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Frequency of Micronutrient Deficiencies in Patients with Inflammatory Bowel Disease

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Abstract

Background: Inflammatory Bowel Disease (IBD), which includes Ulcerative Colitis (UC) and Crohn's Disease (CD), carries an increased risk of micronutrient deficiencies. There are no previous data in this respect regarding Mexican patients, and as genetic and cultural context can make their nutritional state differ.

Objective: The aim of this study is to describe the frequency of Vitamin D (VD), Cobalamin (Cbl), Zinc and folic acid (B9) deficiencies in Mexican patients with IBD.

Methods: We reviewed medical records from 270 patients with IBD belonging to the Inflammatory Bowel Disease Clinic at the National Institute of Medical Science and Nutrition Salvador Zubirán. Clinical and sociodemographic data were registered. Statistical analysis was performed using the following cut points: VD insufficiency (21-29 ng/mL), VD deficiency (<20 ng/mL), Cbl deficiency (<180 pg/mL), Zinc deficiency (<60 µg/dl) and B9 deficiency (<6 ng/mL).

Results: Of the total 270 patients studied, 224 had UC (82.96%) and 46 (17.03%) CD. A total of 225 had VD registered measures, from them, 108 (48%) VD insufficiency and 76 (33.8%) VD deficiency; 159 (58.9%) patients had registered Cbl levels, from them, 22 (13.8%) showed deficient levels. Of the 71 (26.29%) patients with registered Zinc serum levels, 5 (7%) presented deficiency. From the 166 (61.48%) patients with B9 registered levels, deficiency was found in 5 (3.01%) of them.

Conclusion: The frequency of micronutrient deficiencies in IBD patients was: 48% for VD insufficiency, 33.8% for VD deficiency; 13.8% for Cbl deficiency, 7% for Zinc deficiency and 3.01% for B9 deficiency.

Keywords: Micronutrients; Inflammatory bowel disease; Mexico; Vitamin D; Cobalamin; Zinc; Folic acid

Abbreviations: IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn´s Disease; Cbl: Cobalamin; B9: Folic acid; VD: Vitamin D

Introduction

Ulcerative Colitis (UC) and Crohn's Disease (CD) represent the two main types of Inflammatory Bowel Disease (IBD). Genetics, environmental factors and the immune system play important roles in its multifactorial etiology [1]. IBD clinical course is characterized by chronic inflammation of the intestine that implies important consequences in the nutritional status of IBD patients, as malnutrition is one of the major comorbidities, present in up to 85% of them [2]. Disturbances can involve macronutrients related to energy and protein intake during active and severe disease or micronutrients like vitamins, minerals and trace elements, which levels can be diminished even during mild activity or remission [3].

Vitamin D (VD) plays an important role in IBD clinical course and pathogenesis. At least 60% to 70% of the patients have insufficient or deficient vitamin D levels [4]. Its normalization is associated with reduced risk of relapse, IBD-related surgeries and improvement in quality of life regarding Cobalamin (Cbl), patients with CD are thought to be at significant risk for developing this micronutrient deficiency, which has been reported in up to 40% of the cases, as long-term inflammation in these patients can lead to impaired absorption, but also to fibrosis, strictures, and fistulae that require surgical resection of the ileum [5-7]. On the other hand, zinc is an essential mineral, important in immune function, protein and collagen synthesis, and wound healing, and co-factor for various enzymes involved in maintenance of intestinal integrity, regulating autophagy and bacterial clearance in macrophages [3,8]. Its deficiency is reported in up to 22% of the patients, which is associated with more severe colitis and a larger inflammatory burden. It has been proven that administration of zinc improves intestinal barrier function and reduces expression of pro-inflammatory cytokines [8,9]. Finally, folate is involved in the methylation of DNA and may produce epigenetic changes that affect the interaction between the gut microbiota and systemic immune responses, which may be involved in the pathogenesis of IBD [10].

The clinical course of IBD and the micronutrient deficiency it accompanies may be different depending on the ethnic and genetic background, latitude, and food consumed, habits and beliefs that form a basic part of culture, which may have beneficial or detrimental effects on health status [11,12]. For that reason, prompted by the lack of data about micronutrient deficiencies in Mexican patients with IBD, the aim of this study was to describe the frequency of Vitamin D (VD), Cobalamin (Cbl), Zinc and folic acid (B9) deficiencies in patients with IBD.

Materials and Methods

A total of 270 patients with histopathological diagnosis of UC or CD was studied from the IBD clinic at the National Institute of Medical Sciences and Nutrition "Salvador Zubirán". All patients regularly seen in the IBD clinic from January 2014-June 2017 were evaluated to be included, except for those who were taking any vitamin supplements, had any current infection or other inflammatory condition besides

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IBD at the time of vitamins and mineral measurement. We looked at for clinical and sociodemographic data from the 30 days around the day of the sample collection and registered them in a database using SPSS v.24, using the following cut points to classify serum levels of each micronutrient: VD insufficiency (21-29 ng/mL), VD deficiency (<20 ng/mL), Cbl deficiency (<180 pg/mL), Zinc deficiency (<60 µg/dl) and B9 deficiency (<6 ng/mL). The following variables were registered as clinical and sociodemographic characteristics of the sample: histopathological diagnosis of UC or CD, sex, current age, years of evolution of IBD, family history of IBD, positive or negative smoking habit, positive or negative personal history of appendectomy or tonsillectomy, activity of disease at the inclusion of the study, clinical course of IBD (initially active and then inactive, one or less relapses per year, two or more relapses per year), the presence of extraintestinal manifestations such as arthritis, arthralgia, ankylosing spondylitis, Sacroiliitis, Erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis or uveitis, bone densitometry results (classified as normal, osteopenia, osteoporosis or no register), number of hospitalizations registered for IBD, positive or negative history of surgical treatment for IBD.

Statistical analysis was performed using mean and median as measures of central tendency, and Chi squared, Mann-Whitney U test, Spearman's correlation and MANOVA were further used accordingly to study possible differences between groups or possible associations. A value of P≤0.05 was considered statistically significant.

Results

Clinical and sociodemographic characteristics

Of the total 270 patients studied, 224 had UC (82.96%) and 46 (17.03%) CD; 156 (57.77%) women and 114 (42.22%) men; with an average age ± standard deviation of 47.77 ± 15.19 at the moment of the study, with a median (range) of years of evolution of IBD of 10 years (1-43). Table 1 shows demographical characteristics, clinical characteristics are shown in Figures 1 and 2 and medical treatment in Figure 3.

Frequency of micronutrient deficiencies

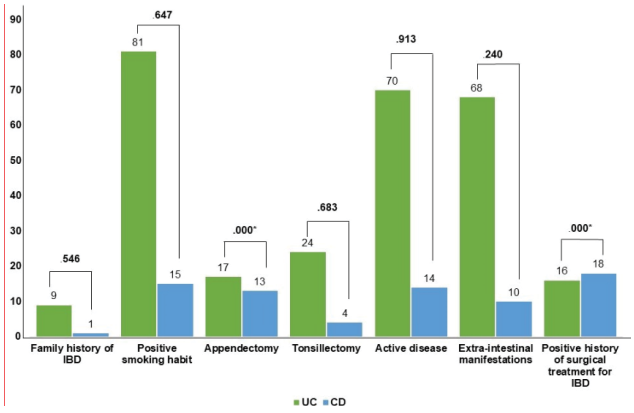
A total of 225 (83.33%) patients had VD registered measures, from them, 108 (48%) had VD insufficiency [93 (41.33%) UC and 15 (6.66%) CD] and 76 (33.8%) VD deficiency [58 (26.2%) UC and 18 (7.55%) CD]. One hundred fifty-nine (58.9%) patients had registered Cbl levels, from them, 22 (13.8%) showed deficient levels [6 (3.8%) UC and 16 (10%) CD]. Of the 71 (26.29%) patients with Zinc serum levels, 5 (7%) presented deficiency, all of them with UC diagnosis. From the 166 (61.48%) patients with B9 registered levels, deficiency was found in 5 (3.01%), all of them with UC diagnosis (Figure 4).

Univariate analysis

We found that CD patients had a greater median age than UC patients (55.5 *vs.* 47 years, p=0.001), were older at diagnosis (46 *vs.* 32 years, p=0.000) and had surgical treatment for IBD more frequently (18 *vs.* 16, p=0.000). On the other hand, UC patients had more years of evolution (11 *vs.* 7, p=0.001) and appendectomy history more frequently (17 *vs.* 13, p=0.000).

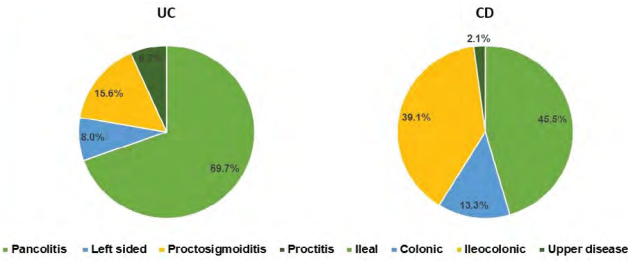
Variables	UC n=224 (%)	CD n=46 (%)	p-value
Female	128 (57.1)	28 (60.9)	0.641
Male	96 (42.9)	18 (39.1)	
Median age (range)	47 (20-92)	55.50 (25-85)	0.001*
Median age at diagnosis (range)	32 (12-77)	46 (18-72)	0.000*
Median Years of evolution (range)	11 (1-43)	7 (1-36)	0.001*

Table 1: Socio-demographic characteristics of Mexican patients with IBD: Inflammatory Bowel Disease, UC: Ulcerative Colitis and CD: Crohn`s Disease.



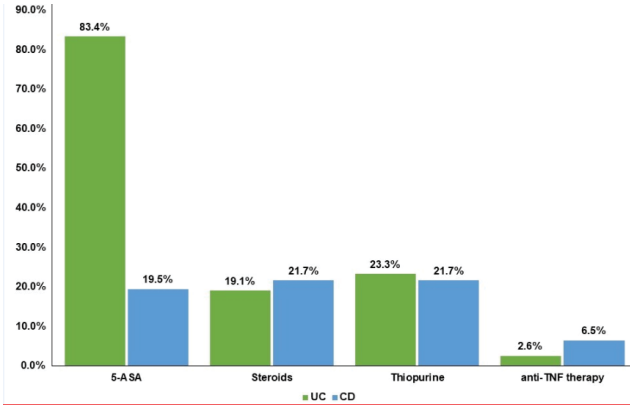
Abbreviations: IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn´s Disease

Figure 1: Clinical characteristics in Mexican patient with IBD.



Abbreviations: US: Ulcerative Colitis; CD: Crohn´s Disease

Figure 2: Extent in UC and disease location in CD.



Abbreviations: IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn´s Disease, anti-TNF therapy: anti-Tumor Necrosis Factor therapy

Figure 3: Treatment in Mexican patient with IBD.

Clinical associations

Regarding the difference among these three categories of VD serum levels (normal, insufficient or deficient) in IBD patients, years of evolution of disease showed a statistically significant linear trend

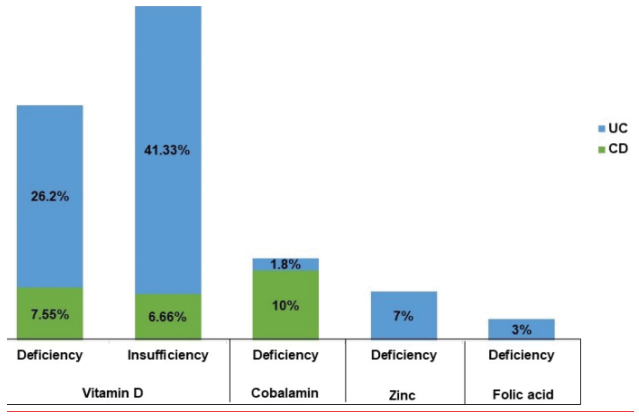


Figure 4: Frequency of micronutrient deficiencies in Mexican patient with IBD.

Abbreviations: UC: Ulcerative Colitis; CD: Crohn´s Disease

F=5.43 (p=0.02), indicating that years of evolution of IBD increase, VD serum levels decrease proportionately. Besides, high smoking rate showed a tendency to statistical significance regarding low VD levels, F=3.075 (p=0.052), showing a linear trend indicating that smoking rate increased serum VD levels decreased proportionately. When the difference between medians of VD serum levels was compared between the seasons of autumn and winter and spring and summer, VD serum levels were significantly lower when measured during the months of spring and summer (p=0.004). Finally, CD patients with deficient levels of Cbl (n=10, 45.5%) had more years of evolution compared to CD patients with normal levels (10 (6-27 years) *vs.* 5 (1-20 years), p=0.01). Due to the low number of deficiency cases, associations could not be studied for Zinc or Folic Acid.

Discussion

This study concludes that the frequency of micronutrient deficiencies for Mexican IBD patients is 48% for VD insufficiency, 33.8% for VD deficiency, 13.8% for Cbl deficiency, 7% for zinc deficiency and 3% for B9 deficiency. Additionally, as high smoking rate and years of evolution increase, VD levels decrease proportionately; VD levels are significantly lower when measured during the months of spring and summer. Besides, CD patients with Cbl deficient levels have more years of evolution compared to the ones with normal levels.

Regarding the frequency of VD insufficiency and deficiency levels, 48 and 33.8% respectively and 81.8% in total, we can observe it is not so different from data reported from the United States, where at least 60% to 70% of the patients with IBD have insufficient or deficient vitamin D levels [4], and from the ones reported in Canada, where only 22% of the patients have sufficient levels of vitamin [13,14]. Besides, VD levels in this study are significantly lower when measured during the months of spring and summer, which supports the already known seasonal variation patterns that can influence disease development, severity and progression [15]. For instance, this pattern had been previously reported in CD, where VD deficiency in winter is present in 50-76% of patients and insufficiency in 73-100%, while in summer VD deficiency appears in 10-19% of patients and insufficiency in 55-59% of them [16-20]. This study also shows that years of evolution and smoking rate are associated with low VD serum levels. The relationship between VD low serum levels and smoking has been stablished not only in the case of IBD patients and its evolution but also in healthy individuals. Precisely, smoking has been stated as a significant determinant of low VD serum levels and as a risk factor for developing IBD [21,22]. The importance of VD in IBD relies on the fact that local activation of VD coordinates the activity of the innate and adaptive arms of immunity and the intestinal epithelium, in a manner that promotes barrier integrity, facilitates the clearance of translocated flora and diverts CD4 T-cell development away from inflammatory phenotypes [23]. Unfortunately, even with this knowledge and the great percentage of VD low serum levels described consistently in IBD patients, it is known that increasing serum VD alone may not be enough intervention, as it has been suggested that maintaining sufficient VD levels in these patients can be particularly difficult, because of many reasons still under research. For instance, diminished epithelial responses to VD during active IBD or, to a lesser extent, genetic variants, as it has been shown that risk alleles explain only 3% of the variance of VD levels in these patients [24,25]. Some of the principal risk factors for VD deficiency in IBD, consistent with the results of this study, include decreased sunlight exposure, disease duration, smoking, and genetics [5].

In this study, Cbl deficiency was observed in 13.8% of the patients, and the frequency of vitamin B9 deficiency was 3%. Results from previous literature regarding Cbl and folate levels in IBD patients are not as consistent as in VD, which is why a recent meta-analysis was made in this regard, which concluded that although serum Cbl concentrations are not different between IBD patients and healthy controls, the average serum folate concentration in IBD patients is indeed significantly lower than the one present in control patients [10]. It is important to note that 10% of Cbl deficient patients come from the CD group and all the 3% of the patients with folate deficiency have UC. Additionally, a statistically significant difference was observed when years of evolution of CD where compared between Cbl deficient patients and the ones with normal levels, which suggests those years of evolution of disease could be a risk factor for Cbl deficiency in CD. These results may be due to the intestinal region affected by CD, which is frequently ileocecal, considering that terminal ileum is the principal region where Cbl uptake occurs [26]. The most important clinical consequences of Cbl deficiency include nervous system dysfunction and megaloblastic anemia [7]. On the other hand, folate deficiency still appears to be relatively common, about 78% of the patients have it, particularly in CD, which contrasts with the low frequency reported in this study [27]. It is important to mention that potential mechanisms of folate deficiency include inadequate dietary intake, malabsorption, and medication interactions, and that in spite of folate fortification programs, IBD patients may be at increased risk of folic acid deficiency compared with the general population [3].

Finally, zinc deficiency was present in 7% of the patients, which differs with the 22% frequency that has been reported in other studies [9]. Zinc deficiency in IBD patients may be related to absorption defects, increased losses or ongoing inflammation [28]. Possible reasons why Mexican IBD patients have no zinc or folate deficiencies in a high frequency of cases may be due to the type food consumed or because de majority of patients in this sample had two or less relapses per year, which may suggest less exposure to intestinal inflammation through time.

Diet has a significant impact on the development and progression of IBD. Nutrition-related factors, together with components of the gut microbiota, genetic predisposition and lifestyle from industrialized countries, emerge as prime environmental triggers for the development and modification of these lifestyle-related chronic diseases of the gastrointestinal tract [29]. To illustrate the importance of diet in the development of IBD, we can mention for instance, carbohydrates, especially refined versions, which are suspected to be the chief

alimentary factor in Crohn's disease, the activity IBD presents in 'Westernized' cultures, in addition to the increased frequency of this disease in 'dairy based' cultures compared to 'soy-based' ones [30].

Conclusion

This study has the strength of being the first one to report the nutritional deficiencies in a Latin American country, which has an important contribution to IBD international knowledge and nutritional status in order to develop further interventions for improving this type of nutritional deficiencies. In conclusion, high prevalence of low VD serum levels was found in the Mexican IBD population. Other deficiencies such as Cbl, B9 and zinc were not as frequent in our population and depend on the type of IBD. Additionally, this study supports the relationship between smoking rate and season of the year with VD serum levels, besides years of evolution of IBD, which are also related to Cbl deficiency in the case of CD.

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