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Correspondence

Gitelman syndrome triggered by proton-pump inhibitor use

Dear Editor,

A 33-years-old male was admitted in July 2017 to our care following a 2-month history of heartburn and dry cough. He underwent upper GI endoscopy, which detected only the presence of hiatal hernia. A daily therapy with 30 mg lansoprazole and sodium alginate was therefore started, with quick resolution of symptoms. Around 20 days later, the patient suffered from diarrhea (10 bowel movements/day), deep asthenia, nocturia, and rapid weight loss of 6 kg.

He was admitted to the Emergency Department, and diagnosed with severe hypokalemia (1.6 mEq/l, n.v. 3.7–4.8 mEq/l) and hypomagnesaemia (1.0 mg/dl, n.v. 1.9–2.5 mg/dl), and treated with intravenous supplement of potassium and magnesium. In the following two months he showed persistent hypokalemia and hypomagnesaemia, and was therefore admitted to the Nephrology Department. During his hospital stay, no significant instrumental or laboratory alteration was found except for persistent hypokalemia and hypomagnesaemia. On suspicion of salt-losing tubulopathy, research of SLC12A3 gene was performed, and biallelic inactivating mutations in this gene were found. Diagnosis of Gitelman syndrome (GS) was therefore posed, and the patient was discharged with oral supplement of potassium and magnesium, and recommendation to avoid proton-pump inhibitors (PPI).

At the last examination (November 2018), the patient was doing well under treatment with oral supplementation of potassium and magnesium and with mucosal esophageal cytoprotector (EsoxxOne^{TM}).

GS is a salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesaemia and hypocalciuria [1]. GS is believed to be the most frequent inherited tubulopathy with a prevalence of 1–10 per 40,000 people [2]. The disease is caused by biallelic inactivating mutations in the SLC12A3 gene encoding the thiazide-sensitive sodiumchloride cotransporter expressed in the apical membrane of cells lining the distal convoluted tubule [3]. To date, >350 mutations scattered throughout SLC12A3 have been identified in GS patients [4]. The majority of patients are compound heterozygous for SLC12A3 mutations, but a significant number of GS patients are found to carry only a single SLC12A3 mutation.

This is the first reported case of GS triggered by PPI, and why this occured is unknown. We can hypothesize that PPI could inhibit not only gastric ion pump H/K-ATPase but also renal ion pump Na/K-ATPase, which are similar. This pathogenetic mechanism, that could also explain some cases of acute kidney injury under treatment with PPI [5] in some genetically predisposed subjects, could trigger GS. This case teaches us therefore that PPI use could be a trigger factor for kidney diseases in genetically predisposed subjects.

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Looking for women in hepatology: Sex authorship differences in clinical practice guidelines and position statements

First female authorship is slowly increasing in scientific publications, but it is still inconsistent and seems to vary across different medical disciplines and specialties [1–4]. When looking at the authorship in gastroenterology and/or hepatology original papers, it was estimated that the proportion of first female authors increased from 9% in 1992 to 29% in 2012, whereas for last authors, the proportion of female authors increased from 5% in 1992 to 14% in 2012 [5]. However, clinical practice guidelines or position statements may potentially adopt different authorship rules when compared to original articles [3,4]. To date, information regarding the representation of first, second and last female authors in hepatological clinical practice guidelines and position statements published in the last five years is scarce. We searched *PubMed* for clinical practice guidelines or position statements on liver disease management/diagnosis/liver imaging, published in English from 1st January 2014 to 31st December 2018. Based on this selection, we found 165 clinical practice guidelines and/or position statements. Subsequently, we excluded from the analysis those in which the authorship list was not clearly reported or those with only panel members (n = 32, 19.4%). As shown in Table 1, of the 133 included documents, 44 were published in 2018, 30 in 2017, 23 in

2016, 19 in 2015 and 17 in 2014. With regard to geographic area, we found 44 European clinical practice guidelines or position statements, 34 from North America, 10 from Central/South America, 30 from Asian countries, whereas 15 were International. With respect to hepatological topics, we found 8 clinical practice guidelines or position statements on cirrhosis, 1 on alcoholic liver disease, 10 on liver transplantation, 11 on non-alcoholic fatty liver disease, 21 on liver cancer, 35 on viral hepatitis, 12 on cholestatic liver disease and 35 on other issues (such as autoimmune hepatitis, diagnostic methods and/or procedures, acute liver injury, hepatotoxic drugs, and management of liver disease in pediatric patients).

Overall, the percentage of hepatological clinical practice guidelines or position statements with first female authors was 18.8% (95% confidence interval [CI] 12.5%–26.5%), the percentage of those with second female authors was 20.5% (95% CI 13.8%–28.5%) and, finally, the percentage of those with last female authors was 14.6% (95% CI 9.0%–22.9%). As reported in Table 1, after stratification by publication year, the percentage of clinical practice guidelines or position statements with first female authors was 18.2% in 2018, 26.7% in 2017, 17.4% in 2016, 15.7% in 2015 and 11.8% in 2014 ($p = 0.798$ for trend, as assessed by Fischer's exact test). Furthermore, after stratification by geographic area, the percentage of clinical practice guidelines or position statements with first female authors was 15.9% in Europe, 29.4% in North America, 30.0% in Central/South America, 3.3% in Asia and 26.6% in International publications ($p = 0.064$ for trend). Interestingly, the percentage of high-impact publications with first female authors was slightly higher when compared to the percentage of mild/low-impact publications with first female authors (25.0% *vs.* 17.7%, respectively, $p = 0.310$) (Table 1). The aforementioned trends in the representation of female authors were substantially similar for second authors. Conversely, the percentage of clinical practice guidelines or position statements with last female authors was very low (14.6%, 95% CI 9.0–22.9%), even after stratification by publication year, country, hepatological topic or high-impact journals (Table 1).

At present, the representation of first, second and last female authors on hepatological clinical practice guidelines or position statements is low and, probably, unacceptable. Importantly, our study also suggests that the representation of female authors has not significantly improved over the last five years as well as among different countries (although Asian countries have the lowest representation of female authors). In addition, albeit not significant, high-impact journals seem to acknowledge better the sex matters in science publications, as the representation of female authors in these journals is 25%.

The present data seem not to be completely justified by the current estimates of the sex composition of physicians. As described in a recent report, the share of female physicians has been increasing for the last 15 years in OECD (Office of Economic Cooperation and Development) countries, spanning from 29% in 1990 to 46% in 2015 [6]. In addition, when the analysis was stratified by countries, in 2015 the lowest percentage of female physicians was observed in Japan and in Korea (approximately 20%), the intermediate percentage in Norway and United Kingdom (nearly 45%), whereas the highest proportion of female physicians was seen in Latvia and Estonia (nearly 75%) [6]. In Italy the percentage of female physicians was 40%. Therefore, a possible explanation of our findings is that, to date, the number of women in academic medicine is still relatively small. However, given that accumulating studies [1,2,5] show that the overall proportion of female first authors of original research is slowly increasing, we believe that multiple and specific impediments to female authorship on the clinical practice guidelines or position statements still exist [3,4]. In this context, it is important to remember that authorships of clinical practice guidelines or position statements (especially as first or last authors) are established in many cases by an informal invitation [3,4]. Undoubtedly, this way contributes to create a sex bias in authorship list [3,4]. However, as reported in Table 1, with regard to the relatively novel topics (*e.g.*, non-alcoholic fatty liver disease), the gap in sex authorship might be less evident, probably due to the presence of new

Table 1
Main characteristics of 133 hepatological clinical practice guidelines or position statements (with available authorship list) published between January 2014, and December 2018.

	Percentages of manuscripts with 1st female author	Percentage of manuscripts with 2nd female author	Percentage of manuscripts with last female author
Overall (from 2014 to 2018), n = 133	18.8% (12.5%–26.5%)	20.5% (13.8%–28.5%)	14.6% (9.0%–22.9%)
By publication year			
2018, n = 44	18.2% (8.2%–32.7%)	21.4% (10.3%–36.8%)	16.3% (6.8%–30.7%)
2017, n = 30	26.7% (12.3%–45.9%)	16.7% (5.6%–34.7%)	10.0% (2.1%–26.5%)
2016, n = 23	17.4% (4.9%–38.8%)	22.7% (7.8%–45.4%)	27.3% (10.7%–50.2%)
2015, n = 19	15.7% (3.4%–39.6%)	11.7% (7.2%–52.4%)	0%
2014, n = 17	11.8% (1.4%–36.4%)	25.0% (7.3%–52.4%)	0%
By country			
Europe, n = 44	15.9% (6.6%–30.1%)	23.8% (12.1%–39.4%)	21.4% (10.3%–36.8%)
North America, n = 34	29.4% (15.1%–47.5%)	28.1% (13.7%–46.7%)	21.2% (8.9%–38.9%)
South America, n = 10	30.0% (6.7%–65.2%)	44.4% (13.7–78.8%)	10.0% (2.5%–44.5%)
Asia, n = 30	3.3% (0.1%–17.2%)	3.4% (0.1%–17.7%)	0%
International, n = 15	26.6% (7.8%–55.1%)	7.1% (0.1%–33.8%)	6.7% (1.7%–31.9%)
By hepatological topic			
Cirrhosis, n = 8	0%	0%	12.2% (0.3%–52.6%)
Alcoholic liver disease, n = 1	100%	0%	0%
Liver transplantation, n = 10	0%	15.5% (12.1%–73.7%)	30.0% (6.7%–65.2%)
Nonalcoholic fatty liver disease, n = 11	27.3% (6.0%–60.9%)	18.2% (2.3%–51.7%)	27.3% (6.0%–60.9%)
Liver cancer, n = 21	19.0% (5.4%–41.9%)	21.1% (6.1%–45.6%)	9.5% (1.2%–30.4%)
Viral hepatitis, n = 35	22.8% (10.4%–40.1%)	27.3% (13.3%–45.5%)	12.1% (3.4%–28.2%)
Intrahepatic cholestatic liver disease, n = 12	8.3% (1.0%–38.5%)	8.0 (1.0%–38.4%)	0%
Other*, n = 35	17.1% (6.6%–33.6%)	14.7% (4.9%–31.1%)	14.3% (4.0%–32.7%)
By impact factor (IF) of journals			
IF < 10, n = 113	17.7% (11.2%–26.0%)	19.6% (12.6%–28.4%)	12.7% (7.1%–20.4%)
IF ≥ 10, n = 20	25.0% (8.7%–49.1%)	25.0% (8.6%–49.1%)	25.0% (8.6%–49.1%)

Data are percentages and 95% confidence intervals. We searched for clinical practice guidelines or position statements in the hepatological field from 1st January 2014 to 31st December 2018.
Note: The term "Other" includes hepatological clinical practice guidelines or position statements regarding liver autoimmune diseases, diagnostic methods and/or procedures, acute liver injury, hepatotoxic drugs, and management of liver disease in pediatrics.

principal investigators, that are in many cases women. Another possible important explanation of our findings is that women are under-represented in leadership scientific positions and that, presumably, they spend more time doing experimentation rather than being in charge of research design [7,8]. For instance, it was estimated that in the US academic medicine only 21% of full professors and only 15% of division chairs were women in 2016 [7]. Such situation may be incidentally evident by the sparse female representation among the panel members of several guidelines (data not shown). This discrepancy might be addressed by actuating different plans at various levels [8].

The present study has some limitations that should be mentioned. Firstly, the included eligible clinical practice guidelines or position statements were not necessarily the highest impact guidelines in hepatology. Secondly, the chosen time frame may be relatively short as well as the number of clinical practice guidelines or position statements found. Therefore, additional studies are needed to keep monitored the percentage of female authors in clinical guidelines in the hepatological filed.

In conclusion, our observations offer new evidence supporting that additional work and energy should be done to empower the representation of female authors in the (hepatological) clinical practice guidelines or position statements. Authorship in science should follow a rigorous and evidence-based procedure including important tools, such as competitive merit-based invitations and illustration of the methods used for author selection in detail [3,4].

Conflict of interest

None declared.

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