MedNut Mail

The How, What, Which, Where, When and Why of pharmaconutrition

Albumin and glucose

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https://medicationsandnutrition.com/mednut-mail/

Editorial

Albumin is a glycoprotein that is the primary, blood-specific carrier in the body's distribution network. It is not a glucose carrier. Increasing evidence indicates that interactions between albumin and glucose confer both benefit and harm.

Albumin-glucose interactions

1. Glycosylation

Glycosylation is the enzyme-driven binding of a sugar to specific amino acids. It is essential for albumin stability. That albumin could be glycosylated was only proven very recently. Consequently, the terms glycation and glycosylation continue to be applied interchangeably and the current glycosylation/glycation claims are unreliable.

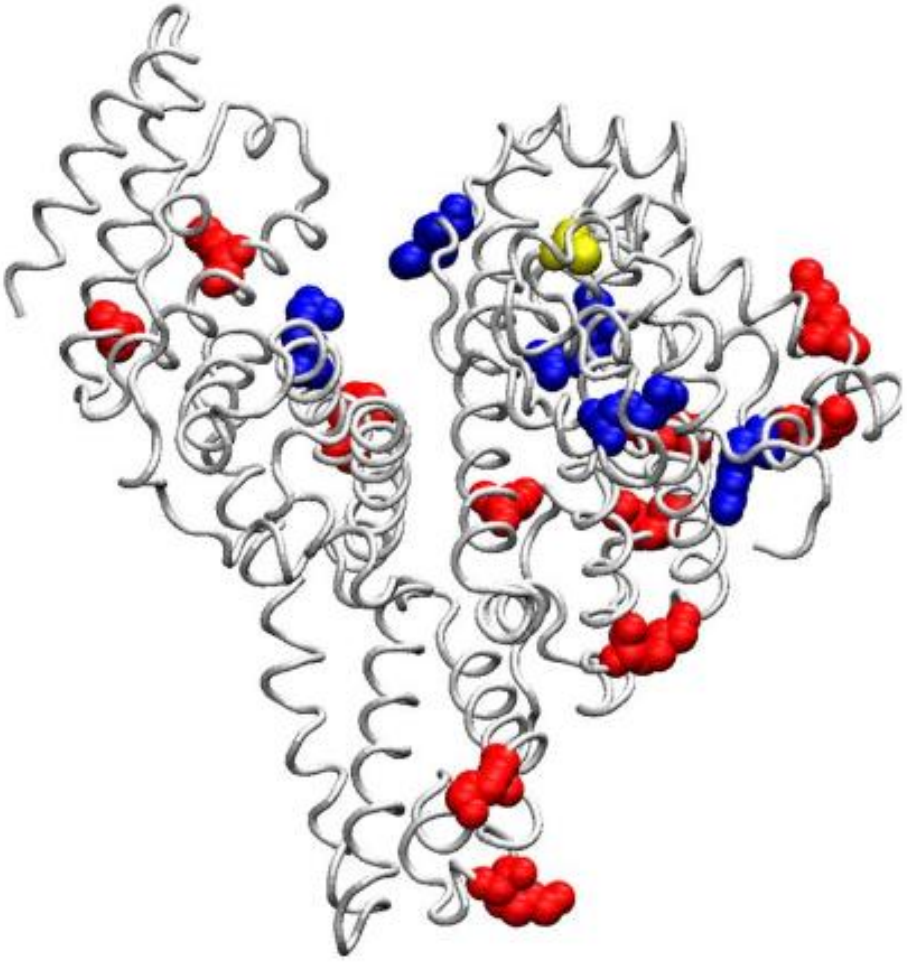
2. Glycation

Glycation is the non-enzymically driven binding of a sugar to a protein during hyperglycemia. Albumin contains more than 60 known glycation sites.

According to some reports, "normal" blood glycation levels are about 10-18%, and "diabetic" blood glycation levels are about 20-40%.

Identified glycation/glycosylation impacts include –

- decreased albumin binding of copper, zinc, iron and a range of other compounds including pharmaceuticals;
- inverse relationship between circulating vitamin D and glycated albumin levels;
- initiation of intracellular signaling;
- toxic impacts on microglia that may contribute to neurodegeneration;
- reduced binding affinity to bilirubin and long-chain fatty acids;
- reduced anti-oxidant properties via AGEs (advanced glycation end-products) formation, and consequent increased ROS (oxidative stress) formation;
- typically alters albumin's structure near Sudlow sites I+II;
- increased intrinsic structural flexibility of domains and secondary structure elements;
- increased albumin clearance.



The main sites of HSA modification. The sites of in vivo glycation are shown in red (lysines) and blue (arginines). The site of redox modification (Cys34) is shown in yellow.
From - **Serum Albumin in Health and Disease: Esterase, Antioxidant, Transporting and Signaling Properties**
https://doi.org/10.3390/ijms221910318

Glycation and nutrients

One of the factors that causes albumin glycation is impaired nutrient availability. Adequate availability of the following nutrients has been found to limit or inhibit albumin glycation – chromium, folate, magnesium, manganese, molybdenum, niacin, pyridoxine, retinol, thiamine, vitamin C, vitamin D metabolites (cholecalciferol and calcitriol), vitamin E, zinc. Their mechanisms of action are currently speculative.

Copper at physiological levels inhibits albumin glycation whilst both excessive and inadequate levels increase albumin glycation.

3. Glucuronidation

Glucuronidation is the covalent binding of acid glucuronide metabolites to albumin to create compounds that are highly hydrophilic. The binding can be reversible or irreversible and occurs in Sudlow's sites I+II.

Glucuronidation essentially supports the removal of unwanted substances from cells and the body by increasing their solubility.

The rate of glucuronidation is controlled by the rate by which glucuronides leave the cells. If glucuronidation rate is increased then so is their formation, and likewise reduced excretion rate means reduced formation. The rate of glucuronidation can directly and indirectly alter drug and nutrient availability and effectiveness.

Being highly hydrophilic, glucuronidation metabolites require transporters to move them through cell membranes. Key membrane transporters include MRPs (Multidrug resistant proteins), BCRP (breast cancer resistance protein), OATPs (organic anion transporting polypeptides), OATs (organic anion transporters), OCTs (organic cation transporters), BSEP (Bile salt export pump).

Factors that impair membrane transporters will consequently slow rate of glucuronidation.

Glucuronidation and nutrients

Some evidence indicates -

- iron and arachidonic acid can indirectly alter glucuronidation via the glucuronosyltransferases (UGTs);

- high-dose vitamin A inhibits UGTs and therefore glucuronidation;

- vitamin D modulates extrahepatic glucuronosyltransferase activity.

Clinical concerns

Speculatively, glycated albumin is a potential mal-nutrition marker. If glycated albumin levels are raised, then we should ascertain whether there is a nutritional contribution. If the Diet History indicates adequate dietary intake of all key nutrients, then direct nutritional contribution is unlikely. However, non-nutritional factors may alter nutrient availability indirectly via mechanisms of action such as inhibition of the membrane transporters.

Many commonly prescribed drugs have been found to impair availability of one or more nutrients associated with inhibiting glycation. For example, clozapine, doxepin, imipramine, and olanzapine inhibit chromium availability.

Polypharmacy combinations often negatively impact one or more common nutrients. Examples include –

- both Proton Pump Inhibitor + metformin negatively impact availability of magnesium, thiamine, and vitamin C;

- Proton Pump Inhibitor + furosemide + digoxin all negatively impact magnesium availability.

Clinical Questions

What actions will you initiate as you a review a person whose prescribed medications profile includes one or more drugs that utilize albumin as a carrier, will you -

- consider requesting glycated albumin as a mal-nutrition marker? And how would you interpret, and act on, the results?
- clarify adequacy of total intake of all nutrients, including both dietary choices and nutrient supplements if glycated albumin is elevated?
- clarify and regularly monitor copper, iron, zinc, and vitamin D levels if glycated albumin is elevated?

Conclusions

Albumin and glucose interact via glycosylation, glycation and glucuronidation. These interactions typically alter albumin's structure and consequently alter nutrient and drug availability.

Case study

Medical History with Nutritional Aspect

Amputation	☐	Constipation	☐	Dysphagia	☑	MND	☐
Anaemia	☐	CVA	☐	Enteral Feed	☐	MS	☐
Arthritis	☐	CVD	☐	Falls	☑	Osteoporosis	☐
Cancer	☑	Dementia	☐	Fracture	☐	PD	☐
CCF	☐	Dentures	☑	Frailty	☐	Pressure Area	☐
Chest Infection	☐	Depression	☑	Gout	☐	Renal	☑
COAD	☐	DM Type 1	☐	Hypertension	☐	Ulcer	☐
Confusion	☐	DM Type 2	☐	Incontinent	☑	UTI	☐

Food Allergies: clams, shellfish, seafoods

Other: peripheral neuritis, schizophrenia, Ca breast, CKD

Biochemistry with PharmacoNutrition Consequences

Na:	147	mmol/l	Hb:	134	g/L	Albumin:	29	g/L	BSL:		mmol/l
K:	4.6	mmol/l	Lymph:	3.0		Total Protein:	59	g/L	HbA1C:	6.0	
Urea:	8.4	mmol/l	MCV:	84	mmol/l	B12:	326	pmol/L	INR:		
Creatinine:	0.90	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 54, Ca 2.19, Ca corr 2.36, phos 1.19, Mg 0.82, Mg corr 0.88, chol 3.9, Tg 1.4, Fe 14, TRF 2.2, satn 25%, ferritin 3

Prescribed medications side effects - biochemistry

Some commonly prescribed medicines and their impacts on some common blood tests												
Drug	Y-yes		↑↓									
	BPP	ana	Alb	BSLs	Na	K	Ca	Mg	Zn	UA	Chol	Tg
Atorvastatin	Y			↑↓								
Calcium carbonate							↑					
Colecalciferol							↑					
Escitalopram		Y		↑	↓						↑	↑
Furosemide	Y			↑	↓	↓	↓	↓		↓	↑	↑
Olanzapine	Y			↑							↑	↑
Omeprazole	Y				↓	↓	↓	↓	↓			
Risperidone	Y			↑								
BPP – binding to plasma proteins ≥ 90%, ana – anaemia, alb – albumin, glyc – glycaemia, Na – sodium, K – potassium, Ca – calcium, Mg – magnesium, Zn – zinc, Cr – chromium, pho – phosphates, UA – uric acid												

Prescribed medications side effects profile

Some commonly prescribed medicines and some of their side effects													
Drug	N/V	C/D	Wt	App	AT	DM	Thir	Dys	SW	Tre	Sal		
Atorvastatin	N/V	C/D	↑	↓	Y								
Calcium carbonate		C											
Colecalciferol													
Escitalopram	N/V	C/D	↑↓	↓	Y	Y	Y		Y	Y			
Furosemide	N/V	C/D		↓		Y							
Olanzapine		C	↑	↑		Y							
Omeprazole	N/V	C/D	↑		Y	Y			Y				
Risperidone	N/V	C	↑								↑		
N – nausea, V – vomiting, C – constipation, D – diarrhoea, Wt – weight, App – appetite, AT – altered taste, DM – dry mouth, Thir – thirst, Dys – dysphagia, SW – sweating, Tre – tremor, Sal - salivation													

Prescribed medications affected nutrients profile

Some commonly prescribed medicines and some of the nutrients that interact with them														
Drug	**Nutrients affected (Y = yes)**													
	B12	**B9**	**B1**	**B2**	**B6**	**VC**	**VD**	**Cr**	**K**	**Mg**	**Zn**	**Ca**	**Fe**	**Na**
Atorvastatin														
Calcium carbonate													**Y**	
Colecalciferol														
Escitalopram														
Furosemide			**Y**						**Y**	**Y**	**Y**	**Y**		**Y**
Olanzapine								**Y**						
Omeprazole	**Y**		**Y**			**Y**			**Y**	**Y**	**Y**	**Y**	**Y**	
Risperidone														
B12 – cobalamin, B9 – folate, B1 – thiamine, B6 -pyridoxine, VC – vitamin c, VD – vitamin D, VK – vitamin K, K – potassium, Mg – magnesium, Zn – zinc, Ca – calcium, Na – sodium														

Transporter-mediated interactions and nutrients matrices

Transporter	**OCT1**		**OCT2**		**OCT3**		**THTR2**		**OCTN1**		**MATE1**		**MATE2**		**SMVT**	
Nutrients - Substrates	B1, choline		B1, choline		B1, choline, carnitine		B1, B6		Carnitine, choline		B1		B1		B5, B7, iodide	
Nutrients - Inh									vit D, choline						B5, B7	
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Aspirin																**Y**
Atorvastatin																
Baclofen																
Colecalciferol																
Folic acid																
Janumet	**Y**	**Y**	**Y**		**Y**		**Y**	**Y**	**Y**		**Y**		**Y**			
Lipidil																
Neo-B12																
Ranitidine	**Y**	**Y**	**Y**		**Y**							**Y**		**Y**		
Ural																
Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide																

Albumin and glucose

Transporter	OAT1		OAT3		BCRP		P-gp		OATP1B1		OATP2B1		GLUT1			
Nutrients - Substrates	B5, pyridoxic acid (B6), B7, B9, B2		B5, B6, B9, carnitine, B2		B2, B9, B5, vit K3		B12, vit D, B6, B3, B5		vit D		Vit D		vit C			
Nutrients - Inh					vit D2		vit A		Vit D def		Vit D def					
Biomarker					B2											
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Aspirin		Y	Y				Y							Y		
Atorvastatin					Y		Y	Y	Y		Y					
Baclofen																
Colecalciferol																
Folic acid																
Janumet																
Lipidil																
Neo-B12																
Ranitidine																
Ural																
Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide																

Comments – medication and nutrition effects only

Data summary

Biochemistry

Recent relevant available biochemistry indicates -

- low albumin – a primary carrier for 3 of the prescribed drugs and hypoalbuminaemia may alter their effects.

Glycaemia

BSLs

- daily range - 5.9-9.1; recommended range 4-10
- tested weekly
- reportable limits: < 3 and > 20
- recent HbA1c indicates good glycaemic control

Diabetes drugs

- Janumet has a duration of > 24 hours

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage from previous morning's dose;
- before evening meal BSLs - covered by current morning's dose.

Currently prescribed 3 non-glycaemia-management medications that alter glycaemia.

Pharmaconutrition

Vitamin C (960 mg/day) attenuates aspirin-induced gastric injury.

Aspirin reversibly decreases gastric vitamin C levels.

Aspirin inhibits vitamin C absorption by either inhibiting vitamin C binding to albumin, or by inhibiting/regulating/modulating GLUT1 (glucose transporter 1) uptake of vitamin C as DHA (dehydroascorbic acid).

If there is concurrent administration of a vitamin C intervention and aspirin then advisable to administer vitamin C (preferably 1 hour) prior to aspirin as aspirin impairs vitamin C absorption whilst vitamin C does not impact drug absorption.

Aspirin has a negative impact on folate status - the mechanism of action remains speculative.

Magnesium stearate, a common excipient (ingredient) has been found to inhibit the effectiveness of aspirin.

Coffee inhibits vitamin D uptake by inhibiting the osteoblasts (bone builders) vitamin D receptors, consequently decreasing calcium and zinc absorption.

Metformin component in Janumet decreases magnesium, zinc, thiamine, pyridoxine, folate and B12; the impact on B12 is progressive ie the decrease persists and grows.

Ranitidine decreases B12 absorption.

Thiamine commenced 12 years ago; each tab provides 100 mg thiamine. Both

Janumet and ranitidine decrease thiamine availability both directly and indirectly. Advisable to clarify status and if well within acceptable ranges then review necessity for its continued prescription.

Megafol has been prescribed for at least 9 years. Both aspirin and Janumet decrease folic acid availability. There is some evidence elevated folate levels impair cognitive function therefore advisable to monitor levels.

Mr ADL is prescribed two hypolipidaemics - being atorvastatin and lipidil. Given his current good lipid status advisable to review current management strategy. Further, statins are contraindicated if there is dysfunctional mitochondria – both diabetes and MS are dysfunctional mitochondria disorders.

Statins interfere early in the cholesterol metabolic pathway and consequently decrease -

- conversion of sun to vitamin D - vitamin D intervention currently prescribed;

- production of CoQ10 - important in cellular energy production; CoQ10 intervention recommended;

- DHEA production - low DHEA associated with increased risk of metabolic syndrome; intervention recommended.

Membrane transporters

Some of the identified membrane transporters alter the absorption and/or organ and cellular uptake of a range of nutrients. Inhibition of membrane transporters means blood test results may be unreliable. To clarify nutrient status advisable to conduct blood tests at least one hour before administration of relevant prescribed medicines. A concurrent detailed Diet History is also essential to corroborate adequacy of intake of all affected nutrients. Further, all affected nutrients to be monitored on a regular basis ie at least annually.

Nutrients that are affected by Mr ADL's prescribed medications include -

- **substrates** – thiamine, riboflavin, niacin, pantothenate, pyridoxine, biotin, folate, B12, choline, carnitine, vitamin C, vitamin D, vitamin K3, iodide;
- **inhibitors** – pantothenate, biotin, vitamin D, vitamin A, choline;
- **biomarkers** – riboflavin is a biomarker for BCRP.

The duration of drug inhibition of transporters currently remains unknown.

Bowel management

- no regular interventions prescribed;
- oral PRN aperient prescribed;
- no Nurse Initiated interventions administered.

Staff comments

Staff advise Mr ADL eats well, and that he does not have food in his room. They also advised that his habit is to sit outside for significant intervals whilst he enjoys his cigarettes.

Observations

Mr ADL is a man of size who was sitting outside in the courtyard enjoying a cigarette - he looks really well in fact the best I have ever seen him. Mr ADL told me he does not have food in his room, has a cask of wine from which he has 2 drinks to help him sleep, that he sleeps well, and that he sits outside every day.

Mr ADL's weight status is currently indeterminate as he was recently hospitalised and may still be in convalescence and regaining some of the lost weight.

Pharmaconutrition comments

Mr ADL is at risk of altered glycaemia due to non-diabetes-related impacts. It is likely much of the altered glycaemia will resolve upon cessation of the relevant medicines. Likely mechanisms of action include -

- **Inhibition of glucose transporters** GLUTs, SGLTX, SWEET1. Currently prescribed aspirin. Duration of inhibition is currently unknown;
- **Thiamine**. Important in carbohydrate metabolism. Currently prescribed Janumet therefore advisable to clarify thiamine status and if low then intervention recommended;
- **Vitamin C**. Has been found to confer beneficial impacts on HbA1c and fasting glucose and insulin levels. Currently prescribed aspirin which, if administered concurrently, prevents vitamin C from accessing albumin. Advisable to administer vitamin C interventions at least one hour prior to aspirin administration;
- **Vitamin D**. Increases the number of insulin receptors on the cells. Currently prescribed a vitmin D intervention, therefore advisable to clarify vitamin D status and if low then review adequacy of the intervention;

- **Iron**. The beta cells in the pancreas do not tolerate inadequate or excessive iron intake and decrease insulin production as a consequence. Currently prescribed aspirin and ranitidine therefore advisable to clarify iron and copper levels and initiate an intervention if either are low;
- **Magnesium**. Is important for activation of thiamine, vitamin C and vitamin D, and regulation of the IR/IRS/PI3K/PDK/Akt/GLUT4 pathway. Currently prescribed Janumet therefore advisable to clarify magnesium status and if low then intervention recommended.

What else would you include?

Please read this as it is important …

The information in this article is provided to support Health Professionals. It is not an exhaustive protocol and Health Professionals are advised that adequate professional supervision is accessed to ensure that Duty of Care obligations with respect to safe administration of medicines is met for each consumer.

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