Hawkinson TR, Gentry MS, Sun R. *Hyperglycosylation is a metabolic driver of Alzheimer's disease.* **Nature Metabolism.** 2026.

Dr. Paul Tervit 2026

| Aspect | Summary |
|---|---|
| **Citation** | Hawkinson TR, Gentry MS, Sun R. *Hyperglycosylation is a metabolic driver of Alzheimer's disease.* **Nature Metabolism.** 2026. |
| **Study Question** | Does abnormal protein glycosylation contribute directly to Alzheimer's disease pathogenesis rather than simply occurring as a consequence of neurodegeneration? |
| **Hypothesis** | Excessive **N-linked protein glycosylation (hyperglycosylation)** is a metabolic driver of Alzheimer's disease. |
| **Study Design** | Mechanistic laboratory study integrating human post-mortem brain tissue, transgenic Alzheimer's mouse models, multi-omics analyses, isotope tracing, genetic manipulation, glucosamine supplementation experiments, and retrospective electronic health record analysis. |

**Study Methods**

| Method | Purpose |
|---|---|
| Spatial metabolomics | Measure metabolic alterations within affected brain regions |
| Spatial glycomics | Quantify glycosylated proteins and glycans |
| Spatial lipidomics | Assess associated lipid metabolic changes |
| Stable isotope tracing | Measure active glycan synthesis |
| Human AD brain tissue | Validate findings in patients |
| 5xFAD mouse model | Amyloid pathology model |
| PS19 mouse model | Tau pathology model |
| Genetic inhibition of glycosylation enzymes | Determine causality |
| Glucosamine supplementation | Increase glycosylation pathway activity |
| Electronic health records | Examine clinical association between glucosamine use and AD outcomes |

**Principal Findings**

| Finding | Evidence | Clinical Significance |
|---|---|---|
| Hyperglycosylation present in AD | Increased N-linked glycans in human and mouse brains | Indicates widespread abnormal protein glycosylation |
| Increased glycan synthesis | Isotope tracing showed increased production rather than impaired clearance | Supports active metabolic dysregulation |
| Hyperglycosylation appears causal | Genetic reduction of glycosylation improved cognition in mice | Suggests therapeutic potential |
| Glucosamine worsened disease | Increased glycosylation and accelerated cognitive decline in AD mice | Raises concern regarding glucosamine supplementation |
| Human observational study | Glucosamine users with MCI/AD had worse outcomes | Hypothesis-generating only; causality not established |

**Proposed Pathophysiological Mechanism**

| Step | Proposed Mechanism |
|---|---|
| 1 | Increased glucose metabolism into the hexosamine biosynthetic pathway |
| 2 | Increased production of UDP-N-acetylglucosamine (UDP-GlcNAc) |
| 3 | Excessive N-linked protein glycosylation |
| 4 | Altered neuronal protein structure and function |
| 5 | Synaptic dysfunction |
| 6 | Neurodegeneration |
| 7 | Cognitive decline and Alzheimer’s disease progression |

**Experimental Interventions**

| Intervention | Result |
|---|---|
| Genetic inhibition of glycosylation enzymes | Reduced hyperglycosylation |
|  | Improved memory |
|  | Improved behavioural performance |
| Glucosamine administration | Increased glycosylation |
|  | Accelerated cognitive decline |
|  | Worsened pathological changes |

**Clinical Implications**

| Potential Application | Comment |
|---|---|
| New therapeutic target | Glycosylation pathways may represent a novel treatment strategy |
| Biomarker development | Hyperglycosylation may become an early biomarker for Alzheimer’s disease |
| Drug development | Enzymes within the hexosamine pathway represent potential pharmacological targets |
| Nutritional implications | Glucosamine supplementation in patients with MCI or AD warrants further investigation |

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**Strengths**

| Strength | Importance |
|---|---|
| Human and animal validation | Improves biological credibility |
| Multiple independent methodologies | Strong mechanistic evidence |
| Demonstrated reversibility | Supports causation rather than association |
| Translational approach | Connects laboratory findings with clinical observations |

**Limitations**

| Limitation | Potential Impact |
|---|---|
| Mouse models may not fully replicate human AD | Limits direct clinical translation |
| Human glucosamine data observational | Cannot infer causality |
| No randomized clinical trials | Clinical recommendations cannot yet be made |
| Mechanism of toxicity incompletely defined | Further mechanistic studies required |

**Clinical Bottom Line**

| Question | Answer |
|---|---|
| **What is the major discovery?** | Hyperglycosylation appears to be a metabolic driver—not merely a consequence—of Alzheimer’s disease. |
| **Should glucosamine now be avoided in Alzheimer’s disease?** | Not yet. The animal data are compelling, but the human evidence is observational. Randomized clinical trials are needed before changing practice. |
| **Most important implication** | Glycosylation biology may represent one of the most promising new metabolic targets for disease-modifying therapy in Alzheimer’s disease. |