MedNut Mail

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

Drug-induced hyperglycaemia

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Editorial

Drug-induced hyperglycaemia is not a formally recognised diagnosis but is a very common side effect of many prescribed medicines.

Diabetes is typically diagnosed on the basis of hyperglycaemia however the causes of hyperglycaemia are not considered.

Drug-induced hyperglycaemia mechanisms

Multiple nutrition-related factors are likely causes of drug-induced hyperglycaemia, ten of which are outlined.

1. Impaired nutrient absorption.

Many nutrients, especially vitamins, are important in carbohydrate metabolism, and many prescribed medicines negatively impact these nutrients. The status of negatively impacted nutrients is not ascertained when hyperglycaemia manifests.

Example of direct effect. Pyridoxine inhibits the activity of a-glucosidase on polysaccharide digestion consequently decreasing the amount of glucose released for absorption. Metformin inhibits pyridoxine absorption.

Example of indirect effect. Magnesium is essential for activating thiamine, vitamin C and vitamin D. Proton pump inhibitors inhibit magnesium absorption.

2. Altered renal nutrient resorption.

Example of direct effect. Digoxin inhibits magnesium resorption.

3. Increased renal nutrient excretion.

Example of direct effect. Furosemide increases magnesium excretion.

4. Inhibited glucose transporters.

If blood tests are conducted during inhibition of the glucose transporter and and their substrate (compound they carry) is stuck in the -

- blood then the results are interpreted as hyperglycaemia;

- cells then the results are interpreted as euglycaemia (normal levels) or hypoglycaemia.

Example of direct effect. Aspirin inhibits GLUT1.

Example of indirect effect. Ertugliflozin is a SGLT1 inhibitor. SGLT1 substrates include thiamine which is important in ATP production. If the AMP/ATP or

ADP/ATP ratios are negatively impacted then ultimately insulin-dependent glucose transporters will not be activated.

5. inhibited nutrient transporters.

Inhibition of intestinal nutrient transporters means nutrients are not absorbed during the period of inhibition.

If blood tests are conducted during inhibition of the nutrient transporter and the substrate is stuck in the –

- blood then the results are typically interpreted as excessive dietary intake, and the advice is to reduce intake;

- cells then the results are interpreted as inadequate dietary intake, and a nutrient supplement is typically prescribed.

Example of direct effect. Amiodarone is a P-gp inhibitor (blocks the transporter function) and its substrates include vitamin D. By inhibiting P-gp transporter, amiodarone decreases vitamin D availability during the period of inhibition.

Example of indirect effect. Pyridoxine transporter (THTR2) requires an acidic environment (ph 5.5) for absorption. It is likely an acid inhibitor changes absorption site acidity, and therefore THTR2 cannot facilitate pyridoxine absorption.

6. Impaired nutrient distribution by carrier.

Example of direct effect. Limited evidence indicates vitamin C has significant beneficial effects on haemoglobin A1c (HbA1c), fasting insulin, and fasting blood glucose. Aspirin inhibits vitamin C access to the carrier albumin.

Example of indirect effect. Iron interventions limit chromium's access to the carrier transferrin. This action decreases cellular uptake of chromium and consequently decreases insulin signalling.

7. Altered pancreatic function

Inadequate or excessive copper intake alters iron availability. Inadequate or excessive iron availability impairs pancreatic beta cell production and consequently reduces insulin production. (MedNut Mail The interdependence of copper-iron interactions)

8. Chromium

Chromium is important in enhancing insulin's signalling thus inadequate chromium status means decreased glucose uptake.

Chromium is typically transported by transferrin and consequently chromium availability is influenced by iron status.

9. Vitamin D

Vitamin D activates the insulin receptor gene to increase the number of insulin receptors on the surface of insulin-responsive cells. This ensures appropriate insulin signalling and thus insulin sensitivity. A consequence of inadequate vitamin D is reduced insulin receptors and therefore decreased glucose uptake.

10. Magnesium

Magnesium is important in 2 key mechanisms in glycaemia management, being –

1. essential for vitamin D synthesis and activation,
2. regulator of the IR/IRS/PI3K/PDK/Akt/GLUT4 pathway (MedNut Mail Glucose transporters and insulin function). Ultimately insulin action is dependent upon intracellular magnesium concentration. As intracellular magnesium levels fall so the requirement for insulin increases in order to metabolise the same glucose load.

Management strategies

Knowing the cause of the drug-induced hyperglycaemia is integral to initiation of appropriate interventions. If the drug-induced hyperglycaemia cause is -

- a mal-nutrition then identifying and addressing that cause is essential,
- due to glucose transporter inhibition what would be an appropriate dietary management strategy during the period of inhibition? Would it be based on a limited intake of slow-release (low Glycaemic Index) carbohydrate, or possibly no carbohydrate?

If the timing of the hyperglycaemia is known, eg prednisolone causes afternoon hyperglycaemia, then should other interventions be initiated such as –

- **thiamine**? Thiamine is important in energy metabolism. If there is a drug-thiamine transporter interaction with any of the prescribed medicines, then identifying the best administration time becomes important;
- **magnesium?** Adequate magnesium status means optimised availability of activated thiamine, vitamin C and vitamin D to support glycaemia-management processes.
- **vitamin C?** The intervention(s) should be administered either -
    - prior to anticipated episodes of hyperglycaemia in order to maximise available vitamin C within cells during hyperglycaemic episodes. For

example, administering extra vitamin C in the morning to maximise cellular content prior to the prednisolone-induced afternoon hyperglycaemic episode;

- after the hyperglycaemia episode once the glucose transporters are available to transport vitamin C again. For example, administering extra vitamin C in the evenings to replace lost content during the prednisolone-induced afternoon hyperglycaemic episode.

Clinical concerns

How many people currently diagnosed with diabetes, were diagnosed on the basis of drug-induced hyperglycaemia? If all their hyperglycaemia-associated prescribed drugs were ceased and the hyperglycaemia resolved then what should have been their diagnosis?

If hyperglycaemia-inducing drugs are essential to therapeutic outcomes, then appropriate management strategies are required to manage drug-induced hyperglycaemia. In order to do that we need to know –

- time from drug administration to commencement of hyperglycaemia,
- duration of hyperglycaemia, and
- mechanism of action causing the hyperglycaemia.

Further, this information needs to be included in the Product Information documents.

Occasionally a paper on drug-induced hyperglycaemia is published in a journal somewhere. The papers typically focus on primary mechanisms of action, namely drug and physiological factors. The contribution of mal-nutrition to drug-induced hyperglycaemia seems to be overlooked.

Do you, or have you heard any doctor, pharmacist, nurse or other health professional, question whether other prescribed medicines are contributing to, or exacerbating, hyperglycaemia or brittle diabetes control? In 30+ years of clinical practice, I haven't.

Managing drug-induced hyperglycaemia does not seem to be integrated into the daily clinical practice of relevant clinicians. Perhaps it is time for all the relevant professional bodies, universities and other training institutions to review and address this profoundly relevant clinical oversight.

Drug-induced hyperglycaemia is a real challenge to clinical skills as pathology results can no longer be considered definitive. Does the combination of acceptable dietary

habit and high/low pathology results indicate a known/unknown negative drug impact or is it due to the disease process?

Clinical Questions

Should all nutrition-related clinical reports include a drug-induced hyperglycaemia section? It would likely include a comment on -

- nutritional adequacy of dietary habit,
- drug-compromised nutrients and transporters,
- relevant management strategies,
- the risk of diabetes diagnosis due to drug-induced hyperglycaemia.

What actions will you initiate as you a review a person whose prescribed medications profile includes hyperglycaemia, will you -

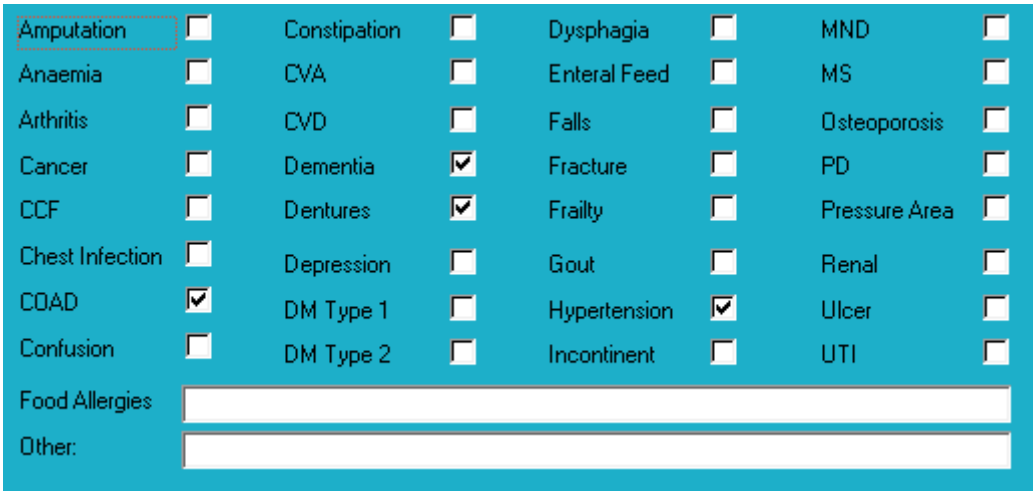
- ask which came first – diabetes, or were they already prescribed other medicines and then diagnosed with diabetes?
- include a drug-induced hyperglycaemia section in your clinical report?

Conclusions

Drug-induced hyperglycaemia is a common side effect of many prescribed medicines that is rarely considered in current glycaemia management strategies.

Case study

Medical History with Nutritional Aspect



Biochemistry with Pharmaconutrition Consequences

No recent relevant results available.

Prescribed medications side effects - biochemistry

Drug			↑↓									
	BPP	ana	Alb	glyc	Na	K	Ca	Mg	Zn	Cr	pho	uri
Amlo	Y			↑								
Auspril		Y			↓	↑						
Progout												
Urex-M	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, uri – uricaemia												

Prescribed medications side effects profile

Drug	N/V	C/D	Wt	App	AT	DM	Thir	Dys	SW	Tre			
Amlo	N/V	C/D	↕	↕	Y	Y	Y	Y	Y	Y			
Auspril	N/V	C/D		↓	Y								
Progout	N/V	D			Y								
Urex-M	N/V	C/D		↓		Y							
N – nausea, V – vomiting, C – constipation, D – diarrhoea, Wt – weight, App – appetite, AT – altered taste, DM – dry mouth, SW – sweating, Thir – thirst, Dys – dysphagia, Tre - tremor													

Prescribed medications affected nutrients profile

Drug	Nutrients affected (Y = yes)												
	B12	B9	B1	B2	B6	C	D	VK	K	Mg	Zn	Ca	Na
Amlo				Y							Y		
Auspril				Y							Y		
Progout													
Urex-M			Y						Y	Y	Y	Y	Y
B12 – cobalamin, B9 – folate, B1 – thiamine, B6 -pyridoxine, C – vitamin c, D – vitamin D, VK – vitamin K, K – potassium, Mg – magnesium, Zn – zinc, Ca – calcium, Na – sodium													

Transporter-mediated interactions and nutrients

Transporter	OAT1		OAT2		OATP1B1		BCRP							
Nutrients - Substrates	B9, B5, pyridoxic acid (B6), B2, B7		B3, B9, vit C		Vit D		B2, B5, B9, vit K3							
Nutrients - Inh			B3		Vit D def		Vit D2							
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Amlo														
Auspril					Y									
Progout				Y			Y							
Urex-M	Y			Y										
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

No recent relevant biochemistry available. Advisable to check plasma proteins (albumin, total proteins) as they are the primary transporters for two of the prescribed drugs and hypoproteinaemia may alter their effects.

Glycaemia

Currently prescribed 2 medications that alter glycaemia.

Pharmaconutrition

Amlo impairs zinc status.

Urex-M increases urinary excretion of calcium, magnesium, potassium and sodium.

Chronic use of Auspril decreases intracellular zinc.

Progout is a CYP1A2 inhibitor (blocks transporter function). CYP1A2 substrates include caffeine, retinol, melatonin, phosphatidylcholine, inhibitors include grapefruit juice and inducers include coffee; drug's metabolism inhibited therefore drug will remain active in the body for longer.

Mr ADH is currently prescribed the trifecta ie 3 drugs that impair zinc availability. Zinc is important in a range of functions, including immune system, wound healing, taste and appetite. Advisable to clarify zinc status and if low then 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 ADH's prescribed medications include -

- substrates - riboflavin, niacin, pantothenate, pyridoxine, biotin, folate, vitamin C, vitamin D, vitamin K3;
- inhibitors – niacin, vitamin D.

The duration of drug inhibition of transporters currently remains unknown.

Bowel management

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

Staff comments

Staff advise Mr ADH has a diminishing appetite as the day progresses ie eats well at breakfast, small lunch and very small evening meal.

Observations

Mr ADH is a pale, well-built, charming northern Italian man who was sitting outside in the sun when I went to speak to him - he told me he eats well, sleeps well, and that the food has an acceptable taste.

Mr ADH is currently weight stable.

Pharmaconutrition comments

If there is loss of weight then advisable to check zinc levels. Zinc is important in sense of taste and release of the hunger hormone Neuropeptide Y. Currently prescribed 3 drugs that negatively impact zinc status.

Mr ADH is at risk of a diagnosis of diabetes as he is prescribed 2 medicines that include altered glycaemia as a side effect. It is likely the hyperglycaemia will resolve upon cessation of the relevant medicines, and unlikely he has developed a metabolic disorder. Further management strategies for drug-induced hyperglycaemia may differ from those for diabetes-induced hyperglycaemia, and likely mechanisms of action include -

- Inhibition of glucose transporters GLUTs, SGLTX, SWEET1. Duration of inhibition is currently unknown;
- Thiamine. Important in carbohydrate metabolism. Currently prescribed Urex-M therefore advisable to clarify thiamine status and if low then intervention recommended;
- Magnesium. Is important for activation of thiamine, vitamin C and vitamin D. Currently prescribed Urex-M therefore advisable to clarify vitamin D 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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