MedNut Mail

The How, When, Where, Which and Why of pharmacotnutrition

Coagulation and pharmaconutrition

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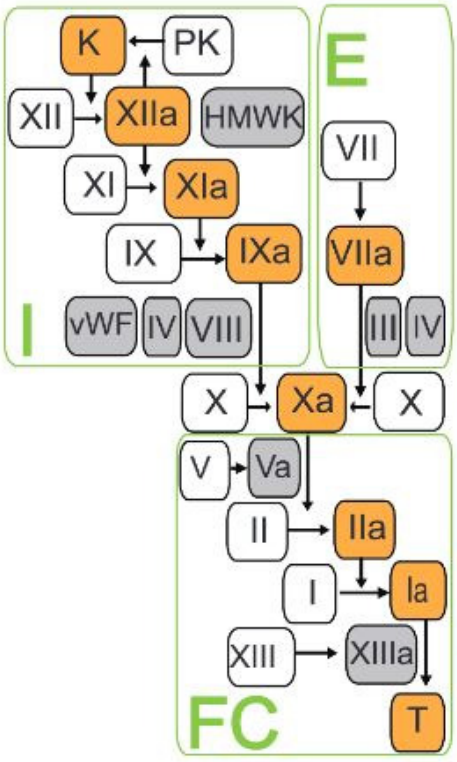
Commentary

Coagulation (blood clotting) is a process that prevents excessive bleeding when a blood vessel is injured. Usually, a blood clot dissolves once the injury has healed however sometimes a clot will form inside a blood vessel without any obvious injury and/or may not dissolve naturally.

Coagulation Factor IX for Hemophilia B Therapy.

Orlova, NA., Kovnir, SV., Vorobiev, II. & Gabibov, AG. 2012. Acta Naturae. 4:2(13) DOI: 10.32607/20758251-2012-4-2-62-73.



#	Name	Features	Pathway
I	Fibrinogen		E, I
II	Prothrombin	VKD, SP	E, I
III	Tissue factor, thromboplastin	NEC	E
IV	Ca++	NEC	E, I
V	Proaccelerin	NEC	E, I
VII	Proconvertin	VKD, SP	E
VIII	Anti-hemophilic factor	NEC	I
IX	Christmas factor	VKD, SP	I
X	Stuart factor	VKD, SP	E, I
XI	Plasma thromboplastin antecedent	SP	I
XII	Hageman factor	SP	I
XIII	Fibrin-stabilizing factor	TG	E, I
vWF	Von Willebrand factor	NEC	I
PK	Prekallikrein, Fletcher factor	SP	E, I
HMWK	High Molecular Weight Kininogen, Fitzgerald factor	NEC	I

Fig. 1. Scheme of blood coagulation cascade and international nomenclature of coagulation factors [2]. *VKD - vitamin K dependent; SP - serine protease, TG - transglutaminase; E — extrinsic pathway; I — intrinsic pathway; NEC - non-enzymatic cofactor, FC - final common pathway.*

Vitamin K is commonly associated with the coagulation process however there are other important nutrients including -

Calcium

Important in the activation of several coagulation factors, including -

- facilitating Factor IV binding to phospholipids,
- conversion of prothrombin to thrombin, Factor XIII to XIIIa, and Factor X to Xa,
- activating thromboplastin.

Magnesium

Reduces platelet aggregation and thereby increases time to clotting.

Low magnesium is prothrombotic and increases the risk of thrombosis by stimulating thromboxane synthesis – thromboxane is produced by platelets.

Factor IX requires both calcium and magnesium, as it has specific binding sites for each. Magnesium accelerates the calcium-dependent activation of factor IX via the intrinsic pathway activator factor XIa.

Magnesium is essential for the activation of vitamin D, and also for its inactivation when levels are too high ie optimal magnesium status is required for optimal vitamin D status.

Magnesium is also essential for the activation of vitamin C.

Vitamin D

Vitamin D both directly and indirectly, affects the coagulation cascade by mechanisms such as -

- downregulating tissue factor (TF) which initiates coagulation activation,
- decreasing platelet aggregation, tumour necrosis factor effects, TNF-α-induced expression, thrombin generation, clot density, fibrinolysis and thrombosis,
- upregulating antithrombin (AT), thrombomodulin (TM), and tissue factor pathway inhibitor (TFPI) expression,
- suppressing NF-κB (Nuclear Factor-κ Beta) activation,
- modulating plasminogen activator inhibitor-1 (PAI-1) and thrombospondin-1 expression in smooth cells.

There is an inverse correlation between vitamin D status and -

- mean platelet volume (MPV),
- development of deep venous thromboembolism (DVT) and unprovoked venous thromboembolism (VTE).

There is a positive correlation between vitamin D status and TFPI level.

Vitamin C

Vitamin C has both pro- and anticoagulatory effects -

Procoagulation

Vitamin C works to lower the plasma levels of nitric oxide.

Anticoagulation

Vitamin C actions include -

- restoring normal platelet function by scavenging Reactive Oxygen Species (ROS) and disrupting the ROS-platelet-activation cycle;
- inhibiting thrombin-induced and P-selectin mediated platelet aggregation and platelet-endothelial adhesion and therefore preventing microthrombus formation;
- inhibiting the pH-dependent thrombin-induced release of plasminogen-activator-inhibitor-1 from platelets;
- inhibiting NF-κB - a transcription factor known to stimulate the production of cytokines, chemokines, leukocyte adhesion molecules.

Copper

Copper is important in the functions of Factors VI and VIII.

Copper deficiency is associated with reactive thrombocytosis.

Copper, alone and in combination with manganese and/or mercury, has been found to adversely affect thrombus formation and consequently potentially increase the risk for thrombotic events in exposed individuals.

Manganese

Can bind to several coagulation cascade components, including laminin, collagen type IV, cellular and plasma fibronectin, plasminogen and fibrinogen.

Vitamin E

Is associated with having indirect anticoagulation properties such as -

- suppressing vitamin K activity – proposed mechanism of action is interference with Vitamin K precursors,
- inhibiting protein kinase C which is important in platelet aggregation,
- inhibiting platelet aggregation, and platelet-mediated thrombus formation,
- decreasing glutamate production – glutamate is required for Factor IX production.

Retinol

Vitamin A and its derivatives (retinoic acid and retinaldehyde) have significant antithrombotic properties through inhibition of thrombin and platelet aggregation.

Omega-3

Omega-3 PUFAs (polyunsaturated fatty acids) exhibit potent antithrombotic effects against -

- platelet activating factors,
- other prothrombotic pathways such as thrombin, collagen, and adenosine diphosphate.

Omega-3 fatty acids also down-regulate NF-κB.

Homocysteine

Homocysteine favours a pro-coagulant state and platelet adhesion.

The effects of homocysteine, directly and indirectly on the coagulation cascade include inducing activation of the coagulation cascade, triggering activation of NF-kB, correlation with interleukin 6 (IL-6), IL-1 receptor antagonist, and fibrinogen, disturbing endothelial function, and reducing thrombus permeability and solubility sensitivity.

Important nutrients in homocysteine formation include – riboflavin, pyridoxine, folic acid, cobalamin, and choline ie inadequate status of any of these results in homocysteine formation.

What actions will you initiate when you see someone prescribed medications that negatively impact the status of nutrients associated with the coagulation cascade, will you recommend regular monitoring of –

- coagulation status ie that it does not become dysfunctional?
- status of key nutrients involved in the coagulation cascade?
- prescribed medications that negatively impact nutrients important in the coagulation cascade?

Conclusions

Coagulation is a very intricate cascade that is at risk of disruption from external factors such as prescribed medications with disruption manifesting as either clotting or inability to clot – both consequences can cause significant harm.

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:

Other: leg ulcers, hernia

Biochemistry with Pharmaconutritional Consequences

Na:	142	mmol/l	Hb:	116	g/L	Albumin:	41	g/L	BSL:		mmol/l
K:	4.9	mmol/l	Lymph:	1.5		Total Protein:	72	g/L	HbA1C:		
Urea:	9.3	mmol/l	MCV:	92	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.112	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 41, Fe 12, TRF 2.8, satn 17%, ferritin 181, ESR 56

Medications That May Adversely Affect Nutritional Status

Drug	Vits + Mins	bpp	>90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drlg	d m	Dys	BSL
ENDONE		☐		NV	CD		↕	☑	↓			☑	☑	☐
LASIX	(20 mg/day) Ca, Cl, K, Mg, Na,	☑		NV	CD		↓	☐				☑	☐	☑
Mirtazapine		☐		N	D	↑	↑	☐				☑	☐	☐
PANADOL OSTEO		☐		NV	CD			☐				☐	☐	☐
RISPERDAL		☑		NV	C	↑		☐		↑		☐	☐	☐
VALIUM		☑		N	C			☐		↓		☑	☐	☐
		▩						▩				▩	▩	▩

Extra drug: multivit, arginaid

Summary of medications, nutrients and transporters

Organ (transporter)	Thiamine	Choline
Inhibitor function		
Liver	Risperidone	Risperidone
Into kidneys	Mirtazepine Risperidone Valium	Mirtazepine Risperidone Valium

Comments – medication and nutrition impacts (direct and indirect) only

Data summary

Biochemistry

Relevant available biochemistry within acceptable ranges.

Glycaemia

Currently prescribed 2 medications that alter glycaemia, being frusemide and risperidone.

Pharmaconutrition

Currently prescribed 5 medications that include nausea as a side effect.

Currently prescribed 4 medications that include constipation as a side effect.

Currently prescribed 3 medications that include hyperglycaemia as a side effect.

Lasix increases urinary excretion of calcium, magnesium, potassium, sodium and thiamine.

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

Dietary levels of caffeine intake in conjunction with paracetamol inhibit antinocieception.

Concurrent ingestion of paracetamol and iron resulted increased rate of iron absorption and decreased extent of drug absorption; the authors advise drug and iron interventions to be administered at different times from each other.

Bowel management

- no regular intervention prescribed

- oral PRRN aperient prescribed

- no Nurse Initiated interventions administered

Staff comments

Staff advise Mrs AGJ typically consumes toast and drinks at breakfast, quarter main course and half dessert at midday, and unable to advise evening meal intake. Staff

commented Mrs AGJ seems to enjoy fruit drinks and milky coffees (half milk + half water)

Observations

Mrs AGJ is a small, slender, pale, colourful lady who was participating in an activity which I interrupted. Mrs AGJ told me she has lost her appetite because she is concerned about family matters (a daughters marriage breakup), she has a nasty taste in her mouth, and her wound is getting worse and could also be impacting on her appetite. Mrs AGJ did tell me she likes milk drinks, and usually enjoys her food.

Mrs AGJ is either remaining weight stable or continuing to lose weight.

Pharmaconutrition comments

Mrs AGJ's diagnoses include chronic pain - nutritional factors that may be useful to consider in pain management include -

- magnesium – proposed mechanism magnesium blocks the NMDA receptor channels in the spinal cord and thus limits the influx of calcium ie reduces the risk of excitotoxicity and consequent exacerbation of pain. Currently prescribed frusemide which increases magnesium excretion.

Mrs AGJ's diagnoses include UTI - nutritional factors that may be useful to include UTI management include -

- zinc – recurrent UTIs deplete immune system and consequently zinc status therefore advisable to check zinc status and if low then short term (90-120 days) intervention recommended. Currently prescribed frusemide which increases zinc excretion.

What else would you include?

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