Is There an Association Between Heparin-Induced Thrombocytopenia (HIT) and Autoimmune Disease?

Brent Klinkhammer, MD, PharmD; Michael Gruchalla, MD

ABSTRACT

Background: Heparin-induced thrombocytopenia (HIT) is a drug-induced, immunoglobulin G medicated autoimmune disorder associated with several negative clinical outcomes including increased morbidity, mortality, and increased medical costs. Previous studies have shown associations between comorbid autoimmune diseases, but there is little known about associations between HIT and autoimmunity.

Purpose: To provide clinical data to suggest an association between HIT and autoimmunity.

Methods: Retrospective chart review of 59 cases with a diagnosis of HIT and 251 matched controls without a HIT diagnosis, comparing the prevalence of autoimmunity in each group.

Setting: A single, large upper Midwest health care system.

Results: Patients with a diagnosis of HIT were significantly more likely to have a comorbid autoimmune disease than those without a HIT diagnosis (55.9% vs 10.8%, $P<0.001$). In disease-specific analyses, patients with a diagnosis of HIT were significantly more likely to have a diagnosis of antiphospholipid syndrome (15.3% vs 0.0%, $P<0.001$), systemic lupus erythematous (8.5% vs 0.4%, $P=0.001$), rheumatoid arthritis (5.1% vs 0.0%, $P=0.007$), Hashimoto's thyroiditis (13.6% vs 3.6%, $P=0.006$), or nonischemic cardiomyopathy (5.1% vs 0.0%, $P=0.007$). Patients diagnosed with HIT were significantly older than controls ($P<0.001$).

Conclusion: This novel study gives evidence to suggest an association between HIT and autoimmune disease and suggests a need for more research into the relationship between HIT and autoimmunity. These results could alter the anticoagulation management of venous thromboembolism and acute coronary syndrome in patients with a previously identified autoimmune disease.

INTRODUCTION

Associations between specific autoimmune diseases have been widely documented and often complicate the management of these disease entities.[1-4] It is also widely believed that autoimmune diseases are grossly underdiagnosed or unrecognized, which further conceals important associations and shared risk factors between these clinical syndromes. Given the current lack of understanding of autoimmunity, the likely shared commonalities in pathogenesis and etiology, and clinical ramifications of autoimmunity on patient outcomes, it is important to elucidate the relationships between autoimmune conditions to improve patient care.[5]

Heparin-induced thrombocytopenia (HIT) is believed to be a drug-induced, immunoglobulin G (IgG) medicated autoimmune disorder, in which autoantibodies are formed against and bind to conformationally altered epitopes on platelet factor 4 (PF4) when complexed with heparin-based therapeutic agents. This clinical syndrome has the potential to lead to several serious complications, most commonly thromboembolic events including deep-vein thrombosis, pulmonary embolism, myocardial infarction, stroke, peripheral arterial thrombosis, and critical limb ischemia.[6] Less commonly, HIT has been associated with bleeding complications, including adrenal hemorrhage and gastrointestinal bleeding.[7,8] HIT also manifests in acute systemic (anaphylaxis and anaphylactoid) reactions, which have the potential to be fatal, and local skin necrosis.[9,10] The mortality associated with HIT is approximately 5% to 10%, usually secondary to thrombotic complications.[6]

The commonly held belief that HIT is an idiosyncratic drug reaction is inadequate. It has been well-documented in the past that anti-PF4 autoantibodies can exist in patients who have never been exposed to a heparin-based therapeutic agent.[11,12] Even more enlightening is the fact that a HIT-like syndrome, meeting both the clinical and serologic features of the disease, has been described in heparin-naïve patients as well.[13,14] This

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Author Affiliations: University of North Dakota School of Medicine and Health Sciences (Klinkhammer, Gruchalla).

Corresponding Author: Brent Klinkhammer MD, PharmD, University of Nebraska Medical Center, 982055 Nebraska Medical Center, Omaha, NE 68198-2055; phone 218.261.0967; email brent.klinkhammer@unmc.edu.

seemingly suggests that a complex autoimmune pathogenesis may indeed underlie the etiology of this disease entity.

In this case-control study, we attempted to describe an association between HIT and autoimmunity, including specific disease-disease interactions between HIT and particular autoimmune diseases. To our knowledge, no prior associations have been made between HIT and autoimmunity in general, and previous published literature into this topic matter has been tenuous.[15]

METHODS

A hospital-based, case-control study was conducted using data from a large, upper Midwestern integrated health system. We performed a retrospective chart review of adults (n=59) 18 years of age and older diagnosed with heparin-induced thrombocytopenia (HIT), between May 1, 2009 and December 31, 2015 at Sanford Health System. The ICD-9 code used to identify HIT cases was 289.84. The primary analysis was a comparison of the prevalence of any autoimmune disease in the group of patients with HIT to the prevalence of any autoimmune disease in a matched control group without HIT (n=251). In order to be included as a case in this study, patients must have met the clinical and laboratory definition of HIT, in that they needed to have either a positive titer of anti-PF4 antibodies or serotonin release assay along with either thrombocytopenia or thrombosis that was not otherwise explained. Control patients were chosen from a random sample of patients who were identified using the ICD-9 code V70.0, which codes for a general medical exam. Secondary analyses were made to examine the association between the prevalence of any one specific autoimmune disease and HIT. For the purposes of this study, "autoimmune disease" was defined as any disease that appears on the American Autoimmune Related Disease Association's (AARDA) "List of Diseases: Autoimmune and Autoimmune-Related Diseases" at the time of data collection.[16] Excluded were patients <18 years of age. Recorded data included the following: age, sex, race, and diagnoses. Informed consent was not required for inclusion in our retrospective study due to the nature of the study, the absence of any direct interventions, and because there was no physical interaction between the principal investigators and the patients whose charts were reviewed at any time. This study protocol [IRB-201601-233 (UND), STUDY00000624 (Sanford Health) received dual IRB approval from the University of North Dakota IRB and from the Sanford Health IRB on January 25, 2016 and March 24, 2016, respectively.

Table 1. Baseline Characteristics of the Study Patients

Explanatory Variable	Patients with HIT N=59	Control Patients N=251	*P*-value
Sex			0.251
Male	32.2% (n=19)	24.7% (n=62)	
Female	67.8% (n=40)	75.3% (n=189)	
Age			
Mean	57.47 (95 % CI: 52.1 to 62.84)	31.75 (95% CI: 31.02 to 32.48)	<0.001
Race			.319
White	98.3% (n=58)	94.4% (n=237)	
Minority	1.7% (n=1)	5.6% (n=14)	
American Indian	1.7% (n=1)	0.8% (n=2)	
Black	0.0% (n=0)	1.6% (n=4)	
Asian	0.0% (n=0)	2.0% (n=5)	
Other	0.0% (n=0)	1.2% (n=3)	

Abbreviation: HIT, heparin-induced thrombocytopenia.

Table 2. Prevalence of Autoimmunity in Heparin-Induced Thrombocytopenia (HIT) Cases and Controls

Explanatory Variable	Patients with HIT N=59	Control Patients N=251	*P*-value
Autoimmune Disease	55.9% (n=33)	10.8% (n=27)	<0.001
Antiphospholipid Syndrome	5.3% (n=9)	0.0% (n=0)	<0.001
Systemic Lupus Erythematous	8.5% (n=5)	0.4% (n=1)	0.001
Rheumatoid Arthritis	5.1% (n=3)	0.0% (n=0)	0.007
Hashimoto's Thyroiditis	13.6% (n=8)	3.6% (n=9)	0.006
Nonischemic Cardiomyopathy	5.1% (n=3)	0.0% (n=0)	0.007
Endometriosis	0.0% (n=0)	1.6% (n=4)	0.738

SPSS 23.0 for Windows was used to analyze demographic and clinical characteristics of patients. Frequencies and relative percentages were computed for each categorical variable. Fisher's exact test was performed to determine statistical significance of categorical data and *t*-test/ANOVA was used to determine the statistical significance of continuous variables. All *P*-values were 2-sided, and P-values < 0.05 were considered significant.

RESULTS

A total of 60 HIT cases were matched with 251 controls without a HIT diagnosis. One case was excluded due to the patient being less than 18 years of age at time of data acquisition. Baseline characteristics of patients in both groups are reported in Table 1. The only statistically significant difference between the two groups was age, in that patients in the HIT group were significantly older

than those in the control (mean age 57.47 vs 31.75 $P < 0.001$).

The results of this study are reported in Table 2. Patients with a diagnosis of HIT were significantly more likely to have a comorbid autoimmune disease than those without a HIT diagnosis (55.9% vs 10.8%, $P < 0.001$). Subgroup analyses were conducted on the most frequently occurring autoimmune diseases. Patients with a diagnosis of HIT were significantly more likely to have a diagnosis of antiphospholipid syndrome (15.3% vs 0.0%, $P < 0.001$), systemic lupus erythematous (8.5% vs 0.4%, $P = 0.001$), rheumatoid arthritis (5.1% vs 0.0%, $P = 0.007$), Hashimoto's thyroiditis (13.6% vs 3.6%, $P = 0.006$), or nonischemic cardiomyopathy (5.1% vs 0.0%, $P = 0.007$). There was no statistical significance between the case and control groups in terms of a diagnosis of endometriosis ($P = 0.738$). A second set of analyses was done to correct for difference in age between HIT case and control groups by eliminating extremes of age in both groups. This second adjusted analysis yielded similar results to the primary analysis reported here.

DISCUSSION

In what we believe is the first of its kind, our study provides evidence to suggest an association between heparin-induced thrombocytopenia and autoimmune disease as defined by the AARDA. It also establishes a relationship between two of the "organ-specific" autoimmune diseases, Hashimoto's thyroiditis and nonischemic cardiomyopathy, and HIT. These findings imply that the underlying disease mechanisms that allow for the development of HIT have some commonality with other autoimmune diseases. Although a cause-and-effect relationship cannot be inferred from a single study, this data provides evidence that comorbid autoimmune disease may indeed be a risk factor for the development of HIT. Additionally, our findings confirm and extend those of other studies that suggested a relationship between HIT and antiphospholipid syndrome.[15,17] Our results are also consistent with a previous report of an increased incidence of HIT in women, although there was no statistically significant difference in sex between the HIT and control groups in our study.[18]

HIT shares several mechanisms with specific autoimmune diseases, which suggests that the development of an autoimmune disease and HIT may have some commonality. First, HIT requires the formation of a specific heparin-PF4 complex "neoantigen," which is similar to the citrullinated proteins that are central to the pathogenesis of rheumatoid arthritis.[19,20] Next, there exists a period of time when IgG antibodies are formed against this complex, similar to a post-vaccination Arthus reaction (type III hypersensitivity reaction).[21] The binding of anti-PF4 antibodies triggers monocyte-mediated response leading to formation release of antigenic PF4, which is similar to the damage mediated release of myelin basic protein in multiple sclerosis.[21,22] Additional features shared between autoimmunity and HIT are the existence of seropositive asymptomatic patients, relapsing-remitting disease course, endothelial cell activation and dysfunction, induced procoagulant effect, inhibition activated protein C, and expression of inflammatory cytokines.[21,23,24,25] HIT also has several shared risk factors with autoimmune disease, such as an increased incidence in women and increasing age.[18,26]

The evidence for this association is supported by the fact that the prevalence of autoimmunity in the HIT group was more than 5 times the rate found in the control group. This association is further supported by the fact that the 10.8% prevalence rate of autoimmunity in the control group in our study is consistent with the estimated nationwide prevalence of autoimmunity suggested by the National Institutes of Health (~7%) and the AARDA (~15%).[27] A similar finding also was observed in our study in the Hashimoto's thyroiditis subgroup.[28]

Our case-control study does have some limitations. In using the V70.0 ICD-9 code in an effort to select appropriately matched controls without other disease or procedure confounders, we developed a statistically significant difference in age between HIT cases and controls. There is a limited amount of data provided by one study to suggest that age is a risk factor for HIT, although little collaborating evidence exists.[29] Nevertheless, age may be an important confounding factor in our study. No other statistically significant difference between cases and controls were found in terms of sex or race. Some potential for selection bias also exists, in that patients with documented autoimmunity may be more likely to have hematological derangements and subsequently be tested for HIT more frequently than patients without an underlying autoimmune disease.

Another limitation of our study is that it does not establish a timeline between the diagnosis of an autoimmune disease and the diagnosis of HIT. However, the validity of designing a study that would accomplish this feat would be in question given that autoimmune diseases are often underdiagnosed and unreported, likely due the lack of provider knowledge of autoimmune disease and the episodic and unspecific presentation of many autoimmune diseases. It also would be difficult to determine at which point an autoimmune disease might confer a risk of HIT given that autoimmune diseases are diagnosed based on both subjective and objective clinical criteria, and that the immunological evidence of an underlying autoimmune disease often predates a diagnosis by a considerable time period. For example, it has also been reported that up to 88% of patients with diagnosed systemic lupus erythematosus (SLE) have a SLE autoantibody present before the diagnosis, sometimes more than 9 years before their eventual diagnosis.[30]

Finally, our study is limited in that only 59 HIT cases were identified using the ICD-9 diagnosis code of 289.84. We would have liked to have an equal amount of cases and controls in our study, however HIT is an uncommonly diagnosed clinical entity. Previous studies have determined the incidence of HIT in trauma patients who receive low-molecular-weight heparin as thromboprophylaxis to be 0.36% and 0.51% in admitted adult medi-

cal patients receiving unfractionated heparin to prevent venous thromboembolism.[31,32]

If the results of our study could be replicated and confirmed, it could have a paradigm-shifting effect on the treatment of venous thromboembolism and its prevention strategies, and the management of acute coronary syndrome in patients with a previously identified autoimmune disease. Based on our data, this may be particularly true in patients with comorbid SLE, antiphospholipid syndrome, rheumatoid arthritis, Hashimoto's thyroiditis, and nonischemic cardiomyopathy. The associated mortality, morbidity, and increased medical costs of HIT potentially could be avoided through the use of agents that have not been associated with HIT.[6] Additionally, many of these agents already have been shown to be a reasonable alternative or even superior to heparin-based therapeutic agents.[6,9,10,32] Thus far, provider unfamiliarity and increased drug costs have prevented some of the non-HIT associated agents from widespread use, however, given that previously published studies have found that a HIT diagnosis increases the cost of a medical admission by more than $30,000, it could make sense to employ these agents more widespread when indicated.[32]

Fondaparinux is a synthetic, parenterally available, factor Xa inhibitor with favorable pharmacokinetic behavior versus low-molecular-weight heparin or unfractionated heparin. Previous studies have shown fondaparinux to be superior to enoxaparin for the treatment of acute coronary syndromes in terms of reducing major bleeding and 30-day mortality.[33,34] Fondaparinux (2.5 mg once daily) also has been shown to be more effective than standard 40-mg once-daily enoxaparin for preventing venous thromboembolism and proximal deep-vein thrombosis following total hip replacement/hip fracture surgery.[35] Caveats to using fondaparinux in HIT patients are that fondaparinux is contraindicated in patients with a creatinine clearance of less than 30 mL/min or a body weight less than 50kg.[33] It also currently lacks approval by the Food and Drug Administration (FDA) for HIT, however previous studies have shown it to be a viable option.[36,37,38]

Currently, the only FDA-approved treatments for HIT are the direct thrombin inhibitors argatroban and bivalirudin (in patients undergoing percutaneous coronary intervention). Lepirudin, another direct thrombin inhibitor, did have an indication for HIT, however it has been discontinued by its manufacturer for nonclinical reasons.[33] Of the FDA-approved options, argatroban has proven to be the therapy of choice, however it is a difficult agent to use clinically.[39] Argatroban is given as a continuous intravenous infusion and has the potential to elevate international normalized ratio (INR), making a therapeutic transition to warfarin or other vitamin K antagonists challenging.[33] Additionally, argatroban is considerably cost prohibitive in that a 10-day infusion costs approximately $7,440 more than fondaparinux.[40]

More recently, the FDA has approved several direct oral anticoagulants that also could be used instead of heparin-based therapeutics for common indications. The orally available factor Xa inhibitors rivaroxaban and apixaban are both FDA-approved for the prophylaxis and treatment of venous thromboembolism and for the stroke prevention in patients with nonvalvular atrial fibrillation; however, they are not FDA-approved for the treatment of HIT at this time.[33] Large randomized trials have shown these agents to be noninferior to treatment with enoxaparin and warfarin for venous thromboembolism with reduced rates of major bleeding.[41,42] The most recent CHEST guidelines have adopted the factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and the oral direct thrombin inhibitor (dabigatran) as their preferred treatment of acute venous thromboembolism.[43]

Given the results our study, the clinical impact of HIT, and the availability and effectiveness of other non-heparin-based therapeutics, we believe that the association between HIT and autoimmunity and specific autoimmune disease, such as SLE, antiphospholipid syndrome, and Hashimoto's thyroiditis, is nontrivial and deserves more study. A longitudinal study to look at long-term outcomes of avoiding the use of heparin-based therapeutics in patients with a history of autoimmune disease and/or other documented risk factors for HIT could shed more light on the management of anticoagulation in this patient population. Furthermore, we believe our study should encourage more research into drug-disease interactions between autoimmune disease and other drugs with what is currently believed to be idiosyncratic adverse events. Further research may help to elucidate the underlying mechanisms that predispose certain patients to adverse drug events given the patient's comorbidities.

CONCLUSIONS

In this novel case-control study, a statistically significant association between the prevalence of heparin-induced thrombocytopenia (HIT) and the prevalence of autoimmune and autoimmune-related disease was found. A statistically significant association also was found between the prevalence of HIT and several specific autoimmune diseases including antiphospholipid syndrome, systemic lupus erythematous, rheumatoid arthritis, Hashimoto's thyroiditis, and nonischemic cardiomyopathy. To our knowledge, our study is also the first to imply a relationship between HIT and two "organ-specific" autoimmune diseases: Hashimoto's thyroiditis and nonischemic cardiomyopathy. Age was an important confounding variable as well. These findings emphasize the need for further research into this relationship and for more study into other drug-disease interactions. The results of this study could suggest a need for change in the management of anticoagulation in patients with a history of autoimmune disease and improved patient outcomes by means of potentially reducing the incidence of HIT in this patient population.

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