640. Prospective Association of Serum Vitamin D Level with Sepsis-Mortality in Postmenopausal Women: Results From the Women's Health Initiative

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Backgrounds. Vitamin D deficiency has been studied in the critically ill, and has been associated with worse morbidity and mortality rates, especially in those admitted with sepsis. Sepsis is a major cause of ICU admissions and accounts for 250,000 deaths per year. Dihydroxyvitamin D can inhibit the production of interleukins, tumor necrosis factor and can also increase the expression of endogenous antimicrobial peptides. This study sought to assess if low serum concentrations of 25(OH)D were associated with higher sepsis mortality rates.

Methods. This is a prospective study composed of participants from the Women's health Initiative (WHI) in the Vitamin D/Calcium trial who have been followed for an average of 15 years. The analysis sample consists of participants who had 25(OH)D measured at baseline. Patients with kidney disease and self-reported cancer at enrollment were excluded. Vitamin D deficiency was defined as levels ² 20 ng/mL, which was categorized into severe deficiency [25(OH)D ²12 ng/mL] and mild deficiency [25(OH) of 12–20 ng/mL]. Cox proportional hazard model was used to study the association between serum Vitamin D and sepsis mortality.

Results. 10,814 participants were included in the study (mean age = 64.4 years). At baseline, 49.26% (n = 5,328) of the sample had vitamin D deficiency and of those who died from sepsis, 57.7% (n = 41) where found to be vitamin D deficient. We found statistically significant increased hazard ratios (HR) for sepsis mortality in mild (HR = 1.19; 95% CI 1.00–1.41) and severe vitamin D deficiency (HR = 1.82; 95% CI: 1.50–2.21) in age adjusted and fully adjusted models (Table 1).

Conclusion. Vitamin D deficiency is associated with increased risk of sepsis mortality in postmenopausal women, which was seen in all ages. A clinical trial evaluating adequate supplementation in patients with sepsis is recommended to assess clinical significance.

Table 1. Cox models for sepsis mortality (Hazards Ratio with 95% CI)

Models	Continuous Vitamin D*	Vitamin D Level		
		Severe deficiency	*Mild deficiency*	*No deficiency*
Model 1: Crude	1.27 (1.17, 1.37)	2.11 (1.76, 2.53)	1.27 (1.08, 1.49)	(ref)
Model 2: Age-adjusted	1.24 (1.15, 1.34)	2.08 (1.73, 2.49)	1.20 (1.02, 1.41)	(ref)
Model 3: Age + SES**	1.19 (1.10, 1.28)	1.94 (1.61, 2.33)	1.17 (0.99, 1.38)	(ref)
Model 4: Age + Behavioral variables***	1.20 (1.11, 1.31)	1.79 (1.48, 2.18)	1.15 (0.97, 1.35)	(ref)
Model 5: Fully adjusted	1.19 (1.10, 1.30)	1.82 (1.50, 2.21)	1.19 (1.00, 1.41)	(ref)

* Vitamin D levels per SD decrease
** SES variables: race/ethnicity, education, income, marital status
*** Behavioral variables: smoking, daily exercise, alcohol intake, BMI, diet.

Fully adjusted: age, race/ethnicity, education, income, marital status, smoking, daily exercise, alcohol intake, BMI, AHEI

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641. Development of Structural Epitope Targeting During B-cell Ontogeny by Exploration of Relatives of Gp41 Structural Epitope Binding Antibody 6F5

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Background. In previous studies, our lab has characterized a number of highly mutated antibodies against structural epitopes of the human immunodeficiency virus (HIV) envelope protein. These antibodies were first isolated from long-term nonprogressors (LTNPs). We have previous mapped 6F5 to a novel structural epitope that encompasses areas in both heptad repeats of GP41, mapping to amino acids of 557, 654 and 657 of reference sequence HXB2. In these studies, three other antibodies that were <90% homologous to 6F5 also resolved amino acid 657. On sequence analysis, 6F5 and its relatives had the same gene usage and general structure. These similarities and the similar epitope mapping implied these were once distantly related to a single B-cell lineage. As fusion of the viral membrane to the target cell depends on these heptad repeat regions associating and forming a six-helix postfusion bundle, antibodies that can interfere in this may be highly useful.

Methods. See results.

Results. Because 6F5 maps to 557 and 654/657 which are widely separated on the primary sequence, we explored if there was differential binding to the postfusion six-helix-bundle form. Two peptides (N36 and C34) each containing one of the heptad repeats can form the post-fusion six-helix-bundle *in vitro*. On sandwich ELISA testing, 6F11 and 7B6 did not bind any form. Interestingly, 4E4 specifically captured both peptides alone, but not the six-helix-bundle and 6F5 only bound the six-helix-bundle but not the other peptide.

A small number of samples were obtained to assess the prevalence of these responses in LTNPs. Antibodies that compete 6F11 are much more prevalent in LTNPs than normal progressors (75% vs. 20%). Functionally, we found that despite being mapped to a similar portion of Gp41 (657), only 6F5 is shown to have significant ADCC activity, however relative 6F11 does not.

Conclusion. If targeting these epitopes correlates with the LTNP state, then these sites may be highly significant as targets of therapeutics or in vaccine strategies. Further studies on a larger cohort of LTNPs are ongoing. Additionally, deep sequencing of antibody sequences are being done to explore the development of structural epitope targeting by this family of antibodies.

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642. B- and T-Cell Responses to Pneumococcal Polysaccharide and Protein Vaccine Antigens in Recently Diagnosed HIV-1-Infected Patients

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Backgrounds. Prevention of serious HIV-1-associated pneumococcal infections may be compromised by the limited magnitude and function of vaccine-induced antibodies. Responses to the T-independent pneumococcal capsular polysaccharide (PPS) + T-dependent diphtheria toxoid (DT) protein conjugate vaccine (PCV-13) may be influenced by CD4+ T follicular helper (TFH) cells which provide specific help for B-cell differentiation.

Methods. We immunized 22 control and 19 newly diagnosed HIV-1-infected adults (median 610 CD4+ T cells/μL (range: 139–1,408) and 69,316 plasma HIV RNA (range 232-806,936) on ART for 1–4 months with PCV13. We measured (i) PPS-specific antibody-secreting cells (ASC) by ELISPOT at Weeks 0 and 1, (ii) serum IgG to 11 PPS serotypes (ST) by multiplex ELISA and (iii) titers of opsonophagocytosis (OP) for four STs at Weeks 0 and 8, and (iv) numbers and activation (ICOS expression) of circulating TFH cells by flow cytometry at Weeks 0 and 1. Values were compared by ANOVA, paired and unpaired t and Mann–Whitney tests.

Results. The number of PPS-specific IgG, IgM and IgA ASC increased significantly from Weeks 0 to 1 post-PCV13 and to similar magnitude in both Controls and HIV+ subjects, returning to baseline by Week 8. Levels of serum PPS-specific IgG increased significantly from Weeks 0 to 8 for 10/11 vs. 7/11 ST in controls and HIV+ subjects, respectively (P = NS), and to comparable levels. Similarly, OP titers increased significantly and similarly to each of four STs in both groups from Weeks 0 to 8. In contrast, although DT-specific IgG ASC increased from Weeks 0 to 1 in HIV+ and controls, these values were lower among HIV-1+ adults (P = .001). Consistent with these limited responses, a key regulatory molecule on TFH cells, elicited largely by T-dependent antigens (DT), was upregulated on cells from Control but not HIV+ at Week 1. Moreover, levels of IL-12, which drives TFH differentiation, were also lower among HIV-1+ at Week 1.

Conclusion. Humoral responses to PPS are largely intact (ASC, serum IgG and killing function) with recently diagnosed HIV-1 infection, highlighting the importance of early HIV-1 recognition. That responses to T-dependent DT and TFH activation are more limited, even with high CD4+ counts and ART, suggests a more rapid and perhaps more recalcitrant HIV-1-associated T-cell defect.

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643. Coronary Artery Aneurysms Are Found on Blindly Read Echocardiograms From Febrile Patients with and Without Kawasaki Disease

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Background. In 2017, the American Heart Association published new Kawasaki disease (KD) guidelines including echocardiographic (echo) criteria for diagnosis of incomplete KD (iKD). Echo is positive if 1 or more coronary arteries (CA) show aneurysmal dilation (Z score of ≥ 2.5), or if a CA has milder dilation (Z score of 2–2.49) plus ≥2 of the following: decreased left ventricular function, mitral regurgitation, and pericardial effusion. While CA dilation is seen commonly in KD and iKD, specificity of this finding is unclear because patients with systemic febrile illnesses may have CA dilation. To assess specificity of the American Heart Association criteria, blinded readers measured CA dimension in patients with KD and iKD and in febrile and healthy patient controls.

Methods. This is a single-center retrospective study. De-identified echo clips of CA from patients age 0–10 years were interpreted blindly and independently by six pediatric cardiologists. KD and iKD diagnoses were based on clinical data and IVIG treatment. Control groups were healthy patients evaluated for a benign murmur and febrile patients with fever ≥72 hours without a KD diagnosis or IVIG treatment. Detection of left ventricular dysfunction, mitral regurgitation and effusion was recorded. An echo was considered positive if the reading from at least one reader met AHA criteria for iKD.