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Original Article

# The impact of intra-articular injection of diprospan at the knee joint on blood glucose levels in diabetic patients

George Habib[1,2], Fadi Khazin[3], Fahed Sakas[4], Geries Hakim[5], Suheil Artul[6]

## Abstract

**Objective:** To evaluate the effect of intra-articular (IA) corticosteroid injection (IACI) of betamethasone dipropionate/betamethasone sodium phosphate (Diprospan) on blood glucose levels in diabetic patients

**Methods:** Patients with type 2 diabetes and symptomatic osteoarthritis of the knee (OAK) in whom medical therapy failed were administered 1 mL Diprospan IACI (5 mg of betamethasone dipropionate + 2 mg of betamethasone sodium phosphate). Patients were asked to monitor blood glucose levels before and 2 h after meals for 1 week before and 12 days after the injection was administered. A control group was administered an IA injection of hyaluronic acid.

**Results:** Twelve patients from the Diprospan group and six from the control group were recruited for the study. Patients in the Diprospan group had significantly increased blood glucose levels with median initial and peak levels of 187.5 mg% and 310 mg%, respectively, at a median of 4 and 11.5 h following IACI, respectively. The last peak level was seen after a median of 45 h following IACI. There was no significant increase in blood glucose levels in the control group.

**Conclusion:** Diprospan IACI is associated with significantly increased blood glucose levels in all diabetic patients with OAK.

**Keywords:** Intra-articular, diprospan, blood glucose

**ORCID ID of the authors:**
G.H. 0000-0001-8134-8575,
F.K. 0000-0002-7913-4871,
F.S. 0000-0001-9923-180X,
G.H. 0000-0002-4337-9714,
S.A. 0000-0002-8621-6034.

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[1]Rheumatology Unit, Laniado Hospital, Netanya, Israel
[2]Rheumatology Clinic, Nazareth Hospital, Israel Institute of Technology School of Medicine, Haifa, Israel
[3]Department of Orthopedics, Carmel Medical Center, Haifa, Israel
[4]Department of Medicine, Rambam Medical Center, Haifa, Israel
[5]Department of Orthopedics, Nazareth Hospital, Bar-Ilan University Gallile School of Medicine, Israel
[6]Department of Radiology, Nazareth Hospital, Bar-Ilan University Gallile School of Medicine, Israel

*Address for Correspondence:*
George Habib, Rheumatology Unit, Laniado Hospital, Netanya, Israel & Rheumatology Clinic, Nazareth Hospital, Israel Institute of Technology School of Medicine, Haifa, Israel

E-mail: gshabib@gmail.com

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## Introduction

Both diabetes mellitus and osteoarthritis of the knee joint (OAK) are relatively common in the general population, particularly among elderly patients (1). Intra-articular (IA) corticosteroid injection (IACI) is a very popular procedure for pain reduction in patients with OAK (2). It is usually used after failure or unsatisfactory response to painkillers and physical therapy. There are different preparations of IA corticosteroids. Methylprednisolone acetate is the most popular worldwide, betamethasone preparations are popular in Europe, and triamcinolone preparations are popular in the United States (3).

IACI could be associated with a wide range of systemic effects (4-8). These effects reflect a substantial amount of steroids reaching the circulation from the knee joint cavity following IACI (9). There are few reports on the effect of IACI on glucose levels in diabetic patients (10-12). In these studies, it has been shown that IACI at the knee joint in patients with symptomatic OAK is associated with significantly increased blood glucose levels in all controlled diabetic patients (10-12). These studies included methylprednisolone acetate (Depo-Medrol), triamcinolones , and betamethasone acetate/betamethasone sodium phosphate (Celestone Chronodose) (10-12). In contrast to triamcinolones and methylprednisolone acetate, following 1 mL Celestone Chronodose IACI (3 mg of betamethasone acetate + 3 mg of betamethasone sodium phosphate), there was a uniform pattern in all patients with a brisk increase in blood glucose levels within the first hour. The significantly increased blood glucose levels lasted for 2-3 days. In the Depo-Medrol group, there was a completely variable pattern between different patients, and the significantly increased glucose levels lasted for up to 5 days. The triamcinolones, particularly triamcinolone hexacetonide, had a more modest effect on blood glucose levels.

Betamethasone dipropionate/betamethasone sodium phosphate (Diprospan) is also a popular depot steroid compound. However, 1 mL of this preparation contains a lower dose of the rapid-acting compound betamethasone sodium phosphate and a higher dose of the long-acting compound betamethasone dipropionate. This difference in composition might have a different effect on blood glucose levels.

## Methods

Patients with type 2 diabetes and glycated hemoglobin (HbA1C) levels of <7.5 during the previous 3 months, as determined using modern versions of blood glucose-monitoring devices, and with knee pain due to OAK for more than 3 months without sufficient response to medical treatment were administered 1 mL Diprospan IACI (Shering-Plough, Belgium) at the knee joint (13). Patients were requested to monitor their blood glucose levels before and 2 h following breakfast, lunch, and dinner every other day for 1 week prior to IACI and daily for 5 days and every other day for 1 week following IACI using the same glucose-monitoring devices. In addition, patients were requested to document blood glucose levels 1 h following IACI. Prior to IACI, all patients had to undergo the following tests: blood chemistry, complete blood count, antinuclear antibodies test, rheumatoid factor test, C-reactive protein test, essential sedimentation rate, and knee X-ray.

All injections were administered 1 h following breakfast, with patients in a supine position with straight legs. The insertion was performed using 23-G needle at the medial aspect of the knee, following local cleaning using chlorhexidine and ethyl chloride spray as a local anesthetic. Prior to IACI, the maximal aspiration of knee fluid, if any, was attempted following the needle insertion. Immediately after IACI, patients were requested to step down and ambulate as usual.

Thereafter, controlled diabetic patients with symptomatic OAK, who were offered 1 mL of hyaluronic acid (20 mg of Suplazyn, Bioniche, Ireland) under the same regimen as the study group, were considered as the control group.

Exclusion criteria included patients who received any type of knee injection, who started or stopped any type of antidiabetic treatment during the previous 3 months, who changed their antidiabetic diet during the previous month, and who started or stopped any type of treatment, such as steroids or thiazides, which may affect glucose metabolism.

For statistical analysis, a significant increase in blood glucose level following IA injection was considered if the level was higher by at least 2-standard deviations than the mean comparable (in reference to meals) glucose level prior to the injection. The Mann-Whitney's U and Fisher's exact tests were used to compare between the continuous and categorical parameters, respectively, of the epidemiologic and clinical data between the two groups.

The study was approved by the Helsinki Committee of the Nazareth Hospital and all the patients signed a consent form.

## Results

Fifteen and seven patients were recruited in the Diprospan and control groups, respectively. Twelve patients in the Diprospan group and six in the control group completed the study. No patient had used or abandoned any medication that could affect blood glucose levels, and no patient reported symptom/s or sign/s suggestive of acute infection.

Table 1 summarizes the epidemiologic and clinical parameters of the patients.

There was no significant difference between the epidemiological and clinical variables of the patient and control groups. Most patients had normal to moderate radiographic changes on X-rays.

**Table 1.** Demographic and clinical parameters of patients in different groups

| Parameter \ Type of preparation | Diprospan | HA | p |
|---|---|---|---|
| - Age, years (median, range) | 48, 40-71 | 52, 46-59 | 0.651 |
| - Female:male | 8:4 | 4: 2 | 0.988 |
| - Duration of DM, years (median, range) | 7, 2-14 | 6, 1-17 | 0.725 |
| - Duration of knee symptoms, years (median, range) | 6, 4-9 | 5, 2-8 | 0.264 |
| - Knee effusion | 3, 2-5 | 3, 1-7 | 0.351 |
| -Kellgren & Lawrence grading | 1.5 (0-3) | 2 (0-3) | 0.407 |
| - HbA1C levels (median, range) | 6.4, 6.1-6.8 | 6.2, 5.8-6.7 | 0.312 |
| - Oral hypoglycemic treatment only | 5 | 3 | 0.764 |
| - Diet only for DM | 1 | 0 | 0.666 |
| - Insulin only | 3 | 1 | 0.755 |
| - Combination therapy | 3 | 2 | 0.737 |

DM: diabetes mellitus; HbA1C: glycated hemoglobin; HA: hyaluronic acid

**Table 2.** Time-relation of glucose levels following Diprospan IACI

| Parameter | Result |
|---|---|
| Median time to earliest significantly increased glucose levels, h (range) | 4.75, (3-21) |
| Median earliest significantly increased glucose levels, mg% (range) | 187.5, (128-326 |
| Median time to peak significantly increased glucose levels, h (range) | 11.5 (3-33) |
| Median significant peak glucose levels, mg% (range) | 310 (227-328) |
| Median time to last significantly increased glucose levels, h (range) | 45 (22-56) |
| Median no. of occasions of significantly increased glucose levels in each patient (range) | 6 (5-8) |
| No. of patients with a significant clinical response (%) | 8 (~72%) |

All patients in the Diprospan group had a significant increase in blood glucose levels compared with levels prior to injection on several occasions (Table 2 and Figure 1). However, patients administered hyaluronic acid showed no significant increase in blood glucose levels, except on one occasion in two patients: in one patient, it occurred 1 h following the injection and in the second patient, on the third day (data not shown). On both occasions, the increased levels were very marginal.

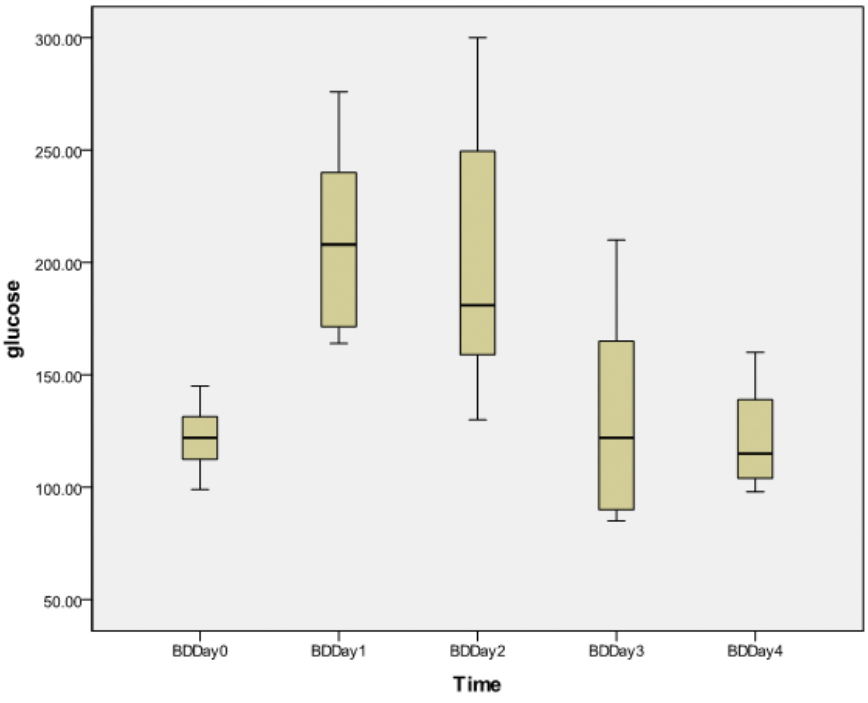


**Figure 1.** Blood glucose levels before dinner prior to and following IACI

BBDay0: blood glucose levels before dinner prior to Diprospan IACI
BBDay1: blood glucose levels before dinner at day 1 following Diprospan IACI
BBDay2: blood glucose levels before dinner at day 2 following Diprospan IACI
BBDay3: blood glucose levels before dinner at day 3 following Diprospan IACI
BBDay4: blood glucose levels before dinner at day 4 following Diprospan IACI

## Discussion

Diprosan IACI at the knee joint was associated with significantly increased blood glucose levels in every diabetic patient with symptomatic OAK, regardless of the duration and severity of osteoarthritis or duration and type of diabetes treatment. The increase in blood glucose levels in the Diprospan group could be attributed to only the steroids, since in the control group with IA injection of hyaluronic acid, there was no significant increase in blood glucose levels, except only on one occasion with marginal levels in two patients.

The median number of occasions of significantly increased blood glucose levels was six, with most of the levels seen on day 1.

The pattern of significantly increased blood glucose levels obtained in the Diprospan group is closer to that seen following Celestone Chronodose IACI at the knee joint. However, there are some differences, particularly in the time to early significantly increased glucose levels: with Celestone, it was seen within the first hour in all patients, while with Diprospan, there was some delay wherein for most of the patients, it was seen 3-5.5 h following IACI. The earliest significantly increased level was seen after 21 h in one exceptional case.

Peak levels were approximately 300 mg% and the last significantly increased glucose levels were seen after a relatively short period of time: 1-3 days.

Hence, for diabetic patients who are candidates for IACI, especially when a betamethasone preparation is considered, Diprospan might be a better choice than Celestone Chronodose due to the gradual increase in glucose levels following Diprospan IACI. Other argument that might provide an advantage for its use over Celestone is the longer duration of the favorable effect in terms of pain relief, following IACI (14).

The main limitation of this study is the small number of patients. However, the consistent findings in either group, the Diprospan or control group, strengthen our conclusions.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of the Nazareth Hospital.

**Informed Consent:** Written informed consent was obtained from all the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - G.H., F.K.; Design - G.H., F.K., G.H., S.A.; Supervision G.H., F.S.,F.K.,; Resources - G.H., G.H., S.A.; Materials - G.H., F.S,. G.H., S.A.; Data Collection and/or Processing -.G.H., F.S., G.H., S.A.; Analysis and/or Interpretation - G.H., F.K., F.S., G.H., S.A.; Literature Search - G.H., F.K.; Writing Manuscript - G.H., F.K., F.S., S.A.; Critical Review - G.H., F.K., F.S., G.H., S.A.

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