ACADEMIA | Letters

Concomitant isotretinoin therapy and whey protein supplementation: an underreported and hepatotoxic combination in adolescents - Literature Review

Alberto Moscona-Nissan

In addition to isotretinoin documented liver toxicity as a side effect and considering acne high prevalence among teenagers and young adults, it is fundamental to examine concurrent food supplements patients may be consuming while undergoing isotretinoin treatment. In recent years, whey protein (WP) products have acquired a fast-rising popularity due to physical performance improval, contribution to protein synthesis and muscle mass gain. Concomitant isotretinoin therapy and WP supplementation might be an underreported combination that could lead to major hepatotoxic effects and transaminase elevation. The present paper aims to review individual isotretinoin and WP hepatotoxicity and concurrent consumption cases that have led to transaminase elevation. Further research should be conducted in order to elucidate the mechanisms, consequences and severity of this preventable adverse effect.

Full Text

Isotretinoin (13-cis-retinoic acid) has remained as the most effective treatment for severe acne since it was introduced in the 1980´s[1,2]. As a retinoid and vitamin A derivative, may lead to a broad spectrum of adverse reactions, which include cheilitis, eczema, tiredness, teratogenicity, mood changes, nosebleeds, elevation of triglycerides and liver enzymes[3].

Several studies [4,5,6] have documented an elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in patients being treated with oral isotretinoin.

Corresponding Author: Alberto Moscona-Nissan, albertomoscona@gmail.com
Citation: Moscona-Nissan, A. (2021). Concomitant isotretinoin therapy and whey protein supplementation: an underreported and hepatotoxic combination in adolescents - Literature Review. *Academia Letters*, Article 1277. https://doi.org/10.20935/AL1277.

A systematic review and meta-analysis4 conducted in 2016, evaluated a total of 1574 patients with acne (26 clinical trails) undergoing oral isotretinoin treatment, with doses of 40 mg/d or more, duration of at least 4 weeks and age from 9 to 35 years.[4] Hepatic panel results showed a mean values of nonbaseline AST of 22.67 U/L (99% CI, 19.94-25.41 U/L) and a difference in mean values of 3.72 U/L between baseline and follow-up measurements (6.6 weeks)[4]. For ALT, the mean value of nonbaseline levels of 21.77 U/L (99% CI, 18.96-24.59 U/L) and a difference in mean values of 3.22 U/L (99% CI, 0.99-5.45 U/L) after follow-up (6.5 weeks).[4]

Furthermore, a retrospective, observational and longitudinal study5 of 130 patients evaluated 70 patients who met the eligibility criteria by completing a minimal 3 month treatment and constant testing was performed in 2012[5]. The population studied had the following characteristics: 39 women (55.7%) and 31 men (44.3%), mean age of 22.2 years (range from 13 to 42), mean weight of 63.3 kg (range from 43 to 120 kg).5 Patients were treated with 20 to 80 mg of oral isotretinoin daily, with a mean dosage of 41.43 ± 10.53 mg during 4 to 12 months.[5] Serum ALT and AST levels were measured at the beginning of the treatment and three months after5. For ALT, the mean of baseline levels were 18.24 ± 8.31 U/L and increased to 23.34 ± 20.02 U/L. For AST, the mean baseline was 20.44 ± 6.25 U/L, and after three months was 24.38 ± 11.9 UL5. A retrospective cohort6 that comprised 13,772 patients from 13 to 50 years undergoing oral isotretinoin reported an incidence of new abnormalities in patients with normal values at baseline of 11% for transaminase levels6.

In addition to liver toxicity caused by isotretinoin, it is fundamental to consider that teenagers and young adults are the population mostly affected by acne, with a reported prevalence of 95%. Therefore, it is fundamental to consider additional food supplements (such as whey protein products) teenagers may be consuming while undergoing isotretinoin treatment. In recent years, whey protein (WP) supplements have acquired a fast-rising popularity. In 2016, whey protein represented a global market value of approximately 7.7 billion USD7. For 2021, its market value is expected to reach 9 billion USD, with an average annual growth of 4%.[7]

Whey protein is an ingredient contained in milk that is considered a useful nutrient.[8] The main two sources of protein in milk are casein and whey protein8. WP supplements contain alpha-lactalbumin, beta-lactalbumin, minerals, big amounts of branched amino acids and glutamine.[8] According to evidence, whey protein is widely used among athletes, with an estimated consumption of 90%.[8] These supplements improve physical performance by contributing to protein synthesis and increasing lean muscle mass gain. Their wide availability at stores and websites has allowed its use without prescription in amateur athletes, that could ignore possible risks associated with chronic and excessive consumption.[8]

Whey protein metabolism consists in the separation of the nitrogenous part from amino

Corresponding Author: Alberto Moscona-Nissan, albertomoscona@gmail.com
Citation: Moscona-Nissan, A. (2021). Concomitant isotretinoin therapy and whey protein supplementation: an underreported and hepatotoxic combination in adolescents - Literature Review. *Academia Letters*, Article 1277. https://doi.org/10.20935/AL1277.

acids in the liver, process called deamination[8]. Then, the nitrogenous part results in ammonia, which is transformed into urea through the urea cycle at the liver and eventually excreted by the kidneys. The resting part of amino acids circulate in the blood stream and reach muscles to increase protein synthesis.[8]

Liver toxicity induced by whey protein has been documented in animal models. Gürgen, et. al (2014)[9] researched short and long-term inflammatory and apoptotic effects of whey protein in non-exercising Wistar rats. A total of 30 young male rats were randomized into three groups as control group, short-term WP consumption (5 days) and long-term WP (6 weeks).[9] Same controlled conditions were applied to each group to eliminate probable variation in histological and biochemical parameters.9 At the end of the experiment, mean IL-1ß values were measured through ELISA and reported to be higher in the long-term WP group (82.14 ± 31.64 ng/mg protein) than in short-term WP (34.48 ± 12.17 ng/mg) and control group (9.51 ± 7.97 ng/mg). IL-6 and TNF-a levels were not significantly distinct between groups. Regarding transaminases levels, higher levels were found in the long-term WP group (mean AST 207.81 ± 68.08 and mean ALT 54.45 ± 13.98), followed by the short-term WP (AST 129.44 ± 16.72 and ALT 45.00 ±10.39) and lower levels in the control group (AST 97.10 ± 9.99 and ALT 8.50± 3.80).[9]

Serum apoptotic Cytokeratin 18 Neoepitope M30 (CK-18 M30) was measured through ELISA. CK-18 M30 is a quantitative indicator of apoptosis in epithelial cells, given by caspase cleavage of intracellular substrates such as keratin 18 (K18). The short-term WP group exhibited a higher mean CK-18-M30 levels (7.18 ± 2.32 ng/mg) than the control group (5.05 ± 2.38 ng/mg) and the long-term WP group (3.80 ± 1.33 ng/mg).9 The above is consistent with the biopsies performed, in which intense CK-18 expression was seen around the central vein of hepatic lobules in the short-term group. Higher apoptosis rates were also demonstrated in the short-term WP group by a higher amount of TUNEL-positive stained cells.[9]

Given isotretinoin and WP documented individual liver toxicity, their combination may synergize major liver toxicity. Considering epidemiological data and its high consumption among teenagers and young athletes concurrent intake is plausible and frequent. Nevertheless, scarce research and few papers have evaluated potential adverse effects of this combination, which could be a preventable cause of hepatic damage.

A retrospective case series, (DeKlotz, et al. 2017)[1] identified eight teenage patients who presented transaminase elevation while undergoing isotretinoin therapy and were concurrently consuming supplements such as protein, creatine or herbal supplements. Recent alcohol consumption was excluded, being concomitant isotretinoin and dietary supplements the most probable cause of transaminitis. However, in 3 out of 8 cases tetracyclines were additionally prescribed and could act as a confusing variable.[9] Among the 8 cases described,

Corresponding Author: Alberto Moscona-Nissan, albertomoscona@gmail.com
Citation: Moscona-Nissan, A. (2021). Concomitant isotretinoin therapy and whey protein supplementation: an underreported and hepatotoxic combination in adolescents - Literature Review. *Academia Letters*, Article 1277. https://doi.org/10.20935/AL1277.

6 of them (75%) reported specific protein supplements consumption, such as protein shakes or bars.

In case 1, DeKlotz, et al. (2017) exposed a 17 year-old boy with normal baseline liver function enzymes (ALT 22 IU/L, AST 28 IU/L) who presented an ALT elevation to 57 IU/L the first month of concomitant 20 mg of isotretinoin per day and protein supplements. Nevertheless, ALT elevation was reversible (44 IU/L) after stopping protein ingestion, but maintaining isotretinoin.[1]

In case 2, a 15 year-old boy with normal baseline liver function enzymes (AST and ALT of 30 IU/L) presented an AST elevation to 49 IU/L and ALT to 55 IU/L after 20 mg of isotretinoin per day and protein supplements for weight training and muscle-building.[1]

In case 6, a 15 year-old boy with baseline AST of 35 IU/L presented an AST elevation of 116 IU/L while undergoing 20 mg of isotretinoin per day and consuming protein shakes concurrently.[1]

In case 8, a 16 year-old boy being treated with 40 mg isotretinoin per day consuming protein supplements concomitantly presented an ALT elevation to 56 IU/L.[1]

Concurrent isotretinoin therapy and whey protein supplementation might be an underreported combination that is causing liver damage among teenagers undergoing acne treatment and protein supplementation regimes to increase muscle mass. This may lead to major hepatotoxicity, since individual liver damage of isotretinoin and WP has been confirmed. Further research should be conducted in order to elucidate the mechanisms, consequences and severity of this possible adverse effect, which could be prevented by completing a thorough clinical history and warning patients before isotretinoin is prescribed.

References:

1. DeKlotz, Cynthia Marie Carver, Keith D. Roby, and Sheila Fallon Friedlander. "Dietary Supplements, Isotretinoin, and Liver Toxicity in Adolescents: A Retrospective Case Series." *Pediatrics* 140, no. 4 (October 2017): e20152940. https://doi.org/10.1542/peds.2015-2940.

2. Bauer, Lindsey B., Jennifer N. Ornelas, Dirk M. Elston, and Ali Alikhan. "Isotretinoin: Controversies, Facts, and Recommendations." *Expert Review of Clinical Pharmacology* 9, no. 11 (November 2016): 1435–42. https://doi.org/10.1080/17512433.2016.1213629.

3. Rademaker, Marius. "Adverse Effects of Isotretinoin: A Retrospective Review of 1743 Patients Started on Isotretinoin: Adverse Effects of Isotretinoin." *Australasian Journal*

Corresponding Author: Alberto Moscona-Nissan, albertomoscona@gmail.com
Citation: Moscona-Nissan, A. (2021). Concomitant isotretinoin therapy and whey protein supplementation: an underreported and hepatotoxic combination in adolescents - Literature Review. *Academia Letters*, Article 1277. https://doi.org/10.20935/AL1277.

of Dermatology 51, no. 4 (November 2010): 248–53. https://doi.org/10.1111/j.1440-0960.2010.00657.x.

4. Lee, Young H., Thomas P. Scharnitz, Joshua Muscat, Allshine Chen, Gaytri Gupta-Elera, and Joslyn S. Kirby. "Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-Analysis." *JAMA Dermatology* 152, no. 1 (January 1, 2016): 35. https://doi.org/10.1001/jamadermatol.2015.3091.

5. Vieira, Andreia Salezze, Vanessa Beijamini, and Ana Carolina Melchiors. "The Effect of Isotretinoin on Triglycerides and Liver Aminotransferases." *Anais Brasileiros de Dermatologia* 87, no. 3 (June 2012): 382–87. https://doi.org/10.1590/S0365-05962012000300005.

6. Zane, Lee T., Wendy A. Leyden, Ann L. Marqueling, and M. Michele Manos. "A Population-Based Analysis of Laboratory Abnormalities During Isotretinoin Therapy for Acne Vulgaris." *Archives of Dermatology* 142, no. 8 (August 1, 2006). https://doi.org/10.1001/archderm.142.8.1016.

7. Keogh, Cian, Chenguang Li, and Zhifeng Gao. "Evolving Consumer Trends for Whey Protein Sports Supplements: The Heckman Ordered Probit Estimation." *Agricultural and Food Economics* 7, no. 1 (December 2019): 6. https://doi.org/10.1186/s40100-019-0125-9.

8. Vasconcelos, Quezia Damaris Jones Severino, Tatiana Paschoalette Rodrigues Bachur, and Gislei Frota Aragão. "Whey Protein Supplementation and Its Potentially Adverse Effects on Health: A Systematic Review." *Applied Physiology, Nutrition, and Metabolism* 46, no. 1 (January 2021): 27–33. https://doi.org/10.1139/apnm-2020-0370.

9. Gürgen, Sg, At Yücel, Aç Karakuş, D Çeçen, G Özen, and S Koçtürk. "Usage of Whey Protein May Cause Liver Damage via Inflammatory and Apoptotic Responses." *Human & Experimental Toxicology* 34, no. 7 (July 2015): 769–79. https://doi.org/10.1177/0960327114556787.

Corresponding Author: Alberto Moscona-Nissan, albertomoscona@gmail.com
Citation: Moscona-Nissan, A. (2021). Concomitant isotretinoin therapy and whey protein supplementation: an underreported and hepatotoxic combination in adolescents - Literature Review. *Academia Letters*, Article 1277. https://doi.org/10.20935/AL1277.