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## **Role of various infections on the cardiovascular risk under special consideration of diabetes mellitus**

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Main objective of this work was to further investigate a possible role of sero-markers of various infections on the risk of cardiovascular diseases (CVD) under special consideration of diabetes. The associations between chronic and non-chronic infections such as *Helicobacter pylori* (HP), cytomegalovirus (CMV), chlamydia species, *Chlamydia pneumoniae* (CP), hepatitis A virus sero-status, and a possible role of human heat-shock protein 60 (h-hsp60) as an intermediate factor on the cardiovascular risk profile were explored in subjects under special consideration of type – 2 diabetes mellitus as some epidemiological studies have suggested an interaction between chronic infections and diabetes in promoting vascular disease.

Three independent study populations were employed to answer the research questions. Firstly, possible associations between sero-positivity to *Helicobacter pylori* (HP), hepatitis A virus (HAV) and prevalent cardiovascular disease and established CVD risk markers (lipids) were explored. The study population consisted of patients with clinically diagnosed type – 2 diabetes mellitus aged 40 – 79 years who were participants of a population based National Health Interview and Examination Survey in Germany in 1998. Subjects were defined as having diabetes if they reported a history of diabetes mellitus, or if they reported intake of anti-diabetic drugs explored by a physician. Overall 365 patients with prevalent diabetes were identified in the study sample. The overall HP prevalence at baseline was 55.8%; for HAV, overall baseline prevalence was 81.4%. At baseline, 32.1% already had a prevalent CVD. The odds ratio for CVD given a positive HP IgG titre or a positive HAV IgG titre was 1.07 (95%

CI 0.66-1.75) and 0.70 (95% CI 0.36-1.35) respectively, after adjustment for covariates. Furthermore, the odds ratio for CVD given a positive combined sero-prevalence (“infection burden” of HP and HAV) was 0.84 (95% CI 0.37-1.92) after full adjustment for covariates.

Although the study had some limitations with respect to study design and limited number of measured infection markers, our results do not support suggestions that sero-positivity to HP or HAV or their combination (“infection burden”) might be strong and independent risk factors for cardiovascular diseases or associated with a more unfavourable lipid profile in patients with type – 2 diabetes mellitus who are at special risk for cardiovascular disease.

Secondly, in a population based sample consisting of participants of a general health check-up (ESTHER-1 study) aged 50 – 74 years and diagnosed with a type- 2 diabetes, the role of HP sero-status including a virulence marker of this infection (CagA positivity) on the prevalence of CVD was investigated. Overall 1312 patients with prevalent diabetes were included in this analysis. The overall HP prevalence at baseline was 50.0% and 30.4% were CagA positive. The prevalence of CVD at baseline was 24.9%. The odds ratio (OR) for CVD given a positive HP IgG titre was 0.89 (95% CI 0.68-1.15) and for a positive HP CagA titre 0.97 (95% CI 0.73-1.29) after adjustment for covariates. Again, it seems unlikely that HP- and HP CagA- sero-status are independent risk markers for the development of cardiovascular diseases in subjects with type – 2 diabetes mellitus.

Thirdly, a prospective cohort study including a large group of patients aged 30-70 years participating in an in-patient rehabilitation program after acute manifestation of coronary heart disease (CHD) was employed to investigate the role of cytomegalovirus (CMV) and chlamydia sero-status on the risk for secondary cardiovascular events under special consideration of type – 2 diabetes mellitus. Overall 1052 patients were included in this study. Baseline sero-prevalence of CP IgA was 37.4%, for CP IgG was 39.3% and for CMV was 56.5%. During the 3 year follow-up period, 6.8% of the patients experienced a secondary CVD.

Results of the study indicate a possibly moderate increase in risk of secondary CVD events among patients with a positive CMV sero-status compared to CMV negative patients (8.1% of CMV sero-positive patients and 5.4% CMV sero-negative patients had a secondary CVD event ( $p=0.07$ )). In addition, the results indicate an increased risk among CMV positive patients with type – 2 diabetes mellitus compared with CMV negative non-diabetic patients (hazard ratio (HR) 2.58, 95% CI 1.32-5.10) after adjusting for covariates. Risk for developing

a secondary CVD for CMV negative patients with diabetes compared with CMV negative non-diabetic patients was HR: 1.16, 95% CI 0.43-3.12.

In the case of CP and ch-hsp60, subjects with diabetes alone and who were sero-negative for the infections had elevated HR that were not statistically different from the HR of subjects who were both sero-positive and diabetic indicating that CP is not related to subsequent CVD end points even in the presence of diabetes. In addition, this study showed that h-hsp60 is very unlikely an intermediate factor for the development secondary CVD events considering mechanisms of autoimmunity.

However, larger studies or meta-analysis of multiple studies are needed to address the interaction between infection sero-status and diabetes with adequate power. Notwithstanding the need of further evidence from such studies, our analyses clearly showed that patients with type – 2 diabetes are at special risk for developing secondary CVD events with HR of 2.00 (95% CI 1.21-3.31) after adjusting for confounders and should be a target group for preventive measures.