Dietary Supplements, Isotretinoin, and Liver Toxicity in Adolescents: A Retrospective Case Series

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abstract

Isotretinoin is the most effective acne therapy available, but has the potential for a number of adverse side effects, including transaminitis. The iPLEDGE isotretinoin program recommends avoiding some herbals and supplements due to potential side effects. However, little is known about the effects of protein supplements on the liver, particularly in patients taking isotretinoin. We designed a retrospective chart review to evaluate the symptoms, diagnosis, treatment, and outcome of patients on or preparing to take isotretinoin therapy who were concurrently ingesting protein or herbal supplementation and who developed transaminitis. In 100% (8/8) of cases, dietary supplementation was determined to be at least a possible cause of elevated liver transaminases. In 75% (6/8) of cases, dietary supplement appears to be the most likely cause at some point in their evaluation. Most of our patients' elevations in aspartate aminotransferase and/or alanine aminotransferase were likely caused by supplementation with protein, creatine, or herbal extracts, rather than prescribed isotretinoin or tetracycline antibiotics for acne. Hence, dietary supplementation may cause liver function abnormalities. As supplement usage appears common in teenagers, clinicians should consider counseling their patients to avoid these products, particularly when prescribing known hepatotoxic drugs.

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Acne vulgaris affects most individuals at some point in life, and moderate to severe disease develops in ∼20% of adolescents.[1] Treatments for moderate to severe disease include oral antibiotics and oral isotretinoin.[2] Although effective, isotretinoin is associated with adverse effects,[3] including elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[4,5]

The iPLEDGE program for isotretinoin recommends avoiding herbals and supplements[6] that young athletes use for supposed health, recovery, and performance enhancement.[7–9] The safety of these supplements and their effects on the liver are incompletely understood.

Our study objective was to assess the effects of protein and herbal supplementation on liver transaminases in adolescent patients and the effects of combined isotretinoin and protein or herbal supplementation on the liver via evaluation of AST or ALT.

METHODS

A retrospective chart review identified 8 adolescent patients with abnormal liver function tests obtained as part of their isotretinoin treatment plan, who were concurrently ingesting supplements. All patients were seen during a 12-month period at Rady Children's Hospital–San Diego Outpatient Dermatology office for the

TABLE 1 Association of Supplements with Transaminitis

Case No.	Age, Sex	Elevated Liver Transaminase(s), IU/L	Cumulative Dose of Isotretinoin at Time of Elevated ALT or AST, mg/kg	Likely Cause of Elevated Liver Transaminase(s)
Supplements most likely caused transaminitis				
1	17, boy	ALT 57 AST 37	13.1	Protein supplements
2	15, boy	ALT 55 AST 49	94.5	Protein and muscle-building supplements and energy drinks
3	16, boy	ALT 50 AST 29	N/A	Initially: protein supplements, creatine supplements, minocycline, and/or viral illness Later causes: protein and/or creatine supplements
4	17, boy	ALT 40 AST 140	N/A	Green tea supplements
5	16, girl	ALT 27 AST 74	N/A	Protein supplements
6	15, boy	ALT 36 AST 187	92	Initially: protein supplements Later causes: protein supplements and/or illness
Supplements possibly caused or contributed to transaminitis				
7	16, boy	ALT 34 AST 65	114.4	Creatine supplements and/or isotretinoin
8	16, boy	ALT 56 AST 41	40.7	Protein supplementation and/or isotretinoin

N/A, not applicable.

treatment of acne vulgaris. Charts for patients who consumed protein or herbal supplementation and manifested abnormal liver function tests, defined as AST >32 IU/L and/or ALT >46 IU/L, noted as part of regular patient care for isotretinoin screening or monitoring, were reviewed. Serial laboratory results, interventions, and treatments were reviewed and assessed with no specific exclusion criteria. The aims of this study were to assess the effects of protein and herbal supplementation on the liver via AST and ALT blood levels and to determine the effects of combined isotretinoin and protein or herbal supplementation on the liver via AST and ALT blood levels. Approval for the study was obtained from the University of California, San Diego, Institutional Review Board.

RESULTS

Eight patients manifested transaminitis either just before or during the course of isotretinoin therapy. Each of these patients admitted to concurrently ingesting protein, creatine, or herbal supplementation (Table 1). Patients were asked about alcohol use (all denied), recent illness, and exercise level to exclude common causes of transient transaminitis. Patients were instructed to discontinue all supplements and, in some cases, oral isotretinoin. At follow-up, 87.5% (7/8) had normalization of liver transaminase levels. One remaining patient refused to discontinue protein supplementation, and continued to exhibit mildly elevated transaminase levels.

Cases in Which Supplements Most Likely Caused Transaminitis

Case 1

A 17-year-old healthy boy with normal baseline transaminases (ALT = 22 IU/L, AST = 28 IU/L) had an elevated ALT 57 IU/L 1 month after initiating isotretinoin therapy, and shortly after starting protein shake supplements. He was advised to stop supplemental protein intake and continue isotretinoin at the previously prescribed dosage of 20 mg daily. After 3 months, his ALT normalized to 44 IU/L. Because his ALT improved after stopping protein supplements despite continuing isotretinoin, the likely cause of elevated liver transaminase is protein supplements.

Case 2

A 15-year-old boy with normal baseline AST and ALT of 30 IU/L, while on a stable dosage of 60 mg per day isotretinoin, presented with a rise in AST to 49 IU/L and ALT to 55 IU/L. The only reported change before the elevated AST and ALT was the use of dietary supplements. The patient had been weight training daily and supplementing with protein and muscle-building supplements and energy drinks. He was instructed to continue isotretinoin but stop all protein supplements and limit weight training. Instead, the patient discontinued isotretinoin but continued protein supplements and intense exercise; months later, his transaminases remained elevated at AST 45 IU/L and ALT 48 IU/L. Because the patient had discontinued isotretinoin but continued protein supplementation, dietary supplements appear the likely cause of elevated liver transaminases.

Case 3

A 16-year-old male football player on 100 mg minocycline presented with an elevated ALT to 50 IU/L noted on pre-isotretinoin evaluation. He admitted taking concurrent protein and creatine supplements and reported a recent mild illness. He was instructed to discontinue minocycline and all supplements; he started isotretinoin 40 mg per day. Two weeks later, his ALT decreased to 44 IU/L; however, he admitted to still taking protein. One month later, off both protein and creatine supplements, his ALT improved to 39 IU/L; the patient continued isotretinoin. Later in the treatment

course, while continuing isotretinoin at 40 mg per day but increasing consumption of protein, his ALT increased to 44 IU/L. On follow-up, while continuing isotretinoin but eating a balanced diet and avoiding protein supplements, his ALT decreased to 33 IU/L. Minocycline and/or viral illness cannot be excluded as contributing to or causing the initially elevated ALT; however, subsequent significant improvement in his liver function tests occurred despite continued isotretinoin therapy and only after discontinuing his supplements. Therefore, the latter elevations are most likely due to protein and/or creatine intake.

Case 4

A 17-year-old boy taking minocycline 100 mg per day was found on prescreening isotretinoin laboratories to have an elevated ALT 40 IU/L and AST 140 IU/L. He acknowledged taking green tea supplements up to 7 glasses per day. His AST decreased to 60 IU/L 2.5 weeks after cessation of green tea, but continuing minocycline therapy, and further decreased to 14 IU/L 2 months later after discontinuation of both green tea and minocycline. He began isotretinoin 20 mg per day, and 1 month later, his AST and ALT were both 12 IU/L. As laboratories dramatically and quickly improved after discontinuing green tea alone but continuing minocycline, green tea supplements appear the most likely cause of transaminase elevation.

Case 5

A 16-year-old female competitive swimmer on doxycycline was found to have an AST of 74 IU/L and ALT of 27 IU/L on pre-isotretinoin screening laboratories. She acknowledged taking large amounts of supplemental protein shakes and bars. Two months after stopping all protein supplements but still continuing doxycycline and vigorous exercise, her AST decreased to 44 IU/L. She was subsequently treated with isotretinoin 40 mg per day and urged to avoid protein supplements. AST on follow-up ranged from 27 IU/L to 37 IU/L. The most likely cause of elevated AST was protein supplementation.

Case 6

A 15-year-old boy with a previous AST of 35 IU/L on 20 mg per day isotretinoin presented with an AST of 116 IU/L while taking daily protein shakes. Two weeks later, after discontinuing supplementation, his AST normalized to 30 IU/L. Subsequently, while on a stable dosage of 30 mg per day isotretinoin, the AST increased to 187 IU/L. The patient at this point admitted to reinstituting daily protein shakes plus 3 hours daily weight training and endorsed a recent illness. He was instructed to hold isotretinoin and all protein supplements and limit weight training to 1 hour daily. Although the patient did not limit weightlifting as recommended, he did stop taking protein supplements and 15 days later, his AST decreased to 29 IU/L. A month later, he restarted isotretinoin, continued working out, but refrained from protein supplements. His AST ranged from 38 to 43 IU/L during remaining treatment. The initially elevated AST of 116 IU/L appears secondary to protein supplements, and the subsequently elevated AST of 187 IU/L appears secondary to protein supplements and/or illness; isotretinoin is an unlikely cause.

Cases in Which Supplements Possibly Caused or Contributed to Transaminitis

Case 7

A 16-year-old male baseball player with baseline AST 35 IU/L had been tolerating isotretinoin treatment well for months and had a normal AST 28 IU/L while on a stable dosage of isotretinoin 60 mg per day. One month after that normal laboratory test, he presented with an elevated AST to 65 IU/L despite continuing the same dosage of isotretinoin. However, he did admit to recently using daily creatine supplements. He was instructed to stop isotretinoin and discontinue creatine supplements. Two weeks later, after stopping both, his AST decreased to 23 IU/L. He did not reinstitute isotretinoin therapy. The only reported change in risk factors before the elevated AST was creatine intake, a likely cause of AST elevation; however, isotretinoin cannot be ruled out as a contributing factor.

Case 8

A 16-year-old boy taking 40 mg per day isotretinoin (increased 1 month previously from 30 mg per day) and daily dietary protein had an elevation of ALT to 56 IU/L. He was instructed to stop both isotretinoin and protein supplements. Four weeks after stopping both, his ALT improved to 39 IU/L. Consequently, the cause of transient elevation could be isotretinoin and/or protein supplementation.

DISCUSSION

We initially chose to investigate the possible association of protein supplements with transaminitis when several patients in our practice were noted to have elevated liver function tests while on supplements, either with concurrent isotretinoin therapy, or on baseline laboratory evaluation before instituting isotretinoin therapy. By using chart review, 8 adolescent patients with elevated liver transaminase levels were identified who admitted to taking protein, creatine, or herbal supplementation while concomitantly taking or preparing to initiate isotretinoin therapy. In all cases in which dietary supplementation was discontinued, elevated liver transaminases were reversible. In 100% of cases, dietary supplementation appears a possible cause of elevated liver transaminases.

In 75% of patients (cases 1–6), dietary supplement appears the most likely cause at some point in the course. In the remaining 2 cases (7 and 8), concurrent isotretinoin precluded categorizing the etiology of their findings with the same certainty; however, we believe in these cases as well, supplements played a contributing or primary role. Patients were not prohibited from exercising; however, their exercise status could not uniformly be confirmed. It is therefore impossible to rule out exercise, or even alcohol consumption, which they did not admit to, as a confounding factor, but it does appear that protein supplements play a distinct role.

Tetracyclines have been reported to cause elevated liver transaminases.[10,11] Three patients in our study (cases 3–5) had improvement of liver enzymes after cessation of supplements while either continuing antibiotic treatment or initiating isotretinoin therapy. Derangement in liver enzymes, therefore, appears likely a result of dietary supplements, not antibiotic hepatotoxicity. This does not, however, eliminate the possibility of antibiotics, supplements, and/or viral illness contributing to these abnormalities. A patient taking minocycline (case 4) presented with significantly elevated liver enzymes while taking an herbal green tea extract. There are several reports of green tea extract, as well as other over-the-counter herbal supplements, leading to hepatotoxicity.[12,13] This patient's AST dramatically improved after discontinuing green tea supplementation.

There are reports of supplemental protein exacerbating acne flares in teenage athletes.[14,15] Our study population was receiving treatment of severe acne, which may have been exacerbated by dietary supplements.

Although the link between herbal supplements and hepatic impairment has been established in the literature,[16–18] to our knowledge, this is the first case series to address the relationship between protein/creatine supplements and elevated hepatic transaminases. Two previous case reports have described acute liver injury subsequent to protein supplemental intake, one with a mixed cholestatic and hepatocellular injury while taking whey protein, creatine, and amino acid,[19] and the other with cholestatic liver injury with minimally elevated transaminases due to whey protein and creatine supplements.[20] Our findings are consistent with these 2 previous reports and add increased evidence to support the association between protein supplements and elevated hepatic transaminases. This retrospective study, however, has some limitations, including a limited number of patients. Also, although there was no known contributing past medical history in our patients, we cannot rule out other potential causes of asymptomatic elevations in liver enzymes, such as vigorous exercise,[21] viral illness, tetracycline use, alcohol use (although denied by our patients), or fatty liver disease.[22] This study was unable to identify all patients taking protein, creatine, or other herbal supplementation in our patient population, thus precluding the ability to determine an exact incidence of liver toxicity in that population overall. The presence of several risk factors (eg, supplements in the presence of viral illness and/or isotretinoin therapy) may be required for liver enzyme elevations in some patients. Also, the significance of transient rises in AST and ALT is currently unknown.

CONCLUSIONS

The results of this small retrospective review support the belief held by many practitioners that protein and herbal supplements can affect liver function laboratory evaluations. This is particularly problematic when patients are concurrently taking isotretinoin and undergoing monthly liver function evaluation to rule out toxicity from that drug. In our study, elevations in AST and/or ALT, likely caused by supplementation with protein, creatine, or herbal extracts rather than prescribed isotretinoin or tetracycline for acne, appeared to be reversible in the vast majority of patients. We cannot eliminate the possibility that exercise or illness were contributing factors, and a larger prospective controlled study is required to confirm these findings. However, in the interim, it would be prudent to specifically ask all patients who will be undergoing isotretinoin therapy if they are taking supplements, and counsel them that this might lead to laboratory abnormalities that could preclude or modify continuing therapy. As protein, creatine, and herbal supplement ingestion appears to be increasing in teenagers, and many patients do not consider them "drugs," it is important to consider counseling patients to avoid these products, particularly when prescribing drugs with known potential for hepatotoxicity.

ABBREVIATIONS

AST: aspartate aminotransferase
ALT: alanine aminotransferase

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