Lichen sclerosus and data science: using an age, site and gender specific disease to define correlation and causality

Colleen M. Reisz1* and Rima Chakraborty2

Abstract

Introduction: Lichen sclerosus (LS) is a site, gender and age specific disease that affects the vulvar region of menopausal women. The menopausal transition is characterized by physiologic changes that impact basic processes, such as weight, sleep and drug clearance. Our current pharmacopeia includes drugs that target basic metabolic processes such as cholesterol, sex steroidogenesis and the gut microbiome. Introduction of drugs engages complex pathways that govern bile salt metabolism and the provision of sex steroid substrate. We hypothesized that lichen sclerosus in the vulva may represent an off target effect of pharmaceutical alteration of sex steroid substrate in some women. We compared biometric and drug data in women with lichen sclerosus with an age matched control group without disease.

Methods: 43 women with lichen sclerosus underwent chart review to determine BMI, Fitzpatrick level, and pharmaceutical burden. This data was compared to 106 randomly selected age matched controls. Logistic regression was adjusted for age, BMI and Fitzpatrick phototyping. The statistical software was R version 3.0.1. Cases were defined as those with diagnosis claims for lichen sclerosus and were obtained from electronic records in a single private practice.

Results: Proton pump inhibitors were noted in 12/43 women (28%) cases and 15/106 (14%) controls: p=0.048, (confidence interval CI=-0.01 to 0.287), adjusted p value 0.33; Hormone therapy 5/43 cases (12%), 26/106 (25%) controls: p value 0.078, (CI=-0.25 to 0.002), adjusted p value 0.02. Antihypertensive medications 17/43 (40%) cases, 29/106 (27%) controls, p value 0.14, (CI=-0.047 to 0.29), adjusted p value 0.8. Statins 16/43 cases (37%), 28/106 controls (26%); p=0.19, (CI=-0.05 to 0.27), adjusted p value 0.89. Average age among cases was 63, average age in the control group was 61. Average BMI was 27.5 in the case group, 23.6 in the control group. Logistic regression analysis was adjusted for age, BMI and Fitzpatrick phototyping.

Conclusions: Borderline statistical significance was seen with proton pump inhibitors and hormone replacement therapy (HRT). The significance seen with proton pump inhibitors went away with adjustment for Fitzpatrick, age and BMI. The significance seen with HRT withstood adjustment, with the control group featuring more women on hormone replacement therapy than the case group.

Keywords: Fitzpatrick phototyping, lichen sclerosus, polypharmacy, drug metabolism

Case presentation

Menopause is characterized by physiologic changes that alter sleep, salt and water metabolism, insulin resistance and drug metabolism [1,2]. Drug metabolism is a complex, overlapping and competitive process that utilizes key components of cholesterol and bile metabolism [3-7]. The transport mechanisms for endogenous steroids also function in the delivery and elimination of HMG-CoA reductase inhibitors (statins), angiotensin receptor II antagonists and cardiac glycosides [8,9]. We hypothesized that lichen sclerosus may relate to competition in steroid and drug transport mechanisms at a time of physiologic change. 7 of the 43 women in this case series suspected that a recent drug change caused the problem; 3 with change in hormones, 3 with change in hormones, 3 with introduction of a beta blocker and 1 with introduction of
thyroid replacement. This number is probably low, as approxi-
mately half of these patients were seen years after their initial
diagnosis and could not remember the sequence of events.
Many underwent months and years of treatment for other
vulvar conditions, such as chronic yeast infections, before the
characteristic features of lichen sclerosus emerged (Figures 1-4).
86% of the patients were on at least one drug, with 58%
on more than one drug. Hypertension was the most treated
comorbid state with over half of this group on a beta blocker.
37% were on HMGCoA reductase inhibitors and 33% were on
a drug(s) that targets the gut. Three women were extreme
athletes with chronic amenorrhea. 79% were very fair, Fitzpat-
rick phototyping classification 1 or 2. 60% had a BMI>25.
All patients were counseled about the effect of diet and
exercise on the need for prescription drugs. Patients with

Figure 1. Drug eruption: 89 year old with polypharmacy and
two year history of painful dermatitis superimposed on lichen
sclerosus.

Figure 2. Drug eruption: 89 year old 4 weeks after
cardiologist guided cessation of amiodarone, amlodipine
and omeprazole.

Figure 3. Lichen Sclerosus: 70 year old obese
female presenting with lichen sclerosus after
weaning Premarin.

Figure 4. Lichen Sclerosus: 70 year old after
applying pioglitazone in ointment.

high BMI and those with a history of large for gestational
age babies (LGA) were offered low dose metformin. Patients
with severe disease resistant to clobetasol were given topical
pioglitazone 30mg/loz of petrolatum [10] (Tables 1 and 2).
were all found more frequently in the case group, they did not meet statistical significance. After logistic regression analysis for age, BMI and Fitzpatrick phototyping, only hormone replacement therapy, seen more frequently in the control group, maintained statistical significance.

We were limited by the inability to accurately note the onset of the disease in some women. The difficulties noting onset complicate the definition of a temporal relationship between drug introduction and onset of disease. It may be that multiple requests for treatment for yeast infections may be a curatable measurement for the onset of lichen sclerosus. In some women, lichen sclerosus is asymptomatic and only recognized on physical exam.

Concurrent changes in medical care could impact the frequency of this disease. Polypharmacy accelerates around the menopausal transition. The utilization of hormone replacement therapy is more controversial. Older, sicker and heavier women often bypass well woman exams and forego discussions on hormone replacement therapy. Off target effects of statins and proton pump inhibitors, introduced in 1987 and 1990, respectively, on diabetes risk and the gut microbiome, are more recent findings.

The work-up of patients presenting with lichen sclerosus should include a complete drug history. Advances in pharmacokinetics pertaining to gender may improve prescribing habits at menopause. Treatments offered to women with lichen sclerosus may include reduction of comorbid states through non pharmaceutical methods, reduction of specific drugs and identification of harmful drug/drug combinations at menopause.

## Competing interests
The authors declare that they have no competing interests.

## Authors’ contributions

| Authors’ contributions         | CMR | RC |
|-------------------------------|-----|----|
| Research concept and design   | ✓   | -- |
| Collection and/or assembly of data | ✓   | ✓  |
| Data analysis and interpretation | ✓   | ✓  |
| Writing the article           | ✓   | ✓  |
| Critical revision of the article | ✓   | -- |
| Final approval of article     | ✓   | ✓  |
| Statistical analysis          | ✓   | -- |

## Publication history
Editors: Konstantinos Dafopoulos, University of Thessalia, Greece. Erich Cosmi, University of Padua, Italy.
Received: 11-Nov-2014 Final Revised: 09-Apr-2015
Accepted: 21-Apr-2015 Published: 30-Apr-2015

## References
1. Murphy R. Lichen sclerosus. Dermatol Clin. 2010; 28:707-15. | Article | PubMed
2. Polotsky HN and Polotsky AJ. Metabolic implications of menopause.
3. Xu C, Li CY and Kong AN. Induction of phase I, II and III drug metabolism/transport by xenobiotics. Arch Pharm Res. 2005; 28:249-68. | Article | PubMed

4. Timsit Timsit YE and Negishi M. CAR and PXR: the xenobiotic-sensing receptors. Steroids. 2007; 72:231-46. | Article | PubMed Abstract | PubMed Full Text

5. de Aguiar Vallim TQ, Tarling EJ and Edwards PA. Pleiotropic roles of bile acids in metabolism. Cell Metab. 2013; 17:657-69. | Article | PubMed Abstract | PubMed Full Text

6. Hernandez JP, Mota LC and Baldwin WS. Activation of CAR and PXR by Dietary, Environmental and Occupational Chemicals Alters Drug Metabolism, Intermediary Metabolism, and Cell Proliferation. Curr Pharmacogenomics Person Med. 2009; 7:81-105. | Article | PubMed Abstract | PubMed Full Text

7. Marino M, di Masi A, Trezza V, Pallottini V, Polticelli F and Ascenzi P. Xenosensors CAR and PXR at work: impact on statin metabolism. Curr Drug Metab. 2011; 12:300-11. | Article | PubMed

8. Klaassen CD and Aleksunes LM. Xenobiotic, bile acid, and cholesterol transporters: function and regulation. Pharmacol Rev. 2010; 62:1-96. | Article | PubMed Abstract | PubMed Full Text

9. Bonf P and Elferink RO. Mammalian ABC transporters in health and disease. Annu Rev Biochem. 2002; 71:537-92. | Article | PubMed

10. Yki-Jarvinen H. Thiazolidinediones. N Engl J Med. 2004; 351:1106-18. | Article | PubMed

11. Li T and Chiang YJ. Bile acid signaling in metabolic disease and drug therapy. Pharmacol Rev. 2014; 66:948-83. | Article | PubMed

12. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005; 352:2211-21. | Article | PubMed

13. Calderon-Larranaga A, Gimeno-Feliu LA, Gonzalez-Rubio F, Poblador-Plou B, Liria-San Jose M, Abad-Diez JM, Poncel-Falco A and Prados-Torres A. Polypharmacy patterns: unravelling systematic associations between prescribed medications. PLoS One. 2013; 8:e84967. | Article | PubMed Abstract | PubMed Full Text

14. Vesper BJ, Jawdi A, Altman KW, Haines GK, 3rd, Tao L and Radosevich JA. The effect of proton pump inhibitors on the human microbiota. Curr Drug Metab. 2009; 10:84-9. | Article | PubMed

15. Blume H, Donath F, Warnke A and Schug BS. Pharmacokinetic drug interaction profiles of proton pump inhibitors. Drug Saf. 2006; 29:769-84. | Article | PubMed

16. Zhou YT, Yu LS, Zeng S, Huang YW, Xu HM and Zhou Q. Pharmacokinetic drug-drug interactions between 1,4-dihydropyridine calcium channel blockers and statins: factors determining interaction strength and relevant clinical risk management. Ther Clin Risk Manag. 2014; 10:17-26. | Article | PubMed Abstract | PubMed Full Text

Citation:
Reisz CM and Chakraborty R. Lichen sclerosus and data science: using an age, site and gender specific disease to define correlation and causality. Res J of Womens Health. 2015; 2:1. http://dx.doi.org/10.7243/2054-9865-2-1