

SHORT COMMUNICATION

Unapproved Weight Gain Supplement as a Cause of Avascular Necrosis: A Cautionary Report

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Received: 12 April 2019

Accepted: 15 October 2019

Abstract

Avascular necrosis of the femoral head (AVNFH) is a leading cause of end-stage joint disease in the young population that can lead to total hip replacement in early life. There are various risk factors, including trauma, corticosteroids, thrombosis, hypertension, and alcohol. There is a growing number of patients with AVNFH and history of self-medication with herbal supplement used for weight gain in Iran. The present study aimed to demonstrate the prevalence rate of using unapproved weight gain supplements (UWGS) in patients with AVNFH.

An observational and cross-sectional study was conducted to estimate the prevalence rate of using UWGSs in patients with osteonecrosis at Imam Khomeini Hospital, Tehran, Iran, from January 2012 to 2018. The data were analyzed in SPSS software (version 24) through descriptive statistics and tests of means.

Out of 207 patients with AVNFH, 115 cases were male. In total, 44 patients (20.95%) had a history of using UWGSs, and there had no other risk factors of osteonecrosis of FH.

In conclusion, UWGSs can be a risk factor for AVNFH, and it is necessary to develop educational programs to alert young population about the side effects of these supplements.

Level of evidence: III

Keywords: Avascular necrosis, Femoral head, Herbal medicine, Weight gain supplement

Introduction

Avascular necrosis of the femoral head (AVNFH), which is also known as osteonecrosis or aseptic necrosis, can lead to the femoral head collapse and subsequent hip osteoarthritis in the young population. It can cause significant hip pain and a limited range of motion which deteriorates the quality of life in young patients (1). The pathogenesis of AVN is blood supply deprivation of femoral head, which in turn induces cellular death of bone tissue (2-4). The main three mechanisms for damage of femoral head blood supply include traumatic fractures or dislocations, intravascular occlusion from blood or

fat emboli, or intraosseous extravascular compression from lipocyte hypertrophy (5). The most common cause of AVN is the direct interruption of femoral head blood supply induced by trauma (6). There are many non-traumatic risk factors for AVNFH, including glucocorticoid medications, alcohol consumption, radiation, and chemotherapy (6-10). Among these risk factors, corticosteroid usage and alcohol abuse are the most common non-traumatic known ones (11).

In the last few years, the utilization of herbal medicine, especially those labeled as supplements of plant origin, is growing in Iran and some countries (12-15). One

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THE ONLINE VERSION OF THIS ARTICLE
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of the common reasons for using herbal medicine in developing countries is gaining weight. Unlike developed countries (16), it is culturally acceptable to weight gain in developing countries (17-19). In addition, the public has broader access to unapproved herbal supplements, such as powder, capsules, and tablets that are used for gaining weight (20).

In recent years, there has been an increasing number of patients with AVNFB who had a history of consuming unapproved weight gain supplements (UWGS) as the only risk factor. Based on our review of the literature in English, there is no previous report on the association between consuming UWGS and AVN. Therefore, we decided to evaluate the prevalence rate of consuming weight gain supplements in patients who visited the clinic with AVNFB and investigate the potential causal relationship.

Materials and Methods

An observational, descriptive, and cross-sectional study was conducted to evaluate the prevalence rate of consuming unapproved medicine in patients who referred to Imam Khomeini Hospital Tehran, Iran, with AVNFB. In total, 207 patients were diagnosed with AVNFB from January 2012 to 2018. Demographic characteristics (i.e., age, gender, weight, height, known risk factors for AVN, medications, and history of trauma) of all patients were obtained in this study. Moreover, the patients were asked carefully whether they consumed any supplements for weight loss, weight gain, or bodybuilding.

All data were analyzed using SPSS software (version 24). The descriptive statistics and mean tests were applied to estimate descriptive information and the prevalence rate of consuming unapproved medicine in patients with AVNFB. It should be noted that written informed consent was obtained from all participants.

Results

This study included 207 patients with AVNFB who referred to Imam Khomeini Hospital, Tehran, Iran. Out of 207 patients, 115 cases were male, and 44 (21%) patients had a history of consuming UWGS (i.e., powders, formulation, syrups, and capsules) without any other known risk factors for AVN. Actually, after corticosteroid usage (39.3%) due to various causes, such as asthma, systemic lupus erythematosus, rheumatoid arthritis, and liver and kidney transplant and idiopathic causes (32.9%), weight gain herbal supplement (21.4%) was the third most common risk factor in patients with AVNFB at Imam Khomeini Hospital, Tehran, Iran [Table 1; Figure 1].

The mean time from the onset of consuming weight gain supplements to the presentation of symptoms was estimated at seven months (range: 1 to 36 months).

Regarding the gender distribution of the patients with AVNFB, 40% (18) and 60% (27) of the cases were female and male in the group consumed UWGSs. In addition, 55% (74) and 45% (89) of the patients with other risk factors were female and male, respectively ($P=0.61$). Moreover, the patients with AVNFB due to

Cause	N	Percent %
Corticosteroid	82	39.3 %
Idiopathic	68	32.9 %
Weight gain supplement	44	21.4 %
Trauma	13	6.4 %

consuming UWGSs were significantly younger than (mean age:29.1±5 years) those with AVNFB due to other causes (mean age:35.5±10.1 years) [$P<0.05$, Table 2].

Furthermore, the mean body mass index (BMI) of all patients was obtained at 25.33±2 kg/m², and the mean values of BMI in the group consuming UWGS and other patients were 23.41±2 and 25.85±3 kg/m², respectively ($P<0.05$). In total, 155 (74.8 %) and 55 (25.2%) patients had bilateral and unilateral ANFB, respectively ($P<0.05$). Out of UWGS users, 37 (84%) and 7 (16%) patients had bilateral and unilateral AVNFB, respectively. In the present study, a core decompression was performed for all patients with a diagnosis of AVNFB without a collapsed head in the first step.

Discussion

There are different pathophysiological mechanisms defined in the AVNFB which lead to direct cell death or indirect cellular injury via circulation impairment (11). Recently, genetic factors and immune system agents have been involved in this process as predisposing factors for AVNFB. Although different risk factors have been described for this pathology, there is no consensus about all potential ones. Corticosteroid and alcohol are the most well-known risk factors; however, there is evidence in which many young patients with AVNFB have no history of previously described risk factors. However, all of them reported the consumption of unapproved medications for gaining weight.

Unapproved herbal medications have several documented liver, kidney, and other organ side effects; however, there has been no report so far about their effect on femoral head blood supply and AVN (21, 22). Based on the present study, 20.95% of patients with AVNFB had a history of consuming UWGSs with no other known risk factors. According to literature, trauma, corticosteroid consumption, and alcohol are the three most common causes of AVNFB. In this study, the consumption of the UWGSs was the third most common cause after trauma and corticosteroid consumption. Furthermore, it is of the utmost importance to gain evidence on the potential side effects of the supplements in populations who purchase unapproved medications for weight gain as over-the-counter medicines [Figure 2].

Another important finding in this study is the young age of the target community who consume UWGSs, compared

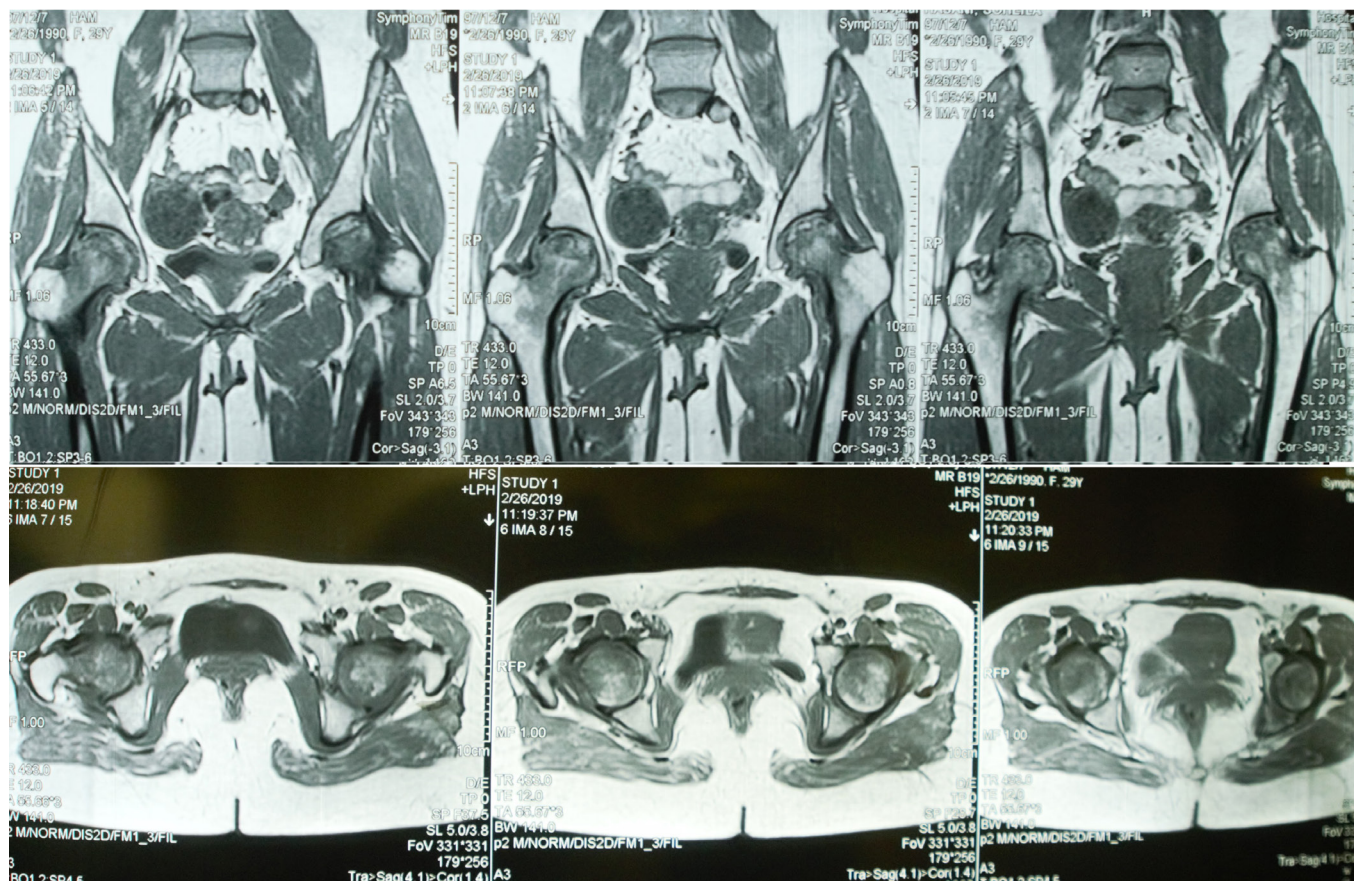


Figure 1. MRI of a patient who had avascular necrosis of femoral neck caused by weight gain capsule under the brand name "Fereshteh".

Table 2. Demographic characteristics of the participants				
		Weight gain supplement	Other risk factors	
Sex	male	26	89	<i>P</i> =0.61
	female	18	74	
BMI		23.41±2.18	25.85±3.01	<i>P</i> =0.001
AVN side	Unilateral	7	48	<i>P</i> =0.001
	Bilateral	37	118	
Age		25.14±5.19	35.58±10.42	<i>P</i> =0.001

to other risk factors of AVNFH (*P*<0.05). Considering the catastrophic consequences of AVNFH, especially in young patients, it is necessary to make efforts to prevent the incidence of this condition.

Based on the present study, the rate of bilateral AVNFH is significantly higher in the group who consume UWGSS (84% vs. 71%) (*P*<0.05). Therefore, it can be concluded that AVNFH which is associated with UWGSS can lead to worse results with unknown mechanisms.

Our evaluation of unapproved medications (i.e., powders, formulation, capsules, and syrups) reveals that most of these supplements consist of glucocorticoids, testosterone, antipsychotics, cyproheptadine, hormonal components, and other medications which induce weight gain and loss (unpublished data).

Saberi et al. revealed that weight gain herbal supplement consisted of cyproheptadine, dexamethasone, sildenafil, tramadol, caffeine, and acetaminophen (23). They

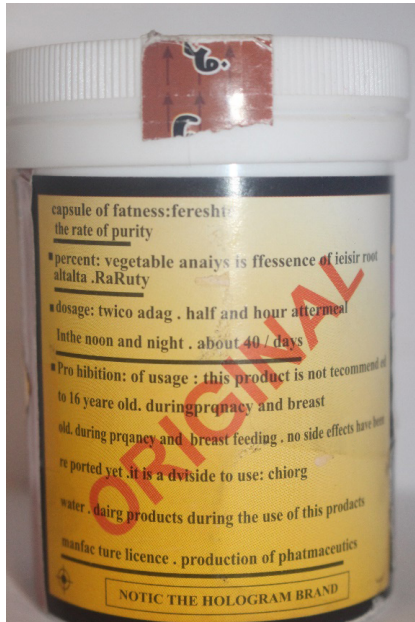


Figure 2. Weight gain capsule under the brand name “Fereshteh is an unapproved medication inducing avascular necrosis of femoral head in many cases.

also showed that the doses of cyproheptadine and dexamethasone were higher than therapeutic doses (23).

Corticosteroids can cause AVN by several mechanisms, such as fat embolism to small vessels and hypercoagulability (6). Many studies suggest that corticosteroids increase the risks of AVN depending on the dosage and applications (24). In the same line, McKee et al. reported 15 cases of AVN due to short term usage of corticosteroids (25).

One of the known process that could cause AVN is the hyperactivity of thyroid glands and adrenal glands due to hormonal medications (26). According to our evaluation, hormonal components and testosterone were observed in UWGSs. Moreover, it is probable that UWGSs which have hormonal components induce AVN with this pathway; however, there is no evidence about such a side effect for hormonal medications.

According to literature, cyproheptadine is one of the ingredients of UWGSs (23). Cyproheptadine is a potent antihistamine and H_1 receptor antagonist which can induce weight gain as a side effect (27). There is no evidence demonstrating that cyproheptadine can lead to AVN; nevertheless, the high percentage of UWGS consumption among patients with AVN in this study in combination with other medications can create new side effects. Self-medications and non-prescription drugs (i.e., formulation, tablet, and capsules) have been used for weight gain in developing countries (20). Unapproved

weight gain medications can induce AVN with several known and unknown mechanisms.

Below are some limitations in this study: As mentioned above, these medicines are unapproved and occasionally handmade with either unknown ingredients or dosage. However, we attempted to evaluate some of these supplements chemically as we had no access to most of them. Therefore, we are not assured of the ingredients of these medications and their potential or side effects.

Furthermore, the majority of the weight gain medications consist of corticosteroid and there was no possibility to reliably confirm which mechanisms other than corticosteroid were the harm factors. Although corticosteroid consumption accounts for 32% of AVN in our patients in this study which is consistent with the results in the literature, about 22% of AVN following UWGS consumption would have causes other than corticosteroid (4).

In conclusion, unapproved weight gain medications may be one of the risk factors of AVN in the young population. The major problem is the consumption of any kind of medicines with unknown ingredients and dosage that could be theoretically harmful to different organs and even AVN (21, 22).

Therefore, it is recommended to develop educational programs to increase people's knowledge about the side effects of unapproved medications and any other herbal supplements that can be found in traditional drug stores since we know nothing about their ingredients and their dosage or whether they are used for weight gain or loss or other uses.

Conflicts of Interest: The authors declare no conflict of interest regarding the publication of the study.

Acknowledgements

This study was performed at the Orthopedic Surgery Ward of Imam Khomeini Hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran. The authors would like to express their gratitude to all patients for their participation.

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