



Toxic hepatitis in a group of 20 male body-builders taking dietary supplements

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ABSTRACT

Dietary supplements have been used for decades for enhancing muscle growth. The harm caused by some of these products is well documented. We investigated and reported toxic hepatitis in 20 male athletes following self-prescribing of a number of dietary supplements which are lesser known. The patients' ages ranged from 24 to 32 with a mean of 28 years. They had taken three kinds of supplements for 1 year including testosterone optimizer agent T Bomb II, a creatine supplement Phosphagen and an amino acid based supplement Cell-Tech. Based on the history, clinical examination, and laboratory findings the cases were diagnosed as toxic hepatitis. After discontinuation of taking the supplements, clinical recovery and improvement of liver function tests were achieved within 30 days. Causality assessment with the CIOMS (Council for International Organization Medical Sciences) scale showed a "possible" grade of causality (+5 points) for these supplements. It can be concluded that these newer anabolic supplements may induce toxic hepatitis. Since the health risks of them may be severe, the use of these kinds of dietary supplements should be discouraged.

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1. Introduction

Athletes are affected in various ways by self-prescription of the over-the-counter medications and by the misuse of food supplements. Dietary supplements and their effects on the performance of the body builders should be a matter of concern to the athletes' health. Despite the fact that these supplements are sometimes associated with serious or deadly adverse effects, they are not generally under serious investigations for their efficacy and safety. Even safe supplements like vitamins, creatine, and protein powders can be toxic particularly if they are taken in high doses for a long time. For example, creatine supplementation may cause renal dysfunction and hepatotoxicity (Bizzarini and De Angelis, 2004). There are four different categories of supplements on the market according to their principal contents (i.e., creatine, prohormones, mental enhancers, and branched chain amino acids). There may be some harmful additives in dietary supplements not indicated on the label of their packages. These added substances may also be the reason of a positive doping test in an athlete during sport competitions (Foster and Tyler, 1999; King et al., 1999; Haller and Benowitz, 2000; Poortmans and Dellalieux, 2000; Kamber et al., 2001). This study was conducted in 2011 for the purpose

of evaluating the possible side effects of some commonly used supplements on the human health.

2. Methods

In this study, we documented the cases of 20 male body-builders with no past medical history, who developed hepatitis secondary to chronic ingestion of Phosphagen, a creatine supplement (Fig. 1); T-Bomb II, an optimizer of testosterone production (Fig. 2) and Cell-Tech, an amino acid and creatine-based supplement (Fig. 3) for 1 year. They were separately referred to a physician with symptoms such as fever, chills, weakness and fatigue. Clinical examinations suggested them as the cases of suspicious toxic hepatitis with no past history of alcohol consumption. Therefore, the following laboratory tests were requested for confirmation of clinical diagnosis: complete blood count (CBC), blood aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (T Bili), urea, creatinine (Creat), prothrombin time (PT), hepatitis B surface antigen (HBS Ag), anti hepatitis B core antibody (Hbc Ab), anti hepatitis C virus antibody (HCV Ab), anti hepatitis E virus antibody (HEV Ab), and anti hepatitis A virus antibody (HAV Ab). Additional test included anti CMV-IgM, anti EBV-IgM, and anti HSV-IgM were performed.

Biochemical tests were performed via colorimetric methods using Technicon RA-1000 chemistry analyzer (Bayer Diagnostics, Ireland). To reject the presence of infectious hepatitis, relevant tests were conducted on the serum samples using commercially available human ELISA kits according to the manufacturer's protocols. All experiments were done in Abou-Reihan clinical laboratory (Mashhad, Iran).

3. Results

The ages of the patients ranged from 24 to 32 years. They had used all three supplements. Briefly, in clinical examinations, they

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Nutrition Facts		
Serving Size 1 1/2 teaspoons		
Servings Per Container 100		
Amount Per Serving		
	Serving	% DV
Creatine Monohydrate (Equivalent to 4.4 g of Anhydrous Creatine Base)	5 g	-
*percent Daily Values are based on a 2,000 calorie diet.		
*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.		

Fig. 1. Information sheet of Phosphagen.

had the symptoms such as fever, chills, weakness, fatigue, itching, jaundice, and elevated blood pressure in common (Table 1). Hemoglobin content, Hct%, WBC and differentiation counts did not show any significant pathological findings (Table 2). Transaminases and total bilirubin were highly elevated as described in Table 3. Creatinine was mildly elevated. Relevant tests for hepatitis A, B, C and E were negative. Tests for anti CMV-IgM, anti EBV-IgM, anti HSV-IgM were negative. In the present study the ratios of ALT:its upper limit of normal range (R_1) and ALP:its upper limit of normal range (R_2) were determined. Then, the ratio (R) of $R_1:R_2$ was calculated. Since the R was more than 5 in all patients, therefore, they had a clear hepatocellular type of liver toxicity rather than a cholestatic or cholestatic-hepatocellular injury (Teschke et al., 2008, 2009). The patients were improved clinically (symptoms free) and their biochemical data returned to near normal values one month after cessation of the supplements at different time intervals (Table 3).

In this study we also used a main-test of a structured causality assessment method suitable for the diagnosis of DDS (drugs and dietary supplements) hepatotoxicity (Teschke et al., 2008, 2009). This main-test represents the quantitative causality assessment and is based on the CIOMS (Council for International Organization of Medical Sciences) scale (Benichou et al., 1993; Danan and Benichou, 1993).

4. Discussion

With the main-test for hepatocellular damage all three supplements were evaluated quantitatively, and the answers were scored from -3 to +3. The total number of the score was +5 points. Therefore, the grade of causality for probable hepatocellular injury caused by these supplements was "possible" (Table 4).

In the last decades, dietary supplements like creatine, prohormones and amino acids have been widely taken by athletes who thought that these products would elevate their physical abilities (Ekblom, 1996; Engelhardt et al., 1998; Appelgate, 1999; Di Luigi et al., 1999; Terjung, 2000; Ziegenfuss et al., 2002; Sundgot-Borgen et al., 2003). T Bomb II is a brand name for a product made by Maximum Human Performance, Inc. (MHP). This product is widely commercially available and marketed on line. It is an optimizer of testosterone production. It has been suggested that oral intake of this product increase circulating testosterone levels and induce muscle gain. Contrary to these claims however, some studies have showed that these compounds are neutral at increasing athletic performance (Brown et al., 2006). According to the manufacturers, T Bomb II is scientifically formulated to help optimize the production and balance of key hormones for male performance. It helps boost the natural production of testosterone, lowers estrogen levels by inhibiting the conversion of testosterone to estrogen, increases free testosterone by lowering SHBG (Sex Hormone Binding Globulin), and inhibits the production of DHT (Dihydrotestosterone). Anabolic steroids such as testosterone have been associated with abnormal liver function tests (Dickerman et al., 1999; Kicman, 2008). There are several different types of herbal medicines in this supplement as hormone optimizing blend. Herbal preparations are widely used as nonprescription medications and thought to be safe because they are "natural". They are classified as dietary supplements and also cannot be sold as a treatment or cure for a particular disease or condition. For this reason they do not require prior approval by the Food and Drug Administration (Stedman, 2002; Willet et al., 2004).

The search for natural products with side effects has provided a clue that some herbal medicines of T Bomb II are hepatotoxic. Saw palmetto extract can reduce the symptoms of enlarged prostate, including frequent urination, painful urination, sudden urge to urinate, and inability to urinate. There are some concerns that saw palmetto extract might cause liver or pancreas problems in some people. There are two reports linking saw palmetto products to hepatotoxicity (Web/MD). Red clover and Puereria root extracts contain "isoflavones" which are changed in the body to "phytoestrogens" that are similar to the hormone estrogen (Web/MD). Isoflavones are a common class of phytoestrogens. They are plant-derived compounds capable of estrogenic or anti estrogenic effects. Isoflavones are structural mimics of endogenous 17 beta-estradiol (Seielstad et al., 1995). Phytoestrogens are hypothesized to induce hepatotoxicity through mechanisms similar to hormonal estrogens (Melgarejo and Cupp, 2000). Thus, Saw palmetto berry, Red clover and Puereria root extracts might cause hepatotoxicity. We didn't find any clear hepatotoxicity report in different medical databases or literature reviews for the remaining herbal medicines of T Bomb II. Nevertheless, hepatotoxicity or drug induced liver injury (DILI) is unpredictable and herbal remedies can cause DILI (Tarantino et al., 2009a,b). On the other hand, hepatotoxicity due to taking natural preparations has become widespread in countries. For example, an internet search revealed that use of these products has continuously increased in the United States over the past decade and that about thirty percent of patients attending a liver center use herbal preparations (Stedman, 2002). However, we collected the side effects of herbal substances used in T Bomb II (Table 5) based on available information on the internet medical databases (Web/MD,¹ Emedicinehealth² and RX list³).

Creatine is an organic compound which is synthesized in the liver and kidneys. It is found in most protein rich foods such as meat (Metzl et al., 2001). Using creatine as a component of athletes'

¹ Web/MD. [<http://webmd.com>].

² Emedicinehealth. [<http://emedicinehealth.com>].

³ Rxlist. [<http://rxlist.com>].

Supplement Facts		
Serving Size 3 Tablets		
Servings Per Container 56		
Amount Per Serving		% DV
Magnesium (as Magnesium Oxide)	15.00 mg	4%
Zinc (as Zinc Aspartate)	25.00 mg	167%
Copper (as Copper Gluconate)	2.00 mg	100%
Optimone 5™: Five Phase Hormone Optimizing Blend	903.00 mg	**
Chrysin		**
Zinc (as Zinc Aspartate)		**
Beta sitosterol		**
DIM (diindolymethane)		**
Stinging Nettle Leaf Extract (4:1)		**
Pygeum Africanum Extract (25% total sterol)		**
Tribulus terrestris (40% furastanol saponins)		**
Fenugreek 4:1 extract (seed)		**
Red clover extract (40% isoflavones)		**
Saw Palmetto berry extract (90% total sterols & free fatty acids)		**
Bioprene® black pepper extract		**
longjack 20:1 extract (root)(Eurycoma longifolia Jack)		**
Avena Sativa 10:1 extract (aerial parts)		**
Pueraria root extract 40% isoflavones.		**
2nd Messenger™ Hormone Amplifiers - Receptor Signal Transduction Blend	625.00 mg	**
Magnesium (as Magnesium Oxide)		**
L-Arginine		**
Glycine		**
L-Methionine		**
NADH (reduced B-nicotinamide adenine dinucleotide)		**
Dipentene (Limonene)		**
Flaxseed (fatty acid profile-linolenic 8.0% linoleic 2.5% & oleic 2.5%)		**
DL-malic acid		**
cordyceps (<i>cordyceps sinensis</i>)		**
** Daily Value (DV) not established		

Fig. 2. Information sheet of T Bomb II.

Table 1
Clinical symptoms of 20 athletes before cessation of the supplements.

Symptoms	Before cessation supplements [*]
Fever and chill	12
Weakness	16
Fatigue	16
Itching	20
Jaundice	20
Elevated blood pressure	10

^{*} Indicates the total number of patients with the relevant symptoms.

nutritional regimen has been admitted. Creatine increases performance in short, high-intensity exercises (van Loon et al., 2003). Side effects of this product include weight gain, could be secondary to water retention (Harris et al., 1992; McNaughton et al., 1998). There is one report of hepatotoxicity associated with creatine supplements (Bizzarini and De Angelis, 2004). These products have

been also reported to increase blood creatinine, which is in agreement with our athletes' mildly elevated levels (Poortmans et al., 1997; Poortmans and Francaux, 1999). However, creatine experimentally appears to be safe, although more trial data are needed.

Considering the types of supplements taken by our athletes, it is difficult to realize which compounds have caused hepatotoxicity. T Bomb II, the testosterone optimizer compound taken by our athletes, and Cell-Tech, the amino acid-based supplement, do not have available safety data. Given the commonly use of these supplements and lack of reliable information on them, it is important to know more about these kinds of products and their possible adverse effects on humans.

This study highlights potential side effects of diverse unchecked muscle-building supplements, which may induce toxic hepatitis. It is strongly advised that there should be some concerns about possible supplement-induced liver injury in all bodybuilders, or other athletes. The most important thing that we have to consider is that T Bomb II, Cell-Tech, Phosphagen and other similar commercially

Supplement fact		
Serving size: 100g		
Serving per container: 30		
Ingredient	Amount	% Daily Value**
Calories	310	
Total Carbohydrate	77g	26
Sugars (from Dextrose)	75g	
Vitamin C	250mg	417
Calcium	80mg	8
Iron	1.8mg	10
Phosphorous (as creatine phosphate and dipotassium phosphate anhydrous)	40mg	4
Magnesium	70mg	20
Chromium (as chromium picolinate)	250mcg	208
Sodium	70mg	3
Potassium	40mg	<2
CreaMax	10000mg	
-Creatine Monohydrate		†
-Creatine Phosphate		†
-Creatine Pyruvate		†
Osmodrol	2608mg	
-Glycine		†
-L-Methionine		†
-L-Arginine		†
-Taurine		†
-L-Glutamine		†
-L-Glutamic Acid		†
-L-Lysine HCl		†
-L-Leucine		†
-L-Isolucine		†
-L-Valine		†
-Alpha-Ketoglutarate		†
InsuloDrive	1000mg	
-L-Aspartic Acid		†
-L-Phenylalanine		†
-Inosine		†
-L-Arginine Pyroglutamate		†
-Inositol		†
-Leaf of Medicago sativa		†
Lipoic-Tech	200mg	
-AlphaLipoic Acid		†

** Percent Daily Value is based on a 2000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.
† Daily Value not established.

Fig. 3. Information sheet of Cell-Tech.

Table 2
Hematological parameters of 20 athletes before and 30 days after cessation of the supplements.

Parameter	Before cessation	After cessation
Hb (g/dl)	16.0 ± 0.3	16.3 ± 0.25
Hct (%)	47.4 ± 0.8	47.9 ± 1.0
WBC (cell/ μ l)	9548 ± 358	8433 ± 458
Neutrophil	6405 ± 254	5805 ± 254
Lymphocyte	2598 ± 205	2440 ± 180
Monocyte	328 ± 28	400 ± 43
Eosinophil	235 ± 38	197 ± 25

Data shown are in terms of mean ± SD.

available supplements are unchecked and not approved by the FDA. The safety of these agents is not known. Any athletes using compounds such as T Bomb II should be warned of the many pos-

sible adverse effects including toxic hepatitis. Since the health risks of them may be severe, the use of these kinds of dietary supplements should be discouraged.

Table 4 (continued)

Hepatocellular injury injury	Score	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20
• Alcoholism (AST/ALT \geq 2)																					
• Acute recent hypotension history (particularly if underlying heart disease)																					
Group II																					
• Complications of underlying disease(s)																					
• Infection suggested by PCR and titre change for CMV (anti-CMV-IgM/IgG), EBV (anti-EBV-IgM/IgG), HSV (anti-HSV-IgM/IgG), VZV (anti-VZV-IgM/IgG)																					
Evaluation of group I and II																					
• All causes-groups I and II – reasonably ruled out	+2																				
• The 6 causes of group I ruled out	+1																				
• 5 or 4 causes of group I ruled out	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
• Fewer than 4 causes of group I ruled out	-2																				
• Nondrug cause highly probable	-3																				
8. Previous information on hepatotoxicity of the drug																					
• Reaction labelled in the product characteristics	+2																				
• Reaction published but unlabelled	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1
• Reaction unknown	0																				
9. Response to readministration																					
• Doubling of ALT with the drug alone	+3																				
• Doubling of ALT with the drugs already given at the time of 1st reaction	+2																				
• Increase of ALT but less than N in the same conditions as for the first administration	+1																				
• Other situation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total points		+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5	+5

Total points/causality: \leq 0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; 8, highly probable. P, patients; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HAV, hepatitis A virus; HBC, hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

Table 5

Side effects of herbal substances used in T Bomb II based on available information on the internet medical databases.

Herbal substances	Side effects/via oral root exposure
Chrysin	No side effects have been reported
Beta sitosterol	Nausea, indigestion, gas, diarrhea, constipation, erectile dysfunction and loss of interest in sex
Diindylmethan	It is safe in small amounts. There is not information about Diindylmethan in larger amounts
Stinging nettle leaf extract	Stomach complaint and sweating. The safety of its using long term is unknown
Pygeum africanum extract	Nausea and abdominal pain. It is safe for most people
Tribulus terrestris	There is no information about Tribulus terrestris safety in a long period of time
Fenugreek extract	Congestion, coughing, wheezing, facial swelling, severe allergic reactions in hypersensitive people, and hypoglycemia
Red clover extract	It can cause rash -like reactions, muscle ache, headache, nausea, and vaginal bleeding
Saw palmetto extract	Mild side effects include dizziness, headache, nausea, vomiting, constipation, and diarrhea. Excessive bleeding in persons who took it before surgery. There have been two reports linking saw palmetto products to hepatotoxicity and one report linking saw palmetto to pancreatitis
Black pepper extract	It might be safe for most people
Longjack extract	There is not enough information about Longjack safety
Avena sativa extract	It is safe for most people. It can cause intestinal gas and bloating
Pueraria root extract	No side effects have been reported in clinical studies
Limonen	Limonen appears to be safe for most people in medicinal amounts
Flaxseed	Bloating, gas, abdominal pain, constipation, diarrhea, stomachache, and nausea
Cordyceps	Cordyceps seems safe for most people

Conflict of Interest

The authors declare that there are no conflicts of interest.

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