Worms and diabetes mellitus – questioning the dichotomy of infectious diseases versus NCDs

Infectious diseases versus NCDs should be no longer understood as a dichotomy, but a complex interrelationship of numerous factors related to the homeostasis of humans.

We are used to distinguishing between infectious- and non-infectious diseases. The latter is commonly abbreviated as NCDs. Often NCDs are characterized as chronic diseases while infectious diseases are thought to be acute and of short duration. This point of view is not entirely valid. There are infectious diseases being chronic, such as tuberculosis. On the other hand, the so-called chronic diseases may be caused, at least partly, by infections. Cervical cancer is a good example, for which human papillomaviruses, HPV 16, and HPV 18, are cofactors (1). The beneficial development, after realizing the interplay amongst cervical cancer and virus is the development of vaccines to protect young females from the malignancy (2). The advantage of the vaccines are still under discussion (3, 4), but vaccination is encouraged by WHO and three vaccines are available all over the world.

Nutritional status, diabetes, and infections

However, infectious diseases and NCDs are not only correlated in that particular infective particle might be the causes for certain NCDs. The present Covid-19 pandemic is a telling example of how general metabolic conditions of the population determine the course of the virus infection through the population (5). The nutritional status, to be overweight and obese, and the prevalence of NCDs, such as diabetes mellitus, elevate the risk to fall seriously sick and eventually succumb to the infection. It seems justified to divert from reflecting infectious diseases versus NCDs as a dichotomy. Public Health should be accustomed to a more holistic view of health and diseases. Not only that infections and NCDs could be linked in such a way, that that one could determine the outcome of the other. A recent publication, about parasitic infections and diabetes mellitus, is an astonishing example of even a 'reverse' interaction of infection and a common NCD triggered by the immune system (6).

Human parasitology

Parasites are organisms belonging to the eucaryotes. Their cells resemble in a number of aspects human cells, such as having a nucleus, and that makes parasites different from viruses and bacteria. They are with us since prehistoric times (7). Many parasites stay within the human organism in a symbiotic relationship, causing only minor discomfort or even are unrecognized. Human parasitology focus on endo- and ectoparasites. Endoparasites are living in selected organs, such as the gut, bladder, liver, or blood or bile ducts. Infections with ectoparasites occur superficially, i.e. at the skin. Among the endoparasites there are protozoan organisms', such as Plasmodium vivax, causing some kind of malaria, and helminth also referred to as intestinal worms. Among the intestinal worms there are tapeworms, such as hookworm, and flukes, such as the small liver fluke.

Worms and insulin resistance

Recently a number of studies showed that those with helminth infections had a lower prevalence of type 2 diabetes mellitus (T2DM) compared with controls without the worms. It seems, that those harboring the worm are somehow protected from T2DM. While testing about 650 adults with and without one or more intestinal worms, insulin resistance (determined by HOMA-IR) was lower in those infected with worms (8). The findings from Flores island, Indonesia was supported by results from a group of Aboriginals from Australia. Those with prior infections with Strongyloides stercoralis (Ss) had a lower risk to develop T2DM than those non-infected (9). Similar results were obtained from different kind of worms affecting different organs such as lymphatic filariasis, highly prevalent in India (10), and schistosomiasis (Schistosoma mansoni) in China (11).

The reverse effect of some worms on diabetes

Why helminthic infection has a reverse effect on the development of T2DM in that non-infected persons tend to have a higher risk to acquire diabetes and show increased insulin resistance. The answer is linked to the immune system. Along with the development of T2DM, a 'pro-inflammatory cytokine's response is activated (10, 12). This ultimately results in insulin resistance and metabolic derangements of glucose and lipid metabolism (13). Helminth infections, however, trigger a so-called Type 2 immune response, elevating regulatory cytokines (14). It appears that the immune response of helminth infections works against the effect of the pro-inflammatory cytokines and chemokines initiated by T2DM, and through this mechanism protect, to a certain extent, those infected by helminth to acquire T2DM.

Rajamanickam et al. (2020) (6) found that individuals with Ss and T2DM had lower levels of pro-inflammatory cytokines and chemokines compared with non-infected T2DM persons., Treating the parasite infection the cytokine and chemokine plasma levels increased significantly in the formerly infected individuals, still retaining T2DM.

The variability of the interrelationship of worms and man

The protective effect of helminths towards T2DM is not shared by all kinds of such worms. Strongyloides stercoralis belongs to the so-called soil transmitted helminth. In tropical areas, particularly in low- and middle-income countries, these worms are highly prevalent. The infected persons pass the eggs of the worm with the feces. In case hygienic standards are low and latrines are not available or used, defecation occurs under the sky. In case the feces are dropped on the soil, suitable for the further development of the parasite, an infective larva eventually enters the host by invading the skin of the barefoot. A number of these kinds of worms settle into the gut. In response to evolution, the parasite cohabitates with the bacterial microbiota modulating host immunity (15). Through these mechanisms 'evolutionary forces' enables the host and the worm to survive over a long time. The result reported here is an example, that not only survival is assured but also comorbidities are modulated involving the host's metabolism. Reactions however might be seriously different from one parasite to the other. Among the intestinal worms, there are species different from the soil-transmitted helminths, called flukes or trematodes. The life cycle of trematodes is complex. For instance, the infective agent of Schistosoma mansoni, prevalent in red China, develops in water and invades humans, by penetrating the skin while standing in the water. The reaction of the metabolism to this trematode is similar as described above for the soil-transmitted helminths. This is not true to Opisthorchis viverrini (Ovi), a fluke prevalent in Thailand and Lao PDR. The parasite survives in the bile duct, is able to neutralize bile acids, and by this prevents being digested. It feds on lipoprotein metabolites, and extensively damage the hepatobiliary system (16). Epidemiological reasoning hints towards T2DM as a factor exacerbating the risk of Ovi infection towards cholangiocarcinoma (CCA) (17). Results from laboratory animals and cell culture investigations strongly support the connection of Ovi, through T2DM towards CCA (18). Supposedly, the Khon Khean Province at the Northeast of Thailand is the center of CCA in the World. As mentioned above, public health, especially for countries like Thailand, infectious diseases versus NCDs should be no longer understood as a dichotomy, but a complex interrelationship of numerous factors related to the homeostasis of humans.

Literature:

1. Boshart M, Gissmann L, Ikenberg H, Kleinheinz A, Scheurlen W, zur Hausen H. A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. EMBO J. 1984;3(5):1151-7.
2. Huh WK, Roden RB. The future of vaccines for cervical cancer. Gynecol Oncol. 2008;109(2 Suppl):S48-56.
3. Rees CP, Brhlikova P, Pollock AM. Will HPV vaccination prevent cervical cancer? J R Soc Med. 2020;113(2):64-78.
4. Zhang S, Zhao F. Comment on "Will HPV vaccination prevent cervical cancer". BMC Med. 2020;18(1):115.
5. Shekhar S, Wurth R, Kamilaris CDC, Eisenhofer G, Barrera FJ, Hajdenberg M, et al. Endocrine Conditions and COVID-19. Horm Metab Res. 2020;52(7):471-84.
6. Rajamanickam A, Munisankar S, Dolla C, Menon PA, Thiruvengadam K, Nutman TB, et al. Helminth infection modulates systemic pro-inflammatory cytokines and chemokines implicated in type 2 diabetes mellitus pathogenesis. PLoS Negl Trop Dis. 2020;14(3):e0008101.
7. Cox FE. History of human parasitology. Clin Microbiol Rev. 2002;15(4):595-612.
8. Wiria AE, Hamid F, Wammes LJ, Prasetyani MA, Dekkers OM, May L, et al. Infection with Soil-Transmitted Helminths Is Associated with Increased Insulin Sensitivity. PLoS One. 2015;10(6):e0127746.
9. Hays R, Esterman A, Giacomin P, Loukas A, McDermott R. Does Strongyloides stercoralis infection protect against type 2 diabetes in humans? Evidence from Australian Aboriginal adults. Diabetes Res Clin Pract. 2015;107(3):355-61.
10. Aravindhan V, Mohan V, Surendar J, Muralidhara Rao M, Pavankumar N, Deepa M, et al. Decreased prevalence of lymphatic filariasis among diabetic subjects associated with a diminished pro-inflammatory cytokine response (CURES 83). PLoS Negl Trop Dis. 2010;4(6):e707.
11. Chen Y, Lu J, Huang Y, Wang T, Xu Y, Xu M, et al. Association of previous schistosome infection with diabetes and metabolic syndrome: a cross-sectional study in rural China. J Clin Endocrinol Metab. 2013;98(2):E283-7.
12. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11(2):98-107.

13. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet. 2011;378(9786):169-81.
14. Allen JE, Maizels RM. Diversity and dialogue in immunity to helminths. Nat Rev Immunol. 2011;11(6):375-88.
15. Reynolds LA, Finlay BB, Maizels RM. Cohabitation in the Intestine: Interactions among Helminth Parasites, Bacterial Microbiota, and Host Immunity. J Immunol. 2015;195(9):4059-66.
16. Young ND, Nagarajan N, Lin SJ, Korhonen PK, Jex AR, Hall RS, et al. The Opisthorchis viverrini genome provides insights into life in the bile duct. Nat Commun. 2014;5:4378.
17. Saengboonmee C, Seubwai W, Wongkham C, Wongkham S. Diabetes mellitus: Possible risk and promoting factors of cholangiocarcinoma: Association of diabetes mellitus and cholangiocarcinoma. Cancer Epidemiol. 2015;39(3):274-8.
18. Chaidee A, Onsurathum S, Intuyod K, Pannangpetch P, Pongchaiyakul C, Pinlaor P, et al. Co-occurrence of opisthorchiasis and diabetes exacerbates morbidity of the hepatobiliary tract disease. PLoS Negl Trop Dis. 2018;12(6):e0006611.

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