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Micronutrients in Chilean Inflammatory Bowel Disease patients: Cross-sectional study

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RESEARCH

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ABSTRACT

Background

Inflammatory Bowel Disease (IBD) patients often present with nutritional disorders that affect both macronutrient and micronutrient levels. Vitamin and mineral deficiencies are typically more frequent in Crohn's disease (CD) patients than other IBD patients. However, some studies have shown that these deficiencies can also be present in ulcerative colitis (UC) patients, even in those in remission.

Aims

To describe the prevalence of micronutrient deficiencies in patients diagnosed with IBD and to correlate these micronutrient deficiencies with demographic, clinical and disease characteristics.

Methods

A cross-sectional study of patients in the IBD program who were 18 years and older was completed. Clinical characteristics and disease activity indexes were assessed. Body Mass Index (BMI), haematocrit, serum albumin, serum iron profile, serum 25(OH) D, vitamin B12, folate, zinc and copper were measured.

Results

Ninety-one patients with IBD were included: 46 patients (50.5 per cent) with UC and 45 patients (49.5 per cent) with CD. At least one micronutrient deficiency was found in 39.5 per cent of patients, 35.1 per cent had two deficiencies, and 12 per cent had three or more deficiencies. Iron, zinc, copper, and vitamin B12 deficiencies were found in 33 per cent, 22 per cent, 11 per cent and 10 per cent of patients, respectively. No folate deficiencies were found. Low levels of serum 25(OH) D were detected in 76 per cent of patients. The mean BMI was 24.3 (SD 3.4), and the mean serum albumin level was 4.0g/l (SD 0.4).

Conclusion

Micronutrient deficiencies were frequent in our study cohort and did not correlate with macronutrient status. Measurement of macronutrients and micronutrients should become a routine assessment in IBD patients to improve patient care and to avoid negative repercussions on disease activity.

Key Words

Inflammatory bowel disease, Crohn`s disease, ulcerative colitis, micronutrients

What this study adds:

1. What is known about this subject?

Micronutrients have been implicated in many inflammatory responses. Studies have observed an association between Vitamin D levels and the risk of disease activity, hospitalization, and surgery in inflammatory bowel disease.

2. What new information is offered in this study?
This is the first micronutrient study in inflammatory bowel disease patients in South America.

3. What are the implications for research, policy, or practice?
Because of the impact of IBD on many physiological functions and on quality of life, we suggest measuring micronutrient levels as a routine assessment in IBD patients to improve patient care.

Background

Inflammatory bowel diseases (IBD), including Crohn´s disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gut with an unknown etiology.[1] It has been suggested that genetic, environmental and microbiome factors are involved in the pathogenesis of IBD.[2] IBD patients often present with nutritional disorders affecting both macronutrient (protein and calorie) intake[3] and micronutrients such as vitamins, minerals and trace elements.[4] Although classical physical manifestations of nutritional deficiencies are not common, laboratory tests indicate that subclinical deficiencies are common.[3] Protein-energy malnutrition occurs more frequently in patients with active, severe disease.[3,4] However, the optimization of therapeutic strategies with the use of immunomodulators and biological therapy has resulted in a higher percentage of patients who achieve remission and therefore acquire a better nutritional status.[5]

The literature describes that vitamin and mineral deficiencies are more frequent in patients with CD, especially in those with fistulas, stenosis, or a history of surgery such as small bowel resections, than in other IBD patients.[3] However, some studies have shown that micronutrient deficiencies can also be present in patients who have not had surgery, in UC patients, in patients with mild disease or in patients who are in remission.[4,5]

Nutritional deficiencies can be explained by multifactorial causes, including chronic inflammation, reduced food intake due to anorexia or to avoid abdominal pain, enteric loss of nutrients, and the effects of medical therapy, among others.[3]

The assessment of micronutrient deficiency is important because it has been associated with disease activity, a history of hospitalization and surgery and quality of life.[6–12] Therefore, supplementation is an important standard of care.

The aim of this study is to describe the frequency of micronutrient deficiencies in IBD patients included in our program and to correlate any of these micronutrient deficiencies with demographic data, clinical and disease characteristics.

Method

This is a cross-sectional study of adult IBD patients included in the IBD Program at Clínica Las Condes, in Santiago, Chile, located 2314 miles from the equator. The study was performed between spring and summer (October 2014 to March 2015).

Patients 18 years and older with a confirmed diagnosis of UC, CD or unclassified IBD based on clinical, endoscopic and histological criteria and who participated in the IBD program during the months indicated above were included. All patients provided verbal informed consent.

Clinical characterization data, including disease extent in UC and phenotype in CD according to the Montreal Classification,[13] were recorded. Disease activity indexes were determined using the Mayo score for UC[14] and the Harvey-Bradshaw index for CD.[15]

Medical treatment and medication dosages were recorded; clinical determination of Body Mass Index (BMI), haematocrit and serum albumin were measured. Micronutrient measurements, including serum iron profile, serum 25-OHD (vitamin D), vitamin B12, folates, zinc and copper, were performed.

Exclusion criteria included regular intake of vitamin supplements, with the exception of folic acid in patients being treated with sulfasalazine and/or methotrexate.

Any comorbidity able to affect nutritional status (e.g., cancer, infection) was considered as a second exclusion criterion.

Vitamin B12 deficiency was considered as levels <200pg/ml. For iron deficiency, both ferritin levels and transferrin saturation were evaluated. If the patient had a clinically active disease, ferritin levels <100ng/ml were indicative of iron deficiency, while in patients who were clinically inactive, ferritin levels <10ng/ml were considered deficient. In addition, patients with transferrin saturation of <20 per cent were considered as iron deficient. Regarding folic acid, levels <120ng/ml for red cell folate or/and <6ng/ml for serum folic acid were considered deficient. For zinc and copper, levels <70ug/dl and <0.70mg/l were considered

indicative of a deficiency, respectively. Vitamin D (VD) levels ≤20ng/ml were considered as insufficient, and levels between 20 and 30ng/ml were considered as deficient. Anaemia was diagnosed when female patients had haemoglobin levels <12.3g/dl or haematocrit <36 per cent and when male patients had haemoglobin levels ≤13g/dl or haematocrit <40 per cent. Albumin levels <3.5g/dl were considered low.

For statistical descriptions of the categorical variables, relative frequency and percentage were used. Continuous variables were analysed using either median and range or mean and standard deviation, depending on their distribution. For comparative statistical analysis of categorical and continuous variables, chi-square and Mann-Whitney tests were used, respectively. Probability levels below 0.05 were considered statistically significant.

Results

The study included 91 patients with IBD, 46 patients (50.5 per cent) with UC, and 45 patients (49.5 per cent) with CD. Of the 91 patients, 50 (54.9 per cent) were women. The median age was 35 years old (range: 18–72).

General demographic data and IBD clinical characteristics are shown in Table 1. Nutritional parameters, including BMI, haematocrit, haemoglobin and albumin, are shown by diagnosis in Table 2. The relationship between the demographic data and clinical characteristics and the prevalent micronutrients deficiencies are shown in Table 3.

In our study, 39.5 per cent of the patients had at least one micronutrient deficiency, 35.1 per cent had two deficiencies, and 12 per cent had three or more micronutrient deficiencies. Iron, zinc, copper, and vitamin B12 deficiencies were found in 33 per cent, 22 per cent, 11 per cent, and 10 per cent, respectively, and no folate deficiencies were found. The distribution of micronutrient deficiencies by diagnosis is shown in Figure 1. There was no statically significant correlation between deficiencies of these micronutrients (iron, zinc, copper, and vitamin B12) and disease activity.

Low levels of VD were found in 76 per cent of the patients, where 50.5 per cent had levels below ≤20ng/ml (insufficiency) and 25.3 per cent had levels between 20 and 30ng/ml (deficiency). Statically significant lower levels of VD were found in those patients who underwent surgery related to IBD (19.1±12.3 versus 24.1±11.1ng/ml, $p<0.02$).

VD was significantly lower in patients with moderate-severe disease compared with patients in remission or with mild disease activity (Figure 2). There was no correlation between VD levels and a history of hospitalization for IBD. Anaemia was present in 30 per cent of IBD patients; no differences between types of IBD, disease activity or among different treatment medications were observed.

The mean BMI was 24.3 (SD 3.4), and no correlation with micronutrient deficiencies was found.

The serum albumin mean was 4.0g/dl (SD 0.4), and as with the BMI, we did not find any correlation with micronutrients, diagnosis, treatment, or disease activity.

Discussion

Micronutrient deficiencies are frequent in IBD patients, and this study corroborates these findings because at least one micronutrient deficiency was found in 39.5 per cent of patients, two deficiencies in 35.1 per cent of patients, and three or more micronutrient deficiencies in 12 per cent of patients.

VD has been implicated in many immune regulatory and inflammatory responses, playing a role in T regulatory lymphocytes, dendritic cells, monocytes, and the intestinal epithelium by regulating the expression of interleukins and transcription factors and by inhibiting the differentiation of CD4+ T lymphocytes into Th1 and, consequently, their function.[16] Vitamin D and its receptor have been shown to play a role in the regulation of tight junctions in the intestinal barrier, preserving the integrity of the intestinal mucosa and therefore in intestinal homeostasis.[17,18] VD treatment has been shown to down regulate TNF-alpha associated genes in the colonic tissue of animal models, suggesting a beneficial effect on inflammation.[19] A recent study observed that CD patients who were treated with infliximab and had low VD levels were more likely to achieve infliximab-induced clinical remission.[20]

In our study cohort, the most common deficiency was VD: up to half of our patients had levels below 20ng/ml. It is important to consider that our study was performed during the spring and summer; therefore, serum VD levels should be affected positively by sun exposure. However, our patients were instructed to use sunscreen or avoid sun exposure due to the increased risk of skin cancer associated with sun exposure and the use of immunomodulators and anti-TNF medication.[21] How this recommendation affected our patients is unknown, because we did not directly assess how many patients followed this recommendation.

Our results are similar to the results reported by Ulitsky et al.[6] in which approximately 50 per cent and 11 per cent of patients exhibited insufficient levels (<30ng/dl) and severe deficiencies (<10ng/dl) of VD, respectively;[6] however, another study showed that only 22 per cent of patients had normal levels of VD.[22]

Some studies have observed an association between VD levels and the risk of disease activity,[6–8] hospitalization, and surgery.[8] In our cohort, we also found that patients with severe disease and who have had surgery experienced lower levels of VD, whereas no differences in VD levels were observed between those patients who have never been hospitalized and those who have been hospitalized.

In addition, recent evidence shows that sufficient VD levels may be related to a lower cancer risk[23–26] and that low VD serum concentration is associated with a lower quality of life.[6,9]

The ECCO guideline regarding VD suggests that serum 25(OH)D concentrations between 30 and 50ng/ml should be the target, as these levels have benefits such as improving bone health, preventing colorectal cancer, and alleviating depression;[16] suggested daily doses in this publication range between 1,800 and 10,000IU of VD according to different risk factors.[16] However, the Endocrine Society suggests that adults who are vitamin D deficient should be treated with 50,000IU of vitamin D2 or D3 once a week for 8 weeks or 6,000IU of vitamin D2 or D3 daily to achieve levels >30ng/ml, followed by maintenance therapy of 1,500–2,000IU daily.[27]

Previous studies have described anaemia as a common complication in patients diagnosed with IBD, occurring in 6 to 74 per cent of these patients.[28] Different aetiologies can explain iron deficiency; malabsorption, impaired dietary intake, disease activity, chronic gastrointestinal bleeding, and drug side effects, among others, should be considered.[4,29] In our cohort, 33 per cent of the patients presented with iron deficiency and 30 per cent with anaemia. Our findings are similar to those reported by Vagianos et al.,[29] in which 39 per cent of their IBD subjects had iron deficiency and 40 per cent had anaemia. However, a study published by Lochs[30] reported that anaemia could be as frequent as 60–80 per cent in patients with CD and 66 per cent in patients with UC. Similarly to our study, Vagianos et al.[29] did not find any differences between UC and CD patients.

Iron deficiency and anaemia are relevant conditions that must be addressed as they have been related to increased health-care costs, including an increased risk of hospitalization and surgery.[31] Additionally, some studies have suggested that these conditions play a role in the patient's quality of life.[10–12]

To correctly diagnose iron deficiency, an important distinction must be made between patients in remission and those who have an active disease. The ECCO guidelines suggest that for patients in remission, ferritin <30ng/ml is an appropriate criterion, whereas in patients who have an active disease, serum ferritin <100ng/ml should be considered.[32]

The ECCO guidelines suggest that for those patients who have a clinically active disease, intravenous iron should be considered as first line of treatment. Intravenous iron should also be considered for patients who need erythropoiesis-stimulating agents. However, oral iron may be used in patients with mild anaemia who have a clinically inactive disease, with maximum doses of 100 mg of elemental iron per day.[32]

We did not find any folate deficiencies. However, one retrospective study found that 28.8 per cent of patients with CD and 8.6 per cent of patients with UC exhibited a level of serum folate <3ng/ml compared with 3.7 per cent of control individuals.[33] Another study of patients with CD in remission reported similar frequencies.[34] We believe that this difference may be due to food fortification or folate supplementation. In Chile, fortification of wheat flour was established as mandatory in January 2000 by the Health Ministry in doses of 2.0–2.4mg of folic acid per kilogram.[35] However, only patients under treatment with methotrexate (3 patients) and/or sulfasalazine (5 patients) received folate supplementation at doses of 5mg for those using methotrexate and 1mg for those using sulfasalazine.

It is well known that the absorption of vitamin B12 occurs in the terminal ileum. Therefore, patients with CD are at increased risk of vitamin B12 deficiency because 30 per cent of the patients present with ileal involvement only and another 30 per cent present with ileocolonic involvement.[4] In addition, many of these patients require surgical resection of the ileum at some point during their disease, increasing their risk.[4] In our study, 10 per cent of the IBD cohort had deficient levels of vitamin B12. If analysed separately, approximately 13 per cent of patients with CD and 7 per cent of patients with UC had deficient levels of

vitamin B12. Several studies have reported a vitamin B12 deficiency prevalence of 11–22 per cent in patients with CD.[4,29] Vitamin B12 deficiency in patients with UC is similar to that of general population.[33] Yakut et al.[33] reported vitamin B12 deficiency in 22.2 per cent of their patients with CD and in 7.5 per cent of their patients with UC, similar to that found in the control group. This last percentage is similar to the vitamin B12 deficiency results found in our study.

Copper deficiency was present in 11 per cent of our patients. Our results disagree with the results of Fillipi et al.,[5] which showed that 84 per cent of 54 patients with CD in clinical remission had lower than reference levels of plasma copper concentrations. In patients with UC, copper levels appear to be similar or even superior to the control population.[36,37] In another study published by Ojauwo et al.[38] of IBD paediatric patients, CD patients had higher levels of copper than those with UC or control individuals. This finding shows that copper deficiency results are contradictory. Different diagnostic criteria for dietary intake may explain these differences.

Zinc deficiency has also been previously described in patients with IBD. In our study, zinc deficiency was the third most common micronutrient deficiency, where 22 per cent of our patients had this micronutrient deficiency. In the study published by Vagianos et al.,[29] zinc deficiency reached up to 20.5 per cent in patients with CD and 4.8 per cent in patients with UC, which was different from our study in which patients with UC and CD had zinc deficiencies in the same proportion. Nevertheless, it is important to consider that clinical disease activity was present in 50 per cent of our patients with UC, and Vagianos et al.[29] did not find a significant difference between active IBD and remission. Other studies do report decreased plasma zinc levels only in patients with severe CD,[37] whereas most of our patients were in remission (91 per cent). It should be considered that, regardless of the data obtained, zinc deficiency assessment is complex because very little zinc is present in serum[4] and this assay probably overestimates the deficiency.[36] An adequate zinc supply is probably of great importance for patients with IBD because zinc promotes tissue repair and healing.[37] Zinc has further been related with skin care,[39] and low levels of serum zinc have been related with hair loss.[40]

Various mechanisms contribute to malnutrition in patients with IBD, including decreased dietary intake, malabsorption and hypercatabolism, among others. Malnutrition in IBD patients is common; it has been previously described that up to 75 per cent of the patients who have an active disease experience weight loss and hypoalbuminemia.[30] However, Filippi et al.[5] studied 54 CD patients in remission with CDAI values <150 and compared these patients with 25 healthy control individuals. They reported that these patients have significantly lower body fat mass than control individuals and that nearly a third of the patients were at risk for malnutrition.

In our cohort, malnutrition was assessed using BMI and albumin as markers; however, we did not find alterations in these parameters or a relationship with micronutrient deficiency. Of note is that nearly 30 per cent of our IBD patients presented with clinical disease activity.

Our study has several limitations. One limitation is related to the fact we did not measure other micronutrients such as vitamin A, vitamin K, and selenium, among others, that could also be deficient in patients with IBD. The majority of our patients were in clinical remission; however, not all patients were assessed endoscopically or with faecal calprotectin. Therefore, we cannot be sure that subclinical inflammation was not playing a role in these patients. In addition, we did not have a healthy population control group to compare our results with, and we did not perform a dietary intake questionnaire. Finally, patients were selected consecutively until the sample was completed (91 patients), which may imply selection bias.

Conclusion

In conclusion, micronutrient deficiencies in our study were frequent, the most important being VD, iron, and zinc. Regarding VD, patients with moderate-severe disease showed significantly lower levels than patients in remission or with mild disease. Neither BMI nor albumin levels were associated with micronutrient deficiencies. Finally, because of the impact of micronutrients on many physiological functions and on quality of life, evaluations by a nutritionist should become part of the routine for patients in an IBD program to improve patient care. Further prospective studies and larger studies assessing micronutrient supplementation in IBD patients will clarify the impact of micronutrients in these patients.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

The study was approved by the Institutional Ethics Committee (M022015).

Figures and Tables

Table 1: Demographic and clinical characteristics

Variable	Ulcerative Colitis n=46	Crohn's Disease n=45	Total n=91
Gender Female/Male	26/20	24/21	50/41
Age (median; range)	33 (18–70)	38 (19–72)	35 (18–72)
Current age at diagnosis (median; range)	25.5 (16–58)	31 (13–66)	28 (13–66)
Years of disease (median; range)	4 (0–24)	6 (0–38)	4 (0–38)
Extraintestinal Manifestations (%)	19 (41)	28 (62.2)	47 (51.6)
Smoking habit (%)	6 (13.0)	4 (8.9)	10 (11.0)
Clinical activity (%)	23 (50.0)	4 (8.9)	27 (29.7)
Hospitalization due to IBD (%)	16 (34.8)	26 (57.8)	42 (46.2)
Surgery due to IBD (%)	1 (2.2)	16 (35.6)	17 (18.7)
Current Treatment (%)			
5-ASA	31 (67.4)	3 (6.7)	34 (37.4)
Immunosuppressors	10 (21.7)	16 (35.6)	26 (28.6)
Biological therapy	5 (10.9)	18 (40.0)	23 (25.3)
Steroids	3 (6.5)	6 (13.3)	9 (9.9)
Other medication	0	4 (8.9)	4 (4.4)

Table 2: Nutritional parameters; BMI, haematocrit, haemoglobin and albumin by diagnosis

Variable	Ulcerative Colitis n=46	Crohn's Disease n=45	Total n=91
Haematocrit (%) (mean; SD)	39.6 (3.4)	39.3 (4.4)	39.4 (4.0)
Haemoglobin (gr/dL) (mean; SD)	13.1 (1.3)	13.0 (1.9)	13.1 (1.6)
Albumin (gr/dL) (mean; SD)	4.1 (0.3)	4.0 (0.3)	4.0 (0.4)
BMI (mean; SD)	24.3 (3.5)	24.2 (3.4)	24.3 (3.5)

SD: Standard Deviation

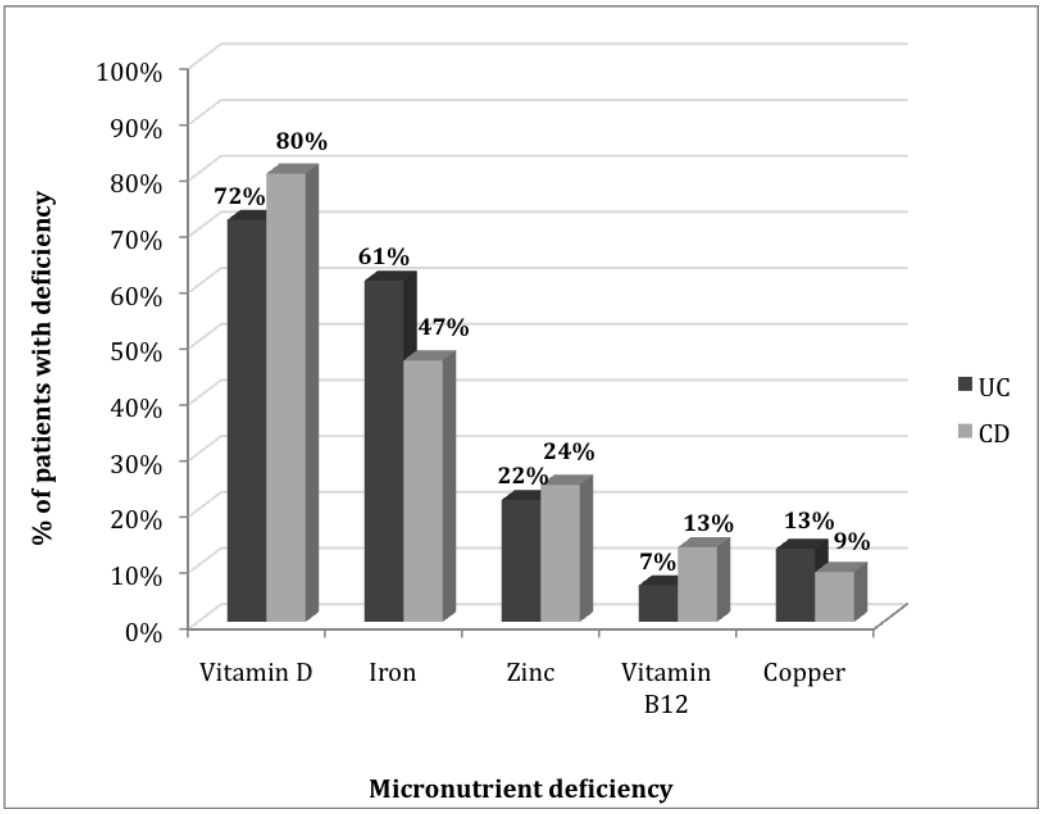
BMI: Body Mass Index

Table 3: Demographic and clinical characteristics in relation to prevalent micronutrient deficiency (Vitamin D, Iron and Zinc) in patients with IBD

Variable (n=91)	Vitamin D n=69 (%)	Iron n=30 (%)	Zinc n=20 (%)
Female/Male	35/34	16/14	15/5
Current age (median; range)	34 (18–70)	30 (19–54)	39 (21–59)
UC patients (%)	33 (47.8)	15 (50)	10 (50)
Age at diagnosis (median; range)	28 (13–62)	25 (13–47)	30 (17–58)
Extraintestinal manifestations (%)	38 (55.1)	14 (46.7)	10 (50)
Smoking habit (%)	6 (8.7)	1 (3.3)	2 (10)
BMI (mean; SD)	24.3 (3.7)	23.8 (3.3)	23.8 (2.1)
Clinical activity (%)	22 (31.9)	12 (40)	9 (45)
Hospitalization due to IBD (%)	35 (50.7)	15 (50)	8 (40)
Surgery due to IBD (%)	22 (31.9)	11 (36.7)	5 (25)
Current Treatment (%)			
5-ASA	24 (34.8)	10 (33.3)	9 (45)
Immunosuppressors	21 (30.4)	8 (26.7)	3 (15)
Biological therapy	18 (26.1)	10 (33.3)	3 (15)
Steroids	8 (11.6)	3 (10)	2 (10)

SD: Standard Deviation
BMI: Body Mass Index

Figure 1: Distribution of micronutrients deficiency by diagnosis



UC=Ulcerative colitis, CD=Crohn´s disease

Figure 2: Mean vitamin D levels analyzed by disease activity