Prevalence of anaemia in inflammatory bowel disease in Switzerland: A cross-sectional study in patients from private practices and university hospitals

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Swiss IBD Cohort Study

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Abstract

Background: Anaemia represents a common complication of inflammatory bowel disease (IBD). Most studies on anaemia in IBD patients have been performed in tertiary referral centres (RC) and data from gastroenterologic practices (GP) are lacking. We investigated the frequency and severity of anaemia in IBD patients from tertiary referral centres and gastroenterologic practices compared to the general population.

Methods: Data were acquired from patients included in the Swiss IBD Cohort Study. IBD activity was evaluated by CDAI and modified Truelove and Witts severity index (MTWSI). Anaemia was defined as haemoglobin ≤ 120 g/L in women and ≤ 130 g/L in men.

Results: 125 patients from RC (66 with Crohn’s disease (CD) and 59 with ulcerative colitis (UC)) and 116 patients from GP (71 CD and 45 UC) were included and compared to 6074 blood donors. Anaemia was found in 21.2% (51/241) of the IBD patients and more frequently in patients from RC as compared to GP and healthy controls (28.8% vs. 12.9% vs. 3.4%; P < 0.01). IBD patients from RC suffered more frequently from active disease compared to IBD patients in GP (36% vs. 23%,...
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1. Introduction

Anaemia likely represents the most common systemic complication in patients with inflammatory bowel disease (IBD). However, precise data on the frequency are lacking and a recently published systematic review reported a wide range of anaemia prevalence values between 6.2% and 73.34%. The mean anaemia prevalence from these studies was 17%. Of note, the anaemia prevalence in outpatients was markedly lower (16%) than in hospitalized patients (up to 68%).

As expected from anaemia data, also iron deficiency was found frequently in IBD patients and its prevalence ranged from 36% up to 90% with a mean of 45%. Anaemia may significantly impair the quality of life even in the absence of specific symptoms. The anaemia in IBD is caused by several factors, of which iron deficiency and anaemia of chronic disease represent the most important mechanisms. Most studies on the prevalence of anaemia in IBD originate from tertiary referral centres. Data on the prevalence of anaemia in IBD from gastroenterological practices, where a considerable proportion of IBD patients is regularly managed, is unfortunately scarce.

We were interested in the frequency and severity of anaemia and supplementation therapy in IBD patients from gastroenterological practices as compared to IBD patients from tertiary referral centres. We hypothesized that the prevalence of anaemia in IBD patients from gastroenterological practices would be lower than from patients in tertiary referral centres and that supplementation therapy would be performed in equal frequencies in both treatment settings.

We therefore performed a cross-sectional study with the purpose of testing these hypotheses and further evaluate the clinical aspects of anaemia in IBD.

2. Materials and methods

2.1. Patients

Since 2006 adult and pediatric IBD patients from most regions of Switzerland, an area with approximately 7 million inhabitants, are included into the Swiss IBD Cohort Study (SIBDC). Inclusion criteria are (i) established and confirmed diagnosis of Crohn's disease (CD), ulcerative colitis (UC) or indeterminate colitis (IC) based on standard endoscopic, histological and radiographic procedures and (ii) written informed consent. The SIBDC project is supported by the Swiss National Science Foundation (SNF) and approved by the local ethics committees. Inclusion criteria for this analysis were confirmed diagnosis of CD or UC and age ≥ 14 years. Subjects < 14 years and patients with indeterminate colitis were excluded.

The data acquisition focused on clinical, biological, socio-economic and psychosocial data. At the time of inclusion, patients underwent a thorough clinical and laboratory assessment including calculation of clinical disease activity scores (CDAI or modified Truelove and Witts severity index) as well as inflammatory markers (CRP, blood leukocytes). Laboratory results and clinical data of patients were obtained from the SIBDC. Data from 120 randomly chosen healthy first time blood donor candidates (HBD) giving their blood between 2004 and 2008 at the Blood transfusion Centre of the Swiss Red Cross, Basel, Switzerland were used as reference.

2.2. Definitions

We followed the World Health Organization definitions that characterize anaemia as haemoglobin concentration ≤ 12 g/dL for non-pregnant women and ≤ 13 g/dL for men. A haemoglobin level below 10 g/dL is commonly considered as severe anaemia. Iron deficiency anaemia was defined by a ferritin level < 30 μg/L. A ferritin level between 30 and 100 μg/L together with active disease (CDAI > 150; MTWSI > = 10) was defined as iron deficiency anaemia in combination with anaemia of chronic disease.

2.3. Statistical analysis

Clinical data were exported from the data centre of the Swiss IBD Cohort Study at the University of Lausanne. All private practice patients whose data were present in the database were included in this study. The university hospital patients were randomly chosen to obtain a sample of similar size as the private practice sample. Continuous, normally distributed data are presented as mean ± SD whereas non-parametric data are presented as median, minimal and maximal values. We used t-tests to compare parametric continuous variables between care settings and the Mann–Whitney two sample rank sum test for non-parametric data. Binary and categorical data were compared by means of chi-squared tests for contingency tables. Fisher's exact test was used in case of small cell sizes (n < 5). Descriptive statistics of anaemia and haemoglobin values of 6074 healthy blood donors were calculated for informal comparison with the cohort patients. Mean haemoglobin levels of blood donors, university hospital patients and private practice patients were formally compared using one-way analysis of variance (ANOVA). In order to create similar sample sizes, a set of 120 randomly chosen blood donors, whose characteristics were representative for the entire sample, were used for these analyses. Pair-wise comparisons of means were performed using the Bonferroni method after statistically significant ANOVA. To test whether the difference of haemoglobin
levels between settings varies between genders, the setting by gender interaction was tested in a two-way ANOVA that included both main factors and the interaction. All statistical analyses were performed with the statistical package Stata vs 9 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Clinical characteristics of the study populations

The clinical characteristics of the study populations are shown in Table 1. Patients from university setting were recruited at the Departments of Gastroenterology of the University Hospitals Basel and Zurich. IBD patients treated in private practice were recruited from 7 board certified experienced gastroenterologists.

We found significantly fewer women being treated at university hospitals compared to men ($P=0.001$). Further, significantly more IBD patients in university hospitals had active disease as compared to patients in private practice ($P=0.032$). Active disease was defined as CDAI $\geq 150$ and a modified Truelove and Witts severity index $\geq 10$ for UC patients.$^{16,17}$ Location of Crohn's disease was grouped according to the Vienna classification where L1 stands for ileal, L2 for colonic, L3 for ileo-colonic, and L4 for disease in the upper gastrointestinal tract.$^{18}$ L1 location was found more frequently in patients from private practice compared to hospitalized patients. No significant differences were observed regarding age distribution.

The current medical therapy of CD and UC patients in university vs. private practice is depicted in Table 2. Infliximab was more frequently prescribed in university hospitals whereas the combination of adalimumab and azathioprine was more frequently applied in private practice. As therapy regimens sometimes overlapped, the total count exceeds one.

Healthy blood donors (HBD) served as controls. Values of anonymized 6074 healthy blood donors were provided by the
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3.3. Frequencies of ferropenia, anaemia due to iron deficiency and chronic disease

Most patients suffer from iron deficiency anaemia and from anaemia of chronic disease. Ferritin-values were obtained in 121 IBD patients (50.2% of the IBD cohort). In the HBD group we observed a gender difference: 80.8% of anaemic females were measured with a low ferritin compared to only 18.8% of males ($P<0.001$). The frequencies of iron deficiency, of iron deficiency anaemia as well as of iron deficiency anaemia combined with anaemia of chronic disease are further illustrated in Table 4. The data may represent an underestimation of the frequency of iron deficiency as ferritin-values were probably determined by clinicians in case of existing or expected anaemia and not as a routine procedure in non-anaemic patients.

It is well known that ferritin is also an acute-phase protein. We therefore assessed the correlation of ferritin with anaemia and acute-phase reactants as well as disease activity. Keeping the limitation in mind that ferritin levels were determined in only 50.2% of the IBD cohort, we found no correlation between ferritin levels and anaemia ($\rho=-0.0657, P=0.474$), active disease ($\rho=-0.0423, P=0.6507$), haemoglobin level ($\rho=0.1028, P=0.2616$), C-reactive protein ($\rho=0.0027, P=0.9771$), or BSR ($\rho=0.2504, P=0.1458$). This correlation analysis demonstrates that ferritin levels had no significant association, neither with anaemia nor with other acute-phase reactants.

Table 3  Frequency of anaemia and haemoglobin levels in IBD patients from university hospitals compared to private practice. Values are given as mean±SD and the corresponding 95% confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>IBD patients at university hospitals</th>
<th>IBD patients in private practice</th>
<th>$P$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia (frequency)</td>
<td>36 (28.8%)</td>
<td>15 (12.9%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>134.1 ± 19.8 (130.6–137.6)</td>
<td>139±14.6 (136.4–141.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>Haemoglobin females (g/L)</td>
<td>128.6 ± 17.4 (123.4–133.7)</td>
<td>134.7 ±10.7 (132–137.3)</td>
<td>0.024</td>
</tr>
<tr>
<td>Haemoglobin males (g/L)</td>
<td>137.3 ± 20.5 (132.7–141.9)</td>
<td>145±16.9 (140.2–149.9)</td>
<td>0.028</td>
</tr>
<tr>
<td>Haemoglobin female CD pts (g/L)</td>
<td>130.7 ± 15.8 (124.3–137.1)</td>
<td>134.2±2.12 (130.2–138.3)</td>
<td>0.424</td>
</tr>
<tr>
<td>Haemoglobin male CD pts (g/L)</td>
<td>138.8 ± 21 (132–145.5)</td>
<td>146.5±16 (140.7–152.2)</td>
<td>0.091</td>
</tr>
<tr>
<td>Haemoglobin female UC pts (g/L)</td>
<td>125.8 ± 19.3 (116.8–134.8)</td>
<td>135.2±8.4 (132.1–138.4)</td>
<td>0.023</td>
</tr>
<tr>
<td>Haemoglobin male UC pts (g/L)</td>
<td>135.7 ± 20.2 (129.1–142.2)</td>
<td>142.1±18.5 (132.3–151.9)</td>
<td>0.277</td>
</tr>
</tbody>
</table>
3.4. Supplementation therapy in private practice and university hospitals

We evaluated the frequency of supplementation therapy stratified according to the treatment setting (university hospitals vs. private practice). Substances provided by the treating physicians to promote haematological recovery included iron, vitamin B12 and folic acid. Blood transfusions and erythropoietin agents were not assessed.

We found that supplementation was more frequently provided in private practice (48/115, 42%, vs. 33/124, 27%). This difference was especially evident in CD patients (35/71, 49% in private practice vs. 17/66, 26% in university hospitals) but no difference could be observed in UC patients (13/44, 30% in private practice vs. 16/58, 28% in university hospitals). Of interest, we observed a gender difference. The frequency of supplementing female IBD patients did not differ between private practice and university hospitals (29/66, 44% in private practice vs. 16/46, 35% in university hospitals), whereas male IBD patients were more often substituted in private practice compared to university hospitals (19/49, 39% in private practice vs. 17/78, 22% in University hospitals).

We were further interested if existing anaemia is associated with supplementation therapy. We found that anaemic patients were supplemented in comparable frequencies in university hospitals compared to private practice (6/15, 40% of anaemic IBD patients in private practice vs. 15/35, 43% in university hospitals). However, in non-anaemic patients, supplementation was more frequently performed in private practice compared to university hospitals (42/100, 42% in private practice vs. 18/89, 20% in university hospitals). We found heterogeneity in the prescription habits of the gastroenterologists in clinical practice. The high frequency of supplementation therapy resulted mainly from one gastroenterologist having provided 39 (34%) of the IBD patients in the private practice cohort who used to perform supplementation therapy in 54% of the IBD patients. If the patients from this colleague are excluded from analysis, the percentage of supplementation in the private practice cohort (data of 6 gastroenterologists) did no longer differ from the university hospitals (35% vs 26%, P=0.192).

3.5. Correlation between clinical disease activity and haemoglobin levels

As secondary outcome we assessed the correlation between the CDAI and MTWSI respectively with the non-parametric Spearman’s rank correlation test and found CDAI inversely correlated with haemoglobin (rho = −0.449, P < 0.001, meaning that higher CDAI levels were correlated with lower haemoglobin levels), however, MTWSI was not significantly correlated with the haemoglobin (rho = −0.076, P=0.443).

4. Discussion

Our cross-sectional study has two messages we consider to have clinical impact. First, with an average prevalence of 21%, anaemia is rather common in IBD patients and is found in higher prevalences in university hospitals compared to private practices. And second, supplementation therapy is performed in only 40% (private practice) to 43% (university hospitals) of anaemic IBD patients.

We present the first data evaluating the prevalence of anaemia stratified according to the treatment setting. We found that IBD patients in tertiary referral centres had significantly more often an anaemia compared to IBD patients in private practice (28.8% vs. 12.9%). As IBD patients in private practice are seen on an outpatient basis, these frequencies can easily be compared with the literature assessing the prevalence of anaemia in patients. The anaemia prevalence in our IBD outpatient cohort is comparable to the IBD outpatient frequencies from Walker et al. (13% anaemia prevalence in 2894 outpatients) and Ershler et al. (13% anaemia prevalence in 7200 outpatients).19,20 We found a wide range of the anaemia prevalence in IBD outpatients, ranging from 9% reported by Niv et al.21 up to 73% as found by Beecken et al.22 The spectrum of anaemia prevalences in hospitalized IBD patients ranges from 44% as reported by Hoffbrand et al.23 up to 74% as found by Werlin and Grand.24 Reilly et al.25 reported a prevalence of 55% in IBD patients compared to 64% as found by Dyer et al.26 Our anaemia prevalence rates for IBD patients treated at university hospitals cannot be directly compared to the above cited frequencies as they represent a cluster from mostly outpatients and some hospitalized patients. The higher anaemia frequency in patients treated at university hospitals is related to the higher proportion of IBD patients with active disease treated at university hospitals.

We report also on the frequency of supplementation therapy in IBD patients. In the overall population, supplementation with either iron products, vitamin B12, and/or folic acid was performed more frequently in IBD patients treated in private practice compared to university hospitals (42% vs. 27%, P=0.014). In contrast, anaemic patients were supplemented in comparable frequencies in both treatment settings (40% in private practice vs. 43% in university hospitals). In our literature search we found no data evaluating the prescription habits of gastroenterologists regarding supplementation therapy in their IBD patients. It is somewhat astonishing that the percentage of IBD patients supplemented is not higher although it is well known that anaemia represents the most common systemic complication of IBD.2 Several factors may contribute to this finding. First,
treatment physicians may still be accepting the concept of "asymptomatic anaemia", claiming that patients would adapt to low haemoglobin levels if anaemia developed slowly as this is typically the case in IBD. Thereby one could assume that the impact of anaemia on the quality of life in IBD patients is limited. However, as demonstrated meanwhile by several studies, the impact of anaemia on the quality of life of both general patients and specifically IBD patients is a major one. Second, treating physicians may argue that anaemia but not ferropenia represents the only relevant laboratory finding and therefore wait to substitute IBD patients until clinical overt anaemia has manifested. The decision to supplement iron in ferropenic IBD patients lacking anaemia is not completely clear and may depend on the clinical scenario and the individual preferences. Third, treating physicians may claim that anaemia but not ferropenia represents the only "asymptomatic anaemia", saying that patients would adapt to low haemoglobin levels if anaemia developed slowly as this is typically the case in IBD. Thereby one could assume that the impact of anaemia on the quality of life in IBD patients is limited. However, as demonstrated meanwhile by several studies, the impact of anaemia on the quality of life of both general patients and specifically IBD patients is a major one. Second, treating physicians may argue that anaemia but not ferropenia represents the only relevant laboratory finding and therefore wait to substitute IBD patients until clinical overt anaemia has manifested. The decision to supplement iron in ferropenic IBD patients lacking anaemia is not completely clear and may depend on the clinical scenario and the individual preferences. Third, treating physicians may claim that anaemia but not ferropenia represents the only

Our study has strengths and limitations. A clear strength is the possibility of evaluating the frequency of anaemia in a prospective patient cohort. Second, the data are less prone to selection bias as patients from representative university hospitals and private practices have been included. A possible limitation with respect to the anaemia frequencies in private practice vs. university hospitals may be that these can be related to the higher percentage of patients with active disease in the latter group. A further limitation may be that we did not systematically assess the frequency of blood transfusions and application of erythropoietin. However, we think that this does not affect the conclusions from our data as these measures are usually not carried out as isolated procedures but are accompanied by a supplementation therapy with iron products and/or folic acid and/or vitamin B12. Additionally, the percentage of IBD patients in which ferritin levels were measured was low.

In conclusion, our prospective cohort study demonstrates that anaemia is frequent in IBD patients both in tertiary referral centres and in private practice. Second, supplementation therapy in anaemic IBD patients is not performed sufficiently often. Physicians caring for IBD patients should be aware of the impact of anaemia and ferropenia on quality of life and work towards a reduction of anaemia's frequency and severity.

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The individual author contributions are summarized below:

1. Conception and design of the study
2. Acquisition of the data
3. Analysis and interpretation of the data
4. Drafting of the article or revising it critically for important intellectual content
5. Final approval of the version to be submitted

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Alex Straumann: 1,2,3,4,5.
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Andreas Buser: 3,4,5.
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