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Comparing the effect of ginger and vitamin D3 supplement on inflammatory factors and pain severity in adults with low back pain

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ABSTRACT

The objective of this study was to evaluate the effect of ginger and vitamin D3 supplement on inflammatory factors and pain severity in adults with low back pain. To achieve the research objectives, 120 patients with chronic low back pain admitted to Akhtar and Imam Hossein Hospitals were selected by random sampling method in 2017. They were randomly divided into three groups: ginger, vitamin D3 and control**.**The drugs were provided for each group in uniform packages with specific code for six weeks. In order to evaluate the variables, visual analogue scale (VAS, CRP, IL-6) was used before the start of the study and six weeks after the study. Data were analyzed using covariance analysis. The results showed no significant difference between ginger and vitamin D3 in the levels of VAS and IL-6, while significant difference was found between the ginger group and the control group and between vitamin D3 group and control group**.** Other results revealed that CRP reduction was significantly higher in both ginger and vitamin D3 groups than that in the control group. In addition, ginger led to significant reduction in CRP factor compared to vitamin D3. It is recommended for physicians to use ginger, which has fewer side effects, as a substitute for chemical drugs.

Keywords: ginger, low back pain, vitamin D3, prescription

INTRODUCTION

Back pain is the second most common reason for admitting to physician (1). Nearly 70-85% of people experience low back pain at least once during their life (2). It seems that pain to be one of the first pathological manifestations for low back pain, which often leads to limited activity. There is a controversy in explaining the exact mechanism in which pain causes disability. The results suggest a high correlation between pain perception and disability, and the fear of recurrent pain limits the activity at different times. People who suffer from low back pain experience disability in returning to their work. As a result, they would suffer both physically and mentally (3). Low back pain in adults can appear suddenly or gradually by one or more strikes and it can be continuous or appear in a particular kind of activity. It can also be exacerbated by physiological stresses (4). Vitamin D is one of the fat-soluble vitamins, which several sources are involved in its supply (5). Its internal source is 7-dehydrocholesterol, converted into Cholecalciferol and vitamin D3 as a result of UV rays (6). This vitamin is also received in the form of ergocalciferol (vitamin D2) through diet. Vitamin D2 and D3 in the liver pathways is converted to 25-hydroxyl-D3 and it can be transmitted to 25-hydroxyl D3 through bonding to a-globulin. The highest level of vitamin D is supplied when one is exposed to sunlight (7). The recommended level of vitamin D depends on the age, gender, and different treatments. However, daily intake of 200-600 IU is necessary for all people (7). As vitamin D plays both roles of vitamin and hormone in the body, it is considered vital for body. The main

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role of vitamin D is regulating calcium homeostasis, which affects the intestine, kidney, and bone. Along with PTH hormone and calcitonin, it regulates the serum calcium level.

Calcium is directly correlated with irritability and nerve conduction, skeletal and smooth muscles and inversely correlated with irritability of cardiac muscles. Vitamin D and calcium play a major role in bone metabolism. However, different factors such as physical activity, chronic acidosis, protein and calorie intake, late puberty and mal-absorption of vitamins and minerals can affect bone mineralization (8). Vitamin D has receptors in the organs including bone, heart, kidneys, nervous system, skin, teeth and thyroid gland, and plays a role in strengthening the immune system (9). Therefore, deficiency of this vitamin has many side effects in all parts of the body. Some studies have shown high prevalence of vitamin D deficiency in patients with skeletal and muscular pains with unknown origin (6). These studies show a clear correlation between unexplained pain and vitamin D deficiency, which this correlation is independent of age (6). Animal studies also show correlation between muscle pains and vitamin D deficiency. Ginger plant with scientific name of Zingiber Officinale Roscoe has an aromatic and pleasant odor and it is bitter and aromatic in terms of flavor. Ginger plant is one of the medicinal plants, especially in Iran, which has been introduced in the Iran's ancient medicine as anti-inflammatory drug. It is also used to treat various diseases including nausea, digestive disorders, respiratory distress, arteriosclerosis, migraine, depression, gastric ulcer, and increased cholesterol. Moreover, some other effects of ginger are reducing pain, treatment of rheumatoid arthritis, anti-inflammatory property, and anti-oxidant and anti-inflammatory properties. Ginger anti-oxidant and anti-inflammatory properties are applied by preventing the synthesis of pro-inflammatory cytokines include 1=IL and TNF (10, 11). The chemical composition of ginger oil contains sesquiterpenes and bisabolene, applying their anti-inflammatory property through direct inhibition of the cyclooxygenase pathway and 5-lipoxygenase. With regard to anti-inflammatory effects of this plant, numerous reports have shown that the active compounds of this plant, such as gingerol, shogaol and curcumin can inhibit the production of prostaglandins, nitrite oxide, and even interleukins involved in inflammation (12). Thus, given the prevalence of low back pain in Iran, the abundance of medicinal plants in Iran, ease of access with minimum cost and time, the current research was conducted to evaluate the effect of ginger and vitamin D3 supplement on inflammatory factors and pain severity in adults with low back pain.

METHODOLOGY

This research is single-blind clinical trial study. The research population included all patients with low back pain (non-neurologic and non-rheumatic). Among them, 120 patients with low back pain admitted to Akhtar and Imam Hossein Hospitals in 2017 were selected using random sampling method. They were randomly divided into three groups (Group D3 group, ginger group and control group).

The inclusion criteria of study included low back pain with score more than 5 based on VAS criterion, idiopathic low back pain disease lasted for three months, negative neurologic and rheumatologic results, aged between 30 and 80 years, walking ability, mental ability for learning, drug use, and ability for speaking and communicating. The research exclusion criteria included pregnancy, kidney and liver diseases, parathyroid and thyroid disorders, various types of disorders associated with calcium metabolism, sarcoidosis, using calcium channel blockers, Type 1 diabetes, use of diuretic, heparin, antiepileptic drugs, malignancies, history of back surgery, morbid obesity, types of mental disorders, and dementia and taking vitamin D3 during 6 months ago. Ethical criteria of this study were observed by approval of ethics committee of Shahid Beheshti University of Medical Sciences.

PROCEDURE

Based on research inclusion criteria, 120 eligible patients were randomly assigned to three groups: vitamin D3 group, the ginger group, and the control group (each contained 40 persons). After explaining the title and objective of the study for patients, it was also explained for them that they can withdraw from study at any stage of study and they were ensured that lack of their cooperation with physicians and hospitals would not affect their treatment and all patient information would remain confidential. A written consent from was provided to patients and all of its cases were completely explained to patients. Then, the patient completed the form and signed it, if she or he was willing. Then, drugs were provided for each group in uniform packages with specific code for six weeks. In order to examine the patients in terms of pain reduction and inflammatory factors, the project collaborator, who was not aware of type and dose of drugs, examined the patients using visual analog scale (VAS) before the onset of the treatment and the sixth week later. In addition, the levels of CRP and IL-6 in blood serum of people were also measured at the time of admission

Table 1: *Descriptive indexes of pre-test and post-test scores in three groups*

variable	status	Group	mean	SD	K-S Z	p
		ginger	5/9	087/0	1/1	88/0
	Pre-test	Vitamin D3	4/9	093/0	99/0	91/0
VAS		Control	5/9	083/0	86/0	12/1
		ginger	1/5	11/0	85/0	08/1
	Post-test	Vitamin D3	58/5	28/0	12/1	87/0
		Control	5/9	99/0	97/0	98/0
		ginger	2.19	0.052	78/0	22/1
	Pre-test	Vitamin D3	2.23	0.048	81/0	1/1
IL-6		Control	2.21	0.012	92/0	97/0
		ginger	1.58	0.019	88/0	05/1
	Post-test	Vitamin D3	1.54	0.0109	86/0	13/1
		Control	1.57	0.011	89/0	98/0
		ginger	1.54	0.014	83/0	14/1
CRP	Pre-test	Vitamin D3	1.48	0.021	95/0	94/0
		Control	1.52	0.015	12/1	83/0
		ginger	0.753	0.014	97/0	91/0
	Post-test	Vitamin D3	1.09	0.058	23/1	75/0
		Control	1.52	0.013	82/0	12/1

Table 2: *The results of single-variable covariance analysis to examine the difference among three groups in the VAS variable*

Source	Sum of squares	df	Mean of squares	F statistic	p	Effect size
Pre-test	2.962	1	2.962	7.583	0.007	0.061
Group membership	540.191	2	270.095	691.439	0.00	0.923
error	45.313	116	0.391			

and six weeks later. To evaluate the effect of independent variables on the dependent variable, VAS, CRP and IL-6 were used as follows.

Visual Acuity Scale: VAS indicates the patient pain in general. This scale is plotted as a 10 cm line and the degree of pain is graded from zero to 10 cm. The zero number does not indicate any pain, score 1 to 3 indicates mild pain, score 4 to 6 indicates moderate pain, and score 7 to 10 indicates severe pain (13). The internal reliability of this tool has been reported 0.85 to 0.95 (14). Measurement of CRP and IL-6: Interleukin-6 anilities on serum were measured by ELISA method and reported quantitatively in picogram per liter. The patient's serum sample, immediately isolated from the clot, was frozen in a -20 C at amount of 1000 microliters. CRP was performed quantitatively using Calimetrics (Hitachi 717). In analyzing data, mean, standard deviation, frequency, table and charts were used to classify and summarize the collected data. To check the normal distribution of the data, Kolmogorov-Smirnov test was used. Regarding the statistical assumptions, independent t-test and two-way variance analysis with repeated measures at 95% confidence level and statistical package (version 22) were used.

RESULTS

The mean and standard deviation of the pretest and posttest scores of the variables in three groups of ginger, vitamin D3 and control are presented in **Table 1**.

This table also reports the results of Kolmogorov-Smirnov test to check the normal distribution of variables. According to this table, the Z-statistic of Kolmogorov –Smirnov for all variables is not significant. Thus, it can be concluded that the distribution of these variables is normal.

One-way analysis of covariance was used to evaluate the effect of zinc and vitamin D3 on inflammatory factors and severity of pain in patients. The results of the homogeneity of regression slope test in pre-test and post-test with regard to VAS variable in three groups showed that regression slope was equal in all three groups ($p > 0.491$, $F_{2,114} = 0.715$).

The results of the Levine test to examine the homogeneity of dependent variable variance in the groups showed that the VAS variable was equal in the groups ($p > 0.762$, $F_{2,117} = 0.273$). **Table 2** reports the results of one-variable analysis of covariance to examine the difference among the three groups in the pre-test with the post-test of the VAS variable. According to **Table 2** of the F statistic, the VAS variable is 691.439 in the post test, which is significant at the level of 0.00, indicating a significant difference among three groups in the VAS level. The effect size also is 0.923, indicating that this difference is large in the community.

Table 3: *The results of single-variable covariance analysis to examine the difference among three groups in the CRP variable*

Source	Sum of squares	df	Mean of squares	F statistic	p	Effect size
Pre-test	0.653	1	0.653	10.904	0.001	0.086
Group membership	14.218	2	7.109	118.699	0.00	0.672
error	6.948	116	0.06			

Table 4: *The results of single-variable covariance analysis to examine the difference among three groups in the IL-6 variable*

Source	Sum of squares	df	Mean of squares	F statistic	p	Effect size
Pre-test	0.326	1	0.326	1.948	0.0165	0.017
Group membership	8.503	2	4.251	25.394	0.00	0.305
Error	6.948	116	0.06			

The F statistic is the pre-test of VAS is also 7.583, which is significant at the level of 0.007. These results indicate that pre-test has a significant effect on post-test scores. The results of covariance analysis show that the corrected mean is significantly different in the three groups. Paired comparisons showed no significant difference in the value of VAS between two groups of ginger and vitamin D3, while significant difference was seen between the ginger group and the control group and between vitamin D3 group and control group (**Table 1**).

With regard to the CRP variable, the results of examining the homogeneity of regression slope of pre-test and post-test in CRP variable in the three groups showed that regression slope was equal in all three groups ($p > 0.085$, $F_{2,114} = 0.991$). The results of the Levin test to examine the homogeneity dependent variable variance in the groups showed that the CRP variable was equal in the groups ($p > 0.625$, $F_{2, 117} = 0.842$).

Table 3 reports the results of single-variable covariance analysis to examine the difference among three groups in the pre-test and post-test of CRP variable. According to **Table 3**, F statistics is118.699 in the CRP variable, which is significant at the level of 0.00. It indicates a significant difference among the three groups in terms of CRP level. The effect size of 0.672 also indicates that this difference is high in the community.

The F-statistic of pre-test for CRP is 10.904, which is significant at the level of 0.001. These results indicate that pre-test has a significant effect on post-test scores. The results of covariance analysis show that the corrected mean is significantly different among three groups. Paired comparisons showed a significant difference between ginger group and vitamin D3 group, between ginger group and control group, and between vitamin D3 group and control group in the level of CRP (**Table 1**). With regard to descriptive statistics of **Table 1**, it can be stated that ginger has caused higher reduction in CRP than vitamin D3 did.

With regard to the IL-6 variable, the results of examining the homogeneity of regression slope of pre-test and post-test in IL-6 variable in the three groups showed that regression slope was equal in all three groups ($p > 0.136$, $F_{2,114} = 2.034$). The results of the Levin test to examine the homogeneity dependent variable variance in the groups showed that the IL-6 variable was equal in the groups ($p > 0.089$, $F_{2, 117} = 1.389$).

Table 4 reports the results of single-variable covariance analysis to examine the difference among three groups in the pre-test and post-test of IL-6 variable. According to **Table 4**, F statistics is 25.394 in the IL-6 variable, which is significant at the level of 0.00. It indicates a significant difference among the three groups in terms of IL-6 level. The effect size of 0.305 also indicates that this difference is high in the community.

The F-statistic of pre-test for IL-6 is 1.948, which is significant at the level of 0.001. These results indicate that pre-test has a significant effect on post-test scores. The results of covariance analysis show that the corrected mean is significantly different among three groups. Paired comparisons showed no significant difference between ginger group and vitamin D3 group, while significant difference was found between ginger group and control group and between vitamin D3 group and control group in the level of IL-6 (**Table 1**).

DISCUSSION AND CONCLUSION

The objective of this study was to evaluate the effect of ginger and vitamin D3 supplements on inflammatory factors and pain severity in adults with low back pain. The results showed no significant difference in the level of VAS between ginger and vitamin D3 group. Significant difference was also seen between the ginger group and the control group and between vitamin D3 group and the control group. These results showed that both ginger and vitamin D3 were effective in relieving pain and the effect of them was similar. Other results revealed that rate of CRP reduction was significantly higher in both ginger and vitamin D3 groups than that in the control and ginger, compared to vitamin D3, which caused more reduction in CRP factor. The results also showed that the IL-6 reduction was more in the ginger and vitamin D3

groups, that that in the control group, while the difference was not seen between the effect of ginger and that of vitamin D3 on IL-6. These results are consistent with the those of studies conducted by Zhang et al (2012) Mazidi et al (2017), et al (2018) Mousa and Agbalalah et al (2017), Maan and Acharya (2018), Alipour et al (2017) (8, 9, 15-18). For example, Mousa et al (2018) concluded that vitamin D supplements may reduce low chronic low-level inflammation in patients with type 2 diabetes (18). Agbalalah et al (2017) found that vitamin D supplements in adults improve the function of biomarkers / inflammatory parameters and endothelial function (9). Vitamin D reduction is also associated with an increase in CRP (19).

Maan and Acharya (2018) showed that prescription of ginger significantly reduced CRP (16). Alipour et al (2017) also reported that ginger reduced pain and satisfaction in patients with knee osteoarthritis (17). Gauss et al. (2009) reported that ginger extract inhibits the secretion of IL-8, IL-6, IL-1β and TNF-α from lipopolysaccharides of peripheral blood mononuclear cells. These results show that ginger extract has anti-inflammatory property and can be useful in stomach cancer (20). Tripathi et al. (2007) also examined the effects of the use of 6-gingerol (an active ingredient in ginger) on the production of inflammatory cytokines of tumor necrosis factor (TNF-α), interleukin-12, interleukin beta-1 in mice and observed that gingerol-6 selectively prevents the production of inflammatory cytokines in activated macrophages (21). Several researchers have stated that ginger supplements, due to anti-inflammatory and anti-oxidant properties, inhibit the synthesis of prostaglandins and stop pro-inflammatory cytokines (22). In addition, the anti-inflammatory effects of this plant prevent arachidonic acid metabolism, inhibit platelet adhesion, and suppress the production of free radicals through blocking the synthesis of leukotriene and prostaglandin pathways (23). As a result, they improve the immune systems and reduce the pressure and inflammation (25). In summary, based on research results, it can be concluded that ginger reduces pain and reduces inflammatory factors in patients with chronic low back pain. Thus, it is recommended for physicians to prescribe ginger, which has fewer side effects, as an alternative to chemical drugs.

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