American Journal of Epidemiology

Vol. 187, No. 1
DOI: 10.1093/aje/kwx210
Advance Access publication: June 30, 2017

Brief Original Contribution

Is Blood Transfusion Linked to Celiac Disease? A Nationwide Cohort Study

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Initially submitted December 22, 2016; accepted for publication March 28, 2017.

The vast majority of patients with celiac disease (CD) have disease-specific antibodies. If such antibodies—or other blood-borne factors that cause CD—are transmissible, it might be reflected by a higher risk of CD in individuals who receive blood from donors with incipient CD. In a retrospective nationwide cohort study of 1,058,289 individuals in Sweden who received a blood transfusion between 1968 and 2012, we examined the risk of transmission of CD (defined as having villous atrophy on small intestinal biopsy) using Cox regression. We also examined whether there were clusters of CD patients who received blood transfusions from the same donor independent of the known donor CD status. Overall, 9,455 patients who had undergone transfusions (0.9%) received a blood transfusion from a donor who had been diagnosed with CD. Of these, 14 developed CD, which corresponds to a hazard ratio of 1.0 (95% confidence interval: 0.9, 1.2) compared with recipients of transfusions from unaffected donors. There were no cases of CD among persons who received plasma or platelet units from donors with CD. We found no evidence of CD clustering among recipients of blood from individual donors (P for trend = 0.28). Our results suggest that CD is not transmitted through blood transfusions.

antibodies; autoimmunity; blood; celiac; gluten; transfusion; transmission

Abbreviations: CD, celiac disease; CI, confidence interval; DES, disease excess score; HR, hazard ratio; SCANDAT2, Scandinavian Donations and Transfusions Database.

Although transfusion-associated risks are at a record low, (1) there remains concern about the transmission of infectious agents (2). Meanwhile, it has been speculated that immune-mediated diseases may be transferred by blood transfusion (3). However, there has been little evidence to support this risk.

Celiac disease (CD) is an immune-mediated disease that occurs in approximately 1 in 100 individuals in the Western world (4, 5). It is a small intestinal enteropathy (6) triggered by exposure to gluten in genetically sensitive individuals (7). In addition to enteropathy, CD is also characterized by the presence of endomysium and tissue transglutaminase antibodies (8). These antibodies are almost universally present in patients with untreated CD (9).

The targets of CD-specific antibodies, gliadin peptides and tissue transglutaminase 2, have important roles in CD (10) and may contribute to disease progression. However, despite much research on CD-specific antibodies, it is still not clear whether they are involved in the pathogenesis of CD or are merely an epiphenomenal indicator of disease activity (11). In a recent study, Kalliokoski et al. demonstrated that tissue transglutaminase 2–specific CD antibodies injected to mice induced inflammation in the small intestine and altered the mucosal morphology (12). In the present study, we examined whether celiac disease may be transmitted by blood transfusion.

METHODS

Data sources

We linked data on biopsy-verified cases of CD (13) with data on blood transfusions (14) through the unique personal identification numbers assigned to all Swedish residents (15). CD diagnoses were ascertained from biopsy records collected from all 28 of Sweden's pathology departments in 2006–2008 and in 2013 (13, 16). These data capture virtually all biopsy-verified CD diagnoses between 1969 and 2013. Validation of

charts from 114 randomly selected patients with a diagnosis of villous atrophy from this database found that 108 (95%) had CD (13).

Data on blood donations and transfusions were obtained from the Swedish component of the Scandinavian Donations and Transfusions Database (SCANDAT2), which contains all electronically available data on blood donors, blood donations, blood transfusions, and transfused patients since 1968. The SCANDAT2 has near-complete nationwide coverage of Sweden records since 1995 (14, 17) and is deemed to be of high quality (14).

Study design and statistical analyses

In this retrospective cohort study, our fundamental assumption was that some factor that may cause CD is transmissible through blood transfusion and is capable of causing CD in transfusion recipients. On the basis of this assumption, we set up 2 separate analyses. First, we tested whether patients who received 1 or more blood units from a CD-affected donor had a higher risk of CD than did patients who only received blood units from unaffected donors. Second, we tested whether multiple recipients of transfusions from the same high-risk donor had a shared higher risk (irrespective of whether this donor was diagnosed with CD during the study period). We have previously used both of these approaches and have shown that the second approach is less sensitive to underascertainment because most donors donate to multiple recipients (18).

The analyses followed an approach similar to that described in a previous assessment of transfusion-transmitted disease (18), but they differed in that we only considered data from the Swedish component of the SCANDAT2. For all patients in the Swedish component of SCANDAT2, we defined an exposure ascertainment period of 180 days from the first transfusion registration, and identified all transfusions received during this period. We then identified all blood donors who had contributed these blood units. We did not consider transfusions outside of the exposure ascertainment period.

Patients who underwent transfusion were followed for the occurrence of CD starting 180 days after the first transfusion. This delayed start of follow-up was implemented to exclude patients with subclinical yet undiagnosed CD (18). Patients who died or were censored before the start of follow-up were thus excluded. Follow-up was extended until death, emigration, first CD diagnosis, or end of follow-up (December 31, 2012). Recipients who received an autologous transfusion or blood from an unknown donor were excluded.

For the first analytical approach, we compared the incidence of CD among patients who received at least 1 blood unit from a donor who had a subsequent CD diagnosis with that among other transfusion recipients who received no CD-affected units. These analyses separated donors with a diagnosis within 5 years of transfusion from those who were diagnosed later. For the second analytical approach, we computed a time-dependent, donor-specific disease excess score (DES), which was the difference between the observed and expected numbers of disease events among all past recipients of each donor. The expected number of events was computed for each donation separately by extracting the predicted probability from a Poisson regression model that incorporated the type of donation, calendar year, and county, as well as recipient age and sex. In this case, an elevated DES indicated that there were more CD cases among past recipients of an individual donor than expected from chance alone. The DES was allowed to change in a time-dependent manner with each donation so that it captured the disease occurrence among all previous recipients of that donor (18, 19).

We used Cox proportional hazards regression models to estimate hazard ratios for CD. In the first approach, we conducted analyses in which we compared patients who received blood from CD-positive donors with those who received blood from CD-negative donors. In the second approach, we compared patients who received blood from donors with different DES. In the latter analyses, the DES was fitted as a categorical term (categorized as <0, 0, 0.1–1.5, or 1.6–3.0). In both instances, analyses were adjusted for total number of transfusions (as a restricted cubic spline with 5 knots) and calendar year of first transfusion (as a restricted cubic spline with 5 knots), as well as the transfused patient's age (as a restricted cubic spline with 5 knots), sex, and ABO blood group (as a categorical term). We also adjusted for geographical region of transfusion.

Lastly, we performed a sensitivity analysis in which each blood transfusion was analyzed as a separate entity but that was otherwise similar to the main analysis. In these analyses, we tested whether the risk of CD in the recipient of each blood unit was associated with the occurrence of CD or with the DES of the contributing donor. In technical terms, the analyses were set up with 1 observation per transfused blood unit and did not use a 180-day exposure ascertainment period, thus avoiding assumptions about how quickly CD might occur in transfused patients. These analyses were conducted using a Cox regression model into which we incorporated only patient blood group, calendar period, and geographical region using the same parameters as in the main model. Because this approach potentially counts each CD diagnosis multiple times, confidence intervals for the hazard ratios were constructed using a bootstrap approach with 10,000 runs (19). We used SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina) for all statistical analyses, with P values < 0.05 regarded as statistically significant. The present study was approved by the Ethics Review Board in Stockholm, Sweden on June 20, 2016.

RESULTS

We identified 1,450,916 patients in the Swedish component of the SCANDAT2 who received a blood transfusion between 1968 and 2012. From these, we excluded 2,770 patients with prior diagnoses of CD, 296,363 patients who died or were censored within 180 days of first transfusion, 573 patients who were diagnosed with CD within 180 days of the first transfusion, 86,332 patients who received a blood transfusion from a donor who could not be identified, and 6,589 patients who received an autologous transfusion. A total of 1,058,289 patients remained for our main analysis. Of these, 9,455 patients (0.9%) received at least 1 blood transfusion from an individual with a previous or subsequent diagnosis of CD (3,611 patients from a donor with a prior CD diagnosis, 1,956 patients from a donor diagnosed within 5 years of donation, and 3,888 patients diagnosed >5 years after donation).

Patients who received a transfusion from a donor with CD were similar to those who did not with regard to age at first

Table 1. Relative Risks of Celiac Disease in Relation to Disease Occurrence in Contributing Blood Donors, by Overall Estimate and Donor Disease Latency, Sweden, 1968–2012[a]

Time of CD Diagnosis	Donor With CD				Donor Without CD		
	No. of Events	Person-Years	HR[b]	95% CI	No. of Events	Person-Years	HR[b]
Overall	14	62,976	1.0	0.9, 1.2	1,748	8,915,705	1.0
Before donation	5	16,219	1.1	0.5, 2.8			
0–5 years after donation	2	11,875	0.7	0.2, 2.7			
>5 years after donation	7	34,882	0.9	0.4, 1.9			

Abbreviations: CD, celiac disease; CI, confidence interval; HR, hazard ratio.

[a] The total number of events and duration of follow-up differed between the 4 outcome groups because of the censoring of patients diagnosed during the first 180 days of follow-up.

[b] Hazard ratios were adjusted for patient age, sex and ABO blood group, as well as calendar year of transfusion, region of residence, and number of transfusions.

transfusion (median age, 68.2 years vs. 69.5 years) and follow-up time (median, 6.3 years vs. 5.9 years). However, in exposed individuals, the proportion of females was lower (50.7% vs. 58.6%) and the median number of transfusions was higher (8 vs. 3).

In Table 1, we present results from analyses in which we evaluated whether patients transfused with blood units from donors with CD had a higher risk of CD. Overall, patients exposed to blood from a donor with CD did not have a higher risk of CD (hazard ratio (HR) = 1.0, 95% confidence interval (CI): 0.9, 1.2). Moreover, hazard ratio estimates were independent of whether the donor was diagnosed with CD before donation (HR = 1.1, 95% CI: 0.5, 2.8), within 5 years of donation (HR = 0.7, 95% CI: 0.2, 2.7), or more than 5 years after the donation (HR = 0.9, 95% CI: 0.4, 1.9). There were no CD events among recipients of plasma (n = 1,625) or platelet units (n = 865) from donors with CD.

The analyses of CD risk in relation to the DES of contributing blood donors (i.e., excess CD occurrence of past recipients of each donor) are presented in Table 2. Compared with patients who exclusively received blood units from donors with a DES less than 0 (i.e., those with no observed CD events among prior recipients but with an expected event frequency >0), patients who received units from at least 1 donor with a DES of 1.6 or more did not have a higher risk of CD (HR = 0.6, 95% CI: 0.2, 2.4). The result of a trend test performed by fitting the maximum DES of all contributing blood donors was nonsignificant (P for trend = 0.28). The highest observed DES in any blood donor was 2.99. Results of the sensitivity analyses in which we considered each blood transfusion as a separate entity were very similar to the overall results, with no evidence of CD transmission (data not shown).

DISCUSSION

In the present retrospective nationwide cohort study that included 9,455 patients transfused with blood from donors with CD, we found no evidence of transfusion transmission of

Table 2. Relative Risks of Celiac Disease in Relation to the Maximum Disease Excess Score Among All Contributing Blood Donors, Sweden, 1968–2012

Maximum DES Among Contributing Blood Donors[a]	No. of Patients	No. of Events	Person-Years	HR[b]	95% CI
<0	963,843	1,580	8,177,357	1.0	Referent
0[c]	18,210	33	222,345	0.9	0.6, 1.3
0.1–1.5	74,013	147	562,923	1.1	0.9, 1.4
1.6–3.0	2,223	2	16,054	0.6	0.2, 2.4
P for trend					0.28

Abbreviations: CI, confidence interval; DES, disease excess score; HR, hazard ratio.

[a] The DES was computed in a time-dependent manner so that for each new donation, we calculated the difference between the observed and expected number of diseased patients among all previous recipients of each donor. Thus, a case DES below zero implies that there are fewer than expected diseased patients among previous recipients and a riskiness DES above zero implies that the number of events is higher than expected. Because most recipients received transfusions from more than 1 donor, the highest case DES of all donors who contributed blood unit to each recipient was used in the statistical model. The donor DES only included the number of diseased patients among previous recipients, but not the disease status of the index patient.

[b] HRs were adjusted for patient age, sex, and ABO blood group, as well as calendar year of transfusion, region of residence, and number of transfusions. Trend tests were performed by fitting the DES as a linear term.

[c] No prior donations.

CD. The main weakness of this study is the small number of CD events in the donor population, which led to a limited statistical power. This was especially true for the first analysis, in which we tested for higher risks of CD among recipients of blood from affected donors. It is worth noting that even though this study was based on a mere 14 transfusion recipients from CD donors who subsequently developed CD, these cases represent the entire computerized transfusion experience in 1 country and resulted in a relative risk estimate with an upper confidence limit of 1.2. This suggests that although this analysis was not powerful enough to rule out small increases in risk, we can exclude even modest risks. We have previously shown that the second analytical approach, in which we tested for transmission of some causative agent from yet undiagnosed blood donors, should have a better statistical power in situations in which the clinical penetrance of the causative agent is likely to be low or underdiagnosis is likely to be common (18). Also, it must be kept in mind that reliance on biopsy results for the classification of CD may have resulted in a limited diagnostic sensitivity, affecting the ascertainment of disease among both donors and recipients, as well as further limiting the statistical power. Because of this, these data do not allow us to formally rule out that CD may be transfusion transmissible in a small number of cases. However, the fact that no cases of CD were diagnosed among patients who received plasma transfusions (some of which likely contained tissue transglutaminase 2 antibodies, particularly among undiagnosed CD patients) is reassuring. Thanks to the large study cohort derived using reliable data sources and the likely random allocation of blood units from affected or high-risk donors (18–20), it is clear that such transmission, if at all possible, would be rare and would only have a negligible public health impact.

The rationale for the conduct of this study was the notion that evidence of transfusion transmission of CD would have important implications for our understanding of the etiology of CD. However, given the limited power of the study, we feel reluctant to draw any wider biologic conclusions from our negative results. Nevertheless, our main conclusion is that CD is unlikely to be transmitted via transfusion.

ACKNOWLEDGMENTS

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This project was supported by grants from the Swedish Society of Medicine and the Stockholm County Council. The assembly of the Scandinavian Donations and Transfusions Database was made possible through support from the Swedish Research Council (grants 2011-30405 and 2007-7469), the Swedish Heart-Lung Foundation (grant 20090710), the Swedish Society for Medical Research (grant to G. E.), the Strategic Research Program in Epidemiology at Karolinska Institutet (grant to G .E.), and the Danish Council for Independent Research (grant 2009B026).

Conflict of interest: none declared.

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