International Urogynecology Journal (2019) 30:363–370
https://doi.org/10.1007/s00192-018-3771-7

REVIEW ARTICLE

The potential role of folate metabolism in interstitial cystitis

Carolyn D. Keagy[1]

Received: 25 May 2018 / Accepted: 14 September 2018 / Published online: 6 October 2018

Abstract

The topic of interstitial cystitis (IC), also known as painful bladder syndrome (PBS), and folate/one carbon metabolism has previously been unaddressed in research. This narrative review highlights a potential connection for those with mast cell-related IC and histamine-mediated pain that is explored through four conceptual sections. The first section focuses on the nature of mast cell involvement and histamine-mediated pain in some interstitial cystitis patients. The second section reviews the literature on folate status in wider allergic conditions. The third section addresses the role of folate and methylation in general in histamine excretion. Finally, folate metabolism and vascular function are addressed because of the vascular abnormalities present in some IC bladders.

Keywords Interstitial cystitis · Painful bladder syndrome · Folate · Histamine · Allergy · Vascular endothelial growth factor

Background

Interstitial cystitis (IC), also known as painful bladder syndrome (PBS), is a bladder condition characterized by pain, urgency, and frequency of urination in the presence of sterile urine culture. This disease is heterogeneous with treatment options, including Botox injections of the pelvic floor muscles, pelvic floor physical therapy, antihistamines, mast cell stabilizers, and heparin. Thus, IC populations likely have multiple disease etiologies wherein the predominant theories are myofascial pelvic floor dysfunction, reduction in the glycosaminoglycan (GAG) layer of the bladder, and/or mast cell activity with histamine-mediated pain [1–4]. This paper review addresses the population that positively responds to antihistamine and mast cell stabilizer treatment, and should not be generalized to the full population of PBS patients that may have symptoms with other causes. IC has documented associations with allergies, irritable bowel syndrome, skin sensitivities, and subsequent implications in stroke and cardiovascular disease [5–7].

Although the predominant manifestation is in the bladder, it is theorized that it might be a systemic condition [8]. Others have gone so far as to put forth the idea that IC is a manifestation of a wider allergic disorder owing to its successful treatment with anti-Immunoglobulin E (IgE) medications [9]. Research has found the IC bladders with ulcers have increased levels of IgE on biopsy [10]. Moreover, the key cell in allergic histamine-mediated responses, mast cells, have been found to play an important role in the pathophysiology of IC bladders [11–19]. This different bladder histology of IC bladders, in those with Hunner's lesions and those without, may present as different clinical subtypes based on the proliferation of mast cells within different layers of the bladder wall and muscle [20]. A subset of IC patients present with an increase in activated mast cells in their bladders, and possibly more generally as mast cell activation syndrome (MCAS) [21].

Other research on MCAS, a systemic allergic disease, has highlighted IC as a possible presentation to be considered in the differential diagnosis because of the common role of mast cells in both IC and MCAS [22, 23]. Additionally, there is evidence that the pain present in IC patients is histamine mediated—a dominant chemical mediator released during mast cell degranulation [4]. The key to almost all allergic responses is the mast cell and it is the key feature that links IC with wider allergic states [24]. Thus, there is sufficient research to theorize that in a subset of IC patients, the nature of their disease is similar to allergy, or an atopic disorder in the bladder with systemic implications, rather than an isolated pathological condition of the bladder. This view of IC being a form of allergic disease then broadens the issue to larger metabolic

✉ Carolyn D. Keagy
Carolyn.Keagy@gmail.com

[1] Kaiser Permanente, 1795 Second Street, Berkeley, CA 94710, USA

systems that may be implicated in allergy and ultimately IC. One metabolic system whose allergic status for which there is a significant amount of research, yet has never been applied to IC, is folate and methylation via its role in one carbon metabolism. The following is a review of how this previous research is related to folate status, and various allergic states or relevant disorders, and how it may relate to the plight of IC patients. Additionally, owing to the vascular involvement found in IC, folate is also reviewed with regard to histamine and homocysteine levels, which have implications for cardiovascular disease. These links, and the role of folate and methylation in IC, have been previously unexplored by the scientific community; therefore, this article aims to highlight the gap in the research so that fruitful research can begin in this area.

Allergy and folate status in gestational and nongestational studies

Allergic disorders have been widely examined for links to aberrant folate status with conflicting results (Table 1). In an effort at the transparency of both negative and positive findings, the below reviews significant results for both sides of an inconclusive yet suggestive field on the relationship of allergic states with folate metabolism. Although some may only be familiar with the relationship between folate and neural tube defects, explicit investigations of the role of folate in allergic states in situ started in 2006, wherein impaired folate correlated positively with atopic states [25]. The question of folate and atopic states, namely asthma, was extended to gestational states in 2009 [26, 27]. Since then, there have been many studies with discrepant results. The discrepancies in results are likely methodological owing to the small sample sizes, analytical measurement issues of serum folate vs red blood cell folate (RBC folate or intracellular folate), estimation of dietary folate, folate supplementation, and genotypic variation of folate-related genes, namely C667T on the methylenetetrahydrofolate reductase (MTHFR) gene [28]. This gene codes for an enzyme that catalyzes the reaction to converting food folate or folic acid, by way of 5,10-methylenetetrahydrofolate, to the biologically active 5-methyltetrahydrofolate. This form of folate, with the assistance of b12, is then involved in the conversion of homocysteine to methionine. Finally, methionine metabolism produces s-adenosylmethionine, which is a methyl donor for histamine ring N-methylation, and the ultimate excretion of histamine (Fig. 1) [29, 30]. Studies of folate status in atopy, asthma, and allergic expression can be broadly grouped into those that measure folate in the gestational environment, and those that measure the folate status of patients experiencing various forms of allergy.

Most of the gestational folate supplementation research has assessed whether folic acid has been implicated in the later development of allergic states. For this review, preference has been given to meta-analysis rather than individual studies owing to their pooled results of multiple smaller studies. A recent (2013) meta-analysis of eight electronic databases for articles on gestational folate status showed through pooled risk analysis that there was no link between maternal folic acid supplementation during the first trimester of gestation, and subsequent asthma in offspring [31]. This study is notable because of its focus on folate in both food reported via diary and in supplement form, in addition to the time of exposure limited to periconception through the first trimester. This is corroborated by another study in (2014) that provided a systemic review, but highlighted that the effect on asthma occurs in the early years of youth and is transient when there is an effect. This study was not able to assess for genetic variant status as only two studies to date have had that data with limited effects, and dismissed it as a concern owing to Mendelian randomization of samples within those studies [32]. Another recent (2015) meta-analysis of previously published work showed that there may be a link between maternal folic acid supplementation and later development of asthma and other allergic disease, but only in those who were homozygous for the T variant on the C667T single-nucleotide polymorphism of MTHFR, a concern that was not addressed in the previous meta-analysis. A significant limitation of this meta-analysis is that it did not specifically address dietary sources of folate, and only looked at supplementation, thus missing total folate consumption in its myriad forms [33].

Another additional major feature of these studies is that there is no consistent measurement of serum folate vs RBC folate in participants, which is a particular concern for the highlighted variants of C667T that may have folate in their plasma that is not being adequately transported intracellularly. One study reports that increased intracellular folate levels in pregnancy, particularly during the third trimester, had an inverse relationship with the development of asthma in offspring by the age of 6 or 7—the age when asthma diagnosis stabilizes from a transient wheeze in early childhood [34]. The distinction between folate found intracellularly in RBC readings or serum is possibly the biggest methodological divide in these studies. This is illustrated by a new shift to examine unmetabolized folic acid and its impact on offspring. Specifically, unmetabolized folic acid in fetal cord blood at birth, rather than total folate or 5-methyltetrahydrofolate in the cord blood, was associated with later food allergies [35].

Most of these studies have focused on serum folate status. One meta-analysis in 2014 of high folic acid doses did not show a general impact of folic acid on asthma, but that the high doses of folic acid in gestation correlated with later asthma development and low doses were protective of later asthma development [36, 37]. Thus, part of the design flaw of these studies is that they do not parse out effects by level of total folate consumption, the types of folate, and the gene status that may not be metabolizing folic acid. One review

Table 1 Primary findings of previous allergy and folate status literature

Publication	Sample size	Measurement	Primary findings
Crider et al. [31]	5 articles	Folic acid use yes/no comparison	No association in periconceptional folic acid exposure and asthma/wheeze
Brown et al. [33]	10 studies	N/A—varies by study	Majority of studies do not show a folate and asthma link in gestation, but there is some evidence of a dose-dependent response
Wang et al. [33]	26 studies	Reported maternal folic acid use, objective measure, or gene polymorphism	Maternal folic acid supplementation during early pregnancy may increase the risk of wheeze in early childhood and MTHFR C677T TT polymorphism may be confer a high risk of asthma development
Magdelijns et al. [34]	2,834 women	Questionnaire and intracellular folate blood measurement at the end of the third trimester	ICF correlated inversely with asthma at 6 or 7 years of age in offspring. No association in the gestational use of folic acid and the development of asthma or allergic disease
McGowan et al. [35]	1,394 children; 502 cord blood; 362 early childhood folate readings	Cord blood and later childhood blood measurement of total folate, unmetabolized folic acid, and 5-MTHF.	Higher levels of unmetabolized folic acid at birth were associated with the development of food allergy. Mean total folate levels at birth were lower among those who developed food allergy. No associations with early life folates of any type and food allergy
Yang et al. [36]	150 infant asthma cases, 212 controls, meta-analysis of 14,438 subjects	Supplementation dose	High dose of maternal folic acid supplementation increases the risk of infant asthma. Low dose of maternal folic acid supplementation has a protective effect on infant asthma
Zetstra-van der Woude et al. [37]	913 pregnancies	Supplementation dose, and asthma medication dispensed to children	High-dose folic acid exposure was associated with increased occurrence of asthma in children
Blatter et al. [38]	N/A	N/A—varies by study	Possible weak to moderate effect of folate on asthma, but the authors do not see a strong enough relationship to modify current recommendations
Blatter et al. [39]	582 Puerto Rican children aged 6 to 14 years	Skin prick test, serum folate, and plasma vitamin D	Positive relationship between folate deficiency and increased degree of atopy and severe asthma; exacerbated by vitamin D status
Montrose et al. [40]	32 Montana children	Dietary questionnaire, spirometry, quality of life assessment, and DNA	Methyl donor status, e.g., folate and B vitamins involved in methylation, may have an impact on genes related to asthma
Husemoen et al. [25]	1,671 Danish participants, aged 30–60 years	MTHFR C677T genotype, plasma total homocysteine, and dietary intake	C667T individuals have a higher rate of allergic expression, and this interacts with dietary intake of methionine, folates, B12, B6, and B2. Homocysteine had no relationship
Thuesen et al. [41]	6,784 Danish participants aged 30–60 years. Follow up of 4,516 five years later	MTHFR C677T genotype, spirometry, serum folate and B12, IgE, and dietary questionnaire	Low serum folate levels and the TT genotype of the MTHFR C677T polymorphism were associated with increased prevalence of self-reported doctor-diagnosed asthma, but not atopy or lung function
Matsui and Matsui [42]	8,083 US subjects aged 2+ years.	Serum folate and IgE	Inverse association of serum folate levels with total IgE levels. IgE levels decreased across quartiles indicating a dose–response relationship of IgE, atopy, wheeze, and asthma with serum folate
Farres et al. [43]	180 Egyptians	Skin prick test, spirometry, serum folate, and total IgE levels	Serum folate is lower in the atopic asthma population than non-atopic asthma and control populations. Folate correlates inversely with degree of atopy

MTHFR methylenetetrahydrofolate

by Blatter et al. in 2014 concluded that the research to date does not support an adjustment to the current folic acid recommendations, whereas there may be a weak effect of gestational folic acid use on gestational allergy outcomes

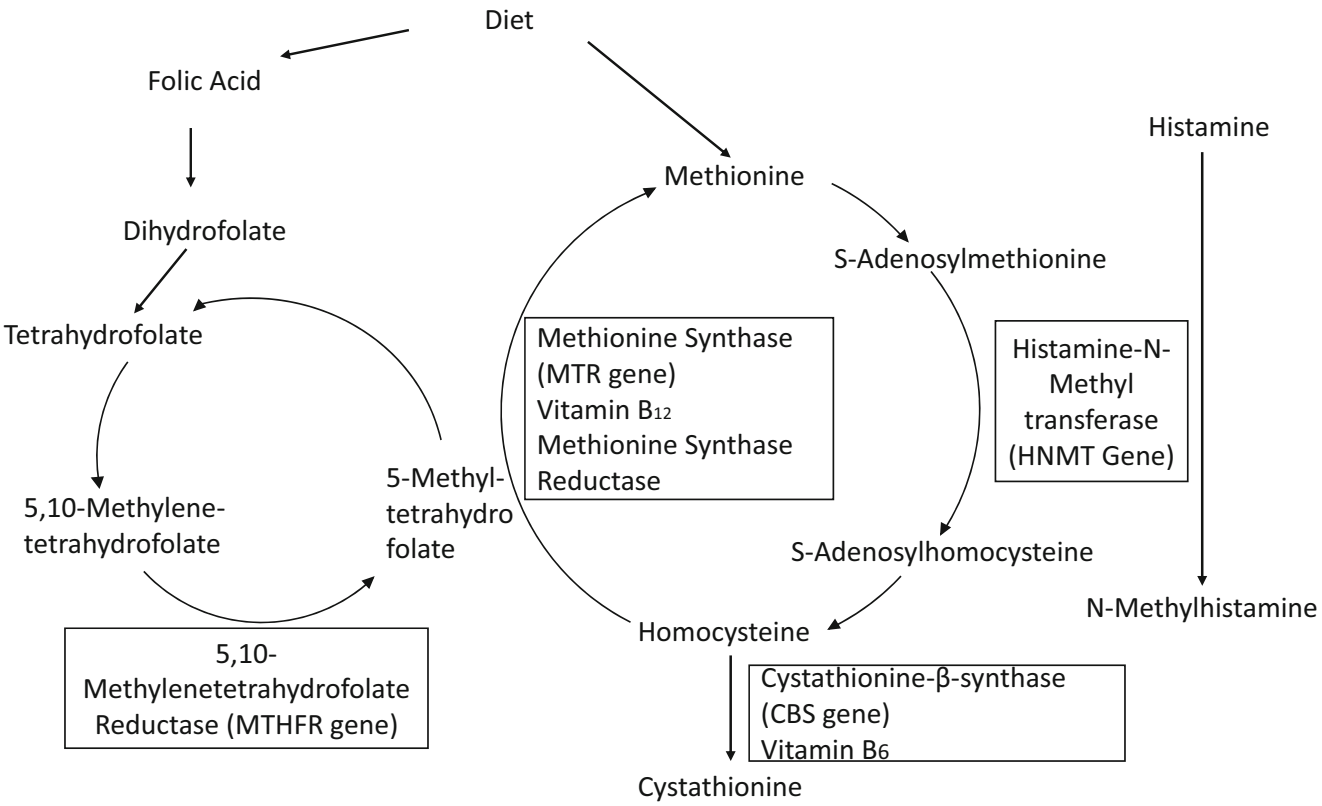

Fig. 1 Folate and histamine metabolism. Adapted from Sharp and Little [29] and Maintz and Novak [30]

[38]. Thus, folate may have an impact on the gestational state with regard to total dose and whether it has been metabolized, as the above results have been conflicting because of the overly general design for large populations without accounting for metabolic nuance.

In nongestational investigations of allergy and folate, there have been several recent publications of note. A relatively large cross-sectional examination of asthma and folate deficiency showed that among Puerto Rican children ($n = 582$) folate deficiency correlated with increased degree of atopy and severe asthma. Additionally, when folate deficiency was compounded by vitamin D deficiency, there was an eight-fold increase in allergic expression [39]. Another study, with a much smaller sample, found that in child asthmatics ($n = 32$) a diet rich in methyl donors, specifically folate, phosphocholine, and betaine, reported significantly higher quality of life metrics regarding their diagnosis than those with low methyl donor diets [40]. The report also found increased methylation of the IFNγ CpG sites, genetic markers involved in the immune response of asthmatics, with higher methyl donor diets. Regretfully, neither of these studies directly investigated the role of MTHFR, particularly the TT genotype, which is a key gene in folate/one-carbon metabolism. Other researchers have suspected the involvement of this gene, and in a large adult population ($n = 1{,}671$) the presence of atopy, as identified by IgE, was examined with regard to MTHFR C667T status, dietary folate intake, and homocysteine levels. The authors found that the homozygous C667T polymorphism was significantly associated with atopy, and that impaired folate metabolism is causally related to the development of atopy, yet homocysteine was not significantly different across groups, suggesting its lack of involvement in atopy. Despite the promising results of this study, it failed to assess supplement intake of participants [25]. Subsequent research has confirmed that the MTHFR C667T TT polymorphism confers an increased risk for asthma, although it found that this did not hold true for lung function, or atopy [41]. In one of the largest cross-sectional studies ($n = 8{,}083$) Matsui and Matsui reported that higher serum folate was inversely correlated with IgE levels and atopic expression [42]. Although this study did not account for MTHFR status, they did assess their results across racial populations and socio-economic status, which were both influential in serum folate levels. In a smaller sample than that of Matsui and Matsui, Farres et al. corroborated this relationship ($n = 60$), wherein an inverse relationship between serum folate and IgE levels existed among a population of Egyptian asthmatics [43]. Thus, some of the conflicting results regarding the role of folate in allergic expression may reflect a difference in baseline folate due to race and class population variation, genotype, in addition to measurement differences. Despite these issues there is enough evidence to suspect the role of folate metabolism in allergic disorders in vivo. Hence, it is possible that folate status plays a role in the pathogenesis and expression of IC patients who have a wider

allergic profile or respond positively to antihistamines and/or Elmiron in the treatment of their IC symptoms.

Histamine, folate, and associated methyl donors

Generally, much of the previous research has focused on serum or RBC folate status, rather than on one carbon metabolism that is widespread physiologically. The effect of folate and associated B vitamins in one carbon metabolism is likely multifaceted, affecting the methylation of CpG sites, cellular development, and other methylation activities. Specifically, metabolizing histamine via enzymatic methylation results in a decreased reactive burden of allergic and pseudo-allergic patients. It is important to note that not all atopic expression is IgE-mediated and can be the result of increased histamine due to impaired excretion via diamine oxidase enzyme (DAO) and methylation—this is the clinical difference between true allergy and pseudo-allergy, which present in a similar manner. Specifically, ring N-methylation via the histamine N-methyltransferase (HNMT) enzyme is one of the principle mechanisms of mammalian metabolism of histamine, which is then excreted in urine [44–46]. A downstream effect of folate's regulation of homocysteine and conversion to methionine is the later donation of a methyl group from s-adenosylmethionine to HNMT for enzymatic activity [47, 48]. Some antifolate medications for chemotherapy have been documented to inhibit HNMT activity and increase ambient histamine levels [49]. Although methyl groups are required for the excretion of histamine, they are also involved in the methylation of phospholipids, which results in a subsequent histamine release from mast cells [50]. Hence, methyl groups are widespread in their effect, and could both increase and decrease histamine levels in patients. The increase appears to be mediated by Ca2+ levels, wherein if there is an absence of Ca2+, then the methylation of phospholipids does not result in a histamine increase [51]. The donation of a methyl group can come from any number of B vitamins (e.g., betaine, folate, and choline), which has implications in the methylation of CpG sites, and histamine metabolism [52]. The secondary path through which histamine is metabolized is through diamine oxidase enzyme (DAO), which predominantly affects dietary histamine that has a similar system-wide effect to endogenous histamine sources from histidine [53]. This may be particularly salient in the management of allergic conditions, such as spontaneous urticaria, that can be a form of histamine intolerance due to additional histamine input in the diet [54]. Hence, increasing methyl donors, while limiting histamine ingestion, may have additional implications in the expression of allergic disease, beyond the more obvious role of folate and instead looking at its larger role as a methyl donor in one carbon metabolism.

Folate and vascular dysfunction

A documented feature of IC is vascular dysfunction within the surface of the bladder [55].This appears to manifest as reduced microvascular density, increased vascular endothelial growth factor (VEGF), and increased endothelial apoptosis. Treatment with 100-U onabotulinumtoxinA injections showed a reduction in VEGF, symptoms, mast cell activity, and apoptosis [56]. Others have documented reduced microvascular density in the suburothelium of women with IC bladders [57]. Yet, contrary to other work, the authors did not find any difference in endothelial cellular proliferation from regular bladders. Further research that was limited to those with pain as the primary presentation of IC showed a documented increase in endothelial apoptosis, as marked by Annexin V binding to phosphatidylserine, and TUNEL staining showed microvascular endothelial apoptosis, but not in the venule [58]. Thus, one perspective of the pathophysiology of IC is its vascular origins marked by increased VEGF, increased apoptosis, and less vascular density. In broader vascular terms, the aforementioned comorbidity with cardiovascular diseases such as ischemic stroke and coronary artery disease suggest a wider vascular syndrome [5, 6].

This may be an interaction with global inflammatory mediators of mast cells, e.g., heparin and histamine, or vascular toxic agents such as homocysteine. To our knowledge, no research has been done to date on homocysteine in any IC population, and pairs with concerns regarding folate due to the role of B vitamins in regulating homocysteine levels. Most importantly, VEGF expression is increased in the presence of ambient homocysteine, as investigated in the case of diabetic retinopathy, and in cellular investigations of THP-1 macrophages [59, 60]. The relationship of homocysteine with VEGF expression is the most direct possible mechanism of folate metabolism on the vascular nature of IC. If homocysteine is elevated because of an impaired folate metabolism, the resulting elevation in VEGF would match the vascular presentation of IC bladders. Homocysteine is documented to have other cardiovascular effects as well. Homocysteine at elevated levels is experimentally documented to remodel the myocardium via fibrosis and by having an impact on endothelial function [61]. In rats with methionine-induced hyperhomocysteinemia, there was an associated increase in mast cells in the heart in addition to cardiac remodeling [62]. This increase in mast cells appears to be somewhat protective, as other research has shown that when mast cell proliferation is hindered, the effects of homocysteine are worse than those with normal mast cell responses [63]. To date, these studies have only been investigated the heart; however, it is possible that other organs may have a similar response to homocysteine that has yet to be researched. Other cardiovascular implicated diagnoses, e.g., stroke, already recognize the importance of B vitamins in the regulation of homocysteine and subsequent endothelial

dysfunction [64]. Additionally, the role of folate and methyl groups in the regulation of homocysteine also has potential cardiovascular effects vis-à-vis the direct impact on histamine levels. High serum histamine is correlated with both coronary artery disease and ischemic stroke [65, 66]. Thus, B vitamins, particularly folate, may have multi-vector effects on cardiovascular disease via homocysteine, and/or the modulation of histamine levels with methylation, that are mast cell-mediated. It is reasonable to postulate that other diseases with strong cardiovascular profiles might benefit from B vitamins to reduce homocysteine, maintain endothelial function, and possibly regulate mast cell activity system-wide.

Discussion

Although it may be an oversimplification, it is undeniably true that folate has many complex functions in the human body, from its role in cell development, to IgE status, to functioning as a methyl donor, and regulating homocysteine. Some may claim that there is no reason to further research it; however, one core conclusion of this review is that previous studies have had major issues with the measurement of folate status (RBC versus serum), form (folic acid versus total folate versus 5-methyltetrahydrofolate), intake measurement (diet and supplements), race and class considerations, and newfound genetic variants. Most of the previous research was done before the accessibility of genetic variant status and has presented issues for current research because of funding and sample sizes. Additionally, though not reviewed here, there is promising research in other disease statuses, namely autism, regarding auto-immune disease and folate receptor antibodies [67, 68]. This review does not discuss this topic, as autism is not a known comorbidity for IC, but there may be similar concerns that antibodies might be a factor in why folate is not metabolized and one carbon metabolism is hindered. In the future, there needs to be folate research that focuses on the wider role of one carbon metabolism that has system-wide effects and examination of other key genetic markers in both phospholipid and histamine methylation that would have an impact on allergic expression downstream. Most importantly, folate status and methyl donors need to be researched in the pathogenesis of histamine-sensitive IC looking at multiple factors in one study: IgE status, RBC folate, unmetabolized folate, homocysteine, VEGF, and mast cell proliferation in the bladder. Similarly, this future research needs to be conscientious of previous design flaws around subtypes of IC with different functional etiologies, comorbid conditions (e.g., allergies), individual folate and histamine metabolism genetic variant status, diet, and measurement of folate. The review of existing literature suggests that folate and one carbon metabolism might have implications for the management and pathogenesis of mast cell-related IC, but this still needs to be tested and validated through further research.

Compliance with ethical standards

Conflicts of interest This work is unfunded, and entirely authored by C. Keagy, with no conflicts of interest.

References

1. Logadottir Y, Fall M, Kåbjörn-Gustafsson C, Peeker R. Clinical characteristics differ considerably between phenotypes of bladder pain syndrome/interstitial cystitis. Scand J Urol Nephrol. 2012;46(5):365–70. https://doi.org/10.3109/00365599.2012.689008.
2. FitzGerald MP, Payne CK, Lukacz ES, et al. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. J Urol. 2012;187(6):2113–8. https://doi.org/10.1016/j.juro.2012.01.123.
3. Cervigni M. Interstitial cystitis/bladder pain syndrome and glycosaminoglycans replacement therapy. Translat Androl Urol. 2015;4(6):638–42. https://doi.org/10.3978/j.issn.2223-4683.2015.11.04.
4. Rudick CN, Bryce PJ, Guichelaar LA, Berry RE, Klumpp DJ. Mast cell-derived histamine mediates cystitis pain. PLoS One. 2008;3(5):e2096. https://doi.org/10.1371/journal.pone.0002096.
5. Chen HM, Lin CC, Kang CS, Lee CT, Lin HC, Chung SD. Bladder pain syndrome/interstitial cystitis increase the risk of coronary heart disease. Neurourol Urodyn. 2014;33(5):511–5. https://doi.org/10.1002/nau.22444.
6. Chung SD, Xirasagar S, Lin CC, Ling W, Li HC, Lin HC. Increased risk of ischemic stroke among women with bladder pain syndrome/interstitial cystitis: a cohort study from Taiwan. Neurourol Urodyn. 2015;34(1):44–9. https://doi.org/10.1002/nau.22515.
7. Alagiri M, Chottiner S, Ratner V, Slade D, Hanno PM. Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. Urology. 1997;49 ((5):52–7. https://doi.org/10.1016/S0090-4295(99)80332-X.
8. Dinis S, de Oliveira JT, Pinto R, Cruz F, Buffington CAT, Dinis P. From bladder to systemic syndrome: concept and treatment evolution of interstitial cystitis. Int J Women's Health. 2015;7:735–44. https://doi.org/10.2147/IJWH.S60798.
9. Lee J, Doggweiler-Wiygul R, Kim S, Hill BD, Yoo TJ. Is interstitial cystitis an allergic disorder?: a case of interstitial cystitis treated successfully with anti-IgE. Int J Urol. 2006;13(5):631–4. https://doi.org/10.1111/j.1442-2042.2006.01373.x.
10. Jhang JF, Hsu YH, Jiang YH, Kuo HC. The role of immunoglobulin E in the pathogenesis of ketamine related cystitis and ulcerative interstitial cystitis: an immunohistochemical study. Pain Phys. 2016;19(4):E581–7.
11. Boucher W, El-Mansoury M, Pang X, Sant GR, Theoharides TC. Elevated mast cell tryptase in the urine of patients with interstitial cystitis. Br J Urol. 1995;76(1):94–100. https://doi.org/10.1111/j.1464-410X.1995.tb07840.x.
12. Letourneau R, Pang X, Sant GR, Theoharides TC. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. Br J Urol. 1996;77(1):41–54. https://doi.org/10.1046/j.1464-410X.1996.08178.x.
13. Bicer F, Altuntas CZ, Izgi K, et al. Chronic pelvic allodynia is mediated by CCL2 through mast cells in an experimental

autoimmune cystitis model. Am J Physiol Renal Physiol. 2015;308(2):F103–13. https://doi.org/10.1152/ajprenal.00202.2014.
14. Spanos C, Pang X, Ligris K, et al. Stress-induced bladder mast cell activation: implications for interstitial cystitis. J Urol. 1997;157(2):669–72. https://doi.org/10.1016/S0022-5347(01)65247-9.
15. Theoharides TC, Sant GR, El-Mansoury M, Letourneau R, Ucci AA Jr, Meares EM Jr. Activation of bladder mast cells in interstitial cystitis: a light and electron microscopic study. J Urol. 1995;153(3):629–36. https://doi.org/10.1016/S0022-5347(01)67669-9.
16. Theoharides TC, Kempuraj D, Sant GR. Mast cell involvement in interstitial cystitis: a review of human and experimental evidence. Urology. 2001;57(6, Suppl 1):47–55. https://doi.org/10.1016/S0090-4295(01)01129-3.
17. Yamada T, Murayama T, Mita H, Akiyama K. Subtypes of bladder mast cells in interstitial cystitis. Int J Urol. 2001;7(8):292–7. https://doi.org/10.1046/j.1442-2042.2000.00197.x.
18. Sant GR, Kempuraj D, Marchand JE, Theoharides TC. The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. Urology. 2007;69(4 Suppl):34–40. doi:https://doi.org/10.1016/j.urology.2006.08.1109.
19. Martin Jensen M, Jia W, Schults AJ, Ye X, Prestwich GD, Oottamasathien S. IL-33 mast cell axis is central in LL-37 induced bladder inflammation and pain in a murine interstitial cystitis model. Cytokine. 2018;110:420–27. https://doi.org/10.1016/j.cyto.2018.05.012.
20. Malik ST, Birch BR, Voegeli D, et al. Distribution of mast cell subtypes in interstitial cystitis: implications for novel diagnostic and therapeutic strategies? J Clin Pathol. 2018;71(9):840–44.
21. Regauer S. Mast cell activation syndrome in pain syndromes bladder pain syndrome/interstitial cystitis and vulvodynia. Translat Androl Urol. 2016;5(3):396–7. https://doi.org/10.21037/tau.2016.03.12.
22. Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. J Hematol Oncol. 2011;4(1):10. https://doi.org/10.1186/1756-8722-4-10.
23. Ratner V. Mast cell activation syndrome. Translat Androl Urol. 2015;4(5):587–8. https://doi.org/10.3978/j.issn.2223-4683.2015.09.03.
24. Castells M. Mast cell mediators in allergic inflammation and mastocytosis. Immunol Allergy Clin N Am. 2006;26(3):465–85. doi:https://doi.org/10.1016/j.iac.2006.05.005.
25. Husemoen LL, Toft U, Fenger M, Jorgensen T, Johansen N, Linneberg A. The association between atopy and factors influencing folate metabolism: is low folate status causally related to the development of atopy? Int J Epidemiol. 2006;35(4):954–61. https://doi.org/10.1093/ije/dyl094.
26. Haberg SE, London SJ, Stigum H, Nafstad P, Nystad W. Folic acid supplements in pregnancy and early childhood respiratory health. Arch Dis Child. 2009;94(3):180–4. https://doi.org/10.1136/adc.2008.142448.
27. Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J Epidemiol. 2009;170(12):1486–93. https://doi.org/10.1093/aje/kwp315.
28. Tsang BL, Devine OJ, Cordero AM, et al. Assessing the association between the methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism and blood folate concentrations: a systematic review and meta-analysis of trials and observational studies. Am J Clin Nutr. 2015;101(6):1286–94. https://doi.org/10.3945/ajcn.114.099994.
29. Sharp L, Little J. Polymorphisms in genes involved in folate metabolism and colorectal neoplasia: a HuGE review. Am J Epidemiol. 2004;159(5):423–43. https://doi.org/10.1093/aje/kwh066.
30. Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr. 2007;85(5):1185–96. https://doi.org/10.1093/ajcn/85.5.1185.
31. Crider KS, Cordero AM, Qi YP, Mulinare J, Dowling NF, Berry RJ. Prenatal folic acid and risk of asthma in children: a systematic review and meta-analysis. Am J Clin Nutr. 2013;98(5):1272–81. https://doi.org/10.3945/ajcn.113.065623.
32. Brown SB, Reeves KW, Bertone-Johnson ER. Maternal folate exposure in pregnancy and childhood asthma and allergy: a systematic review. Nutr Rev. 2014;72(1):55–64.
33. Wang T, Zhang H-P, Zhang X, Liang Z-A, Ji Y-L, Wang G. Is folate status a risk factor for asthma or other allergic diseases? Allergy Asthma Immunol Res. 2015;7(6):538–46.
34. Magdelijns FJH, Mommers M, Penders J, Smits L, Thijs C. Folic acid use in pregnancy and the development of atopy, asthma, and lung function in childhood. Pediatrics. 2011;128(1):e135–44. https://doi.org/10.1542/peds.2010-1690.
35. McGowan EC, Hong X, Selhub J, et al. The association between folate/folic acid metabolites and the development of food allergy (FA) in children. J Allergy Clin Immunol. 2018;141(2, Supplement):AB86. https://doi.org/10.1016/j.jaci.2017.12.277.
36. Yang L, Jiang L, Bi M, et al. High dose of maternal folic acid supplementation is associated to infant asthma. Food Chem Toxicol. 2015;75:88–93. https://doi.org/10.1016/j.fct.2014.11.006.
37. Zetstra-van der Woude PA, De Walle HEK, Hoek A, et al. Maternal high-dose folic acid during pregnancy and asthma medication in the offspring. Pharmacoepidemiol Drug Saf. 2014;23(10):1059–65. https://doi.org/10.1002/pds.3652.
38. Blatter J, Han YY, Forno E, Brehm J, Bodnar L, Celedon JC. Folate and asthma. Am J Respir Crit Care Med. 2013;188(1):12–7. https://doi.org/10.1164/rccm.201302-0317PP.
39. Blatter J, Brehm JM, Sordillo J, et al. Folate deficiency, atopy, and severe asthma exacerbations in Puerto Rican children. Ann Am Thor Soc. 2016;13(2):223–30. https://doi.org/10.1513/AnnalsATS.201508-549OC.
40. Montrose L, Ward TJ, Semmens EO, Cho YH, Brown B, Noonan CW. Dietary intake is associated with respiratory health outcomes and DNA methylation in children with asthma. Allergy Asthma Clin Immunol. 2017;13:12. https://doi.org/10.1186/s13223-017-0187-8.
41. Thuesen BH, Husemoen LLN, Ovesen L, et al. Atopy, asthma, and lung function in relation to folate and vitamin B12 in adults. Allergy. 2010;65(11):1446–54. https://doi.org/10.1111/j.1398-9995.2010.02378.x.
42. Matsui EC, Matsui W. Higher serum folate levels are associated with a lower risk of atopy and wheeze. J Allergy Clin Immunol. 2009;123(6):1253–1259.e1252. https://doi.org/10.1016/j.jaci.2009.03.007.
43. Farres MN, Shahin RY, Melek NA, El-Kabarity RH, Arafa NA. Study of folate status among Egyptian asthmatics. Intern Med. 2011;50(3):205–11. https://doi.org/10.2169/internalmedicine.50.4424.
44. Gustafsson A, Forshell G. Studies on the enzymic methylation of histamine. Acta Chem Scand. 1964;18:2069–76.
45. Schayer RW, Karjala S. Ring N methylation; a major route of histamine metabolism. J Biol Chem. 1956;221(1):307–14.
46. Granerus G. Urinary excretion of histamine, methylhistamine and methylimidazoleacetic acids in man under standardized dietary conditions. Scand J Clin Lab Invest. 1968;104:59–68.
47. Selhub J. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. J Nutr Health Aging. 2002;6(1):39–42.
48. Brown DD, Tomchick R, Axelrod J. The distribution and properties of a histamine-methylating enzyme. J Biol Chem. 1959;234:2948–50.
49. Duch DS, Edelstein MP, Nichol CA. Inhibition of histamine-metabolizing enzymes and elevation of histamine levels in tissues

by lipid-soluble anticancer folate antagonists. Mol Pharmacol. 1980;18(1):100.
50. Ishizaka T, Hirata F, Ishizaka K, Axelrod J. Stimulation of phospholipid methylation, Ca2+ influx, and histamine release by bridging of IgE receptors on rat mast cells. Proc Natl Acad Sci. 1980;77(4):1903–6.
51. Hirata F, Axelrod J, Crews FT. Concanavalin a stimulates phospholipid methylation and phosphatidylserine decarboxylation in rat mast cells. Proc Natl Acad Sci U S A. 1979;76(10):4813–6.
52. Sharma S, Litonjua A. Asthma, allergy, and responses to methyl donor supplements and nutrients. J Allergy Clin Immunol. 2014;133(5):1246–54. https://doi.org/10.1016/j.jaci.2013.10.039.
53. Manzotti G, Breda D, Di Gioacchino M, Burastero SE. Serum diamine oxidase activity in patients with histamine intolerance. Int J Immunopathol Pharmacol. 2016;29(1):105–11. https://doi.org/10.1177/0394632015617170.
54. Wagner N, Dirk D, Peveling-Oberhag A, et al. A popular myth—low-histamine diet improves chronic spontaneous urticaria—fact or fiction? J Eur Acad Dermatol Venereol. 2017;31(4):650–5. https://doi.org/10.1111/jdv.13966.
55. Saban R. Angiogenic factors, bladder neuroplasticity and interstitial cystitis—new pathobiological insights. Transl Androl Urol. 2015;4(5):555–62. https://doi.org/10.3978/j.issn.2223-4683.2015.08.05.
56. Peng CH, Jhang JF, Shie JH, Kuo HC. Down regulation of vascular endothelial growth factor is associated with decreased inflammation after intravesical OnabotulinumtoxinA injections combined with hydrodistention for patients with interstitial cystitis—clinical results and immunohistochemistry analysis. Urology. 2013;82(6):1452.e1451–6. https://doi.org/10.1016/j.urology.2013.09.003.
57. Rosamilia A, Cann L, Dwyer P, Scurry J, Rogers P. Bladder microvasculature in women with interstitial cystitis. J Urol. 1999;161(6):1865–70.
58. Yamada T, Nishimura M, Mita H. Increased number of apoptotic endothelial cells in bladder of interstitial cystitis patients. World J Urol. 2007;25(4):407–13. https://doi.org/10.1007/s00345-007-0174-7.
59. Roybal CN, Yang S, Sun CW, et al. Homocysteine increases the expression of vascular endothelial growth factor by a mechanism involving endoplasmic reticulum stress and transcription factor ATF4. J Biol Chem. 2004;279(15):14844–52. https://doi.org/10.1074/jbc.M312948200.
60. Maeda M, Yamamoto I, Fujio Y, Azuma J. Homocysteine induces vascular endothelial growth factor expression in differentiated THP-1 macrophages. Biochim Biophys Acta Gen Subj. 2003;1623(1):41–6. https://doi.org/10.1016/S0304-4165(03)00161-2.
61. Herrmann M, Taban-Shomal O, Hübner U, Böhm M, Herrmann W. A review of homocysteine and heart failure. Eur J Heart Fail. 2006;8(6):571–6. https://doi.org/10.1016/j.ejheart.2005.11.016.
62. Singh AP, Singh M, Balakumar P. Effect of mast cell stabilizers in hyperhomocysteinemia-induced cardiac hypertrophy in rats. J Cardiovasc Pharmacol. 2008;51(6):596–604. https://doi.org/10.1097/FJC.0b013e31817ae60f.
63. Joseph J, Kennedy RH, Devi S, Wang J, Joseph L, Hauer-Jensen M. Protective role of mast cells in homocysteine-induced cardiac remodeling. Am J Physiol Heart Circ Physiol. 2005;288(5):H2541–5. https://doi.org/10.1152/ajpheart.00806.2004.
64. Spence JD. Homocysteine lowering for stroke prevention: unravelling the complexity of the evidence. Int J Stroke. 2016;11(7):744–7. https://doi.org/10.1177/1747493016662038.
65. Clejan S, Japa S, Clemetson C, Hasabnis SS, David O, Talano JV. Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis. J Cell Mol Med. 2002;6(4):583–92.
66. Zdravkovic V, Pantovic S, Rosic G, et al. Histamine blood concentration in ischemic heart disease patients. J Biomed Biotechnol. 2011;2011:8. https://doi.org/10.1155/2011/315709.
67. Frye R, Sequeira J, Quadros E, James S, Rossignol D. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol Psychiatry. 2013;18(3):369.
68. Ramaekers VT, Rothenberg SP, Sequeira JM, et al. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. N Engl J Med. 2005;352(19):1985–91.