Felodipine Therapy May Not Alter Glucose and Lipid Metabolism in Hypertensives

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Abstract The effects of long-term monotherapy with felodipine, a calcium antagonist, on blood pressure, glucose tolerance, and serum lipid profiles were prospectively investigated in 51 hypertensive patients: 13 with normal glucose tolerance and 38 with glucose intolerance. The levels of plasma glucose, serum lipids, and glycosylated hemoglobin A1c were determined before and during long-term therapy with felodipine. A 75-g oral glucose tolerance test was performed before and during long-term felodipine therapy. Significant decreases in both systolic and diastolic blood pressures in both patient groups were maintained during the therapy. Neither fasting nor post-glucone load venous plasma glucose levels were altered in either group of patients, and no patients with normal glucose tolerance developed diabetes mellitus during the study. Serum lipid levels did not change significantly in either group of patients except for significant decreases in high-density lipoprotein cholesterol and apolipoprotein A-I in the group with normal glucose tolerance tests, but those changes remained within the normal range. Furthermore, neither serum lipid nor apolipoprotein levels were altered, even in patients with hypercholesterolemia (total cholesterol levels, >5.69 mmol/L = 220 mg/dL). These results suggest that long-term therapy with felodipine may not alter glucose and lipid metabolism in hypertensive patients, and felodipine appears to be useful as an antihypertensive agent for hypertensive patients with either dyslipidemia or impaired glucose metabolism. (Hypertension. 1994;23[suppl I]:I-215-I-219.)

Key Words • glucose metabolism • lipid metabolism • hypertension, essential • calcium-antagonist • long-term felodipine therapy

Chronic therapy with diuretics or β-blockers in hypertensive patients has been shown to be associated with reversible deterioration in glucose tolerance and in lipid metabolism. These adverse effects have been of particular concern because deterioration in glucose and/or lipid metabolism may pose additional risk for cardiovascular diseases. Recently, Ferrannini and coworkers reported that patients with essential hypertension may have an insulin-resistant state that contributes to the development of glucose intolerance, dyslipidemia, and cardiovascular disease. Several investigators examining the effects of antihypertensive drugs on glucose and lipid metabolism and/or insulin resistance in essential hypertension have found that angiotensin-converting enzyme inhibitors and α1-blockers may improve glucose and lipid metabolism. There are several reports that calcium antagonists may have neutral effects on glucose and lipid metabolism in humans. On the contrary, there are some reports that calcium antagonists may suppress insulin secretion from isolated pancreatic β-cells. Moreover, some calcium antagonists may cause glucose intolerance. Felodipine is a long-acting calcium antagonist, and it has been suggested that felodipine is a useful antihypertensive agent. The present study, which was conducted in several centers, is a prospective evaluation of long-term felodipine therapy on blood pressure, glucose, and lipid metabolism in hypertensive patients with and without glucose intolerance and with and without hypercholesterolemia.

Methods The subjects included 51 outpatients (24 men and 27 women; Table 1) with essential hypertension. Secondary causes of hypertension were excluded by endocrinological and radiological examinations, including renoscintigraphy, adrenoscintigraphy, and computed tomography in some patients. Thirteen of the 51 patients had normal glucose tolerance tests (NGT group). The remaining 38, designated the IGT group, included 14 patients with a diagnosis of non-insulin-dependent diabetes mellitus, all of whom had abnormal glucose tolerance tests, and 24 with impaired glucose tolerance using the criteria of the World Health Organization. Informed consent was obtained from all patients, and the study was approved by each hospital’s ethics committee. All antihypertensive medications and drugs affecting lipid metabolism were discontinued throughout the study. Patients were seen every month in the outpatient clinic, and blood pressure (BP) was measured three times with the patient in a sitting position at each visit. The average BP of the last two visits before the initiation of felodipine was higher than either 160 mm Hg systolic or 95 mm Hg diastolic in all patients. Basal levels of plasma glucose, serum insulin, glycosylated hemoglobin A1c (HbA1c), serum total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and apolipoproteins were determined in the morning after a 12- to 16-hour overnight fast. After BP was measured, blood samples were drawn at 30, 60, 120, and 180
Results

There were no significant differences in clinical variables between the NGT and IGT groups except for fasting plasma glucose and hemoglobin A1c. *P<0.05 vs NGT group.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein. Data are expressed as mean±SD. There were no significant differences in clinical variables between the patient groups with normal glucose tolerance tests (NGT) and impaired glucose tolerance tests (IGT) except for fasting plasma glucose and hemoglobin A1c.

The mean treatment period with felodipine was 7.5±0.5 months (range, 6 to 9 months). Three patients were withdrawn from the study because of palpitation, flushing, dizzi-
in BP and pulse rate after initiation of felodipine therapy in the NGT group are shown in Fig 1A, and those for the IGT group are shown in Fig 1B. Throughout long-term felodipine therapy, both systolic and diastolic BP decreased significantly and similarly in both groups without significant change in pulse rate. Fig 2 (A and B) illustrates the changes in mean plasma levels of glucose and serum levels of insulin after glucose loading in each group, before and during long-term felodipine treatment. Plasma glucose and serum insulin responses to a glucose load did not deteriorate in either group during therapy. The insulinogenic index (ΔIRI/ΔBS) was calculated as the ratio of the difference between the fasting and 30-minute post-glucose-load serum insulin levels and venous plasma glucose levels. Long-term felodipine therapy did not alter the insulinogenic index in either patient group. The concentrations of HbA1c also did not show any significant change in either group during long-term therapy. The mean values of serum lipids and apolipoproteins are shown in Table 2. No significant changes in those values were found in either group during long-term felodipine therapy, except for decreases in HDL-C and apolipoprotein A-I in the NGT group (Table 2A). When the subjects were subdivided into two groups (Table 2B) — one with serum TC levels of less than 5.69 mmol/L (220 mg/dL) and the other with levels of more than 5.69 mmol/L (hypercholesterolemia) — long-term therapy did not alter serum lipid and apolipoprotein levels in either patient group with or without hypercholesterolemia. There were no remarkable changes in body mass index, peripheral blood cell counts, serum electrolytes, creatinine, or enzymes during the long-term therapy.

**Discussion**

Certain antihypertensive agents may cause impairment of glucose tolerance, worsening of diabetic control, and hyperlipidemia when administered over an
extended period. These metabolic effects of diuretics may reduce or abolish their ability to lower morbidity and mortality.\textsuperscript{1,2} Several reports have suggested that \(\beta\)-blockers also impair glucose metabolism in normal and diabetic hypertensive patients.\textsuperscript{3,7,8} The Framingham cohort analysis\textsuperscript{21} noted that an increase in plasma glucose from 70 to 79 mg/dL to 90 to 99 mg/dL was associated with an increase in the incidence of cardiovascular diseases of 11\% in men and 21\% in women. This finding indicates that minor increases in plasma glucose are associated with a higher incidence of cardiovascular mortality and morbidity even if fasting glucose levels remain within the normal range. In addition, the hyperglycemic effect of diuretics has been found to be augmented by concomitant use of \(\beta\)-blockers.\textsuperscript{22} A reduction in HDL-C as well as increases in serum triglyceride and TC levels are considered to be risk factors for the development of coronary artery diseases.\textsuperscript{1,2,21,23,24} It is known that \(\alpha\)-blockers have a favorable effect on serum lipid profiles.\textsuperscript{25} We and other investigators\textsuperscript{5,6,8-10} have reported that long-term treatment with several angiotensin converting enzyme inhibitors may have beneficial effects on glucose and lipid metabolism through improving insulin sensitivity. Recently, calcium antagonists have been established as one of the first-line drugs as well as diuretics, \(\beta\)-blockers, angiotensin-converting enzyme inhibitors, \(\alpha\)-blockers, and \(\alpha\beta\)-blockers for the treatment of hypertension because of their promising depressor effect and relative tolerability;\textsuperscript{26} however, the metabolic effects on glucose are controversial during treatment with calcium antagonists.\textsuperscript{11,12,16} Some investigators have reported that calcium antagonists may worsen glucose metabolism through suppression of pancreatic insulin secretion, and other investigators have pointed out that glucose metabolism improved slightly with calcium antagonists. There are also some reports that calcium antagonists may have neutral effects on glucose metabolism,\textsuperscript{13,14} although some studies indicate a decrease in TC and LDL-C levels.\textsuperscript{17} In the present study, glucose tolerance was not affected by long-term therapy with felodipine, regardless of the glucose tolerance of the patients and their insulinogenic index. The values of HbA\(_1c\) in both NGT and IGT groups did not alter from their baseline values, indicating that long-term therapy does not affect glucose metabolism. Serum lipid levels did not change significantly in either group of patients, except for significant decreases in HDL-C and apolipoprotein A-I in the NGT group, but those changes remained within the normal range. Furthermore, fasting serum levels of lipids and apolipoproteins did not change during chronic therapy in patients with or without hypercholesterolemia. Overall, our results suggest that treatment with felodipine may have a metabolic neutral effect on glucose and lipid metabolism in hypertensive patients with or without glucose intolerance or hypercholesterolemia. It is known that the effects of lifestyle modification may not only decrease...
blood pressure but also improve glucose and lipid metabolism. As there was no control group treated with placebo in the present study, interference by factors other than felodipine per se cannot be entirely excluded, ie, these results regarding glucose and lipid metabolism may be explained in part as results of the better attention given to daily diet and exercise by the patients even though there were no significant changes in body mass index during long-term therapy with felodipine. Although some antihypertensive drugs unfavorably influence carbohydrate and lipid metabolism, felodipine has an advantage in that it can be used without worsening glucose and lipid metabolism regardless of whether the patient has glucose intolerance and/or hypercholesterolemia.

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References
15. Wollheim CB, Sharp GWG. Regulation of insulin release by calcium. Physiol Rev. 1987;61:945-973.

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