

No evidence of transfusion transmission of Celiac disease

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List of abbreviations: CD, Celiac disease; CI, Confidence Interval; DES, Disease excess score; HR, Hazard ratio

ABSTRACT

The vast majority of patients with Celiac disease (CD) have disease-specific antibodies. If such antibodies—or another blood-borne factor involved in the causation of CD—are transmissible, it might be reflected by an increased risk of CD in individuals receiving blood from donors with incipient CD. In a retrospective nationwide cohort study of 1,058,289 individuals who received a blood transfusion between 1968 and 2012 in Sweden we examined the risk of transmission of CD (here defined as having villous atrophy on small intestinal biopsy) using Cox regression. We also examined if there were clusters of CD patients receiving blood transfusions from the same blood donor, independently of the known CD status of that donor.

Some 9455 transfused patients (0.9%) received a blood transfusion from a blood donor diagnosed with CD. Of these, 14 developed CD, corresponding to a hazard ratio of 1.0 (95% confidence interval, 0.9-1.2) compared to recipients of transfusions from unaffected donors. There were no CD events among recipients of plasma or platelet units from donors with CD. We found no evidence of CD clustering among blood recipients of blood from individual donors (p for trend = 0.28).

This study suggests that CD is not transmitted through blood transfusions.

Keywords: *antibodies, autoimmunity, blood, celiac, gluten, transfusion, transmission*

INTRODUCTION

While transfusion-associated risks are at a record-low(1) there is still concern about 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 about 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). Besides enteropathy, CD is also characterized by presence of endomysium and tissue transglutaminase antibodies (8). These antibodies are almost universally present in untreated CD(9).

The targets of CD-specific antibodies, gliadin peptides and tissue transglutaminase 2 (TG2), have important roles in CD(10), and it has been suggested that these antibodies contribute to disease progression. Despite much research on CD-specific antibodies it is however still not clear whether such antibodies are involved in the pathogenesis of CD or whether they are merely an

epiphenomenon or a marker of disease activity(11). A recent paper however demonstrated that TG2-specific CD antibodies injected to mice induced small-intestinal inflammation and altered the mucosal morphology(12).

In this paper we examined whether celiac disease may be transmitted by blood transfusion.

METHODS

Data sources

We linked data on biopsy-verified CD(13) with data on blood transfusions(14) through the unique personal identity number assigned to all Swedish residents. (15)

CD diagnoses were ascertained from biopsy records collected from all of Sweden's 28 pathology departments in 2006-2008 and in 2013(13, 16). This data captures virtually all biopsy-verified CD diagnoses between 1969 and 2013. A patient chart validation of 114 randomly selected patients from this database, with a diagnosis of villous atrophy 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 (SCANDAT2) database which contains all electronically available data on blood donors, blood donations, blood transfusions, and transfused patients since 1968, with near-complete nationwide coverage in Sweden since 1995.(14, 17) The SCANDAT2-database is deemed to have a high quality (14).

Study design and statistical analyses

The fundamental assumption of this retrospective cohort study was that some factor, which may cause CD, is transmissible through blood transfusion and is capable of causing CD in transfusion recipient. Based on this assumption, we set up two separate analyses. First, we tested whether patients who received one or more blood units from a CD-affected donor would have an increased risk compared to patients who only received blood units from unaffected donors. Second, we tested whether multiple recipients of the same high-risk donor might have a shared increased risk (irrespective of whether this donor is diagnosed with CD during the study period or not). We have previously used both these approaches and have shown that the second approach is less sensitive to under-ascertainment because most donors donate to multiple recipients.

The analyses followed a similar approach as in previous assessment of transfusion-transmitted disease(18), with the difference that we only considered data from Swedish component of the SCANDAT2-database. For all patients in the Swedish part of SCANDAT, we defined an exposure ascertainment period of 180 days from the first transfusion registration, and identified all transfusions they 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.

Transfused patients 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 sub-clinical, yet undiagnosed CD(18). Patients who died or were censored before start of follow-up were thus excluded. Follow-up was extended until death, emigration, first CD diagnosis, or end of follow-up (31st December, 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 in patients who received at least one blood unit from a donor with a later CD diagnosis to other transfusion recipients who received no such units. These analyses were also conducted separating donors with a diagnosis within 5 years, or later. For our second approach we computed a time-dependent, donor-specific “disease excess score” (DES) as 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 incorporating type of donation, calendar year, recipient age and sex, as well as county. In this case, an elevated disease excess score thus indicates that there are more CD cases among past recipients of an individual donor than expected from chance alone. The DES was allowed to change time-dependently with each donation so that it, at each donation, captured the disease occurrence among all previous recipients of that donor(18, 19).

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) for CD. For the first approach, analyses compared patients who received blood from donors with CD to donors without CD. For the second approach, analyses compared patients who received blood with different DES. For the latter, the DES was fitted as a categorical term (categorized as <0, 0, 0.1-1.5, and 1.5-3.0). In both instances analyses were adjusted for total number of transfusions (as a restricted cubic spline with 5 knots), 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 also performed a sensitivity analysis where each blood transfusion was analyzed as a separate entity. The analyses were otherwise similar to the main analysis in that it tested whether the risk of CD in the recipient of each blood unit was associated with the occurrence of CD, or DES in the donor that contributed that unit. In technical terms, the analyses were set up with one observation per transfused blood unit and did not employ a 180-day exposure ascertainment period, thus avoiding assumptions about how quickly CD might occur in transfused patients. The analyses were conducted using Cox regression, incorporating only patient blood group, calendar period and geographical region using the same parameterizations as the main model. Since 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 9.4 (SAS institute, Cary, NC) for all statistical analyses with p-values <0.05 regarded as statistically significant.

Ethical aspects

The current 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 part of the SCANDAT2 database who received a blood transfusion between 1968 and 2012. From these, we excluded 2770 with a prior diagnosis of CD, 296,363 who died or were censored within 180 days of first transfusion, 573 who were diagnosed with CD during within 180 days of first transfusion, 86,332 who received a blood transfusion from a donor that could not be identified, and 6589 patients who received an autologous transfusion. A total of 1,058,289 patients remained for our main analysis. Of these, 9455 (0.9%) received at least one blood transfusion from an individual with a previous or later diagnosis of CD (3611 from a donor with a prior CD diagnosis, 1956 from a donor diagnosed within 5 years of donation, and 3888 diagnosed >5 years after donation).

Patients who received a transfusion from a donor with CD, and those who did not, were similar with regards to age at first transfusion (median age 68.2 vs 69.5 years). They also had similar follow-up (median 6.3 vs. 5.9 years). However, the proportion of females was lower in exposed individuals (50.7 vs. 58.6%) and the median number of transfusions was higher (8 vs. 3).

Table 1 presents results from analyses considering whether patients transfused with blood units from donors with CD were at increased risk of CD. Overall, patients exposed to blood from a donor with CD were not at increased risk of CD themselves (HR, 1.0; 95% CI, 0.9-1.2). Moreover, HR 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 >5 years after the donation (HR, 0.9; 95% CI, 0.4-1.9). There were no CD events among recipients of plasma (n=1625) or platelet units (n=865) from donors with CD.

The analyses of CD risk in relation to disease excess score (DES) of contributing blood donors (i.e. excess CD occurrence of past recipients of each donor) are presented in Table 2. Compared to patients who exclusively received blood units from donors with a DES < 0 (i.e., from donors with no observed CD events among prior recipients, but with an expected event frequency >0), patients who received units from at least one donor with a DES \geq 1.6, were not at increased risk of CD (HR, 0.6; 95% CI, 0.2-2.4). A trend test performed by fitting the maximum DES of all contributing blood donors was non-significant, (p for trend=0.28). The highest observed DES in any blood donor was 2.99.

Results of the sensitivity analyses where we considering 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 this retrospective, nationwide cohort study that included 9455 patients transfused with blood from donors with CD, we found no evidence of transfusion transmission of CD.

The main weakness of this study is the small number of CD events in the donor population, leading to a limited statistical power. This was especially true for the first analysis, where we tested for increased risks of CD among recipients of affected donors. While this analysis was clearly underpowered to be able to rule out small risk increases, it is worth noting that even though it was based on a mere 14 transfusion recipients from CD donors who then developed CD, these cases represent the entire computerized transfusion experience in one country and resulted in a relative risk estimate with an upper confidence interval of 1.2, indicating that we can exclude even modest risks. We have previously showed that the second analytical approach, where we tested for transmission of some causative agent from yet undiagnosed blood donors, should have a better statistical power for a situation such as this one, where the clinical penetrance of the causative agent is likely to be low, or where under-diagnosis should be common(18). Also, it must be kept in mind that the reliance of 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, further limiting the statistical power. As such, these data do not allow us to formally rule out that CD may be transfusion transmissible in a small number of cases. At the same time, the fact that no cases of CD were diagnosed among patients who received plasma transfusions (some of which likely contained TG2 antibodies, particularly among undiagnosed CD patients) is reassuring. Thanks to the large study cohort derived using reliable data sources, and 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 have only 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. Given the limited power of the study, however, we feel reluctant to draw any wider biologic conclusions from our negative results. Nevertheless, our main conclusion is that CD is unlikely to be transfusion transmitted.

Acknowledgments

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Conflict of interest

None. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf.

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Table 1. Relative risks of celiac disease in relation to occurrence of the same disease in the contributing blood donor(s), presented overall and by latency in the donors. Sweden 1968-2012 ^a.

Time of CD diagnosis	Donor with CD				Donor without CD		
	Events	Person-years	Hazard ratio ^b	95% CI	Events	Person-years	Hazard ratio ^b
Overall estimate	14	62,976	1.0	0.9, 1.2	1,748	8,915,705	1.0
<i>CD diagnosed before donation</i>	5	16,219	1.1	0.5, 2.8			
<i>CD diagnosed 0-5 years after donation</i>	2	11,875	0.7	0.2, 2.7			
<i>CD diagnosed >5 years</i>	7	34,882	0.9	0.4, 1.9			

after donation

^a The total number of events and duration of follow-up differs between the four outcome groups due to 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, calendar year of transfusion, region of residence, as well as number of transfusions.

CD, celiac disease

Table 2. Relative risks of celiac disease in relation to the maximum disease excess score among all contributing blood donors. Sweden 1968-2012.

Maximum disease excess score among contributing blood donors ^a	Number of patients	Events	Person-years	Hazard ratio ^b	95% CI
< 0 recipients	963,843	1,580	8,177,357	1.00 (ref)	
0, i.e. no prior donations	18,210	33	222,345	0.9	0.6, 1.3
0.1-1.5 recipients	74,013	147	562,923	1.1	0.9, 1.4
1.6-3.0 recipients	2,223	2	16,054	0.6	0.2, 2.4
<i>P for trend</i>					0.28

^a The diseases excess score was computed time-dependently 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 excess score below zero implies that there are fewer than expected diseased patients among previous recipients and a riskiness score above zero implies that the number of events is higher than expected. Because most recipients received transfusions from more than one donor, the highest case excess score of all donors who contributed blood unit to each recipient was used in the statistical model. The donor disease excess score only included the number of diseased patients among previous recipients, i.e. not the disease status of the index patient.

^b Hazard ratios were adjusted for patient age, sex and ABO blood group, calendar year of transfusion, region of residence, as well as number of transfusions. Trend tests were performed by fitting the diseases excess score as a linear term.