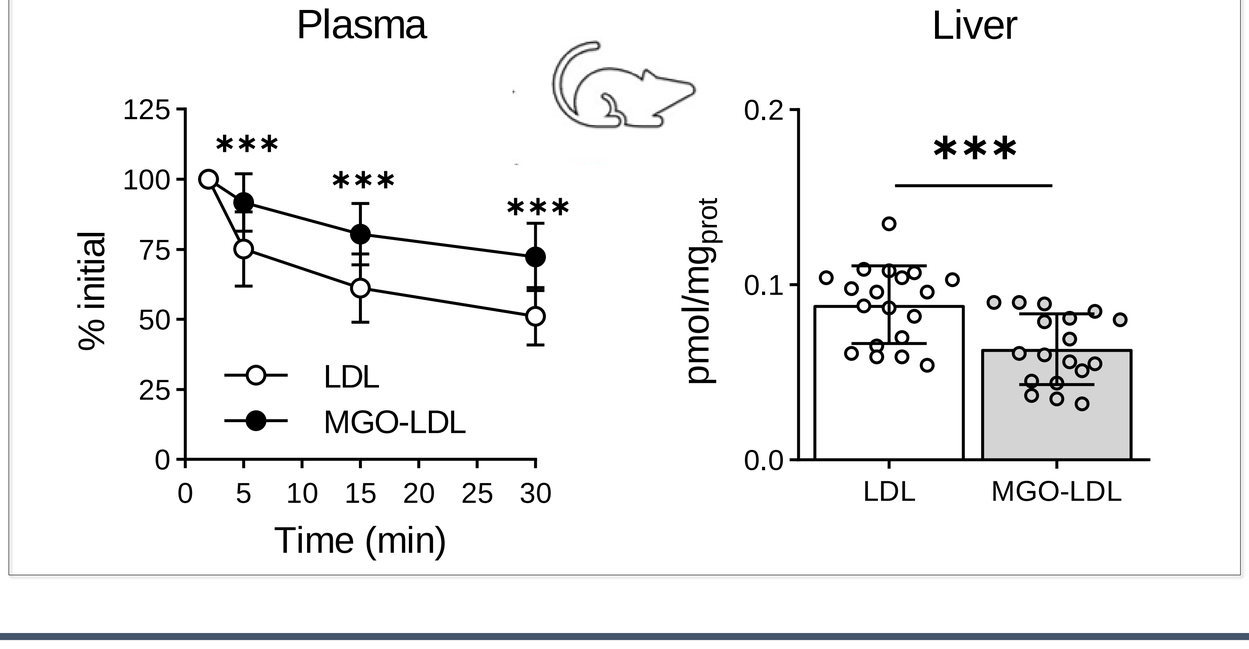
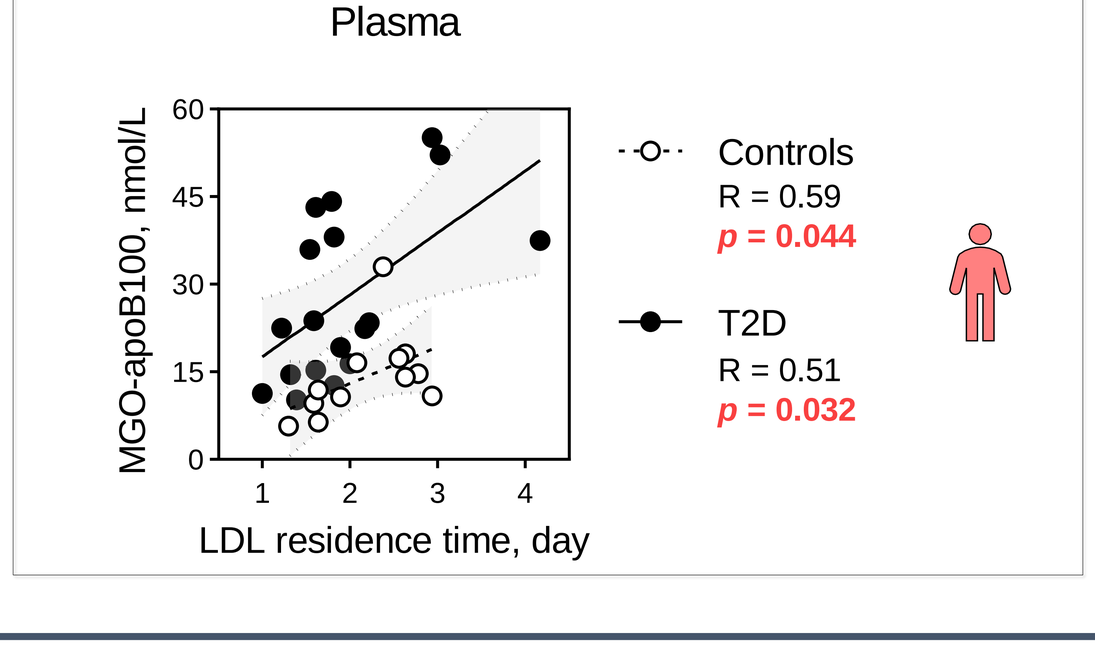


Figure 4. MGO-glycated apoB100 (MGO-apoB100) is positively correlated with LDL residence time in both controls and T2D patients (***in vivo***)



❺ Conclusion

We have identified a peptide biomarker of MGO-glycated apoB100 associated with a reduced catabolism of LDL by hepatocytes in both *in vitro* and *in vivo* models. MGO-glycated apoB100 is also positively corelated with an increased LDL residence time in humans.

References

1. Chen *et al*, *Nat Rev Endocrinol*, **2011**
2. Hanssen *et al*, *Diabetes Care*, **2018**