

The role of the bisphosphonate (Alendronate) as an adjuvant therapy in patients with type 2 diabetes mellitus: a case-control study

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Abstract

Background: Type 2 diabetes mellitus is an extremely common health problem affecting Iraqi population. The mainstay in treating type 2 DM includes lifestyle modification, diet, and drug treatment. Metformin is a common agent used in treating type 2 DM; however, side effects such as lactic acidosis and the need for higher doses with advancing age, in addition to lack of a single form of treatment that can cure type 2 diabetes and involvement of inflammatory process in DM, make mandatory, the search for new approaches to treat type 2 DM.

The aim of the study: To evaluate the role and the mechanism of action of alendronate in a case-control study on the glycemic control in type 2 diabetes patients.

Patients and methods: A case-control study included 60 patients with type 2 diabetes mellitus. They were divided into two groups; the first group included 30 patients who were given metformin (500 mg two times a day) only and served as a control group, whereas, the second group included 30 patients who were given metformin (500 mg two times a day) plus alendronate (70 mg a week) and served as a study group. Baseline estimations of fasting blood sugar (FBS) and serum tumor necrosis factor alpha (TNF- α) were done before starting the treatment and then 2 months from onset of treatment. The study was conducted in Al-Diwaniyah Teaching Hospital, Al-Diwaniyah province, Iraq and started in June 2015 and ended in December 2017.

Results: Mean FBS was significantly reduced from 180.92 \pm 8.86 mg/dl to 130.58 \pm 8.87 mg/dl in the control group ($P < 0.001$) and from 178.08 \pm 16.62 mg/dl to 93.75 \pm 5.71 mg/dl in the study group ($P < 0.001$), however, the magnitude of reduction was substantially greater in study group ($P < 0.001$ versus $P = 0.039$). The rate of improvement in FBS level, expressed as the number of patient with FBS level of < 100 mg/dl, was significantly higher in the study group than in the control group, 66.7% versus 36.7%, respectively ($P = 0.02$). The level of serum TNF- α was not changed significantly following the use of metformin only, 221.39 (59.44) ng/ml versus 221.18 (61.08) ng/ml ($P = 0.646$), however, the use of alendronate as an adjuvant therapy resulted in significant reduction of serum TNF- α from 226.26 (47.35) ng/ml to 163.69 (11.97) ng/ml ($P = 0.002$).

Conclusion: Alendronate is an effective adjuvant agent in treating type 2 diabetic patients may be by reducing TNF- α .

Keywords: Alendronate, type 2 DM, TNF-alpha

INTRODUCTION

Diabetes mellitus is a very common metabolic disorder; by 2011, the estimated burden of DM was 366 million patients and it is anticipated that this figure will rise to 552 million patients by 2030 [1]. The prevalence of diabetes is increasing especially in developing countries and this disease is responsible for substantial morbidity and mortality in these countries [1]. There is some variation in the incidence of diabetes according to geographical distribution [3]. Lifestyle factors and genetics are the main contributory factors in the etiology of type 2 DM [4]. Sedentary lifestyle, physical inactivity, alcohol consumption and cigarette smoking are among the principal lifestyle factors that are responsible for type 2 DM [5]. Obesity has been observed to be responsible for approximately 55% of type 2 DM cases [6]. High rate of obesity among people between 1960s and 2000s is believed to be responsible for the high rate of type 2 diabetes all over the world [7]. It has been suggested that exposure to certain environmental toxins such as bisphenol A, "a constituent of some plastics" may increase the incidence of type 2 DM in certain communities [8]. The main pathologic defect in type 2 DM is resistance to insulin action in addition to reduced insulin production and subsequent beta cell function failure [9, 10]. These pathologic derangements as a whole will lead to reduced delivery of glucose to the liver, adipocytes and muscle cells and subsequent hyperglycemia and increased fat breakdown [11]. The mainstay in management includes lifestyle, diet modification and drug therapy. Biguanides, of which metformin is one of the most frequently used drugs in obese and overweight diabetic individuals. It acts by suppression of hepatic glucose production, increasing sensitivity to insulin, enhancement of glucose uptake by "phosphorylating GLUT-enhancer factor", increasing oxidation of fatty acid, and decreasing the glucose absorption from the intestine [12]. Articles published in 2008 demonstrated additional mechanism of action of metformin such as "activation of AMP-activated protein kinase, an enzyme that plays a role in

the expression of hepatic gluconeogenic genes" [13]. Because of the potential of development of lactic acidosis, metformin must be taken with caution in elderly diabetic patients especially in the setting of renal compromise. Metformin has a low rate of hypoglycemia in comparison to sulfonylureas [12]. Search for new agents to treat type 2 diabetes mellitus makes a substantial budget in both clinical and experimental researchers because no single agent has been proved superior to others and because of the associated side effects.

The most frequently used preventive agent for reduced bone density in diabetic individuals is bisphosphonates [14]. These agent's selectivity incorporate into mineral surfaces of bones where they prevent osteoclast-directed bone resorption [15] and inhibit fractures of bones [16]. Previous researchers supposed that bisphosphonates not only prevent osteoclast-directed bone resorption but they also prevent osteocyte and osteoblast death [17], so these agents are extremely beneficial in elderly diabetic individuals. Experimental studies have reported that bisphosphonates protect "rodent-derived osteoblasts from advanced glycation end products (AGE)-induced death (previously shown elevated in diabetic bone)" [18]. It has been found that TNF- α play role in the induction of insulin resistance. From a clinical point of view, women with or without type 2 diabetes taking bisphosphonates experienced a benefit in general bone health [19]. However, insufficient information is raised regarding the role of bisphosphonates in controlling blood sugar level in those diabetic patients, so the present study was conducted to investigate the role of alendronate, a bisphosphonate, in relation to blood sugar level in patients with type 2 diabetes mellitus through a case-control study.

PATIENTS AND METHODS

The present case-control study included 60 patients with type 2 diabetes mellitus. They were divided into two groups; the first group included 30 patients who were given metformin (500 mg two times a day) only and served as a control group, whereas, the second group included 30 patients who were given metformin

(500 mg two times a day) plus alendronate (70 mg a week) and served as a study group. Baseline estimations of fasting blood sugar (FBS) and serum tumor necrosis factor alpha (TNF- α) were done before starting the treatment and then 2 months from onset of treatment. The study was conducted in Al-Diwaniyah Teaching Hospital, Al-Diwaniyah province, Iraq and started in June 2015 and ended in December 2017.

Statistical analysis

Statistical analysis was carried out using statistical package for social sciences (SPSS) version 23.0 and Microsoft Office Excel 2010. Numeric variables were expressed as mean, standard deviation, median and inter-quartile range (IQR) while nominal variables were expressed as number and percentage. Paired t-test and Wilcoxon test were used to compare FBS and TNF- α before and after treatment for the same group. Independent samples t-test and Mann Whitney U test were used to compare FBS and TNF- α between control and study groups at the same onset of time from treatment. Chi-square test was used to compare the rate of improvement in FBS between study and control groups. The odds ratio was used to evaluate the potency of alendronate added to

metformin in comparison with metformin only with respect to FBS control. The level of significance was considered at $P \leq 0.05$.

RESULTS

Mean FBS was significantly reduced from 180.92 \pm 8.86 mg/dl to 130.58 \pm 8.87 mg/dl in the control group ($P < 0.001$) and from 178.08 \pm 16.62 mg/dl to 93.75 \pm 5.71 mg/dl in the study group ($P < 0.001$), however, the magnitude of reduction was substantially greater in study group ($P < 0.001$ versus $P = 0.039$), as shown in figure 1 and table 2. The rate of improvement in FBS level expressed as the number of patient with FBS level of < 100 mg/dl, was significantly higher in the study group than in the control group, 66.7 % versus 36.7%, respectively ($P = 0.020$), as shown in table 1. The level of serum TNF- α was not changed significantly following the use of metformin only, 221.39 (59.44) ng/ml versus 221.18 (61.08) ng/ml ($P = 0.646$), however, the use of alendronate as an adjuvant therapy resulted in significant reduction of serum TNF- α from 226.26 (47.35) ng/ml to 163.69 (11.97) ng/ml ($P = 0.002$), as shown in figure 2 and table 2.

Table 1: Rate of improvement in FBS level after treatment in control and study groups

| FBS category | Group 2 n = 30 Metformin and alendronate | Group 1 n = 30 Metformin only | P | OR (95% CI) |
|---|---|----------------------------------|-------|------------------|
| Non-diabetic range (< 100 mg/dl), n (%) | 20(66.7) | 11 (36.7) | 0.020 | 3.45 (1.19-9.99) |
| Diabetic and pre-diabetic range (≥ 100 mg /dl), n (%) | 10 (33.3) | 19 (63.3) | | |

FBS: Fasting Blood Sugar; n: number of cases; OR: Odds ratio; CI: Confidence Interval.

Table 2: Fasting blood sugar and tumor necrosis factor alpha levels in control and study groups before and after treatment

| Characteristic | | Group 1 n = 30 Metformin only | Group 2 n = 30 Metformin and alendronate | P |
|------------------------------------|------------------|----------------------------------|--|-----------|
| FBS (meanSD) mg/dl | Before treatment | 180.92 \pm 8.86 | 178.08 \pm 16.62 | 0.039 |
| | After treatment | 130.58 \pm 8.87 | 93.75 \pm 5.71 | < 0.001 |
| TNF- α , median (IQR) ng/ml | Before treatment | 221.39 (59.44) | 226.26 (47.35) | 0.954 |
| | After treatment | 221.18 (61.08) | 163.69 (11.97) | < 0.001 |

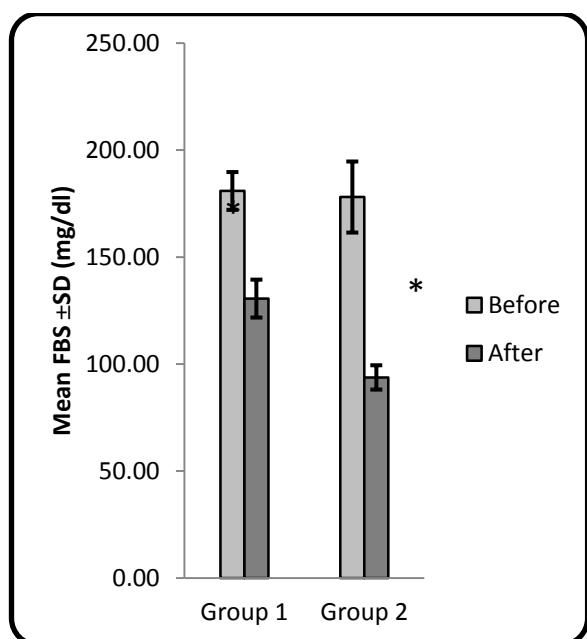


Figure 1: Fasting blood sugar levels in control and study groups before and after 2 months treatment.

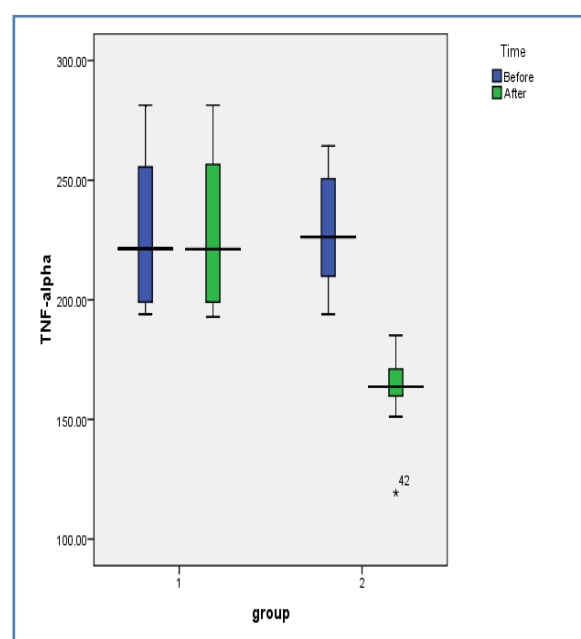


Figure 2: Tumor necrosis factor alpha levels in control and study groups before and after treatment

DISCUSSION

The present study showed that the use of alendronate resulted in significant improvement in control of fasting blood sugar control when used as an adjuvant therapy in addition to metformin; moreover, alendronate resulted in significant reduction in serum TNF- α . A link is suggested between TNF- α reduction and improvement of diabetes control. Several studies, experimental and clinical, have shown that the use of alendronate is accompanied by significant reduction in the serum level of TNF- α [20-22].

Tumour necrosis factor alpha (TNF- α) is an adipocytokine involved in systemic inflammation and stimulates the acute phase reaction [23]. TNF- α is primarily secreted by macrophages, and also by a broad variety of other cells including adipocytes [24, 25]. "TNF- α inhibits insulin transduction and has an effect on glucose metabolism" [26, 27]. Disturbances in the TNF- α metabolism have been implicated in metabolic disorders, such as obesity and insulin resistance [28], "indicating that perturbations of TNF- α metabolism may affect the onset of type 2 diabetes mellitus and the progression of the disease" [29]. Increased TNF- α is thought to contribute to a number of diabetic complications including microangiopathy and neuropathy, cardiovascular diseases, retinopathy, and increased inflammation associated with infection and periodontitis [30].

Bisphosphonates bind to bone, decrease osteoclast activity, and are considered primarily anti-resorptive agents; however, both bone resorption and bone formation are affected by bisphosphonate treatment and additional mechanisms may play a role. One such pathway may be the osteoprotegerin (OPG)/receptor activator of nuclear factor-kappaB (RANK)/RANK ligand (RANKL) system [31, 32]. "Another potential mechanism of action of bisphosphonates is the effect on inflammation. Inflammatory cytokines, IL-6 and TNF- α , are potent stimulators of osteoclast activity and have been implicated in the uncoupled bone resorption seen in some patients with osteoporosis" [33, 34]. In a cohort of patients with chronic idiopathic neutropenia, a condition associated with increased TNF- α concentrations and bone loss, bisphosphonate treatment was associated with marked decreases in TNF- α and IL-1 β , which correlated with decreases in bone resorption markers and increased in BMD [35].

CONCLUSION

This finding suggests that alendronate helps as an adjuvant therapy in type 2 DM may be by reducing insulin resistance and improve insulin sensitivity in response to reduction of TNF- α , of high benefit in osteoporotic patients. Alendronate seems to reduce TNF-alpha produced by monocytes derived inflammatory cells. However, the mechanism is unknown and further experimental studies are needed to disclose the exact molecular mechanism by which alendronate causes reduced TNF-alpha by macrophages.

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