ASSOCIATION OF BLOOD PRESSURE AND BODY WEIGHT DECLINE DURING ONE-YEAR TREATMENT WITH THE INCRETIN ANALOGUE EXENATIDE

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Summary

Exenatide treatment is related to lower blood pressure. It is explained by different pathophysiological pathways. We explored the dynamics of blood pressure and weight loss during one-year therapy with exenatide. Forty-nine type 2 diabetic patients previously treated with a combination of metformin and sulfonylurea were included in this open-label, intention to treat study. Five μg of exenatide was administered twice daily for 4 weeks, and then 10 μg twice daily as adjunctive therapy to the pre-existing treatment. Patients in whom antihypertensive therapy was modified were excluded from analysis. At the end of 52 weeks, systolic blood pressure decreased significantly, with a 4.65 mm Hg reduction (P=0.008582) in exenatide treated patients. There was a positive correlation between body weight and systolic blood pressure drop (Pearson coefficient 0.675254). The interesting blood pressure curve could have relied on various antihypertensive mechanisms of exenatide: drop of blood pressure at first 16 weeks could have been connected with natriuresis and the second one with later vasodilatation.

INTRODUCTION

The introduction of incretin mimetics in daily therapy has opened a new perspective in the treatment of type 2 diabetes mellitus. Incretins, substances secreted from the gut, have many levels of action. They lower blood glucose without fear from hypoglycemia and preserve first-phase insulin secretion. They are also efficient in reducing weight by slowing gastric emptying rate and reducing appetite (1). Glucagon-like peptide 1 (GLP1) receptors are found all over the body, including kidneys (2). There is evidence that the GLP1 mimetic exenatide has a potential blood pressure lowering effect (3). At the beginning of 2010, an extensive analysis was published in the American Journal of Hypertension,
presenting results from six trials including 2171 subjects treated with exenatide for at least 6 months (4). A significantly greater reduction in systolic blood pressure was confirmed, although the exact antihypertensive mode of action remained unknown. Considering these facts, we explored the dynamics of blood pressure during one-year treatment with exenatide. The idea was to demonstrate the possible association between blood pressure and body weight reduction. Patients that were participating in a bigger study supported by Eli Lilly and Company (GWAD study) were analyzed separately during 52 weeks of the study. A sub-analysis was made with approval of the named company (5).

SUBJECTS AND METHODS

Study population

Forty-nine patients (25 female and 24 male) were included in the study. Study group characteristics at randomization are shown in Table 1. All patients had type 2 diabetes treated with a combination of metformin and sulfonylurea for at least 3 months. Inclusion criteria were stable body weight, stable blood pressure (61% of them were treated for hypertension) and no change in antihypertensive therapy for 3 months before randomization. Patients with weight variation of up to 10% in the past 3 months, men with creatinine higher than 132 µmol/L and women with creatinine higher than 110 µmol/L were not included.

METHODS

It was an open-label, intention to treat phase 3 trial with the primary endpoint of blood pressure lowering, with assumed therapeutic benefit in terms of HbA1c decline and weight reduction as manifested by body mass index (BMI) decrease. The trial lasted for 52 weeks (following 2 pre-randomization screening weeks). Nine patients failed to present for follow up visits. Patients were administered 5 µg exenatide twice daily for 4 weeks, and then 10 µg twice daily as adjunctive therapy to the pre-existing metfo-

min/sulfonylurea treatment. In patients that experienced hypoglycemia, the prescribed dose of sulfonylurea was reduced, while maintaining the exenatide dosage. Blood pressure was measured on each of 11 follow up visits (including 2 pre-randomization visits). Patients were instructed to measure blood pressure at home in-between the visits. Patients that had their antihypertensive therapy modified by family physician during the study were excluded from analysis, since change in their blood pressure curve could have been explained by the new treatment. Those patients had otherwise the same characteristic as the other ones.

On statistics analysis, descriptive statistics, Student’s t-test, correlation and analysis of variance were employed.

RESULTS

At the end of 52 weeks, 40 patients completed the study protocol. Data analysis showed their systolic blood pressure to have decreased from 133.4 mm Hg to 128.75 mm Hg (-4.65 mm Hg) and diastolic blood pressure from 78.95 mm Hg to 77.47 mm Hg (-1.48 mm Hg), yielding a statistically significant difference (ANOVA: \( p=0.008582 \) and \( p=0.006286 \), respectively). The interesting dynamics of the systolic blood pressure curve is illustrated in Figure 1 and the dynamics of weight reduction on exenatide therapy in Figure 2. At study entry, the participants were generally overweight, with a long history of diabetes and poor glycemic control. Table 2 shows improvements in HbA1c and body weight from week 0 to week 52, as analyzed by t-test that yielded a statistically significant difference. Exenatide treated patients experienced steady body weight reduction.

Both body weight and blood pressure declined constantly during the 52 study weeks. There was positive correlation between body weight and blood pressure decrease during 52 weeks of therapy (Pearson coefficient 0.675254) (Fig. 1).
DISCUSSION

Type 2 diabetes mellitus and metabolic changes lead to a higher risk of cardiovascular disease. There are well-documented facts demonstrating that rigorous treatment of type 2 diabetes is beneficial for both microvascular and macrovascular complications (6). If other metabolic parameters are corrected, the final outcome is even better (7). Adipose and diabetic patients have glomerular hyperfiltration and enhanced reabsorption of sodium in the kidneys, leading to fluid retention and hypertension. It is already known that obese mice (db/db) have salt retention and elevated intrarenal angiotensin II (8), and that the mechanism of salt retention is similar to the one described in humans. In the experimental study from 2009 performed by Hirata et al., hypertension was artificially induced (acute sodium-loading and angiotensin II-infusion) in both obese type 2 diabetic db/db mice and nonobese db/m mice. The two groups of mice were treated with exendin-4 or a vehicle for 12 weeks. Obese type 2 diabetic db/db...
mice showed high salt sensitivity. Exendin-4 demonstrated antihypertensive effect in db/db mice and angiotensin II-infused mice, related to attenuation of high salt sensitivity. This observation confirmed exendin-4, a GLP-1 analogue, to have an extra-islet effect including regulation of salt handling (9). In 2004, Gutzwiller et al. included 15 healthy subjects and 16 obese men (mean BMI, 36 kg/m²) in a double-blind, placebo-controlled, crossover study. After overnight fasting, hypertonic saline was infused, followed by 3-h infusion of GLP-1. Intravenous infusion of GLP-1 enhanced sodium excretion, reduced H+ secretion, and reduced glomerular hyperfiltration in obese men. These findings suggested an action at the proximal renal tubule and a potential renoprotective effect (10). Two years later, Gutzwiller et al. embarked upon another study in which they compared intravenous salt load alone to the effect of GLP-1 infusion administered together with hypertonic saline. The extracellular volume expansion induced by intravenous infusion of hypertonic saline was partially compensated for by the increase in urinary sodium and water excretion with GLP-1. The authors explained that volume expansion was associated with an increase in renal perfusion, glomerular filtration and filtered sodium load. It was noted that GLP-1 was able to increase renal sodium excretion by 69% and urine volume by 86% (11). All these findings clearly indicate that GLP-1 has a natriuretic effect. Finally, there are also observations on the impact of GLP-1 on endothelial function (12). Decreased blood pressure could be a consequence of enhanced diuresis and natriuresis; however, a new pathophysiological moment has been recognized, i.e. improved endothelial dysfunction through GLP-1 receptor-dependent pathway (13,14). Although there are many speculations, the exact antihypertensive effects of GLP-1 analogues and their clinical usefulness remain unclear.

In our study, systolic pressure declined rapidly during the first 16 weeks of treatment, just as body weight that declined more rapidly during the same period. A strong positive correlation between weight loss and systolic blood pressure was confirmed. Are the first phase of weight loss and blood pressure decrease a result of the natriuretic effect of GLP-1? Is the first phase of weight loss actually dehydration?

The rapid decline of systolic blood pressure in the first 16 weeks was followed by partial elevation and then a much slower decline. The dual curve of systolic pressure could be a consequence of dual GLP-1 antihypertensive action: natriuretic effect followed by GLP-1 receptor reliant endothelial-dependent vasodilatation mentioned in earlier observations.

**CONCLUSION**

We recorded a steady decline in systolic blood pressure, along with body weight loss during the one-year treatment with exenatide. A strong positive correlation confirmed the relationship between these two phenomena. Earlier animal and human studies described the natriuretic effect of GLP-1 and gave the possible clue to this association: natriuresis lowers blood pressure and produces slight dehydration partially responsible for weight loss. The pressure curve relies on the dual antihypertensive mechanism of GLP-1: drop in the first 16 weeks is connected with natriuresis and the late one with later vasodilatation. Additional clinical evaluation of GLP-1 action on blood pressure is definitely needed.

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REFERENCES


