

## Glucocorticoids-Induced Hypertension: The Prevalence and Risk Factors

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### Original Article

### Abstract

**Introduction:** Despite benefits in the treatment of most autoimmune and inflammatory diseases, glucocorticoids (GCs) have proved side effects including hypertension, diabetes, osteoporosis and lipid disorders. Determining the risk factors for hypertension can facilitate the identification of high-risk individuals and lead to effective control of the side effects. The present study aimed to determine the risk factors for hypertension in individuals receiving high-dose GCs.

**Methods:** This prospective study recruited 140 adults (age > 18 years) requiring prednisolone or equivalent more than 30mg daily for at least three months. The participants' blood pressure was monitored every month and correlations between the incidence of hypertension and variables such as serum calcium levels, weight, underlying diseases, body mass index (BMI), and folic acid use were investigated by repeated measure analysis.

**Results:** While none of the subjects were hypertensive at baseline, 55 patients (39.28%) developed hypertension during the course of the study. Baseline weight and BMI, cumulative GC dose, family history of hypertension, and age were significantly higher in hypertensive patients.

**Conclusion:** High BMI, male gender, elderly, family history of hypertension may have impact on development of hypertension in patients taking GCs.

**Key words:** Glucocorticoids, Hypertension, Side Effects

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### Introduction:

Glucocorticoids (GCs) are affordable and powerful medications with anti-inflammatory and immuno regulatory properties which turn them into favorable treatment options for not only rheumatologic and allergic diseases, but also some malignancies. Owing to their confirmed anti-

inflammatory and immunosuppressive properties, GCs are the first line treatment for most rheumatologic disorders like lupus, vasculitis, and myositis. In other words, most rheumatologic diseases will not be controlled in the absence of corticosteroids. As a result, the application of GCs has constantly increased, especially over the past two decades (1-3). Despite advancements in our

understanding of GCs' mechanism of action and potential side effects and development of new drugs, our knowledge about their side effects, e.g. cardiovascular accidents, neural and gastrointestinal disorders, myopathies, hyperglycemia, and dyslipidemia, remains insufficient (4-6).

Although there are some reports of GC-induced hypertension, there is still controversy over the role of GCs in the development of hypertension. Low dosages of synthetic GCs show limited mineralocorticoid properties and thus low potential for water and salt retention. However, hypertension has even been documented in patients under treatment with low dosages of GC (6-9). While genetic plays a major role in GC-induced hypertension (10-12), the effects of other risk factors such as cumulative dose of corticosteroids and patients' weight, body mass index (BMI), age, sex, serum calcium levels, family history of hypertension, and use of various supplements should not be neglected in this regard (12,13). Therefore, patients receiving GCs are generally recommended to be monitored for the incidence of side effects (3,6).

The present study aimed to investigate the prevalence of GC-induced hypertension in patients receiving oral prednisolone ( $\geq 30$  mg/day) for at least three months. It also sought to identify the risk factors of hypertension, particularly the preventable and curable ones, in the hope to minimize patient visits and cardiovascular incidents and decrease corticosteroids dosage in the mentioned group of patients.

## Methods:

This prospective cohort study recruited all adult patients (age  $\geq 18$  years) who had been referred to the rheumatologic clinic or admitted to the rheumatology ward of Rasool-e-Akram Hospital (Tehran, Iran) and required at least three months of oral prednisolone at a dosage of  $\geq 30$  mg/day. All GC doses administered from the beginning of the study including methylprednisolone pulses were converted to prednisolone equivalents for determining cumulative doses. The exclusion criteria were pregnancy, history of hypertension or records of hypertension in previous visits, human immunodeficiency virus (HIV) infection, use of

medications which may raise or lower blood pressure (e.g. non-steroid anti-inflammatory drugs, ACE inh, Angiotensin receptor blocker, diuretic and tacrolimus), history of corticosteroids over the past six months, acute or chronic renal failure causing elevated serum creatinine levels (GFR  $< 60$ ) "electrolyte imbalance (hypokalemia, hyperkalemia, hypernatremia, hyponatremia) and glomerular diseases. Written informed consent was obtained from all patients.

Data on demographics, disease diagnosis, weight, body mass index (BMI;  $\text{kg}/\text{m}^2$ ), lab tests, treatment history including cumulative total dose of prednisolone and blood pressure during the first visit and then in monthly visits for three months were recorded. Blood pressure was measured with a standardized mercury sphygmomanometer with an adequate cuff size based on the patient's right arm size arm after 15 minutes rest in a sitting position. An average of the 2 stable measurements was recorded as the patient's blood pressure. If the patient has smoked, consumed caffeinated materials (tea, cola) or other stimulants or exercised prior to appointment, we postponed our measurement to next day, while emphasizing on keep in mind these points for the following visit. Hypertension was defined as diastolic blood pressure (DBP)  $\geq 90$  mmHg or systolic blood pressure (SBP)  $\geq 140$  mmHg in two visits. Family history of hypertension was present if the patient had a hypertensive parent. The patients were provided with a paper containing details on proper drug (oral prednisolone) use and asked to follow the exact instructions. The mean, standard deviation, maximum, and minimum values of quantitative variables were calculated and compared using t-tests. Chi-square tests were carried out to compare qualitative variables. Multiple logistic regression analysis was used to identify odds ratios for development of hypertension. This study was approved by the Institutional Review Board on research. P values of 0.05 or less were considered statistically significant. All analyses were performed in SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

## Results:

A total of 140 patients were studied during one year. The mean age of the patients was 36.69

years [95% confidence interval (CI): 34.41-38.85]. The mean BMI of the patients was 22.61 kg/m<sup>2</sup> (95% CI: 21.3-23.27) at the beginning of the study. The most common underlying disease was systemic lupus erythematosus (61 patients, 43.57%), renal involvement was not detected in any of the patients. Others, however, suffered from scleritis, uveitis, Behcet's disease, granulomatosis with polyangiitis (Wegener's granulomatosis), temporal arthritis, sarcoidosis, polymyositis, dermatomyositis, and inflammatory bowel disease (IBD). Patient characteristics are summarized in Tables 1 and 2.

**Table 1. Clinical and demographic characteristics of the participants**

Variable	Patients (All counted)
Age	36.69 ± 8.5 year
Height	163.47 ± 10.1 cm
Gender (male/female)	102/38
Primary weigh (Kilogram)	60.60 (95% CI ,58.74-62.27)
Calcium (mg/dL)	8.94 (95% CI,8.89-8.99)
Folic acid usage	55 (39.28%)
Familial hypertension history	46 (32.85%)
Diabetes	5 (3.57%)
Methylprednisolone pulse	78 (55.71%)
Cumulative dose in 3 months	5428.90 mg (95% CI ,5157.37-5725.87)
Hypocalcemia	15 (10.71%)

Hypertension developed in Fifty five (39.28%) patients. In the first month, 52 out of 55 patients were hypertensive. Three out of 55 patients became hypertensive in the second month. Hypertensive patients had significantly higher age compared to the subjects with normal blood pressure (40.93±14.10 vs. 33.99±10.48 years; P=0.005). The frequency of hypertension in patients aging below and over 50 years was 32.29% and 62.21%, respectively (chi<sup>2</sup>, P=0.004)

Baseline weight was significantly higher in hypertensive patients than in subjects with normal Blood pressure (69.51±8.51 vs. 54.94±5.61 kg; P<0.001). Similarly, hypertensive patients had significantly higher BMI compared to individuals with normal blood pressure (26.55±2.89 vs. 20.11±1.60 kg/m<sup>2</sup>; P<0.001). The mean cumulative GC dose was 6085.31±1445.82 mg in hypertensive subjects and 5011.99±1549.22 mg in others (P<0.001).

There was not a significant difference in serum calcium levels between subjects with high and normal blood pressure (8.93±0.28 vs. 8.94±0.25 mg/dl; P=0.777). There was no significant relation between hypocalcemia and hypertension (chi<sup>2</sup>, P=0.24).

Hypertension was significantly more prevalent in men than in women (53.12% vs. 33.34%; chi<sup>2</sup>, P=0.049).

**Table 2. Patient characteristics at different time intervals**

Variable / Time	First visit	End of 1 <sup>st</sup> Month	End of 2 <sup>nd</sup> Month	End of 3 <sup>rd</sup> Month
Weight	60.60 ±2.8	63.92 ±3.1	64.71 ±3.6	65.25 ±4.2
Systolic BP (mmHg)	111.81 ±2.3	128.42 ±3.3	129.83 ±2.9	128.63 ±3.1
Diastolic BP (mmHg)	73.30 ±1.8	85.49 ±1.7	87.19 ±1.9	86.57 ±2.1
Hypertensive	None	43.57%	42.14%	38.57%
Cumulative dose (mg)	-	2786.57 ±287.1	1569.04 ±191.4	1073.28 ±231.1

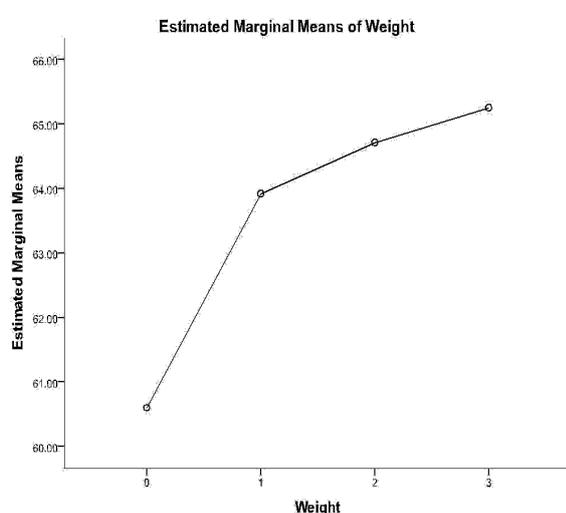
BP: Blood Pressure

In contrast, the presence of underlying diseases had no significant correlation with becoming hypertensive (chi<sup>2</sup>, P=0.152). Hypertension was diagnosed in 34.33%, 40.00%, 41.00%, 57.28%,

20.00%, 23.69%, and 25.00% of patients with SLE, sarcoidosis, scleritis and uveitis, dermatomyositis, IBD, temporal arthritis, and polymyositis, respectively.

Overall, 46.80% of hypertensive patients and 33.34% of individuals with normal blood pressure used folic acid ( $\chi^2$ ,  $P=0.140$ ). However, family history of hypertension was significantly more frequent in hypertensive patients than in participants with normal blood pressure (74.35% vs. 21.25%;  $\chi^2$ ,  $P<0.001$ ). Since only five patients (four with high and one with normal blood pressure) had diabetes, the analysis would have not yielded valid results.

Repeated measures analysis of variance (ANOVA) revealed that GC therapy caused significant increments in patients' weight during the three-month course of the study (Mauchly's  $W=0.279$ ;  $P<0.001$ ) (Figure 1).



**Figure 1.** Changes in patients' weight during the three-month course of the study

Likewise, analysis of the participants' SBP and DBP suggested that the subjects' SBP increased significantly over time (Mauchly's  $W=0.502$ ;  $P<0.001$ ). Nevertheless, there was no significant relationship between receiving pulse GC therapy and becoming hypertensive, i.e. 34.32% of patients receiving pulse GC therapy and 44.44% of other patients developed hypertension ( $\chi^2$ ,  $P=0.256$ ).

## Conclusion:

Despite the benefits of GCs in the treatment of most inflammatory and autoimmune diseases, their substantial side effects, including hypertension and weight gain, have been less studied. Hypertension is a dose-dependent side effect of GCs which

occurs in 37% of patients (13-16).

In the present study, patients who developed hypertension had significantly higher weight and BMI compared to patients with normal blood pressure. The correlation between heavy weight and hypertension has been proved in previous studies (17,18). Furthermore, underlying metabolic abnormalities, such as heavy weight (obesity), insulin resistance, and sleep apnea, can multiply the negative effects of GCs on blood pressure (19,20).

Fardet et al. assessed the incidence of side effects in 80 patients who had received 20 mg/day prednisolone for at least three months. They found GC-induced hypertension to be an uncommon complication presenting in only 8.7% of the patients (2). Such a low prevalence of hypertension can be justified by the lower dosage of GCs and the simultaneous administration of antihypertensive drugs in 23 patients. Besides, changes in other involved variables (e.g. baseline weight, familial history of hypertension, and BMI), which were not analyzed by the above-mentioned researchers, might have been responsible for the low incidence of GC-induced hypertension.

The hypertension caused by the usage of corticosteroids generally occurs during the first days or weeks after drug administration (12,20). In the current study, the mean time for the assessment of GC-induced hypertension was one month. Hypertension could not be diagnosed sooner than one month. Therefore, studies incorporating daily blood pressure measurements can better clarify the mean time for the development of GC-induced hypertension.

Miao et al. investigated the effects of folic acid on blood pressure in rats receiving corticosteroids (dexamethasone or Adrenocorticotrophic hormone). This study showed that folic acid consumption prevents the incidence of hypertension in rats using dexamethasone or ACTH. (21). In the present study, however, folic acid usage had no significant effects on the incidence of GC-induced hypertension. Such an inconsistency can be attributed to different dosages of folic acid in the two studies (40 mg in the study by Miao et al. vs. 1-5 mg in our research) and the simultaneous usage of folate antagonist medications (methotrexate) in our study. Differences in genetic parameters, GC receptor responses, and metabolism of medications

between rats and human might have also been responsible for the observed discrepancy. Nevertheless, the identification of the exact mechanisms requires further investigation (22).

A study evaluated the incidence of hypertension in 35 elderly patients (age > 65 years) who were treated with corticosteroids. While none of the patients was hypertensive at baseline, 1.37% of the subjects developed hypertension during the course of the study. This group of patients had significantly higher family history of hypertension, but lower serum calcium levels (13). Although we found a similar relation between family history of hypertension and the risk of developing the condition during GC use, we failed to establish a significant difference in serum calcium levels between hypertensive and non-hypertensive patients. Meanwhile, both studies identified older age as a risk factor for corticosteroid-induced hypertension.

Weight gain is a major side effect of treatment with GCs. Wung et al. investigated the side effects of corticosteroids in 157 patients with Wegener's granulomatosis. Although 3.22% of the participants gained at least 10 kg in the first year of treatment, weight gain had no correlation with cumulative dose of corticosteroids (23). We observed slightly higher changes in the mean weight during the three-month period of the current research. A number of dissimilarities between the two studies can justify the observed inconsistencies. First, while our participants had different diseases, Wung et al. only recruited patients with Wegner's granulomatosis. On the other hand, individuals studied by Wung et al. had more active diseases, but most of our subjects required lower doses of prednisolone over the course of the study (i.e. they started to recover). In addition, we administered a higher cumulative dose compared to Wung et al. (5428 vs. 3000 mg). Finally, in our study all the participants were new patients while in mentioned study, patients had already been on steroids. In fact, the presence of chronic diseases can be a reason for less weight gain.

Hypertension was developed in 39.28% of our patients taking high dose of GC. BMI, cumulative GC dose, male gender, family history of hypertension was correlated with occurring hypertension. Considering the potential side effects

of long-term treatment with GCs, physicians are recommended to obtain complete patient history and perform thorough physical examinations to identify the risk factors and possible underlying conditions in patients before initiating treatment. Moreover, since GC-induced hypertension generally develops during the first days or weeks of taking the medicine, future studies are suggested to monitor the patients on a daily basis to diagnose any changes in their blood pressure as soon as possible

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