



Synovitis in Haemophilia: A Factor Think Tank Podcast Series

Episode 1. Definition and pathophysiology
Slide summary

Disclaimer

- The Factor Think Tank is an educational activity funded by Sobi. Synovitis in Haemophilia: A Factor Think Tank Podcast Series was developed by the Factor Think Tank working group and the accompanying slide deck is only intended for healthcare professionals
- Slides 6–8 summarise content from the e-Delphi consensus article by Mancuso et al.;¹ wording closely resembles that of the article to reflect the e-Delphi consensus discussions
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Synovitis in Haemophilia: A Factor Think Tank Podcast Series (1)

- Findings from the e-Delphi consensus study on synovitis and joint health in haemophilia have been published in [Haemophilia](#) and provide the basis for the podcast series

HAEMOPHILIA

Synovitis and joint health in patients with haemophilia:
Statements from a European e-Delphi consensus study

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Synovitis in Haemophilia: A Factor Think Tank Podcast Series (2)

- The e-Delphi consensus examined five key domains relevant to synovitis in haemophilia:
 - Definition and pathophysiology
 - Diagnosis
 - Impact on joint health
 - Monitoring and follow-up
 - Prevention and treatment
- Based on these key domains an educational [series of five podcasts](#), featuring lead author Dr Maria Elisa Mancuso and co-authors or expert guest speakers, is available to healthcare professionals

This slide deck provides supporting information for [Episode 1. Definition and pathophysiology](#) of the podcast series on synovitis in haemophilia



An overview of synovitis in haemophilia

- Synovitis is defined as inflammation of synovial tissue within the joint¹
- It is common in patients with haemophilia in response to blood within joints and is the first step towards the development of chronic arthropathy¹
- One bleeding episode can initiate synovial inflammation, which may develop into chronic synovitis if bleeds recur frequently and are not adequately prevented²
- Synovitis is highly relevant to joint health in haemophilia; however, knowledge gaps exist regarding definition, pathophysiology, diagnosis, prevention, follow-up and treatment³
- Delphi methodology, which is often used to produce best-practice guidelines where evidence is missing, was employed to conduct a European e-Delphi consensus study on synovitis in haemophilia³

1. van Vulpen L, et al. Haemophilia. 2021;27(Suppl. 3):96–102; 2. van Vulpen L, et al. Osteoarthritis Cartilage. 2015;23:63–9;
3. Mancuso M, et al. Haemophilia. 2023;29:619–28

e-Delphi consensus article

Domain: Definition and pathophysiology of synovitis (statements 1–4)

Definition and pathophysiology of synovitis in haemophilia

e-Delphi consensus statements 1–4: Background

- There is a lack of data to indicate the time point/clinical stage at which synovitis becomes persistent and irreversible, and the definition of chronic synovitis is unclear
- The WFH and GTH define chronic synovitis as synovial inflammation persisting beyond 3 months^{1,2}
- Elsewhere in the literature, chronic synovitis has also been related to multiple bleeds over 6 months and thus the presence of target joints^{3,4}
- Intra-articular iron and haemosiderin are the main triggers of the pro-inflammatory response, together with hydroxy radicals and cytokines, leading to synovitis and ultimately apoptosis of chondrocytes and bone rearrangement^{5–17}
- Not all underlying pathophysiological mechanisms have been elucidated, and both basic and translational research is critical to increase knowledge in this field

GTH, German Society for Thrombosis and Hemostasis; WFH, World Federation of Hemophilia

1. Srivastava A, et al. Haemophilia. 2020;26(Suppl. 6):1–158; 2. Boddenberg-Pätzold B, et al. Available at: https://www.awmf.org/uploads/tx_szleitlinien/086-005l_S2k_Synovitis-bei-Haemophilie_2019-07.pdf. Accessed July 2023; 3. Hanley J, et al. Haemophilia. 2017;23:511–20; 4. Di Minno MND, et al. Br J Haematol. 2022;196:871–83; 5. van Vulpen LF, et al. Osteoarthritis Cartilage. 2015;23:63–9; 6. Roosendaal G, et al. J Bone Joint Surg Br. 1998;80:540–5; 7. Wojdasiewicz P, et al. Cytokine Growth Factor Rev. 2018;39:71–91; 8. Pulles AE, et al. Pharmacol Res. 2017;115:192–9; 9. Hakobyan N, et al. Haemophilia. 2008;14:804–9; 10. Hooiveld MJ, et al. Arthritis Rheum. 2003;48:396–403; 11. Morris CJ, et al. Ann Rheum Dis. 1986;45:21–6; 12. Ovlisen K, et al. Haemophilia. 2009;15:802–10; 13. Roosendaal G, et al. Arthritis Rheum. 1999;42:1033–9; 14. Roosendaal G, et al. Arthritis Rheum. 1999;42:1025–32; 15. Sen D, et al. J Thromb Haemost. 2013;11:293–306; 16. Tajima T, et al. J Orthop Res. 2005;23:891–8; 17. van Vulpen LF, et al. Blood. 2015;126:2239–46

Definition and pathophysiology of synovitis in haemophilia e-Delphi consensus statements 1–4

1

Synovitis is the synovial hypertrophy generated in response to the inflammatory trigger represented by the presence of haemoglobin and iron deposition in the joint

2

Haemoglobin, iron deposition, cytokines, hydroxyl radicals and neoangiogenesis contribute to synovitis

3

The pathophysiology of synovitis in patients with haemophilia is still poorly understood and needs more basic research

4.1

Chronic synovitis is synovial hypertrophy, which is persistent for at least 3 months*

Podcast discussion points

Synovitis in Haemophilia: A Factor Think Tank Podcast Series
Episode 1. Definition and pathophysiology

Episode 1. Definition and pathophysiology

- This episode focuses on four topics relevant to the definition and pathophysiology of synovitis in haemophilia:
 - Defining synovitis and its importance in haemophilia
 - Focus on chronic synovitis
 - Known causes of synovitis in haemophilia
 - Knowledge gaps in the pathophysiology of synovitis in haemophilia
- Host Dr Maria Elisa Mancuso leads the discussion with Factor Think Tank member Dr Robert Klamroth



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Topic 1. Defining synovitis and its importance in haemophilia

- A full joint bleed, microbleed or silent bleed can trigger synovial inflammation
- The presence of haemoglobin and iron deposition in the joint can lead to cytokine activation, triggering inflammation and subsequent synovitis
- Synovitis is the first step in the process of developing irreversible joint damage
- Long-term inflammation can damage joints; therefore, it is important to treat acute and chronic synovitis promptly and adequately

“Synovitis is inflammation in the synovia, and this results in hypertrophy and chronic inflammation”

Topic 2. Focus on chronic synovitis

- The various definitions of chronic synovitis often specify how long synovial hypertrophy and inflammation must have occurred for
- Through the e-Delphi process, chronic synovitis was defined as synovial hypertrophy, confirmed by medical imaging, and persistent for at least 3 months

“If you look in the literature there are different definitions for chronic synovitis”

Topic 3. Known causes of synovitis in haemophilia

- A joint bleed can cause acute synovitis, and if not treated adequately can result in chronic synovitis
- Preclinical evaluations of joint bleeds in mice have shown that haemoglobin, iron deposition and cytokines are involved in the pathogenesis of synovitis
 - Hydroxyl radicals and neoangiogenesis can also contribute to synovitis
- Synovial hypertrophy can lead to neoangiogenesis and the associated higher blood flow can be observed using Doppler ultrasound

“The problem with the pathophysiology of synovitis is that it is still poorly understood”

Topic 4. Knowledge gaps in the pathophysiology of synovitis in haemophilia

- It is poorly understood why some patients develop synovitis after one bleed and why others do not
- It is known that multiple pathways drive joint inflammation in rheumatoid arthritis
- It is likely that other pathological mechanisms are involved in haemophilic synovitis
- Based on our current understanding, treatment of bleeds and chronic inflammation is used to tackle synovitis
- A better understanding of the pathophysiology may lead to new treatments for synovitis

“I think more basic research and translational research is needed to fully understand these processes”

Conclusions

- Synovitis is synovial inflammation and hypertrophy that can lead to irreversible joint damage in patients with haemophilia
- The definition of chronic synovitis is still unclear and through a recent e-Delphi survey, it has been defined as synovial hypertrophy, which is persistent for at least 3 months
- The pathophysiology behind synovitis development is still poorly understood; however, we know that haemoglobin, iron deposition, cytokines, hydroxyl radicals and neoangiogenesis contribute to its development

Listen to the whole series

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More in the series

- If you enjoyed this podcast and want to find out more about the Factor Think Tank, please visit the website: www.factorthinktank.com
- All episodes in the series can be found here:
 - Episode 1. Definition and pathophysiology (Dr Maria Elisa Mancuso and Dr Robert Klamroth)
 - Episode 2. Diagnosis (Dr Maria Elisa Mancuso and Prof Dario Di Minno)
 - Episode 3. Impact on joint health (Dr Maria Elisa Mancuso and Dr Sébastien Lobet)
 - Episode 4. Monitoring and follow-up (Dr Maria Elisa Mancuso and Dr Katharina Holstein)
 - Episode 5. Prevention and treatment (Dr Maria Elisa Mancuso and Dr Gianluigi Pasta)