Can dietary modification and SGLT2 inhibition alleviate PHTS symptoms? #337

Ambery P[1*], Ambery L[2], Bågenholm R[3]

1) University of Cambridge Hospitals Trust and AstraZeneca Late Stage CVRM research Gothenburg, 2) Gap year student Gothenburg,
3) Drottning Silvia's Children's Hospital, Gothenburg * email: phil.ambery@nhs.net

Introduction

- PTEN Hamartoma Tumor Syndrome (PHTS) is a rare hereditary condition caused by a heterozygous loss-of-function germline variant in the Phosphatase and Tensin homolog gene (*PTEN*) [1]. This leads to constitutive activation of the PI3K/AKT/mTOR signalling pathway, which is important for the regulation of cellular growth and proliferation. Clinical manifestations of PHTS are diverse and include a range of vascular anomalies (VAs), which occur in 30-50% of patients [2,3] and can cause significant morbidity and even mortality.
- Surgical and interventional radiology procedures (sclerotherapy or embolization) are the mainstay of treatment for VAs in patients with PHTS, but these do not address the underlying genetic driver, and progression/recurrence is usual.
- Medical treatment of PHTS has centred on direct inhibition of mTOR with agents such as sirolimus. The response to sirolimus agents tends to be slow (6-24 months) [4] and complete resolution rarely occurs. Responses tend to plateau and recurrence/regrowth usually occurs rapidly if treatment is stopped. Although promising efficacy has been seen in PHTS-VAs [4-8], new therapies that are more active and better tolerated than sirolimus are still needed.
- Indirect inhibition of mTOR offers a potential novel approach. This can be achieved by increasing gluconeogenesis via intermittent fasting and pharmacologic modulation. Fasting is however difficult, particularly for patients with PHTS who also have neurodevelopmental delay.
- A number of medicines either in use or in development for cardiometabolic conditions may help drive gluconeogenesis.
- SGLT-2 inhibitors are licensed for the treatment of type 2 diabetes, chronic kidney disease and heart failure. They drive increased excretion of blood glucose and are not thought to lead to hypoglycaemia when used as monotherapy [9].
- GLP-1 agonists are licensed as agents to reduce blood glucose in type 2 diabetes, and to reduce weight in obesity. They potentiate mealtime insulin release and are not thought to increase risk of hypoglycaemia when used as monotherapy or with an SGLT2 inhibitor [10].
- Glucagon agonism is thought to increase gluconeogenesis and fatty acid oxidation. Dual glucagon and GLP-1 agonists are currently in clinical development. They are not thought to increase risk of hypoglycaemia [11].
- With regards to patients with neurodevelopmental delay (NDD) and PHTS, limited evidence from PET scanning suggests disrupted neuronal glucose uptake may contribute to symptoms [12], metabolically active agents may also be of value in this population.
- Evidence from animal studies suggests that this approach has an advantage over sirolimus in that CNS mTOR inhibition can be achieved [13]. However, neurobehavioral manifestations of PHTS may limit the feasibility of prolonged fasting in some individuals.
- Here we present the case of a 17-year-old woman with normal cognitive function, presenting with a low flow limb vascular malformation.
- She has been managed with an overnight and morning fasting regimen, combined with SGLT2 inhibitor therapy taken in the evening to augment ketone formation and gluconeogenesis.

Case Background

- A 17-year-old female presented to her general practitioner with multiple complaints over nearly 2 years.
- Symptoms included:
  - Severe aching pain affecting the left leg from the groin to the knee
  - Leg swelling
  - Daily fevers often above 39 °C
  - Frequent respiratory tract infections
  - Goitre
  - Menorrhagia
- Multiple blood tests were normal, including thyroid function. The only abnormality identified was a low-normal IgA.
- Multiple thyroid ultrasound scans confirmed the presence of thyroid masses and cysts, with fine needle aspiration confirming no features suggestive of malignancy.
- Approximately 14 months after the onset of pain, an MRI of the left knee was performed. Although initial interpretation suggested the possibility of sarcoma, further contrast MRI scanning confirmed presence of an extensive venous malformation beginning in the left groin and extending to the left knee.
- Genotyping based on biopsy samples taken at the time of knee arthroscopy and validated with blood testing confirmed the presence of a germline c.48 T>G PTEN mutation and a diagnosis of PHTS.
- The venous malformation was too large to consider surgical or interventional radiological treatment, leaving medical therapy the initial option of choice.
- The patient discussed with her paediatrician the fact that her symptoms had significantly improved a few years earlier when she lost a substantial amount of weight (10kg over a period of a few months). A decision was made to attempt nutritional modulation of mTOR as a treatment approach to improve symptoms.
- The patient agreed to attempt overnight fasting from 10pm each night until as late as possible the following day (usually 11am-12pm or later).
- To enhance overnight fasting and stimulate gluconeo-genesis, she also commenced treatment with the SGLT2 inhibitor dapagliflozin 10mg taken at 6pm each evening in September 2025.
- Treatment is ongoing with no current plans to stop.

Results

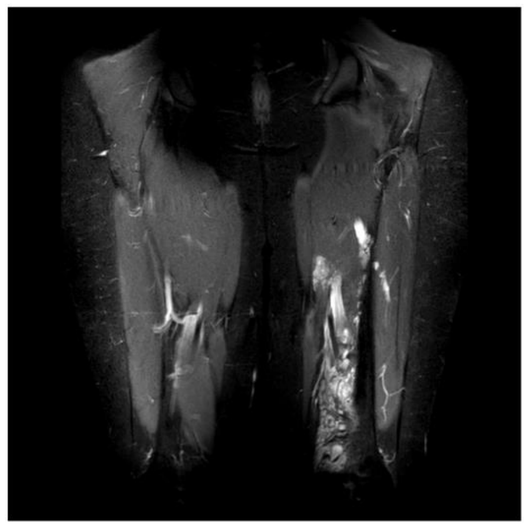

Fig 1. MRI with contrast, end of month one treatment.

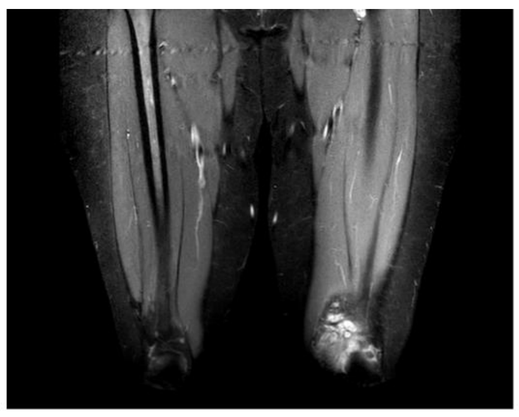

Fig 2. Extensive low flow venous malformation affecting the proximal left leg to the knee, end of month one treatment.

Table 1. Key blood results

	Sept 2025 (BL)	Sept 2025 (2)	Oct 2025	Nov 2025	Dec 2025	Jan 2026*	Mar 2026	Apr 2026
Fasting glucose (mmol/l)	5.0	4.2	4.5	-	-	-	-	4.9
ALT (microkat/l)	0.63	0.36	0.43	0.33	0.42	0.39	0.33	0.38
LDL cholesterol (mmol/l)	3.4	3.1	3.5	3.0	3.4	3.5	2.7	3.4
Triglycerides (mmol/l)	1.0	0.5	0.9	0.5	1.0	0.8	1.1	0.99
D-dimer (mg/l)(<0.45)	0.51	0.64	0.36	0.41	0.39	0.57	0.37	0.37

*Jan 2026 includes monitoring post Christmas and an appointment for progesterone secreting IUD insertion.

Table 2. Gluconeogenic aminoacids

	Sept 2025 (BL)	October 2025	January 2026	March 2026
Alanine‡	250	330	450	450
Glutamine‡	500	520	520	600
Serine‡	100	120	120	130
Glycine‡	230	240	240	270
Aspartate‡	1.9	2.5	2.5	1.9
Glutamate‡	27	29	29	28
Histidine‡	67	77	77	88

‡µmol/l

Intermittent home monitoring using a Roche ketone meter showed that an overnight rise in ketones from approximately 0.1 to 1.4 mmol/l in the morning could be achieved.

Walking distance improved rapidly, from 100m maximum before commencing SGLT2 inhibitor treatment to over 10km within 6 weeks. Pain, which had occurred for more than 12hrs per day, resolved 3 weeks after starting treatment. The patient has now taken up running.

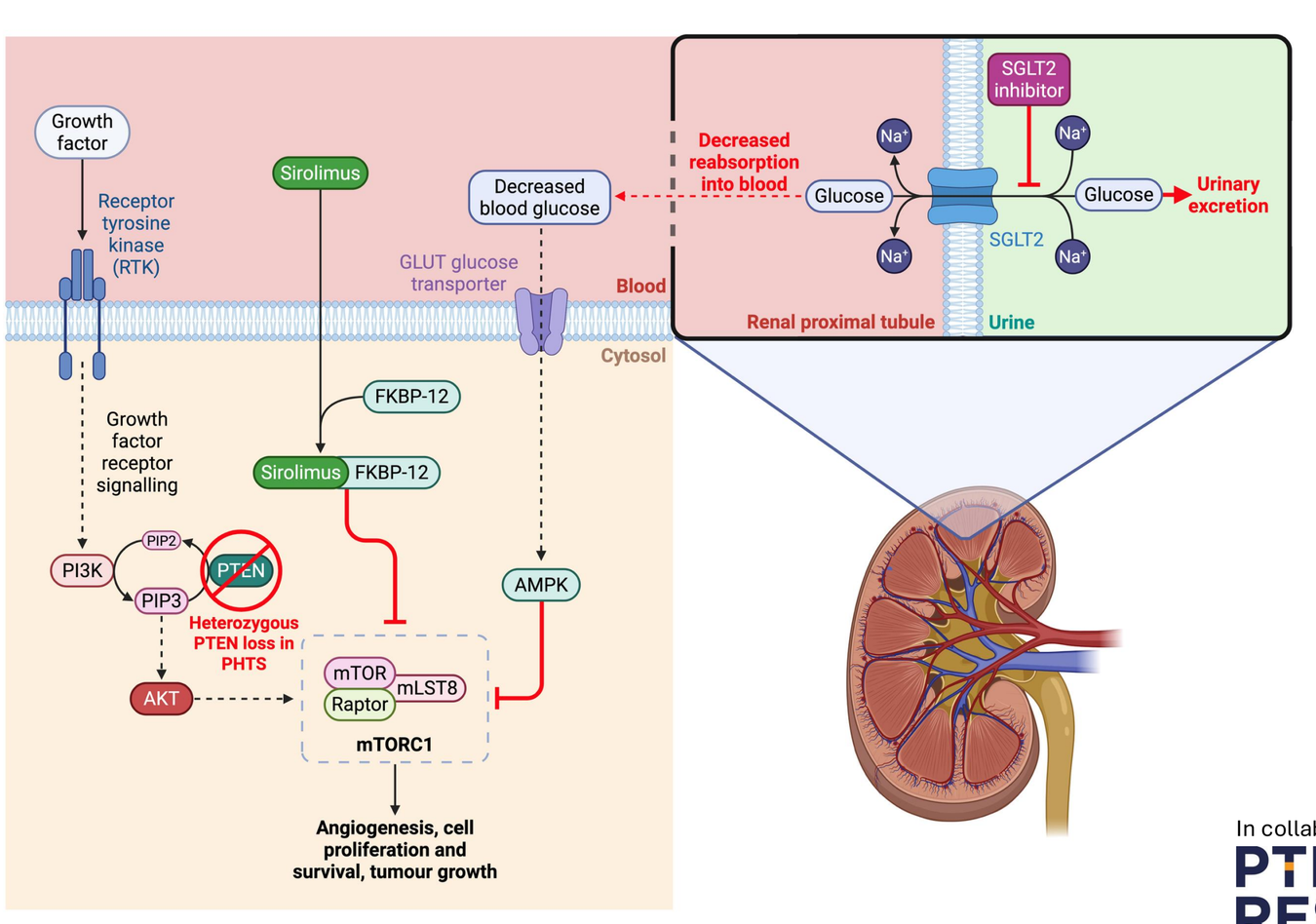

Fig 3. Comparison of the mode of action of SGLT2 inhibition and sirolimus

Discussion

- These data demonstrate durable symptomatic improvement in a 17-year-old woman with PHTS treated with a combination of overnight fasting and dapagliflozin.
- Symptomatic improvement was associated with a reduction in D-dimer, used as a marker of disease activity.
- The rise in ketones observed are consistent with a successful fast, which is likely to have driven, in combination with the SGLT2 inhibitor, gluconeogenesis in the overnight period.
- Reassuringly, no clear trends were seen in gluconeogenic aminoacids consistent with an overnight ketosis and gluconeogenesis being successfully achieved without risking significant protein catabolism and lean muscle mass. (The observation of a modest deterioration in D-dimer and a rise in alanine over the Christmas period fits with a relaxed diet. Concurrent insertion of a progesterone secreting IUD may also have led to a transient rise in D-dimer given they are recognized to increase decidualization of the endometrial lining.)
- No adverse effects of dapagliflozin therapy have so far been seen on glucose or lipid biomarkers.
- Body weight has remained stable throughout the treatment period.
- Although promising data is available for the mTOR inhibitor everolimus in patients with PHTS and neurodevelopmental delay [14,15], indirect modulation of mTOR may provide an alternative approach using agents with extensive clinical experienced for the treatment of T2DM. Indirect modulation may also result increased mTORC2 modulation relative to the the use of rapalogs.

Future work

- The effect of overnight fasting and SGLT2 inhibition in patients with PHTS and VAs warrants further evaluation.
- A prospective randomized controlled trial with a factorial design evaluating both pharmacology intervention and fasting is planned.
- Given the mechanism by which dapagliflozin and overnight fasting is expected to improve symptoms of PHTS, it may well be complementary to direct mTOR inhibitors.
- Further work is planned to evaluate the effect of metabolically active agents in patients with other manifestations of PHTS such as NDD.
- Metabolically active agents such as dapagliflozin have been shown to have a range of other activities that could be important in PHTS-VAs eg. lysosomal function, raising the possibility that overnight fasting and SGLT2 inhibition may be of particular value in this population, impacting a range of symptoms

References

1. Yehia L, Eng C. PTEN hamartoma Tumor Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. Gene Reviews (internet). 1993rd-2025. ed. Seattle: Internet; 2025.
2. Gurunathan A, et al. Impact of vascular anomalies on the PTEN phenotype in children and young adults. Pediatr Blood Cancer. John Wiley and Sons Inc.; 2020;67. https://doi.org/10.1002/pbc.28258
3. Tan WH, et al. The spectrum of vascular anomalies in patients with PTEN mutations: Implications for diagnosis and management. J Med Genet. 2007;44:594–602. https://doi.org/10.1136/jmg.2007.048934
4. Triana P, et al. Sirolimus Early Treatment in Vascular Anomalies Leads to a Better Response. Journal of Vascular Anomalies. 2023;4:e065. https://doi.org/10.1097/JOVA.0000000000000065
5. Queisser A, et al. Genetic Basis and Therapies for Vascular Anomalies. Circ Res. 2021;129:155–73. https://doi.org/10.1161/CIRCRESAHA.121.318145
6. Adams DM, et al. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. Pediatrics. 2016;137. https://doi.org/10.1542/peds.2015-3257
7. Hammer J, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet J Rare Dis. 2018;13:191. https://doi.org/10.1186/s13023-018-0934-z
8. Seront E, et al. Preliminary results of the European multicentric phase III trial regarding sirolimus in slow-flow vascular malformations. JCI Insight. 2023;8. https://doi.org/10.1172/jci.insight.173095
9. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. Clin Diabetes. 2014;32:4-11. https://doi.org/10.2337/diaclin.32.1.4.
10. Castellana M, et al. Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: A meta-analysis. Sci Rep. 2019;9:19351. https://doi.org/10.1038/s41598-019-55524-w
11. Stachteas P, et al. Efficacy of Dual Glucagon and Glucagon-like Peptide-1 Receptor Agonists Across the Cardiometabolic Continuum: A Review of Current Clinical Evidence. Rev Cardiovasc Med. 2025;26:39691. https://doi.org/10.31083/RCM39691
12. Grangeret J, Frismand S, Muller M, Renaud M, Verger A. Brain 18F-FDG PET in Cowden Syndrome. Clin Nucl Med 2022;47:e118–9. https://doi.org/10.1097/RLU.0000000000004025
13. Alirezaei M, et al; Short-term fasting induces profound neuronal autophagy. Autophagy. 2010;6:702–710. https://doi.org/10.4161/auto.6.6.12376
14. Srivastava S, et al; Developmental Synaptopathies Consortium. A randomized controlled trial of everolimus for neurocognitive symptoms in PTEN hamartoma tumor syndrome. Hum Mol Genet. 2022;31:3393-3404. https://doi.org/10.1093/hmg/ddac111
15. Liu Y, et al. Sensitivity Analysis of the Efficacy of Everolimus for Neurocognitive Symptoms in PTEN Hamartoma Tumor Syndrome. Adv Ther. 2026;43:666-687. https://doi.org/10.1007/s12325-025-03441-y

Disclosures

Dr Ambery is an employee of AstraZeneca, his contribution to the poster results from work conducted outside his work with the company. Dapagliflozin is not indicated for treatment of PHTS.

In collaboration with
PTEN RESEARCH
Funding research to support people with PHTS