Postprandial Hyperinsulinemia in Patients with Mild Essential Hypertension

PETER SINGER, WOLFGANG GODICKE, SIEGFRIED VOIGT, IRMGARD HAJDU, AND MICHAEL WEISS

SUMMARY Glucose tolerance tests and diurnal profiles of glucose, insulin, free fatty acids, serum triglycerides, total and high-density lipoprotein cholesterol levels were performed in 8 male patients with mild essential hypertension as well as in 20 normotensive subjects. Although glucose tolerance and postprandial glucose levels appeared equal in both groups, the insulin response after a glucose load and after each meal was significantly increased in hypertensive subjects as compared with the controls (p < 0.01). The levels of free fatty acids were higher in the postabsorptive phase of patients with hypertension in comparison to normotensive subjects, but decreased markedly when plasma insulin levels rose after meals. In both subject groups serum triglyceride levels showed the typical postprandial increase. Total and high-density lipoprotein cholesterol levels showed neither diurnal variations nor differences between hypertensive subjects and normotensive controls. Postprandial hyperinsulinemia in patients with mild essential hypertension possibly may provoke lipid accumulation in the arterial wall and therefore may be a relevant risk factor for atherosclerosis in these subjects. (Hypertension 7: 182-186, 1985)

KEY WORDS • free fatty acids • glucose tolerance • hypertension

HYPERINSULINEMIA has been shown to be related to cardiovascular diseases irrespective of other risk factors. Enhanced insulin response to oral glucose has been observed after myocardial infarction and in subjects with disease of coronary, cerebral and peripheral arteries. Although basal glucose levels and blood sugar during glucose tolerance tests (GTT) appeared to be similar, abnormally raised serum insulin levels after oral and intravenous glucose loads have also been demonstrated in patients with essential hypertension when compared with normotensive controls. As the groups used in these studies were heterogeneous for such factors as age, body weight, hypertensive drug treatment and concomitant diseases — the study of Welborn and colleagues included no data on sex differences and serum lipid levels — the interpretation of the results remains uncertain.

The purpose of this study was to determine whether conclusions drawn from the results of standardized GTT to circadian variations of blood glucose and insulin are justified. Therefore, blood glucose and insulin levels during GTT and diurnal profiles were compared in healthy volunteers and patients with mild essential hypertension.

Methods

Of 22 healthy male subjects and 12 male patients with mild essential hypertension (diastolic blood pressure 90–104 mm Hg) 20 volunteers and 8 hypertensive subjects were chosen for the study on the basis of normal GTT results and normal body weight. None of the subjects had concomitant diseases, and none was receiving therapy. Two healthy subjects and four patients were eliminated because of mild hypertriglyceridemia (> 1.70 mmol/L), which was unmasked during the study.

The diagnosis of essential hypertension was based on the results of physical examination, electrocardiogram, x-ray film, and extensive laboratory studies to exclude secondary hypertension. The most important clinical and biochemical data obtained from the subjects are summarized in Table 1. Three of eight hyper-
TABLE 1. Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertensive subjects (n = 8)</th>
<th>Controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.4 ± 2.7</td>
<td>25.0 ± 2.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.9 ± 2.1</td>
<td>74.6 ± 1.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180 ± 2</td>
<td>178 ± 1</td>
</tr>
<tr>
<td>Ideal body weight (%)</td>
<td>109 ± 2</td>
<td>107 ± 2</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>160 ± 3*</td>
<td>129 ± 5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>95 ± 2*</td>
<td>82 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79 ± 2*</td>
<td>67 ± 4</td>
</tr>
<tr>
<td>Serum triglyceride levels (mmol/L)</td>
<td>1.20 ± 0.07</td>
<td>1.03 ± 0.09</td>
</tr>
<tr>
<td>Total cholesterol levels (mmol/L)</td>
<td>4.14 ± 0.15</td>
<td>5.14 ± 0.31</td>
</tr>
<tr>
<td>LDL cholesterol levels (mmol/L)</td>
<td>2.76 ± 0.17</td>
<td>3.74 ± 0.35</td>
</tr>
<tr>
<td>HDL cholesterol levels (mmol/L)</td>
<td>1.14 ± 0.06</td>
<td>1.19 ± 0.09</td>
</tr>
<tr>
<td>FFA levels (μmol/L)</td>
<td>281 ± 32</td>
<td>285 ± 54</td>
</tr>
</tbody>
</table>

*p < 0.01, compared with the control group.
Values are mean ± SEM.
FFA = free fatty acids; LDL = low-density lipoproteins; HDL = high-density lipoprotein.

GTT and serum glucose levels during diurnal profiles were estimated by glucose oxidase; plasma insulin levels (immunoreactive insulin — IRI) with Rotoradioliotest; plasma FFA levels according to the method of Duncombe; serum triglyceride levels according to a method modified from Royer and Ko; total and HDL cholesterol levels (after precipitation with phosphotungstate and MgCl₂) enzymatically (cholesterol oxidase para-amino phenazone, Boehringer, Mannheim, FRG); low-density lipoprotein cholesterol was calculated by Friedewald's formula.

Values are given as means ± SEM. The data of the two groups were compared and analyzed with the unpaired t test. Analysis of variance was used to detect possible diurnal variations within each group. A p value of less than 0.05 or 0.01 was accepted as significant.

Results

Glucose Tolerance

Capillary blood glucose levels during GTT were within the normal range in both groups (Figure 1). Basal plasma insulin levels in both groups were similar. After a glucose load, however, the level of insulin was markedly higher in hypertensive patients.

Blood pressure was measured at hourly intervals in triplicate by one observer (I.H.), who used the same mercury manometer with standard cuff (13 x 53 cm) placed about midpoint of the subject's contralateral arm while the subject was recumbent. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase 5).

The meals (at 0800, 1300, and 1900 hours) were identical for all participants and consisted of 600 calories each. Their carbohydrate/fat/protein ratio was 40:40:20. The subjects were permitted free activity within the confines of the ward, although no formal exercise was prescribed.

Levels of the various parameters were obtained by the following methods: Blood glucose levels during GTT and serum glucose levels during diurnal profiles were estimated by glucose oxidase; plasma insulin levels (immunoreactive insulin — IRI) with Rotoradioliotest; plasma FFA levels according to the method of Duncombe; serum triglyceride levels according to a method modified from Royer and Ko; total and HDL cholesterol levels (after precipitation with phosphotungstate and MgCl₂) enzymatically (cholesterol oxidase para-amino phenazone, Boehringer, Mannheim, FRG); low-density lipoprotein cholesterol was calculated by Friedewald's formula.

Values are given as means ± SEM. The data of the two groups were compared and analyzed with the unpaired t test. Analysis of variance was used to detect possible diurnal variations within each group. A p value of less than 0.05 or 0.01 was accepted as significant.

Results

Glucose Tolerance

Capillary blood glucose levels during GTT were within the normal range in both groups (Figure 1). Basal plasma insulin levels in both groups were similar. After a glucose load, however, the level of insulin was markedly higher in hypertensive patients.

Blood pressure was measured at hourly intervals in triplicate by one observer (I.H.), who used the same mercury manometer with standard cuff (13 x 53 cm) placed about midpoint of the subject's contralateral arm while the subject was recumbent. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase 5).

The meals (at 0800, 1300, and 1900 hours) were identical for all participants and consisted of 600 calories each. Their carbohydrate/fat/protein ratio was 40:40:20. The subjects were permitted free activity within the confines of the ward, although no formal exercise was prescribed.

Levels of the various parameters were obtained by the following methods: Blood glucose levels during GTT and serum glucose levels during diurnal profiles were estimated by glucose oxidase; plasma insulin levels (immunoreactive insulin — IRI) with Rotoradioliotest; plasma FFA levels according to the method of Duncombe; serum triglyceride levels according to a method modified from Royer and Ko; total and HDL cholesterol levels (after precipitation with phosphotungstate and MgCl₂) enzymatically (cholesterol oxidase para-amino phenazone, Boehringer, Mannheim, FRG); low-density lipoprotein cholesterol was calculated by Friedewald's formula.

Values are given as means ± SEM. The data of the two groups were compared and analyzed with the unpaired t test. Analysis of variance was used to detect possible diurnal variations within each group. A p value of less than 0.05 or 0.01 was accepted as significant.

Results

Glucose Tolerance

Capillary blood glucose levels during GTT were within the normal range in both groups (Figure 1). Basal plasma insulin levels in both groups were similar. After a glucose load, however, the level of insulin was markedly higher in hypertensive patients.

Blood pressure was measured at hourly intervals in triplicate by one observer (I.H.), who used the same mercury manometer with standard cuff (13 x 53 cm) placed about midpoint of the subject's contralateral arm while the subject was recumbent. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase 5).

The meals (at 0800, 1300, and 1900 hours) were identical for all participants and consisted of 600 calories each. Their carbohydrate/fat/protein ratio was 40:40:20. The subjects were permitted free activity within the confines of the ward, although no formal exercise was prescribed.

Levels of the various parameters were obtained by the following methods: Blood glucose levels during GTT and serum glucose levels during diurnal profiles were estimated by glucose oxidase; plasma insulin levels (immunoreactive insulin — IRI) with Rotoradioliotest; plasma FFA levels according to the method of Duncombe; serum triglyceride levels according to a method modified from Royer and Ko; total and HDL cholesterol levels (after precipitation with phosphotungstate and MgCl₂) enzymatically (cholesterol oxidase para-amino phenazone, Boehringer, Mannheim, FRG); low-density lipoprotein cholesterol was calculated by Friedewald's formula.

Values are given as means ± SEM. The data of the two groups were compared and analyzed with the unpaired t test. Analysis of variance was used to detect possible diurnal variations within each group. A p value of less than 0.05 or 0.01 was accepted as significant.

Results

Glucose Tolerance

Capillary blood glucose levels during GTT were within the normal range in both groups (Figure 1). Basal plasma insulin levels in both groups were similar. After a glucose load, however, the level of insulin was markedly higher in hypertensive patients.

Blood pressure was measured at hourly intervals in triplicate by one observer (I.H.), who used the same mercury manometer with standard cuff (13 x 53 cm) placed about midpoint of the subject's contralateral arm while the subject was recumbent. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase 5).

The meals (at 0800, 1300, and 1900 hours) were identical for all participants and consisted of 600 calories each. Their carbohydrate/fat/protein ratio was 40:40:20. The subjects were permitted free activity within the confines of the ward, although no formal exercise was prescribed.

Levels of the various parameters were obtained by the following methods: Blood glucose levels during GTT and serum glucose levels during diurnal profiles were estimated by glucose oxidase; plasma insulin levels (immunoreactive insulin — IRI) with Rotoradioliotest; plasma FFA levels according to the method of Duncombe; serum triglyceride levels according to a method modified from Royer and Ko; total and HDL cholesterol levels (after precipitation with phosphotungstate and MgCl₂) enzymatically (cholesterol oxidase para-amino phenazone, Boehringer, Mannheim, FRG); low-density lipoprotein cholesterol was calculated by Friedewald's formula.

Values are given as means ± SEM. The data of the two groups were compared and analyzed with the unpaired t test. Analysis of variance was used to detect possible diurnal variations within each group. A p value of less than 0.05 or 0.01 was accepted as significant.

Results

Glucose Tolerance

Capillary blood glucose levels during GTT were within the normal range in both groups (Figure 1). Basal plasma insulin levels in both groups were similar. After a glucose load, however, the level of insulin was markedly higher in hypertensive patients.
Diurnal Variations

In diurnal profiles serum glucose levels — including the postprandial increase — again were equal in hypertensive subjects and controls (Figure 2). Insulin response was significantly higher \( (p < 0.01) \) after each meal in hypertensive patients as compared with normotensive subjects. Postprandial insulin peaks were greatest after breakfast in both groups and were least after lunch in normotensive subjects and after dinner in hypertensive subjects.

In the postabsorptive phase the levels of FFA appeared higher in hypertensive subjects but were significant only in the late forenoon \( (p < 0.01 \) and 0.05, respectively; Figure 3). They decreased after each meal and reached the same level in both groups 2 hours later. The levels of FFA again increased when the postprandial plasma insulin returned to basal levels (see Figure 2). This increase was more pronounced in hypertensive subjects.

Serum triglyceride levels showed the typical postprandial increase without major differences between the two groups (Table 2). Total and HDL cholesterol levels remained unchanged in the diurnal profiles (not shown). Blood pressure and heart rate revealed no significant variations during the test period (not shown).

Discussion

Increased insulin response after a glucose load despite the demonstration of normal glucose tolerance has been associated with several cardiovascular diseases, as described by many authors.\(^{1-12,19}\) It remains unclear, howevet, whether hyperinsulinemia represents a feature of manifest atherosclerosis or stimulates development of atherosclerosis in a very early stage of the vascular process. According to epidemiological studies a relationship exists between high insulin levels after administration of a standardized glucose load and the incidence of coronary heart disease irrespective of other risk factors.\(^{1,2}\) As our hypertensive subjects revealed no symptoms of atherosclerosis, severe degenerative lesions of the pancreatic arterial wall as a primary defect leading to postprandial hyperinsulinemia in subjects with mild essential hypertension seem unlikely. On the contrary, it can be speculated that the continued presence of high insulin levels in hypertensive subjects after each meal might provoke lipid accumulation in the vessel wall. In a review of the published experimental data, Stout\(^{19}\) discussed possible pathogenetic factors that could account for the anti-lipolytic and lipogenic action of insulin. Increased lipid synthesis\(^{19}\) and proliferation of smooth muscle cells\(^{20}\) as well as decreased stimulated lipolysis\(^{21,22}\) and prostaglandin synthesis\(^{23}\) mediated by insulin have been shown to contribute to lipid infiltration in the arterial wall.

The higher mean age and body weight of the hypertensive subjects as compared with the controls were not significant and seem to be without major influence on glucose tolerance. Moreover, in hypertensive patients with normal body weight and normal serum lipid levels the well-known reasons for a low peripheral insulin effect (obesity, hypertriglyceridemia) can be excluded. This is consistent with the observation of
Singer and Voigt, who found no differences in adipose cell volume between hypertensive subjects of normal body weight and normotensive controls. Consequently, none of the metabolic factors usually leading to peripheral insulin resistance could be found in the patients with mild essential hypertension. This finding is different from that in subjects with type II diabetes and hypertriglyceridemia of normal body weight in whom increased adipose cell volume is assumed to be the cause of peripheral insulin resistance with competitive hyperinsulinemia. Nevertheless, other factors, such as a reduced number of insulin receptors or increased sympathetic activity, in the hypertensive subjects presented might be relevant for insulin resistance and, consequently, for hyperinsulinemia. Moreover, since in patients with mild essential hypertension insulin levels are only increased after a glucose load or after defined meals, an insulin oversecretion mediated by β-adrenergic receptors of pancreatic beta cells could be involved. Whether postprandial hyperinsulinemia in these subjects is a transient or permanent phenomenon remains unclear, because data from longitudinal studies or from patients with sustained hypertension are not available.

It might be helpful to compare our results with those obtained in spontaneously hypertensive rats (SHR), which are accepted as a suitable model for essential hypertension. Elevated levels of FFA in 4-week-old SHR, impaired glucose tolerance in 6-week-old SHR, and transient hyperinsulinemia in 8-week-old SHR have been described. These findings might be more than a temporal chain of links. It was concluded that increased sympathetic activity associated with high FFA levels can initiate impaired glucose tolerance, the high glucose concentration being adequate stimulus for enhanced insulin secretion. On the other hand, a generalized hypersensitivity of β-adrenergic receptors, which is a common feature in early stages of hypertension, might include pancreatic islets and thus stimulate insulin secretion. In older SHR with sustained hypertension, however, insulin levels are decreased as compared with controls, which has been assumed to be a sign of exhaustion of beta cells, although the remaining islet function does not permit diabetes to develop. Nevertheless, in view of major metabolic differences between SHR and patients with essential hypertension, it is unclear whether these experimental data can be extrapolated to pathogenesis of essential hypertension in humans.

Despite wide variations the FFA levels in hypertensive subjects were increased when compared with the controls. The postprandial hyperinsulinemia was associated with a fall of FFA levels, which appeared more pronounced in hypertensive subjects. The ensuing increase of FFA levels 2 to 3 hours after meals again was more pronounced in hypertensive subjects. This finding is in agreement with recent data of Dewailly and colleagues. Thus, it might be speculated that an enhanced postprandial uptake of FFA into the vessel wall can play a role in accelerated atherogenesis in patients with mild essential hypertension. Further studies that include plasma catecholamine and cortisol levels are needed to elucidate the mechanisms involved. According to the findings of Rowe and co-workers a catecholamine-induced hyperinsulinemia seems especially likely. On the other hand, an increased norepinephrine release after insulin administration at a constant level of blood glucose has been described recently. Furthermore, it seems worthwhile to study the action of β-blockers on insulin release simultaneously with serum lipid levels in hypertensive subjects because published data are equivocal.

### Conclusion

In spite of several uncertainties concerning its causal role, an increased insulin response after each meal can be relevant in patients with mild essential hypertension from the clinical point of view. Although mild essential hypertension does not necessarily proceed to sustained hypertension, the long-term presence of postprandial hyperinsulinemia in subjects with early stages of the hypertensive disease may increase lipid infiltration in the arterial wall, which suggests a hitherto underestimated influence on the cardiovascular risk of patients with mildly elevated blood pressure.

During the day the insulin response in hypertensive subjects appeared most pronounced after the morning meal, a finding that so far has been described only in normotensive subjects. Although atherogenesis has been assumed to be predominantly a postprandial phenomenon based on the internalization of chylomicron...
remnants into the arterial wall, the occurrence of hyperinsulinemia after major meals, which might intensify lipid accumulation during many hours in the course of 1 day, should be considered from a synoptic point of view. Moreover, because of the striking fact that complications from high blood pressure (e.g., heart insufficiency, stroke) in subjects with mild hypertension were found to be reduced by effective hypotensive drug treatment, while atherosclerotic complications (e.g., ischemic heart disease) were not necessarily influenced, it could be speculated that not all factors favoring atherosclerosis in coronary vessels (e.g., hyperinsulinemia) can be eliminated by drug therapy.

Acknowledgments
The authors are grateful to Mrs. I. Berger and Mrs. R. Neumann for skilled technical assistance and Mrs. H. Taraska for secretarial assistance.

References
1. Pyarala K. Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. Diabetes Care 1979;2:131–141
14. Thybusch D. Enzymatische Mikrobestimmung der Blutglu-
23. Lasche EM, Larson RE. Interaction of insulin and prosta
glandin production in the rat. Diabetes 1982;31:454–458
25. Bernstein RS, Grant N, Kipnis DM. Hyperinsulinemia and enlarged adipocytes in patients with endogenous hyperlipopro
teinemia without obesity or diabetes mellitus. Diabetes 1975;24:207–213
30. Rowe JW, Young JB, Minaker KL, Stevens AL, Palotta J, Landsberg L. Effect of insulin and glucose infusions on sympa
Postprandial hyperinsulinemia in patients with mild essential hypertension.
P Singer, W Gödicke, S Voigt, I Hajdu and M Weiss

Hypertension. 1985;7:182-186
doi: 10.1161/01.HYP.7.2.182

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/7/2/182