

Possible effects of agent orange and posttraumatic stress disorder on hyperglycemia in Korean veterans from the US-Vietnam war

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Abstract

This study was conducted to examine whether Korean veterans from the US-Vietnam War who had a diagnosis of type II diabetes mellitus (T2DM) as well as past history of exposure to agent orange (AO) are vulnerable to hyperglycemia when receiving intra-articular corticosteroid injection (IACI) for pain relief.

The current study included a total of 49 patients ($n=49$) who received an injection of triamcinolone 20 or 40 mg to the shoulder under sonographic guidance or did that of dexamethasone 10 mg or triamcinolone 40 mg combined with dexamethasone 20 mg to the spine under fluoroscopic guidance. Their 7-day fasting blood glucose (FBG) levels were measured and then averaged, serving as baseline levels. This is followed by measurement of FBG levels for 14 days of IACI. Respective measurements were compared with baseline levels. The patients were also evaluated for whether there are increases in FBG levels depending on insulin therapy as well as $HbA1c \geq 7\%$ or $HbA1c < 7\%$.

Overall, there were significant increases in FBG levels by 64.7 ± 42.5 mg/dL at 1 day of IACI from baseline ($P < .05$). $HbA1c \geq 7\%$ and $HbA1c < 7\%$ showed increases in FBG levels by 106.1 ± 49.0 mg/dL and 46.5 ± 3.8 mg/dL, respectively, at 1 day of IACI from baseline ($P < .05$). In the presence and absence of insulin therapy, there were significant increases in them by 122.6 ± 48.7 mg/dL and 48.0 ± 20.4 mg/dL, respectively, at 1 day of IACI from baseline ($P < .05$). But there were decreases in them to baseline levels at 2 days of IACI.

Clinicians should consider the possibility of hyperglycemia when using corticosteroids for relief of musculoskeletal pain in Korean veterans from the US-Vietnam War who had a history of exposure to AO.

Abbreviations: AO = agent orange, DM = diabetes mellitus, FBG = fasting blood glucose, IACI = intra-articular corticosteroid injection, MSD = musculoskeletal disorder, PTSD = posttraumatic stress disorder, T2DM = type II diabetes mellitus.

Keywords: agent orange, diabetes mellitus, musculoskeletal pain, posttraumatic, steroids, stress disorders, Vietnam conflict

1. Introduction

During the US-Vietnam War ending in 1973, the number of deaths of Vietnamese and Americans were estimated at 1.5 million and 58,000, respectively.^[1] Approximately 320,000

Korean soldiers also served in Vietnam, who were exposed to Agent Orange (AO), a herbicide that was sprayed to defoliate areas of Vietnam, during that period. To date, possible long-term health consequences of exposure to AO have been of great concern among Korean veterans.^[2] Previous studies have shown that its detrimental effects include cancer, birth defects, skin disorders, hepatic dysfunction, porphyria, peripheral neuropathy, impaired immune function and diabetes mellitus (DM).^[3–5]

It is generally known that the US-Vietnam War veterans are afflicted with chronic pain, anxiety, posttraumatic stress disorder (PTSD) and other troubling symptoms. Most of them therefore use diverse types of pharmacological treatments to control the symptoms due to AO exposure; these include non-steroidal anti-inflammatory agents, tranquilizers, gastrointestinal drugs, neuropsychiatric agents, anti-diabetic agents and cerebrovascular metabolic agents.^[6–9] But clinicians should consider the possibility of hyperglycemia when using steroids for pain relief in those with a past history of exposure to AO. Although unclear, the possible association between AO and DM has been implicated.^[10,11] Moreover, it has been shown that there is a positive correlation between DM and musculoskeletal pain arising from the body trunk, extremities, such as trigger finger, adhesive capsulitis of the shoulder, carpal tunnel syndrome and osteoarthritis.^[12–14] This is serious because such pain may impair the quality of life of affected individuals.

Local corticosteroid injections are often used as the first-line of treatment regimens for the purposes of improving pain,

Editor: Kukuh Noertjojo.

The authors have no funding and conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Hong P, Song YG, Paek S. Possible effects of agent orange and posttraumatic stress disorder on hyperglycemia in Korean veterans from the US-Vietnam war. *Medicine* 2021;100:25(e26508).

Received: 29 September 2020 / Received in final form: 4 March 2021 /

Accepted: 12 May 2021

<http://dx.doi.org/10.1097/MD.00000000000026508>

inflammation and mobility in patients with musculoskeletal pain, such as bursitis, tendinopathy and osteoarthritis; their advantages include ease of administration, low cost and low risk to the patient. Still, there is a controversy as to long-term effects of local administration of corticosteroids; treatment effects are not sustained or may be prolonged.^[15–17]

It is well established that systemic corticosteroids affect blood glucose levels; this is notable in patients with altered glucose metabolism. Still, however, there is a paucity of data regarding effects of local corticosteroid injections on blood glucose control in patients with DM. Moreover, the American Academy of Orthopedic Surgeons, American College of Sports Medicine, American Diabetes Association and American Medical Society for Sports Medicine have not provided recommendations on steroid injections in patients with DM.^[18]

Given the above background, this study was conducted to examine whether Korean veterans from the US-Vietnam War who had a diagnosis of type II diabetes mellitus (T2DM) as well as past history of exposure to AO are vulnerable to hyperglycemia when receiving intra-articular corticosteroid injection (IACI) for pain relief.

2. Methods

2.1. Study patients and setting

The current single-center, retrospective study was conducted in a total of 60 patients (n=60) who were admitted to department of physical medicine and rehabilitation of our medical institution between August of 2018 and December of 2019.

Inclusion criteria for the current study are as follows:

1. Korean veterans from the US-Vietnam War registered with the Korean Ministry of Patriots and Veterans Affairs
2. The patients with a history of exposure to AO
3. The patients presenting with symptoms of PTSD
4. The patients with a diagnosis of T2DM
5. The patients presenting with musculoskeletal pain in the shoulder or spine
6. The patients receiving IACI in the shoulder or spine
7. The patients who were currently taking anti-hyperglycemic drugs or insulin.^[19]

Excluding 11 patients lost to follow-up, we included a total of 49 patients (n=49) in the current study; it was conducted in compliance with the relevant ethics guidelines and then approved by the Internal Institutional Review Board of the Korea National Institute of Bioethics Policy (2019-01-226-031). Written informed consent was waived due to its retrospective nature.

2.2. Intra-articular corticosteroid injection protocol

The patients presenting with pain of the shoulder received an injection of triamcinolone 20 or 40 mg under sonographic guidance. In addition, the patients presenting with pain of the spine received an injection of dexamethasone 10 mg, dexamethasone 10 mg combined with triamcinolone 40 mg or dexamethasone 20 mg combined with triamcinolone 40 mg under fluoroscopic guidance.

2.3. Patient evaluation and criteria

The current study performed a retrospective review of medical records of our clinical series of the patients. Their baseline

characteristics include age, sex, follow-up period, length of hospital stay, sites and dose of injection, types of corticosteroids injected, HbA1c levels prior to injections, the use of insulin and factors affecting blood glucose levels following injections.

At the time of admission, the patients were initially evaluated for HbA1c levels. Their blood glucose levels were monitored by a well-trained nurse throughout the hospitalization period. Thus, 7-day fasting blood glucose (FBG) levels were measured and then averaged. Results served as baseline levels. This is followed by measurement of FBG levels for 14 days of IACI. Respective measurements were compared with baseline levels. The patients were allowed to take anti-hyperglycemic medications and insulin even after injections as they did prior to injections.

2.4. Subgroup analysis

Clinically, HbA1c levels have been reported to be a significant indicator of the status of glycemic control and the degree of response to anti-hyperglycemic therapy over a 3-month period.^[20,21] Patients with HbA1c $\geq 6.5\%$ are commonly diagnosed with DM. Previous studies have shown that diabetic patients with HbA1c $\geq 7\%$ are at increased risks of developing complications. Such patients are therefore recommended to lower HbA1c levels to $<7\%$.^[22] Therefore, the patients were also evaluated for whether there are increases in FBG levels depending on HbA1c $\geq 7\%$ within 3 months of IACI.

2.5. Statistical analysis

All data was expressed as mean \pm standard deviation. Data analysis was performed using the SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). Time-dependent differences in FBG levels were tested for statistical significance using the repeated measures analysis of variance and Duncan's post-hoc analysis. A Pearson's correlation analysis was performed to examine whether HbA1c $\geq 7\%$ and insulin therapy had significant correlations with FBG levels. A *P* value of $<.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the patients

A total of 49 patients (n=49) met inclusion/exclusion criteria; they had a mean age of 71.6 ± 3.8 years old. Baseline characteristics of the patients are represented in Table 1.

Disposition of the study patients is illustrated in Fig. 1.

3.2. Changes in fasting blood glucose levels after intra-articular corticosteroid injection

Overall, there were significant increases in FBG levels by 64.7 ± 42.5 mg/dL at 1 day of IACI from baseline ($P < .05$). At 2 days of IACI, however, there were significant decreases in them to baseline levels. Thereafter, there were no significant increases in them from baseline levels (Fig. 2).

3.3. Changes in fasting blood glucose levels depending on HbA1c after intra-articular corticosteroid injection

At 1 day of IACI, both HbA1c $\geq 7\%$ and HbA1c $< 7\%$ showed significant increases in FBG levels. HbA1c $\geq 7\%$ showed

Table 1**Baseline characteristics of the patients (n = 49).**

Variable	Value
Age (y)	71.6 ± 3.8
Sex (male-to-female ratio)	49:0
BMI (kg/m ²)	25.7 ± 3.3
Duration of T2DM (y)	13.6 ± 11.1
Use of insulin therapy	5 (10.2%)
HbA1c (%)	7.1 ± 1.4
HbA1c ≥ 7%	17 (34.7%)
HbA1c < 7%	32 (65.3%)
FBG (mg/dL)	117.82 ± 22.24
History of exposure to AO	49 (100%)
Causative diseases	
Herniated nucleus pulposus	15 (30.6%)
Rotator cuff disease	13 (26.5%)
Spinal stenosis	13 (26.5%)
Adhesive capsulitis	8 (16.4%)
Underlying diseases	
HTN	45 (91.8%)
PN	4 (8.2%)
Drugs and doses of injection	
Shoulder	20 (40.8%)
Triamcinolone 20 mg	5 (10.2%)
Triamcinolone 40 mg	15 (30.6%)
Spine	29 (59.2%)
Dexamethasone 10 mg	13 (26.5%)
Dexamethasone 10 mg + triamcinolone 40 mg	4 (8.2%)
Dexamethasone 20 mg + triamcinolone 40 mg	12 (24.5%)
Sites of injection	
Shoulder	20 (40.8%)
Spine	29 (59.2%)
C4/5/6	2 (4.1%)
L1/2/3	3 (6.1%)
L2/3/4	1 (2.0%)
L3/4/5	10 (20.4%)
L4/5	9 (18.4%)
L4/5/S1	2 (4.1%)
L5/S1	1 (2.0%)
Coccyx	1 (2.0%)
Length of hospital stay (d)	36.3 ± 8.3

AO = agent orange, BMI = body mass index, FBG = fasting blood glucose, HbA1c = glycated hemoglobin, HTN = hypertension, PN = peripheral neuropathy, T2DM = type 2 diabetes mellitus. Values are mean ± standard deviation or the number of cases with percentage, where appropriate.

increases in them by 106.1 ± 49.0 mg/dL from baseline levels. In addition, HbA1c < 7% showed increases in them by 46.5 ± 3.8 mg/dL from baseline levels. These differences reached statistical significance ($P < .05$). At 2 days of IACI, however, there were decreases in them to baseline levels with no respect to HbA1c ≥ 7% or HbA1c < 7% (Fig. 3).

3.4. Changes in fasting blood glucose levels depending on insulin therapy after intra-articular corticosteroid injection

At 1 day of IACI, there were significant increases in FBG levels with no respect to insulin therapy. In the presence of insulin therapy, there were increases in FBG levels by 122.6 ± 48.7 mg/dL from baseline levels. In the absence of insulin therapy, there were increases in them by 48.0 ± 20.4 mg/dL from baseline levels. These differences reached statistical significance ($P < .05$). At 2 days of IACI, however, there were decreases in them to baseline levels with no respect to insulin therapy (Fig. 4).

4. Discussion

War veterans are more vulnerable to co-morbidities as compared with their age-matched controls.^[2,3] According to a meta-analysis of the previous published studies, performed by Pacella et al, PTSD had significant correlations with greater risks of symptoms and a higher incidence and a greater severity of pain and cardio-respiratory and gastrointestinal symptoms.^[24] Moreover, according to Buhmann, there were physical disabilities and chronic pain in refugees with PTSD sustaining specific injuries arising from torture.^[25]

Our clinical series of the patients comprise 15 cases of herniated nucleus pulposus, 13 cases of rotator cuff disease, 13 cases of spinal stenosis and 8 cases of adhesive capsulitis. This is partly supported by a possible relationship between PTSD and increased muscular tension. That is, emotional stress, arising from interactions in the central nervous system and then leading to painful muscular tension, may be involved in the pathogenesis of myofascial pain syndrome.^[26] War veterans' vulnerability to musculoskeletal disorder (MSD) is advocated by a prior publication showing that they are more likely to have MSDs, such as arthritis, lower back pain, hip pain and knee pain, as compared with non-military civilians.^[27] MSDs are so serious as to cause chronic pain and long-term physical disability in affected individuals. In more detail, approximately 4% to 5% of total adults have physical disabilities associated with MSDs.^[28]

Still, there are inconsistent results of epidemiologic studies about a biologically plausible relationship between AO exposure and DM.^[29] 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a contaminant of AO. The possible relationship between TCDD and DM has been of great concern, which is based on an animal study suggesting that it affects glucose transport.^[30] This is also advocated by a previous published study conducted in humans exposed to TCDD.^[10] Henriksen et al examined DM and glucose and insulin levels in Air Force veterans with a history of an exposure to AO during the Vietnam War. The veterans of Operation Ranch Hand (n = 989), the unit responsible for aerial herbicide spraying in Vietnam between 1962 and 1971, served as the trial group. The Air Force veterans who were not involved in spraying herbicides in Southeast Asia during the same period served as the control group (n = 1276). The median serum dioxin level was 12.2 (range, 0–617.8) ppt in the trial group and 4.0 (range, 0–10) ppt in the control group. According to these authors, there were increases in glucose abnormalities (relative risk = 1.4; 95% confidence limits [CL]: [1.1, 1.8]), diabetes prevalence (relative risk = 1.5; 95% CL: [1.2, 2.0]) and use of oral anti-hyperglycemic medications (relative risk = 2.3; 95% CL: [1.3, 3.9]) but decreases in time-to-diabetes-onset. These authors also noted that there were increases in serum insulin abnormalities (relative risk = 3.4; 95% CL: [1.9, 6.1]).^[10]

Possible effects of PTSD on the occurrence of T2DM need another attention. There is an emerging evidence of a possible relationship between PTSD and T2DM.^[31] Moreover, PTSD has also been reported to have a significant correlation with the metabolic syndrome that serves as a risk factor of developing insulin resistance and DM.^[32] Such associations may be explained by chronic perturbations of the hypothalamic-pituitary-adrenal axis, which is potentially followed by an increased amount of the visceral fat, inflammation and insulin resistance.^[33] Patients with PTSD may also be vulnerable to DM because of detrimental health behaviors, such as sedentary lifestyle, poor dietary habits, sleep problems and excessive

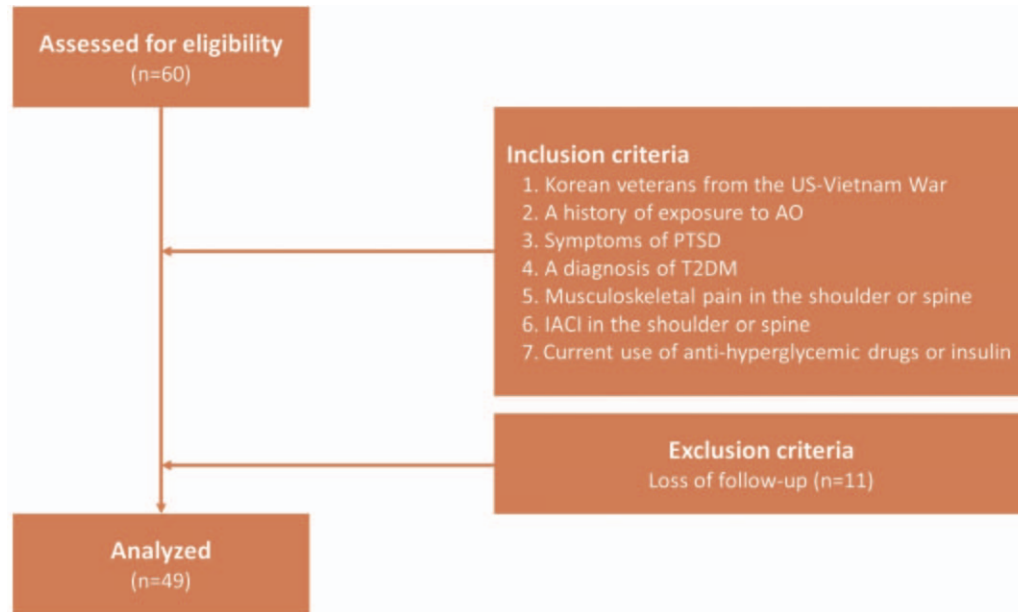


Figure 1. Disposition of the study patients. AO = agent orange, IACI = intra-articular corticosteroid injection, PTSD = posttraumatic stress disorder, T2DM = type II diabetes mellitus.

alcohol ingestion. This is also closely associated with genetic predisposition and familial factors.^[34] It can therefore be inferred that pathophysiologic mechanisms underlying the vulnerability to DM in patients with PTSD might also be associated with genetic pathways, as described in those with depression and cardiovascular disease.^[35] Vidović et al conducted a prospective study in a total of 76 subjects (39 patients with PTSD serving as the patient group and 37 age- and sex-matched normal healthy controls serving as the control group), for which these authors measured levels of hormones and cytokines using a radioimmunoassay and an immunoenzyme assay, evaluated immune functions of the subjects using in vitro natural killer cell cytotoxicity (NKCC) against 51Cr-labeled K562 target cells and determined lymphocyte counts and immunophenotype and intracellular levels of glucocorticoid receptor using a three-color

flow cytometry. Thus, they showed significant changes in immune and endocrine functions in patients with PTSD as compared with their controls.^[36]

When injected in the knee, shoulder, and spine, corticosteroids have short-term effects in raising blood glucose levels. But their long-term effects on blood glucose control have not been described in the literature.^[37-39] Although unclear, complex mechanisms are involved in the effects of corticosteroids on glucose homeostasis. It is known, however, that increased insulin resistance, increased gluconeogenesis in the liver and impaired insulin synthesis and secretion in pancreatic β -cells might be involved in the complex pathophysiologic mechanisms underlying corticosteroid-induced hyperglycemia.^[40-42] Moreover, it is also known that metabolic effects of corticosteroids on blood glucose levels are closely associated with several stages of insulin signaling pathway.^[43] Pagano et al reported a 50% decrease in insulin sensitivity using the insulin clamp method after a 7-day injection of prednisolone in healthy subjects.^[44] Corticosteroids reduce peripheral glucose absorption in the muscle and fat.^[45,46] The liver is a pivotal organ in the context of glucose metabolism; corticosteroids directly act on genes that are involved in carbohydrate metabolism and thereby promote gluconeogenesis in the liver. This leads to the increased endogenous glucose production.^[45,47] Moreover, corticosteroids have direct effects in inhibiting insulin synthesis and secretion in pancreatic β -cells in proportional to the dose of and the period of exposure to corticosteroids.^[48-50] Furthermore, corticosteroids promote proteolysis in the muscle and lipolysis in the adipocytes, thus altering body compositions. This eventually leads to systemic insulin resistance and hyperglycemia.^[40] Finally, concurrent inflammatory diseases may also cause functional insufficiency of pancreatic cells.^[51]

In the current study, FBG levels were significantly increased until 1 day after IACI but decreased to baseline levels at 2 days. Thus, there were no significant increases in them as compared

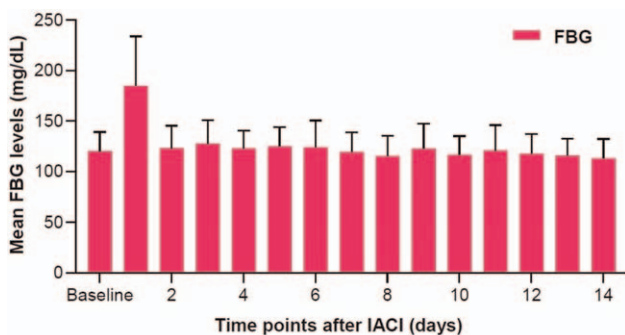


Figure 2. Changes in fasting blood glucose (FBG) levels after intra-articular corticosteroid injection (IACI). Overall, there were significant increases in FBG levels by 64.7 ± 42.5 mg/dL at 1 day of IACI from baseline ($P < .05$). At 2 days of IACI, however, there were significant decreases in them to baseline levels. Thereafter, there were no significant increases in them from baseline levels.

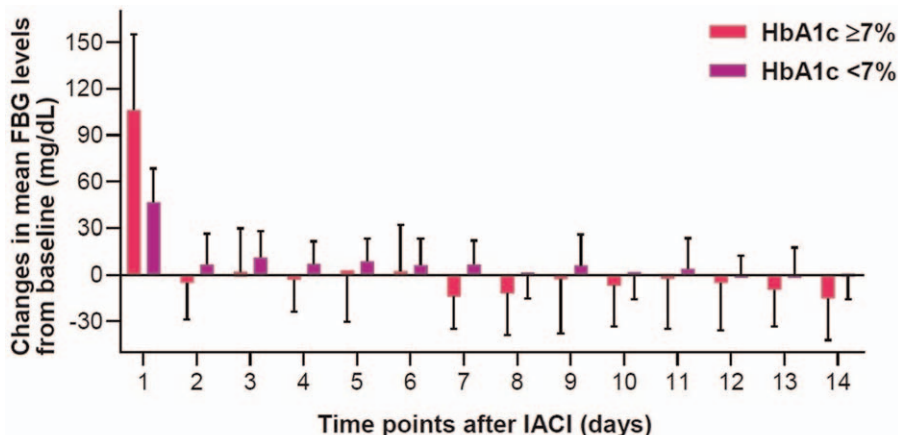


Figure 3. Changes in fasting blood glucose (FBG) levels depending on HbA1c after intra-articular corticosteroid injection (IACI). At 1 day of IACI, both HbA1c ≥ 7% and HbA1c < 7% showed significant increases in FBG levels. HbA1c ≥ 7% showed increases in them by 106.1 ± 49.0 mg/dL from baseline levels. In addition, HbA1c < 7% showed increases in them by 46.5 ± 3.8 mg/dL from baseline levels. These differences reached statistical significance ($P < .05$). At 2 days of IACI, however, there were decreases in them to baseline levels with no respect to HbA1c ≥ 7% or HbA1c < 7%.

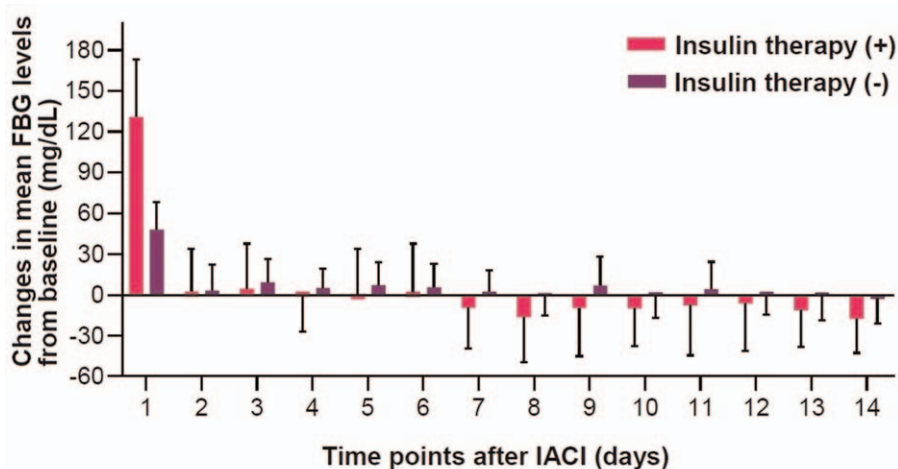


Figure 4. Changes in fasting blood glucose (FBG) levels depending on insulin therapy after intra-articular corticosteroid injection (IACI). At 1 day of IACI, there were significant increases in FBG levels with no respect to insulin therapy. In the presence of insulin therapy, there were increases in FBG levels by 122.6 ± 48.7 mg/dL from baseline levels. In the absence of insulin therapy, there were increases in them by 48.0 ± 20.4 mg/dL from baseline levels. These differences reached statistical significance ($P < .05$). At 2 days of IACI, however, there were decreases in them to baseline levels with no respect to insulin therapy.

with baseline levels. Moreover, the current study also showed that HbA1c had a significant correlation with FBG levels. It can be inferred that HbA1c ≥ 7% might be an indicator of increases in FBG levels in the Korean veterans from the US-Vietnam War. This is in agreement with a previous study showing that patients presenting with symptoms of PTSD were at significantly greater risks of having HbA1c > 7% as compared with non-symptomatic controls even after the adjustment of clinical and demographic factors that known to affect HbA1c levels.^[52]

To summarize, the current results are as follows: Overall, there were significant increases in FBG levels by 64.7 ± 42.5 mg/dL at 1 day of IACI from baseline ($P < 0.05$). HbA1c ≥ 7% and HbA1c < 7% showed increases in FBG levels by 106.1 ± 49.0 mg/dL and 46.5 ± 3.8 mg/dL, respectively, at 1 day of IACI from baseline ($P < .05$). In the presence and absence of insulin therapy, there were significant increases in them by 122.6 ± 48.7 mg/dL and

48.0 ± 20.4 mg/dL, respectively, at 1 day of IACI from baseline ($P < .05$). But there were decreases in them to baseline levels at 2 days of IACI.

But there are some limitations of the current study as follows:

1. A small number of patients were included in the current study.
2. The current study was conducted under the retrospective design.
3. The patients who were hospitalized at the secondary medical institution were evaluated. The possibility of selection bias could not therefore be completely ruled out.

Based on the current results, it can be concluded that clinicians should consider the possibility of hyperglycemia when using corticosteroids for relief of musculoskeletal pain in Korean veterans from the US-Vietnam War who had a history of exposure to AO.

Author contributions

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