General overview of cardiovascular disorders and tuberculosis

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Content

- Key facts
- Overlaping epidemics
- Infection, including *Mycobacterium tuberculosis* and CVD
- Conclusions

This presentation is largely based on the following review article:

Huaman MA, Henson D, Ticona E, Sterling TR, Garvy BA. Tuberculosis and cardiovascular disease: linking the epidemics. Tropical Diseases, Travel Medicine and Vaccines (2015) 1:10 DOI 10.1186/s40794-015-0014-5; available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729377/

Key facts

- Noncommunicable diseases (NCDs) kill 41 million people each year, equivalent to 71% of all deaths globally*
- Each year, more than 15 million people die from a NCD between the ages of 30 and 69 years. 85% of these "premature" deaths occur in low- and middle-income countries*
- 77% of all NCD deaths are in low- and middle-income countries*
- Cardiovascular diseases (CVD) account for most NCD deaths, or 17.9 million (43.7%) people annually, followed by cancers (9.3 million; 22.7%), respiratory diseases (4.1 million; 10%), and diabetes (1.5 million; 3.7%)*
- A total of 1.4 million people died from tuberculosis (TB) in 2019 ¶

* *World Health Organization [Internet]. Geneva: Key Facts 13 April 2021. Accessed 2021 August 20. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases*

¶ *World Health Organization [Internet]. Geneva: Key Facts 14 October 2020. Accessed 2021 August 20. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis*

Overlaping epidemics

- CVD rates are increasing in low- and middle-income countries
- Public health programs challenged with the overlapping TB and CVD epidemics
- Risk of dying from a NCD increases with:
  - ***tobacco use***
  - physical inactivity
  - ***harmful use of alcohol***
  - ***unhealthy diets***

Overlaping epidemics

- Traditional risk factors for development of CVD:
  - Obesity, hypertension, ***diabetes***
  - ***studies indicate that the burden of infection may also contribute to the development of CVD****
- Factors which impact a larger section of the population and accelerate progression to TB disease:
  - **Diabetes, alcohol, malnutrition, tobacco smoke, and indoor air pollution**
- Environmental factors: poverty, occupation, diet, smoking, alcohol and drug abuse, place of residence (urban vs. rural), etc.;

- *Epstein SE, Zhu J, Najafi AH, Burnett MS. Insights into the role of infection in atherogenesis and in plaque rupture. Circulation. 2009;119(24):3133–41. doi:10.1161/CIRCULATIONAHA.109.849455.*
- *Rieder HL. Epidemiological basis of tuberculosis control. Paris: International Union Against Tuberculosis and Lung Disease; 1999.*

Infection and CVD

- In 1978, first evidence that infection with an avian herpesvirus, caused atherosclerotic lesions in coronary arteries*,¶
- Further research showed that other infections induce atherosclerosis, such as Chlamydia pneumoniae, Helicobacter pylori, HIV, hepatitis B virus, hepatitis C, Epstein Barr virus, cytomegalovirus and periodontal bacteria#

** Fabricant CG, Fabricant J, Litrenta MM, Minick CR. Virus-Induced Atherosclerosis. J Exper Med. 1978;148(1):335–40.*

¶ Minick RC, Fabricant CG, Fabricant J, Litrents MM. Atheroarteriosclerosis 30. Induced Infection With a Herpesvirus. Am J Pathology. 1979;96(3):673–700

 # Huaman MA, Henson D, Ticona E, Sterling TR, Garvy BA. Tuberculosis and cardiovascular disease: linking the epidemics. Tropical Diseases, Travel Medicine and Vaccines (2015) 1:10 DOI 10.1186/s40794-015-0014-5; available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729377/

Acute, latent or chronic infection and CVD

- Most of the pathogens implicated in CVD pathogenesis are intracellular organisms and/or may be able to establish chronic or latent infection in humans
- Local or systemic inflammation can lead to atherosclerotic plaque formation
- Latent tuberculosis infection (LTBI) is associated with chronic inflammation*,¶
- A large population-based retrospective study conducted in the United Kingdom showed that acute lower respiratory tract infections are risk factors of subsequent acute myocardial infarction (AMI) or stroke#

*Sullivan ZA, Wong EB, Ndung'u T, Kasprowicz VO, Bishai WR. Latent and Active Tuberculosis Infection Increase Immune Activation in Individuals Co-Infected with HIV. EBioMed. 2015;2(4):334–40. doi:10.1016/ j.ebiom.2015.03.005.

¶Cowan J, Pandey S, Filion LG, Angel JB, Kumar A, Cameron DW. Comparison of interferon-gamma-, interleukin (IL)-17- and IL-22-expressing CD4 T cells, IL-22-expressing granulocytes and proinflammatory cytokines during latent and active tuberculosis infection. Clin Exp Immunol. 2012;167(2):317–29. doi:10.1111/j.1365-2249.2011.04520.x.

#Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. N Engl J Med. 2004;351(25):2611–8.

Mycobacterium tuberculosis and CVD

- A large population-based retrospective cohort study conducted in Taiwan showed that patient with history of TB had a 40 % increased risk of the unstable angina and AMI compared to the non-tuberculosis group. This elevated risk persisted for the entire study period of up to 14 years*

- However, developing TB may be a marker of dysfunctional immune responses in susceptible hosts, as these same abnormal responses may also predispose to CVD

**Chung WS, Lin CL, Hung CT, Chu YH, Sung FC, Kao CH, et al. Tuberculosis increases the subsequent risk of acute coronary syndrome: a nationwide population-based cohort study. Int J Tuberc Lung Dis. 2014;18(1):79–83. doi:10.5588/ijtld.13.0288.*

Mechanisms of the effect of infection on CVD

- An increase in inflammation leading to coronary artery plaque formation and/or plaque rupture

  Possible that the infection triggers host immunologic responses similar to those implicated in atherogenesis

- Autoimmune disease

  - *An additional hypothesis is that pathogens inhabit growing atherosclerotic plaques, and cause direct vascular damage**

**Epstein SE, Zhu J, Najafi AH, Burnett MS. Insights into the role of infection in atherogenesis and in plaque rupture. Circulation. 2009;119(24):3133–41. doi:10.1161/CIRCULATIONAHA.109.849455.*

Mechanisms of the effect of infection on CVD: autoimmune disease

- The most common cross reaction of antibodies from infection to self-proteins in atherosclerosis centers on the heat shock protein (HSP)
- There is cross- reaction between antibodies produced to bacterial HSP such as E. coli HSP60, chlamydial HSP60 or mycobacterial HSP65, and the self HSP60 in humans
- A study showed that antibodies to HSP65 were the only antibodies significantly tied to CVD*
- Endothelial cells express HSP on their surface when they are activated by infection or other stressors providing a target for the immune reaction to HSP, which can lead to plaque development*

** Xu Q, Willeit J, Marosi M, Kleindiest R, Oberhollenzer F, Kiechl S, et al. 70. Association of serium antibody to heat-shock protein 65 with carotid atherosclerosis. The Lancet. 1993;341:255–9*

Evidence connecting TB disease and CVD

- Hypothesis that TB leads to CVD comes from:
  - case studies of TB causing cardiovascular death
  - population based studies that show increased risk of cardiovascular events
- Reports rare cause of myocardial infarction in young patients due to tuberculous granuloma formation affecting the coronary arteries has been described*,¶
  - *possibly contributing to premature cardiovascular death in areas of high tuberculosis prevalence?*

*Rodriguez Y, de Armas Y, Capo V, Wissmann G, Goldani LZ, De Waard JH. Sudden death related to tuberculous coronary arteritis. Int J Cardiol. 2012;156(2):e28–9. doi:10.1016/j.ijcard.2011.08.002

¶Kinare SG, Bhatia BI. Tuberculosis Coronary Arteritis with Aneurysm of Ventricular Septum. Chest. 1971;60(6):613.

Mycobacterium tuberculosis and myocarditis

- *M. tuberculosis* may also affect the myocardium
  - *Tuberculous myocarditis and related sudden cardiac death (SCD)*
  - *Proposed underlying mechanism leading to SCD was ventricular tachyarrhythmia from extensive tuberculous septal involvement or ventricular wall necrosis*

Liu A, Hu Y, Coates A. Sudden cardiac death and tuberculosis - how much do we know? Tuberculosis (Edinb). 2012;92(4):307–13. doi:10.1016/j.tube.2012.02.002.
Wallis PJ, Branfoot AC, Emerson PA. Sudden death due to myocardial tuberculosis. Thorax. 1984;39(2):155–6.
Amonkar G, Rupani A, Shah V, Parmar H. Sudden death in tuberculous myocarditis. Cardiovasc Pathol. 2009;18(4):247–8. doi:10.1016/j.carpath.2007.12.016.

Granuloma formation and CVD

- Granuloma formation relies on inflammatory chemical mediators to bring other immune cells to the site of infection. After the initial innate immune reaction develops an adaptive immune response:
  - CD4+ T cells become activated and release cytokines to modulate the immune response against M. tuberculosis
  - TNF-α and IFN-γ are important in TB and inflammatory responses related to CVD
  - Patients with tuberculosis disease have a significant elevation in IL-1, IL-2, IL-6 and IL-22.
  - The total level of T cells is decreased, but those present shift strongly to a T helper type 1 (Th1) lymphocytes and readily produce IL-17, IL-22 and IFN-γ*
- This Th1 inflammation matches the inflammatory profile of plaque formation
- It is possible that immune responses to TB may have a pathogenic role in atherogenesis

** Cowan J, Pandey S, Filion LG, Angel JB, Kumar A, Cameron DW. Comparison of interferon-gamma-, interleukin (IL)-17- and IL-22-expressing CD4 T cells, IL-22-expressing granulocytes and proinflammatory cytokines during latent and active tuberculosis infection. Clin Exp Immunol. 2012;167(2):317–29. doi:10.1111/j.1365-2249.2011.04520.x.*

Latent tuberculosis infection and CVD

- A link between LTBI and CVD via chronic inflammation seems biologically plausible
- Classic model of LTBI stipulates that mycobacteria in the inflammatory capsule do not divide but remain in stasis, enduring the environment unsuitable for growth
- Isoniazid, commonly used in treatment of LTBI is effective against dividing mycobacterium both in vitro and in vivo
- Gill et al.*demonstrated that there is continued replication of mycobacterium in chronically infected mice and a dynamic equilibrium between the host immune system and the bacteria is established during latency.
- From above said, a degree of chronic inflammation driven by LTBI is possible

** Gill WP, Harik NS, Whiddon MR, Liao RP, Mittler JE, Sherman DR. A replication clock for Mycobacterium tuberculosis. Nat Med. 2009;15(2):211–4. doi:10.1038/nm.1915.*

LTBI may induce long-term persistent inflammation

- The authors of a study in India concluded that LTBI may induce long-term persistent inflammation, even in the absence of TB*
- The same researchers found similar monocyte/macrophage activation markers in persons cured from TB¶
- This may explain the increased risk for AMI and unstable angina years after recovery from TB in the Taiwan cohort study

**King CAS, John K, John, Mehta S. Mycobacterium tuberculosis infection induces persistent non-resolving inflammation. Am J Trop Med Hyg. 2014;91(5S):390.*

¶ Babu S, Bhat SQ, Kumar NP, Kumaraswami V, Nutman TB. Regulatory T cells modulate Th17 responses in patients with positive tuberculin skin test results. J Infect Dis. 2010;201(1):20–31. doi:10.1086/648735.

#Chung WS, Lin CL, Hung CT, Chu YH, Sung FC, Kao CH, et al. Tuberculosis increases the subsequent risk of acute coronary syndrome: a nationwide population-based cohort study. Int J Tuberc Lung Dis. 2014;18(1):79–83. doi:10.5588/ijtld.13.0288.

Summary: possible mechanisms of CVD in TB

- Direct effect on the myocardium (tuberculous myocarditis)
- Direct effect on coronary arteries (tuberculous arteritis)
- Increased expression of pro-inflammatory cytokines (i.e., IL-1, IL-2, IL-6, IFN-γ, TNF-α)
- Monocyte/macrophage immune activation
- CD4+ TH1 and TH17 cell immune activation
- Auto-immunity mediated by antibodies against mycobacterial HSP65

Abbreviations: HSP65 heat shock protein 65, IL interleukin, IFN interferon, TH1 T helper 1, TH17, T helper 17, TNF tumor necrosis factor

Conclusions

- There is increasing evidence that many infections, including TB contribute to the pathogenesis of CVD
- A potential mechanistic model for association is based on persistent immune activation in latent and active TB
- Antibodies to mycobacterial HSP65 cross-reacting with self-antigens in human vessels leading to autoimmunity may also have an effect on CVD risk