Fasting Insulin in Relation to Subsequent Blood Pressure Changes and Hypertension in Women

Lauren Lissner, Calle Bengtsson, Leif Lapidus, Karl Kristjansson, and Hans Wedel

The role of hyperinsulinemia in the development of hypertension is not well understood, particularly insofar as both conditions relate to obesity. The present analysis examines the hypothesis that hyperinsulinemia, independent of obesity, precedes hypertension and natural blood pressure increases in women. The subjects were 50-year-old women from a prospective population study in Gothenburg, Sweden. Fasting insulin levels were determined at baseline (1968–1969) and were evaluated in relation to subsequent hypertension. Blood pressures were measured at the initial physical examination and at the 6- and 12-year follow-up examinations. The first analysis presented here (n=278) identified incident cases of hypertension during the 12-year follow-up period, whereas the second analysis (n=219) examined continuous changes in blood pressure. In both analyses, degree, type, and changes in obesity were considered as possible confounding factors. High fasting insulin values were predictive of subsequent incidence of hypertension over the 12-year follow-up period. Subjects with insulin values above the 75th percentile experienced three times more hypertension than did those below the 25th percentile. There was also a significant association between insulin at baseline and increases in diastolic (but not systolic) blood pressure. The positive relations between fasting insulin, on one hand, and diastolic blood pressure changes and hypertension, on the other, could not be explained by confounding effects of body mass index, waist/hip ratio, or weight gain. These findings are consistent with the hypothesis that fasting insulin levels may be one predisposing factor in the etiology of hypertension. (Hypertension 1992;20:797–801)

Key Words • insulin • hypertension, essential • obesity • women

A number of cross-sectional studies have observed associations between hypertensive and hyperinsulinemic states, the mechanisms of which are not clearly established.1-5 There is some evidence that elevated insulin levels might raise blood pressure by enhancing renal absorption of sodium.6-8 It has also been proposed that insulin-induced changes in intracellular electrolyte balance might affect heart muscle and arteriolar contractility, causing peripheral resistance and hypertension.9-10 Alternatively, insulin may exert hypothalamic effects, with increased sympathetic activity raising heart rate and blood pressure.11,12 Finally, rather than being linked by a causal pathway, insulin and blood pressure might be associated due to confounding by a third factor. Because obesity has been associated with both conditions, its possible explanatory role in the association between hyperinsulinemia and hypertension has been an additional topic of interest.13-15 Two recent reports have suggested that the association between insulin resistance and hypertension may be specific to certain ethnic groups16 or vary as a function of obesity.17

A few recent epidemiologic studies have studied this issue prospectively, with mixed results. Salomaa et al18 observed a small impairment of glucose tolerance in normotensive men before the onset of clinical hypertension. Skarfor et al19 observed that fasting and glucose-stimulated insulin levels were risk factors for subsequent hypertension in men, independent of concomitant weight changes. Conversely, McPhillips et al20 observed that elevated systolic blood pressure was a risk factor for subsequent impairment of glucose tolerance in both men and women, and Haffner et al21 illustrated that both hyperinsulinemia and hypertension are present in prediabetic subjects before the onset of clinical diabetes. Two other prospective studies showed no associations between serum glucose levels and the development of arterial hypertension22 or changes in blood pressure.23 The aim of the present analysis was to examine the hypothesis that hyperinsulinemia may be a risk factor for hypertension in women studied prospectively, with specific attention to possible confounding by generalized, central, and dynamic obesity.

Methods

Population and Protocol

The subjects were a group of 50-year-old women who constituted one age stratum of a larger cohort study in Gothenburg, Sweden.24 All female residents born during the year 1918 on day numbers that were evenly divisible by six were identified in the population registry and invited to participate. At the time of the baseline examination between fall 1968 and spring 1969, there were 416 participating 50-year-olds, representing 91.4%...
of those originally sampled. Three hundred and fifty-five of them returned between late 1968 and early 1970 for additional testing of glucose metabolism. At the time of the 6- and 12-year follow-up studies, the rate of reexamination among surviving members of this subgroup of the cohort was 91.4% (1974–1975) and 86.3% (1980–1981).

Fasting insulin levels were determined from blood samples drawn at the beginning of a glucose tolerance test between late 1968 and early 1970. Serum insulin concentration was determined by a double antibody method. Blood pressure measurements were taken by a single examiner (C.B.) at baseline but by multiple examiners at subsequent examinations. Systolic and phase 5 diastolic blood pressure measurements (sitting and lying), body weight, height, and circumferences (waist and hip) were measured at the initial physical examination in 1968–1969 and at the 6- and 12-year follow-up examinations in 1974–1975 and 1980–1981, respectively. To minimize the impact of measurement error in the blood pressure data, sitting and lying values have been averaged. At each examination, subjects were questioned by a physician regarding their use of antihypertensive medications as well as their history of hypertension. All three phases of the study were approved by the Ethics Committee of the University of Göteborg and commenced after informed consent.

The first analysis presented here identifies incident cases of hypertension during the 12-year follow-up period in a group of initially normotensive women, whereas the second analysis examines natural changes in blood pressure among a subgroup of women who were not taking antihypertensive medications at any of their three physical examinations. This selection procedure resulted in two distinct but partially overlapping samples as described below.

Analysis 1: Hypertension Onset

A subject was defined as hypertensive if she met any of the following criteria: 1) a mean systolic value greater than or equal to 160 mm Hg, a mean diastolic reading greater than 95, or both, as measured at the time of the examination; 2) current, untreated hypertension as reported by the subject to the examining physician; or 3) any type of antihypertensive therapy at the time of the visit. This definition was used both to identify a cohort that was normotensive at inception and to identify incident cases of hypertension (treated or untreated) for the prospective analyses.

The first analysis included 278 subjects who were initially normotensive by this definition and who returned for at least one follow-up visit. Those subjects in whom hypertension had developed by the time of the 6- or 12-year follow-up examinations were then compared, with respect to their initial fasting insulin values, with those who remained normotensive. There were 77 prevalent cases of hypertension at baseline (excluded from this analysis) and 70 new cases during the 12-year follow-up that were compared with noncases. Logistic regression was used to examine the relation between baseline insulin and subsequent hypertension.

Analysis 2: Changes in Blood Pressure

In the second analysis, a continuous variable was used to describe natural developments in blood pressure during the follow-up period. This analysis selected those subjects who were examined three times and were not undergoing antihypertensive treatment at any of their physical examinations, resulting in a reduced sample size of 219. Again, the key independent variable was fasting insulin level at baseline. The end point of interest was subsequent change in blood pressure between visits 2 and 3 (3 minus 2). Because the glucose tolerance test was generally scheduled several months after the first physical examination (range, 16–355 days), this chronology was necessary to do a prospective analysis in which blood pressures are measured after the baseline insulin reading.

Role of Obesity

In both of the analyses outlined above, three aspects of obesity were considered for their possible confounding effects. Generalized obesity was defined as body mass index (weight [kg]/height [m²]) at the baseline examination. Centralized obesity was defined as the waist-to-hip circumference ratio, also at baseline. Dynamic obesity was defined as weight change during the relevant follow-up period (see below). In both analyses, these three indexes of obesity were entered as covariates in the regression models. In addition, analyses 1 and 2 were repeated after stratification on the group median body mass index, waist/hip ratio, and weight change. These median values are shown in Table 1. The only significant intercorrelation among these three covariates was between body mass index and waist/hip ratio (r = 0.3).

As mentioned above, the covariate weight change was studied using the time periods of most relevance to each analysis. The period between examinations 1 and 2 is used for the first analysis (hypertension) because the hypertension diagnoses could occur any time after the
first visit; this maximizes the number of weight changes that occurred before hypertension diagnosis. On the other hand, we used the period of time between examinations 2 and 3 for the second analysis because this corresponded exactly to the time of the measured blood pressure changes. This difference in time periods explains why the average weight gains are higher between visits 1 and 2 (the perimenopausal period for the majority of these women) than between visits 2 and 3 (the postmenopausal period, associated with less weight gain).28

Results

Description of Study Population

The left side of Table 1 includes selected descriptive information on the 278 initially normotensive subjects who returned for at least one examination 6 and/or 12 years later. The right portion of Table 1 includes the same information on the 219 subjects not taking antihypertensive medications who were examined three times and thus included in the second analysis.

Insulin and Hypertension Onset

Hypertension developed in 70 of the initially normotensive subjects over the 12-year follow-up period. Fasting insulin level at visit 1 was found by logistic regression analysis to be a significant predictor of subsequent hypertension in these women (p=0.003). Division of the sample into quartiles of basal insulin level indicated that the relative risks were elevated in the top quartile (RR=3.2, 95% CI 1.5–7.1), as shown in Table 2. This suggests that subjects with insulin levels of 17 microunits/l and higher had over three times higher risk of hypertension developing than did those with the insulin levels below the 25th percentile. Further analysis revealed that this association remained statistically significant after adjustment for the following covariates: initial body mass index, waist/hip ratio, and weight change between the first two examinations. These obesity-adjusted results are also shown in Table 2. The group mean levels of insulin at baseline were 14.7 microunits/l among incident cases of hypertension as compared with 12.8 microunits/l in the other women.

Insulin and Blood Pressure Changes

In those subjects who were not using antihypertensive medication at any of the three examinations, fasting insulin at baseline was found to be positively associated with later changes in diastolic (p=0.01) but not systolic blood pressure (See Table 3). Multivariate regression analysis (also Table 3) suggested that this association between fasting insulin and diastolic blood pressure change was statistically independent of baseline body mass index, baseline waist/hip ratio, and change in body weight between visits 2 and 3. Although weight change alone was clearly the best single predictor of changes in blood pressure, baseline insulin played an independent explanatory role that could not be attributed to subsequent weight gain.

Stratification by Obesity

Analyses 1 and 2 were repeated after stratifying at the group median of available obesity-related indicators (cutoff points shown in Table 1). In both analyses, stratification on waist/hip ratio suggested stronger associations in the below-median group, whereas stratification on weight change showed that stronger associations were present in those gaining more weight. In contrast, the obesity level–stratified results yielded no consistent differences between the associations for heavier versus leaner women. Based on these results, we cannot draw any strong conclusions regarding effect modification by obesity. However, it may be tentatively noted that the insulin–blood pressure connection appears to be stronger in women with a less centralized fat distribution or during the process of weight gain.

Other Potential Confounders

It may be speculated that those subjects who became hypertensive or experienced increased diastolic blood pressure during follow-up had higher blood pressures from the onset. Although not shown in Tables 2 or 3, we further controlled for blood pressure at baseline and found that neither result (analyses 1 and 2) could be explained by preexisting elevated blood pressure levels. Similarly, glucose response to the oral load was not found to be a confounder of the associations between fasting insulin, on one hand, and subsequent hypertension or diastolic blood pressure changes, on the other. The glucose disappearance rate (k value) was not a significant predictor of either end point, while the fasting insulin level remained a risk factor for both, independent of the k value and the indexes of overall and centralized obesity at baseline.

Discussion

This prospective analysis indicates that fasting insulin level in women is associated with subsequent hypertension and increases in diastolic blood pressure. One of the subjects in this sample was identified as diabetic at the time of the glucose tolerance testing, but inclusion or exclusion of this subject in the analysis presented here had no impact on the results. The association is statistically independent of baseline body mass index, waist/hip ratio, and weight change. In other words, the fact that the women with highest insulin levels may also be more obese, centrally obese, or gaining weight does not account for their significantly larger increases in
Table 3. Results of Sequential Multivariate Analysis (Five Models): Partial Regression Coefficients and t Statistics (below) for Changes in Systolic and Diastolic Blood Pressure from Visits 2 to 3 as a Function of Baseline Insulin and Selected Covariates

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*p<0.001; †p<0.01.

Potential limitations of our results are now considered. Regarding hypertension onset (analysis 1), we observed no dose-response. However, we did find evidence of a possible threshold effect in which increased risk of hypertension was observed above the upper quartile of fasting insulin concentration (>17 microunits/l); a similar observation was made in a cross-sectional analysis of insulin and blood pressure in this same cohort (unpublished results from our group).

Secondly, with respect to the analysis of blood pressure changes, the lack of association with systolic changes decreases the likelihood that the association is causal. Furthermore, the magnitude of the association between insulin and subsequent diastolic blood pressure increase was small, although it must also be remembered that this second analysis consists mostly of normotensive subjects, so large changes would not be expected. Finally, in spite of the high participation rates in this study, the nonparticipants appear to have differed from the participants in some respects. For instance, those who refused to attend the 1980–1981 examination or could not be contacted had significantly higher systolic blood pressure at baseline and were more likely to be unmarried and smokers. Although there were no differences in the proportion of participants and nonparticipants taking antihypertensive therapy at baseline, the apparent self-selection with respect to baseline blood pressure may limit the generalizability of our findings.

In conclusion, the two main analyses presented here are consistent with the hypothesis that fasting insulin level is one predisposing factor in the etiology of hypertension. Although the obese, hyperinsulinemic, and hypertensive states frequently coexist, the associations described here cannot be attributed to more obesity in women with insulin resistance and high blood pressure. Despite the statistical independence of these results with respect to obesity in its various manifestations, the stratified results raise the possibility of some effect modification by adipose tissue distribution and weight gain. We hope that further follow up of this cohort will enable us to clarify these observations.

Acknowledgments

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References

12. Landsberg L: Diet, obesity and hypertension: An hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. *Q J Med* 1986;83:1081-1090
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