Blood Cells, Molecules and Diseases 76 (2019) 40–44

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Scurvy, an old story in a new time: The hematologist's experience

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ARTICLE INFO

Editor: Mohandas Narla

Keywords:
Bleeding disorder
Hemostasis
Scurvy
Vitamin C
Ascorbic acid
Nutritional deficiency

ABSTRACT

Background: Scurvy is a rare entity in developed countries and the diagnosis may often be delayed resulting in unnecessary investigations and/or potentially severe complications. A recent increase in the number of patients diagnosed with scurvy in our hematology clinics indicated the need to review the literature on the diagnosis and optimal management of similar patients.

Methods: We conducted a retrospective chart review of patients referred to hematology at our tertiary care centre between 2010 and 2018, who were ultimately diagnosed with scurvy. Data collected from electronic medical records included baseline characteristics, clinical features on presentation, bloodwork results from initial consultation, treatment plan as well as response to treatment.

Findings: Twenty-two adults patient had a diagnosis of scurvy with a mean vitamin C level of 6 μmol/L. Iron deficiency anemia (54%) and gastrointestinal disorders (54%) were the most common comorbidities noted in our cohort. Proton-pump inhibitors use was noted in 54% of patients. Bleeding (45%) and bruising (45%) were the most commonly reported clinical features. Eleven patients received oral supplementation, five had intravenous (IV) vitamin C and six were not treated. Two patients required a transition from oral to IV supplementation. Vitamin C dosing ranged between 250 and 2000 mg and the frequency varied from daily for oral therapy to every few weeks or months for IV.

Interpretation: Awareness of scurvy and its associated risk factors and clinical presentation is important in the evaluation of a patient with bleeding tendency. Treatment plan should be individualized, and a careful review of patients' diet, medial history and medications is warranted.

1. Introduction

Scurvy is one of the oldest described diseases. Caused by a deficiency of vitamin C, it is historically associated with sailors who contracted the condition due to the paucity of fruit and vegetables available during long voyages [1,2]. Since the realization that consumption of vitamin C- rich food prevents scurvy, it has been, considered a rare entity in developed countries.

Vitamin C, also known as ascorbic acid, plays a major role as a cofactor in collagen biosynthesis which ensures integrity of blood vessels, as well as other tissues [2–4]. Poor intake and/or absorption of vitamin C leading to deficiency has been associated with a range of clinical features, including bleeding tendencies that can vary in severity and may be life-threatening. Skin and musculoskeletal manifestations are also typical of the disease process. Most of these clinical manifestations associated with scurvy can be explained by an alteration in collagen structure. Vitamin C also promotes iron absorption and mobilization [4]. Consequently, iron deficiency anemia may be observed with scurvy. Vitamin C is also involved in fatty acid metabolism, catecholamine and tyrosine synthesis, and free radical elimination.

Unlike most mammals, humans cannot synthetize or store vitamin C and are dependent on a minimal daily intake, which comes mostly from fresh fruit and vegetables [3]. Ascorbic acid is a water-soluble vitamin that is absorbed in the ileum and rapidly transported in the blood for distribution in variable amounts to all tissues [5]. The majority of vitamin C is reabsorbed in the renal tubules to maintain an approximate

Abbreviations: aPTT, activated partial thromboplastin times; DMARDs, Disease-modifying antirheumatic drugs; EAR, estimated average requirements; GERD, Gastoesophageal reflux disease; IBS, Irritable bowel syndrome; NSAIDS, Nonsteroidal Anti-inflammatory Drugs; PPI, proton-pump inhibitors; PT, prothrombin time; RDA, recommended dietary allowances

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https://doi.org/10.1016/j.bcmd.2019.01.004
Received 8 January 2019; Received in revised form 23 January 2019; Accepted 23 January 2019
Available online 24 January 2019

body reserve of 1500 mg, which can prevent the development of scurvy for about four to six weeks [3]. Regular intake is required as urinary excretion eliminates additional vitamin C when plasma concentration is over 14 mg/L.

International recommendations regarding daily requirements of vitamin C are lacking. As little as 10 mg daily was previously shown to be sufficient to prevent scurvy but all food and health organizations recommend a daily intake of higher amounts [3,6]. Health Canada has individualized the estimated average requirements (EAR) and recommended dietary allowances (RDA) based on age, gender, pregnancy and lactation status, as well as smoking status [7]. Such recommendations take into account physiological and psychosocial factors. Whether additional supplementation of vitamin C can offer any health benefits remains unclear and controversial.

In developed countries, scurvy has been described to be associated with various specific clinical problems. The most commonly associated conditions include alcohol use disorder, gastrointestinal or malabsorption disorders, neuropsychiatric disorders, as well as food faddism or avoidance [8–12]. Other at-risk populations described in the literature include patients on hemodialysis, transfusion-dependent patients due to iron-overload, patients receiving chemotherapy or post-transplantation status [9].

Scurvy remains a clinical diagnosis based on good history taking and physical examination skills documenting the most frequent clinical manifestations and the patient's dietary history [12]. Laboratory tests are available and can help establish the diagnosis quickly and avoid a battery of unnecessary investigations when the clinical scenario is consistent with scurvy. The two tests most commonly reported are the plasma ascorbic acid level, which is affected by recent dietary intake, and the leukocyte ascorbic acid level which is indicative of the patient's total body content of vitamin C [12].

Unexplained bruising and bleeding are common reasons for referral to a hematologist. Recommendations for evaluation of such presentations typically do not include vitamin C testing [13]. There are no known published guidelines or good quality studies that address the work-up or the management of vitamin C deficiency. The optimal vitamin C replacement regimen is also unclear and not evidence-based [3]. Both oral and parenteral supplementation can be provided and it is unknown whether one of these methods is more efficacious than the other.

We have recently encountered an increased number of patients ultimately diagnosed with and treated for scurvy by the hematology service of The Ottawa Hospital. We aimed to review these cases in hopes of eliciting common themes in presentation and history of these patients as well as response to therapy. We hope our work can increase awareness of vitamin C deficiency in the work-up of a patient with bruising and/or bleeding and help determine when testing for the condition is indicated.

2. Methods

Following approval by our institutional research ethics board, we reviewed the medical records of all adult patients diagnosed with scurvy in the years 2010–2018. Patients were included in our review if they presented to hematologists affiliated with The Ottawa Hospital and were ultimately diagnosed with vitamin C deficiency. Patients were identified from individual hematologists' clinical practices. For each patient, data collected from the electronic medical records included their clinical presentation, any underlying medical conditions and medications, dietary and lifestyle habits, the initial laboratory investigations including the vitamin C levels at diagnosis, and the initial treatment and response. At our institution, vitamin C levels are determined using high performance liquid chromatography assays. The lower limit of detection of this test is 5 μmol/L and levels below 25 μmol/L are considered indicative of vitamin C deficiency. For statistical analysis, vitamin C levels < 5 μmol/L were considered to be equal to zero.

To inform our analysis, a systematic search of medical literature was conducted by an information specialist at The Ottawa Hospital.

3. Results

During the period of January 2010 and June 2018, our hematology service was involved with 22 adult patients diagnosed with scurvy. The mean age at diagnosis was 53 years and ranged between 31 and 76 years of age. There were 18 female patients and 4 male patients.

3.1. Vitamin C levels

For our cohort, the mean vitamin C levels was 6 μmol/L and ranged between 0 and 22 μmol/L. Eleven patients had undetectable levels (< 5 μmol/L).

3.2. Dietary history

Nine patients reported an adequate diet and no specific restrictions. Four patients acknowledged limited intake of fresh fruits and vegetables. Other documented restrictions included limited oral intake (two patients), fluid-based diet (two patients) and food aversion (one patient). A detailed description regarding these dietary restrictions was unfortunately not available. Four patients had undocumented dietary histories. Concomitant deficiencies of vitamin B12 and 25-hydroxy vitamin D were identified in two patients. Both had undetectable vitamin C levels and no dietary restrictions reported. The patient with B12 deficiency had a history of bariatric surgery and the patient with vitamin D deficiency had a confirmed diagnosis of Ehlers-Danlos syndrome.

3.3. Underlying patient conditions

Table 1 shows the breakdown of comorbidities reported for our patient cohort. Concomitant iron deficiency with or without anemia was noted in twelve patients. Similarly, gastrointestinal disorders were reported in twelve patients. Gastoesophageal reflux disease (GERD) and functional disorders such as Irritable bowel syndrome (IBS) were the

Table 1
Comorbidities listed in order of frequency for all patients with scurvy.

Comorbidities	All patients with vitamin C deficiency (levels < 25 μmol/L)	Patients with undetectable levels of vitamin C (< 5 μmol/L)
	N = 22	N = 11
Iron deficiency with or without anemia	12 (54%)	4 (36%)
Gastroinstestinal disorders	12 (54%)	6 (55%)
Psychiatric disorders	10 (45%)	4 (36%)
Musculoskeletal disorders	10 (45%)	4 (36%)
Neurologic disorders	9 (41%)	5 (45%)
Endocrinologic disorders	9 (41%)	3 (27%)
Metabolic disorders	8 (36%)	3 (27%)
Cardiovascular disorders	7 (32%)	5 (45%)
Gastrointestinal surgeries	6 (27%)	2 (18%)
Chronic lung disorders	6 (27%)	4 (36%)
Chronic pain disorders	5 (22%)	3 (27%)
Genitourinary disorders	4 (18%)	2 (18%)
Dermatologic disorders	4 (18%)	1 (9%)
Collagen/connective tissue disorders	2 (9%)	2 (18%)
Malignancies	2 (9%)	1 (9%)
Hematologic disorders	1 (5%)	1 (9%)

Table 2
List of medications and supplements taken by our patients with scurvy.

Medications	All patients with vitamin C deficiency (levels < 25 μmol/L)	Patients with undetectable levels of vitamin C (< 5 μmol/L)
	N = 22	N = 11
Proton-pump inhibitors	12 (54%)	6 (55%)
Antidepressants	12 (54%)	4 (36%)
Iron supplementation (oral or parenteral)	10 (45%)	4 (36%)
Vitamins (excluding Vit C)	10 (45%)	3 (27%)
NSAIDS	9 (41%)	5 (45%)
Antihypertensive	6 (27%)	4 (36%)
Benzodiazepines/hypnotics	6 (27%)	3 (27%)
Opioid analgesics	5 (22%)	2 (18%)
Thyroid replacement therapy	5 (22%)	2 (18%)
Inhalers	5 (22%)	3 (27%)
Anticonvulsant	4 (18%)	2 (18%)
Antiplatelets/anticoagulants	4 (18%)	2 (18%)
Statins	4 (18%)	2 (18%)
Contraceptives/hormonal therapies	3 (14%)	1 (9%)
H2 blockers	2 (9%)	2 (18%)
A1 blockers	2 (9%)	2 (18%)
DMARDs	2 (9%)	1 (9%)
Antihyperglycemic agents (including insulin)	2 (9%)	0 (0%)
Antipsychotics	2 (9%)	1 (9%)
Bisphosphonates	1 (5%)	0 (0%)
Diuretics	1 (5%)	0 (0%)
Triptans	1 (5%)	1 (9%)
None	1 (5%)	1 (9%)

most commonly noted problems. Other important comorbidities seen in 30–50% of our patients included psychiatric disorders (ten patients), musculoskeletal disorders (ten patients), neurologic and endocrinologic disorders (nine patients each), metabolic disorders (eight patients), as well as cardiovascular disorders (seven patients). Only six patients had gastrointestinal surgeries in their medical history and all of them involved the stomach. Interestingly, two patients diagnosed with scurvy had a previously documented diagnosis of Ehlers-Danlos syndrome, a type of collagen disorder. One of the two patients had associated GERD requiring long-term therapy with a proton-pump inhibitor (PPI).

3.4. Medications and supplements use

A total of 17 patients reported taking three or more medications and supplements. Only one patient was not using any medications prior to the diagnosis of scurvy. Most commonly prescribed medications were proton-pump inhibitors (PPI) and antidepressants. Each of these classes of medications was noted in the record of twelve patients, respectively. Table 2 provides a list of all medications and supplements identified in our patient population.

3.5. Signs and symptoms on initial presentation

Bleeding and bruising were the most common clinical features reported. Ten patients were referred to hematology for investigation of bruising and ten for evaluation of bleeding. Among the patients with a bleeding history, five patients described heavy menstrual bleeding, four patients had mucocutaneous involvement, another four patients had deep soft tissue bleeding, and two patients experienced excessive bleeding after an invasive procedure. Review of bruising complaints shows that three patients had description of large bruises, three patients had bruises at unusual sites such as the abdomen and back, and descriptive features were not available for four of the patients.

Table 3
Signs and symptoms reported by patients with scurvy on initial referral to a hematologist.

Clinical features	All patients with low levels (< 25) N = 22	Patients with undetectable levels (< 5) N = 11
Bleeding	10 (45%)	7 (63%)
	5/10	3/7
- Heavy menstrual bleeding	2/10	2/7
- Post-procedural/surgical	4/10	3/7
- Mucocutaneous	5/10	4/7
- Deep/soft tissue		
Bruising	10 (45%)	7 (63%)
	4/10	2/7
- At unusual sites	4/10	3/7
- Large	4/10	3/7
- Unspecified		
Gastrointestinal	9 (41%)	4 (36%)
Fatigue	7 (32%)	2 (18%)
Cardiorespiratory	7 (32%)	4 (36%)
Cutaneous abnormalities	6 (27%)	3 (27%)
Edema	6 (27%)	5 (45%)
MSK pain	4 (18%)	3 (27%)
Oral/gingival issues	3 (14%)	2 (18%)
Poor healing/wound infections	2 (9%)	1 (9%)
Weight loss	1 (5%)	1 (9%)
Memory impairment	1 (5%)	1 (9%)

Gastrointestinal symptoms were also common and noted in nine patients and included symptoms such as reflux, postprandial abdominal pain or cramps, diarrhea, and constipation. Other clinical features identified are reported in Table 3.

3.6. Laboratory features

All patients had a complete blood count performed on initial presentation. Fifteen patients had evidence of anemia with a mean hemoglobin value of 106 g/L (range 57–145 g/L). All patients had normal white blood cell and platelet counts. As previously mentioned, iron-deficiency was a common comorbidity noted in our patients' medical history. Iron deficiency, defined by WHO criteria as a ferritin value under 30 μg/L, was noted in thirteen patients. The mean ferritin value in tested patients (n = 20) was 55 μg/L (range of 2 to 221 μg/L). Hypoalbuminemia, defined as an albumin value below the 35 g/L which is the lower limit of the reference interval in our laboratory, was noted in ten of the 16 patients in whom it was tested at their initial presentation. The mean albumin level was 32 g/L (range of 22 to 43 g/L). All patients had normal prothrombin time (PT) and activated partial thromboplastin times (aPTT). Tests of liver and kidney function, transaminases and creatinine, were within reference intervals in all patients.

3.7. Treatment and response

Six of the 22 patients had no vitamin C replacement therapy initiation or follow-up vitamin C levels documented in their charts. Three of these patients had follow-up clinic visits addressing their iron deficiency. One patient was admitted to the hospital for a spontaneous epidural hematoma and had a prior history of spontaneous subarachnoid hemorrhage. His vitamin C level was noted to be undetectable after his hospital discharge and no evidence of follow up was found in our review of his electronic medical record. It is worth noting that our electronic medical record enables review of laboratory testing done at private facilities but offers no information about admission to hospitals outside The Ottawa Hospital 3 campuses.

A total of five patients were treated with intravenous (IV) vitamin C immediately following diagnosis. Dosing ranged from 500 mg up to

1500 mg per treatment. Frequency of administration also varied from every two weeks to every two months. Length of follow-up varied too, from seven months up to six years. Documented clinical responses were available for two of these five patients and described resolution in bruising symptoms, decreased frequency of oral sores and improvement in fatigue. From a laboratory perspective, one patient who had a confirmed diagnosis of Ehlers-Danlos syndrome had persistently low levels of vitamin C (< 25 μmol/L) despite ongoing IV therapy. Levels normalized in two patients with follow-up lab tests performed at eight at 26 months after therapy initiation. Two patients had no follow-up vitamin C levels performed.

Oral supplementation was initiated at diagnosis in eleven patients. Two of these patients required a change in therapy to IV vitamin C replacement. One failed to achieve symptomatic or laboratory improvement with oral therapy. Her initial presentation included significant gastrointestinal symptoms and a history of large bruises at unusual sites and following minor medical procedures. When switched to the IV formulation at 500 mg weekly, the vitamin C levels normalized, and clinical findings resolved. Attempt to transition the patient back to oral supplementation failed with decrease in vitamin C levels and recurrence of mucocutaneous bleeding. Resolution was again noted when therapy was changed back to IV Vitamin C 500 mg every 2 weeks. The other patient had no documented clinical or laboratory indication for a change to IV vitamin C. The initial presentation consisted of mucocutaneous bleeding and bruising, and treatment initially consisted of a 1000 mg of oral vitamin C. The therapy was then modified to monthly IV vitamin C when the patient was found to have iron-deficiency anemia requiring IV iron infusions.

The other nine patients were treated with oral vitamin C supplements only. Dosage was highly variable ranging from 250 mg to 2000 mg daily. Clinical follow-up ranged from 3 to 32 months. Five patients had no follow-up clinical visit or vitamin C levels documented. The other 4 patients showed improvement in bruising and bleeding symptoms when vitamin C levels normalized. Two patients had evidence of normal vitamin C levels within two months of initiation of oral therapy, while the other had normal levels at seven months.

4. Discussion

4.1. Risk factors and associated conditions

Our cohort of adults with vitamin C deficiency presented with a wide range of comorbidities. As described in prior retrospective studies, gastrointestinal, psychiatric and neurologic disorders play an important role in the etiology of the disease but can also be manifestations of it. Organic GI disorders are likely to interfere with vitamin C absorption and luminal transportation especially if the small bowel is involved. However, the association of scurvy and functional GI disorders is less clear. Although not well understood, interplay between the central nervous system and the GI system has been well described. All patients with the latter also had documented neuropsychiatric disorders likely contributing to the development of scurvy through restrictive dietary habits.

In a pediatric cohort vitamin C deficiency was noted to occur concurrently with iron overload [14]. However, we observed the converse situation with more than half of our adult patients with scurvy having evidence of iron-deficiency. It has previously been established that an increased iron load can hasten vitamin C metabolism which may explain the pediatric findings [14]. Iron deficiency may present more frequently in patients with scurvy when malnutrition or malabsorption are present. Iron supplementation has been shown to improve vitamin C levels as well as iron levels [14]. Another possible connection between the two disorders may that chronic bleeding from friable blood vessels of the gastrointestinal mucosa seen in scurvy can result in iron deficiency. Leukopenia has been described to be a symptom of scurvy but was not seen in any patients in our cohort [15].

The two patients in our cohort who had a documented diagnosis of Ehlers-Danlos syndrome also had concomitant severe vitamin C deficiency. In these cases, the cause of the vitamin C deficiency is likely to be related to inadequate intake due to avoidance of acidic foods which resulted in gastrointestinal manifestations such as reflux. Some authors have suggested using nutritional supplements, such as vitamin C, to target and improve various clinical features associated with Ehlers-Danlos syndrome. Dosing of 1500 mg has been suggested to reduce bruising and bleeding symptoms in this patient population [16,17].

A dietary history remains an important element of the medical assessment and may help guide diagnostic investigations. When scurvy, or any nutritional deficiency is suspected, thorough review or dietary intake is of critical importance in determining etiology. This also serves as tool to counsel patient on their behaviors and promote adequate intake of vitamin C-rich food. Unfortunately, the dietary history in our cohort was quite limited and often lacking. Given this surprising increase in the number of cases encountered in recent years, we feel that awareness of vitamin C deficiency as the possible cause of a bleeding diathesis is warranted. Perhaps with improved awareness, a thorough dietary history may be routinely incorporated in patients' assessment when indicated.

Vitamin C has been reported to interact with certain medications by increasing their toxic effect, as is the case with deferoxamine, or by decreasing their therapeutic effects, which is known to occur with use of bortezomib and cyclosporine. The converse, drugs interfering with vitamin C metabolism has not been described. Proton-pump inhibitors were the most commonly used medications in our cohort, which is not an unexpected finding given the frequency with which these drugs are prescribed [18,19]. PPIs create an alkaline gastric environment which could possibly interfere with vitamin C absorption. Alternatively, those with reflux symptoms may be consciously restricting their citrus intake given the acidic nature of these foods and their potential for exacerbating GI symptoms. Further evaluation of vitamin C levels in chronic PPI use could help better understand this interaction.

4.2. Clinical manifestations and laboratory features

Signs and symptoms of scurvy tend to manifest when the body's vitamin C stores drop below 300 mg [12]. This can occur within as few as one to three months of absence of vitamin C from one's diet [9]. Given the myriad possible presentations of scurvy, establishing a diagnosis solely on clinical features is very difficult. Bruising and bleeding were common findings and no other cause for these manifestations could be identified in our cohort. Several patients suffered from gastrointestinal symptoms which may again reflect the importance of gut disorders and the development of scurvy. Fatigue, noted in one third of our population, is often a challenging symptom for patients and clinicians alike. It is often reported in the scurvy literature and has been associated with interference in the tyrosine and catecholamines synthesis [5]. The unique features of scurvy, such as follicular hyperkeratosis and perifollicular hemorrhage are typically the initial physical findings and most commonly described in the lower extremities [10,12]. These classic and specific signs were not documented in our patients' clinical records. Other symptoms related to defective collagen, such as poor wound healing, edema and musculoskeletal pain were also less commonly documented. Many patients in our cohort underwent testing for both rare and common coagulation factor deficiencies and many also had tests of platelet function done. Awaiting results of these tests before continuing to vitamin C testing can contribute to a delay in the diagnosis. With adequate vitamin C supplementation, the majority of signs and symptoms our patients exhibited resolved quickly making the diagnosis scurvy definitive at that time.

Albumin is the most abundant of the circulating plasma proteins. Decreased levels are often associated with diseases of the liver or kidneys, inflammatory conditions, and malnutrition. More than half of our patients with scurvy had varying degree of hypoalbuminemia when

tested. None of our patients had documented disturbances in serological markers of liver or kidney disease suggesting malnutrition as a primary contributor. This marker may be useful when assessing patients with suspected nutritional deficiencies and perhaps may be used as follow-up marker of improvement. Recognizing signs of malnutrition or unusual symptoms unique to scurvy, or uncommonly seen in other bleeding disorders can aid in timely diagnosis. Features of a nutritional assessment associated with malnutrition include weight loss, change in dietary habits from the patient's norm and the presence of persistent gastro-intestinal symptoms. The physical findings of malnourishment include presence of edema and/or ascites and muscle wasting [20].

4.3. Management

Recommendations for how to dose vitamin C replacement differ among studies. The most commonly recommended treatment dose is 300 mg daily in divided doses [8,12,21]. Other regimens including doses as high as 1–2 g have also been used and are followed by tapering doses and maintenance of a daily low-dose supplementation [11,21,22]. It is unclear if clinical resolution is dose-dependent, occurring faster with more intensive regimens. Moreover, supplementation can be provided via oral or intravenous routes. Practice among the hematologists treating our cohort of patients also varied. Most patients were started on oral supplementation with doses above 500 mg daily. To our knowledge, there are no studies addressing the difference between the two routes of administration with regards to clinical improvement and vitamin C level recovery. Patients failing oral supplementation were generally treated with parenteral vitamin C therapy. This indicates the importance of patient follow up including assessment for resolution of symptoms and verification of vitamin C level improvement with laboratory testing.

Clinical resolution generally occurs over a period of days to weeks. Various case reports and series reported improvement in subjective generalized symptoms such as fatigue and musculoskeletal involvement within the first week of therapy [8,11,12,22]. Cutaneous lesions and hair changes tend to resolve within the first month [8,11,12,21]. Gingival lesions and anemia are both reported to take between several weeks to three months to resolve [8,12,21,23]. While prognosis of scurvy is reported to be excellent, we were not able to determine time to resolution for our patients due to lack of documentation [22]. Only one patient died in the time period evaluated. As death from scurvy usually occurs from cardiovascular collapse and multiorgan dysfunction or secondary infections of cutaneous lesions and our patient had none of these at the time of death, it is not likely that scurvy was the cause of his demise [21,22].

5. Conclusions

While uncommon, scurvy should be recognized as a possible etiology of a bleeding tendency. Knowledge of the unique signs and symptoms associated with the disease as well as a general increased awareness can help shorten the time to diagnosis and effective treatment of this condition. The finding of high rates of PPI use in our cohort suggests that the effect of such drugs on vitamin C levels merits further investigation.

Declaration of interests

No financial or personal conflicts of interests to declare by any of the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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