Hyperinsulinemia in a Normal Population as a Predictor of Non–Insulin-Dependent Diabetes Mellitus, Hypertension, and Coronary Heart Disease: The Barilla Factory Revisited

I. Zavaroni, L. Bonini, P. Gasparini, A.L. Barilli, A. Zuccarelli, E. Dall'Aglio, R. Delsignore, and G.M. Reaven

The study was initiated to evaluate the ability of hyperinsulinemia (as a surrogate measure of insulin resistance) to predict the development in a previously healthy population of three putative outcomes of this abnormality—glucose intolerance, hypertension, and coronary heart disease (CHD). The study involved defining the incidence at which these changes occurred between 1981 and 1993 to 1996 in 647 individuals who were free of any disease when initially studied. The study population consisted of approximately 90% of the subjects evaluated in 1981, divided into quartiles on the basis of the plasma insulin response to a glucose challenge as determined in 1981. The results indicated that the 25% of the population with the highest insulin response in 1981 had significant ($P < .001$) increases in the incidence of impaired glucose tolerance (IGT) or type 2 diabetes (eightfold), hypertension (twofold), or CHD (threefold). Furthermore, the ability of hyperinsulinemia to predict the three clinical endpoints was independent of differences in age, gender, or body mass index (BMI). Finally, if CHD is considered the clinical endpoint, multiple logistic regression analysis indicates that the values for plasma triglyceride (TG) and mean arterial blood pressure ([MAP] as measured in 1981) also predict the development of CHD. These results indicate that the untoward clinical effects of insulin resistance and/or compensatory hyperinsulinemia, glucose intolerance, hypertension, and CHD clearly can develop in less than 15 years.

WE REPORTED the results of an epidemiologic survey in 1989 that established a relationship between the plasma insulin response to an oral glucose challenge and various metabolic and hemodynamic variables in a healthy population of factory employees.[1] On the basis of these data, we suggested that hyperinsulinemia, as a surrogate measure of resistance to insulin-mediated glucose disposal, was associated with higher plasma glucose and triglyceride (TG) concentrations, a lower high-density lipoprotein (HDL) cholesterol concentration, and an increase in both systolic and diastolic blood pressure. All of these changes have been shown to increase the risk[2-9] of coronary heart disease (CHD).

The results of our study played an important conceptual role in the genesis of the notion of syndrome X,[10] ie, the proposal that the resistance to insulin-mediated glucose disposal and the cluster of abnormalities associated with it represent a previously unrecognized syndrome that plays an important role in the development of CHD. Several publications since that time have validated the general principles articulated in the description of syndrome X,[11-13] and there is now evidence that insulin resistance and/or compensatory hyperinsulinemia are associated with other changes that appear to increase the risk of CHD, including smaller, denser low-density lipoprotein (LDL) particles,[14] higher levels of plasminogen activator inhibitor-1,[15] and an increase in the magnitude of postprandial lipemia.[16]

Although these observations provide substantial support for the view that insulin resistance and/or its associated metabolic abnormalities increase the risk of CHD, it is always dangerous to formulate causal relationships based on cross-sectional data. Consequently, we initiated the current study in 1993, in which we recalled for evaluation individuals from the same factory population divided into four quartiles on the basis of the plasma insulin response to a glucose challenge as measured in 1981, and determined the incidence at which previously healthy individuals developed glucose intolerance, hypertension, or CHD.

SUBJECTS AND METHODS

In 1981, we surveyed 732 factory workers for a variety of metabolic and hemodynamic risk factors for CHD. At that time, all subjects were instructed to consume 300 g carbohydrate daily for 3 days preceding the measurements. A complete medical history was obtained and a physical examination performed. Blood pressure was measured with a sphygmomanometer with the subjects recumbent for at least 10 minutes; diastolic blood pressure was defined as the disappearance of Korotkoff sounds (phase 5). In addition, subjects were classified as moderately or intensely physically active in their working or leisure time on the basis of a self-report questionnaire as described by Saltin and Grimby[17] Venous blood was drawn after an overnight fast for determination of plasma glucose,[18] insulin,[19] TG,[20] cholesterol,[21] and HDL cholesterol.[22] In addition, plasma glucose and insulin concentrations were measured 1 and 2 hours after a 75-g oral glucose load. At the end of the survey, complete data were available in 720 subjects.

In 1993, a decision was made to recall these individuals for reevaluation. Between 1993 and 1996, outcome data were collected from 647 of the original subjects, including 32 individuals who died during the period of observation. The presence of diabetes, hypertension, or CHD was determined from medical records of these individuals. None of them developed type 2 diabetes or impaired glucose tolerance (IGT), 11 developed hypertension, and 10 developed CHD. In 615 subjects evaluated in person, the diagnosis of IGT was based on the results of an oral glucose tolerance test using World Health Organization (WHO) criteria. Type 2 diabetes was diagnosed if subjects were treated with oral antidiabetic medication and/or insulin, or by glucose tolerance test criteria (WHO). Hypertension was determined to be present if subjects either were treated with antihypertensive medication or had blood pressure greater than 150/90 mm Hg. The presence of CHD was based on a review of the medical record, using both enzymatic and electrocardiographic evidence.[23]

From the Department of Internal Medicine and Biomedical Science, Parma University, Parma, Italy; Stanford University School of Medicine, Stanford, CA; and Shaman Pharmaceuticals, South San Francisco, CA.

Submitted April 1, 1998; accepted February 15, 1999.

Supported by research grants from University and Scientific Research, Italian Ministry, and the National Institutes of Health (HL-08506).

Address reprint requests to I. Zavaroni, MD, Department of Internal Medicine and Biomedical Science, Via Gramsci 14, 43100 Parma, Italy.

0026-0495/99/4808-0011$10.00/0

Table 1. Baseline Characteristics of the Study Population in 1981

Characteristic	Insulin Quartile I	II	III	IV	P
No. of subjects	155	172	159	161	
Gender (female/male)	47/108	69/103	66/93	50/111	NS
Age (yr)	41.3 ± 0.7	41.6 ± 0.7	40.5 ± 0.7	43.5 ± 0.7	<.05
BMI (kg/m²)	25.3 ± 0.2	25.1 ± 0.2	25.2 ± 0.2	27.3 ± 0.2	<.001
Physical activity (%)					
Work					
Moderate	91.6	91.2	89.3	90.7	NS
Intense	8.4	8.8	10.7	9.3	NS
Leisure					
Moderate	83.7	85.0	76.7	89.4	<.05
Intense	16.3	15.0	23.3	10 6	<.05
Smokers (%)	49.0	43.6	42.8	35.4	NS

Abbreviation: NS, nonsignificant.

For analytical purposes, subjects studied between 1993 and 1996 were divided into quartiles on the basis of the plasma insulin concentration 2 hours after the glucose load as determined in 1981. Quartile I represents the group with the lowest insulin response and quartile IV those with the highest response. Results are expressed as the mean ± SEM. Mean values for cross-sectional data were compared by two-way ANOVA and covariance analysis. The event frequency was evaluated by chi-square test. In these analyses, the insulin quartile was used as the grouping variable. Clinical outcomes were analyzed by multiple logistic regression. The odds ratio for gender was calculated considering females as the reference category. In the analyses, actual values were used except for insulin and TG. For these two variables, the analyses were performed on the natural logarithms to improved the skewed distribution, and the values were then back-transformed to their natural units for presentation in Table 2.

RESULTS

Baseline characteristics of the current study population divided into four insulin quartiles as determined in 1981 are summarized in Table 1. It should be emphasized that the information in Table 1 represents 1981 values for 647 individuals who were available for evaluation between 1993 and 1996, divided into quartiles based on the original insulin response. Eighty-five percent, 94%, 87%, and 88% of the original four groups are included in this report. These data demonstrate that the 25% of the population with the highest insulin response were older and had a higher body mass index (BMI) than the individuals in the first three quartiles. In addition, intense leisure-time activity was lower in individuals in quartile IV compared with quartile III.

A comparison of these same individuals in terms of metabolic and hemodynamic characteristics in 1981 is shown in Table 2. The values were adjusted for differences in age, gender, and BMI. There were no differences in fasting plasma glucose or LDL cholesterol concentrations in any of the quartiles. Every quartile was different from the others in terms of the remaining measures for the glucose concentration and all measures for insulin metabolism ($P < .5$ to .001). Subjects in quartile IV had higher values for mean arterial pressure (MAP) and heart rate than individuals in quartiles I, II, and III ($P < .05$ to .001). Plasma TG concentrations were higher in quartile IV versus quartiles I and II ($P < .05$ to .001), and HDL cholesterol levels were significantly lower in quartile IV compared with quartile I ($P < .05$).

Nineteen subjects (eight women and 11 men) developed type 2 diabetes or IGT in the interval between 1981 and the time of reevaluation. The incidence of glucose intolerance is shown in Fig 1. The incidence was approximately eight times greater in hyperinsulinemic subjects, with the highest incidence in quartile IV (relative risk [RR]: quartile IV *v* quartiles I, II, and III, $P < .001$).

Figure 2 shows the incidence of hypertension that developed in the period of observation (93 subjects, 24 women and 69 men), and approximately twice as many subjects in quartile IV developed high blood pressure during the follow-up period (RR: quartile IV *v* quartiles I, II, and III, $P < .05$).

Twenty-three subjects (five women and 18 men) developed CHD since 1981 (Fig 3). These data indicate that CHD increased more than threefold in subjects in quartile IV in 1981. This difference was also statistically significant (RR: quartile IV *v* quartiles I, II, and III, $P < .05$).

Table 2. Metabolic and Hemodynamic Comparisons Between Quartiles in 1981 Adjusted for Age, Gender, and BMI

Variable	Insulin Quartile I	II	III	IV
Glucose (mg/dL)				
Fasting	86 ± 1	88 ± 1	88 ± 1	88 ± 1
1 h	99 ± 3	104 ± 3	117 ± 3	133 ± 3*
2 h	67 ± 2	76 ± 2	85 ± 2	102 ± 2*
Insulin (μU/mL)				
Fasting	12 ± 0.5	14 ± 0.5	16 ± 0.5	20 ± 0.5*
1 h	66 ± 4	81 ± 4	94 ± 4	126 ± 5*
2 h	18 ± 2	31 ± 2	52 ± 2	111 ± 2*
TG (mg/dL)	116 ± 8	130 ± 7	141 ± 8	156 ± 8‡
HDL cholesterol (mg/dL)	54 ± 1	53 ± 1	50 ± 1	51 ± 1§
LDL cholesterol (mg/dL)	120 ± 4	129 ± 4	120 ± 4	130 ± 4
Uric acid (mg/dL)	4.3 ± 0.1	4.4 ± 0.1	4.6 ± 0.1	4.8 ± 0.1‡
MAP (mm Hg)	97 ± 1	97 ± 1	97 ± 1	100 ± 1†
Heart rate (bpm)	65 ± 1	67 ± 1	67 ± 1	70 ± 1†

*Every quartile significantly different *v* all other quartiles ($P < .05$-.001).

†Quartile IV significantly higher *v* quartiles I, II, and III ($P < .05$-.001).

‡Quartile IV significantly higher *v* quartiles I and II ($P < .05$).

§Quartile IV significantly lower *v* quartile I ($P < .05$).

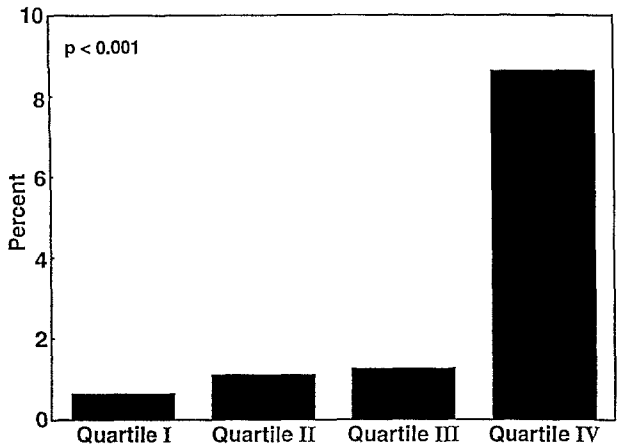

Fig 1. Incidence of IGT or type 2 diabetes onset between 1981 and the time of reevaluation as a function of insulin response in 1981.

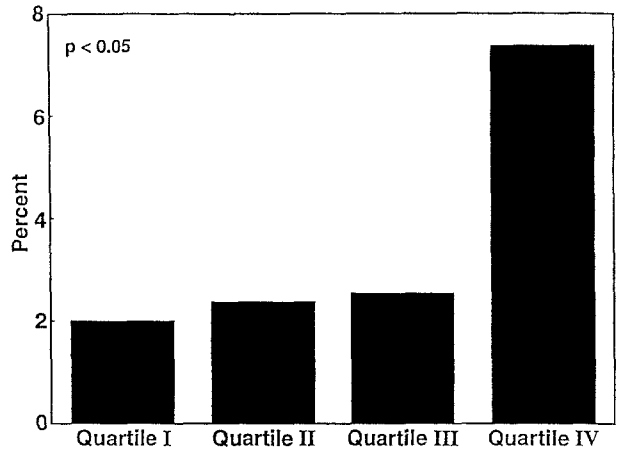

Fig 3. Incidence of CHD onset between 1981 and the time of reevaluation as a function of insulin response in 1981.

To account for the impact of differences in age, BMI, and gender on the development of type 2 diabetes and IGT, hypertension, or CHD, as distinguished from the insulin response, multiple logistic regression analysis was performed. The results in Table 3 demonstrate that the magnitude of the insulin response was a predictor of each of the three clinical endpoints independently of differences in age, BMI, or gender. The results of this analysis were similar if ln-fasting insulin replaced ln-2-hour insulin in the model; however, the level of statistical significance decreased slightly. Specifically, the *P* values between ln-fasting insulin and the development of IGT and diabetes, hypertension, and CHD were .01, .02, and .06, respectively.

As defined in 1988,[10] syndrome X refers to a cluster of abnormalities secondary to insulin resistance and compensatory hyperinsulinemia that increase the risk of CHD. To evaluate the impact of the other components of syndrome X on the development of CHD, multiple logistic regression analysis was also performed with plasma glucose, TG, and HDL cholesterol levels and MAP as independent variables. In addition, the relationship between CHD and both LDL cholesterol and smoking was also evaluated. Table 4 indicates that two syndrome X variables, plasma TG and MAP as well as LDL cholesterol and a history of smoking one pack of cigarettes per day, were significantly related to CHD when adjusted for differences in age, gender, and BMI. It should also be noted that the relationship between the 2-hour glucose concentration and CHD approached the level of statistical significance ($P < .07$).

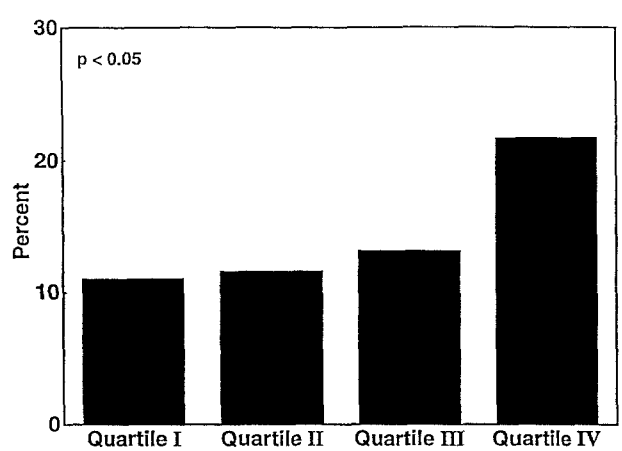

Fig 2. Incidence of hypertension onset between 1981 and the time of reevaluation as a function of insulin response in 1981.

A similar analysis was performed, but in this instance, the endpoint was the development of glucose intolerance (IGT and diabetes). In contrast to CHD, the 2-hour plasma glucose concentration was highly correlated with the appearance of IGT and type 2 diabetes, whereas LDL cholesterol was not. In addition, as with the development of CHD, plasma TG and MAP were significantly correlated with the state of glucose intolerance (Table 5).

DISCUSSION

The study performed in 1981[1] was undertaken to test the hypothesis that "a cluster of risk factors for coronary artery disease would be found in persons with normal glucose tolerance who were insulin-resistant and hyperinsulinemic." This original formulation has been corroborated, and it is now clear that there are many other abnormalities associated with insulin resistance and compensatory hyperinsulinemia, including smaller and denser LDL particles,[14] a higher level of plasminogen activator inhibitor-I,[15] a greater degree of postprandial lipemia,[16] a higher uric acid concentration,[24] and an enhanced sympathetic nervous system activity.[25] Since all of these changes have also been associated with an increased risk of CHD, there is substantial theoretical support for our initial speculation that "insulin resistance and hyperinsulinemia have central and etiologic roles in the development of a series of events leading to an increased risk of coronary artery disease." At that time, we further stated that "whether or not this is true remains to be seen, but the current results suggest that this formulation is worth pursuing."

Given the hypothesis outlined in 1981, the data emerging from this follow-up study seem to be of substantial value. We have been able to show in an unselected population that the risk, over a relatively short time span, of developing glucose

Table 3. Multiple Logistic Regression Analysis of the Effect of 2-Hour Insulin on the Development of Type 2 Diabetes and IGT, Hypertension, or CHD

Condition	β Coefficient	SE	Wald χ^2	OR	95% CI	$P(\chi^2)$
Type 2 Diabetes + IGT						
ln insulin 2 h	1.5661	0.3786	17.1159	4.7880	2.280-10.056	.0000
Age	0.2976	0.2730	1.1877	1.3466	0.789-2.299	.2758
BMI	0.4787	0.3052	2.4602	1.6140	0.887-2.936	.1168
Gender	−0.7604	0.5617	1.8321	0.4675	0.155-1.406	.1759
Hypertension						
ln insulin 2 h	0.3312	0.1618	4.1893	1.3926	1.008-1.924	.0407
Age	0.0922	0.1301	0.5019	1.0966	0.850-1.415	.4787
BMI	0.5085	0.1819	7.8141	1.6627	1.164-2.375	.0052
Gender	0.3309	0.2712	1.4882	1.3922	0.818-2.369	.2225
CHD						
ln insulin 2 h	0.6993	0.3071	5.1839	2.0123	1.102-3.674	.0228
Age	0.8499	0.2331	13.2963	2.3395	1.481-3.694	.0003
BMI	0.5729	0.3168	3.2705	1.7734	0.953-3.300	.0705
Gender	−0.2566	0.5937	0.1869	0.7736	0.242-2.477	.6655

NOTE. The age interval is 10 years. The BMI interval is 5 kg/m^2. The ln insulin 2 h interval is 1 ln unit.
Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; ln, logarithm.

intolerance states, hypertension, or CHD is increased if apparently healthy individuals are hyperinsulinemic and presumably insulin-resistant. These observations are consistent with previous studies showing that insulin resistance and/or compensatory hyperinsulinemia predict the development of type 2 diabetes, hypertension, or CHD.[4,5,26-31] On the other hand, we are not aware of any prospective study showing that these abnormalities of insulin metabolism predict the development of all three clinical syndromes within one population. As such, the current results provide additional support for the view that the common diseases of Western civilization, glucose intolerance, hypertension, and CHD, all share a common relationship with insulin resistance and/or compensatory hyperinsulinemia.

Finally, it should be emphasized that although hyperinsulin-

Table 4. Multiple Logistic Regression Analysis of the Effect of Each Variable on the Development of CHD

Variable	β Coefficient	SE	Wald χ^2	OR	95% CI	$P(\chi^2)$
Glucose 2 h	0.1188	0.0670	3.1415	1.1261	0.988-3.000	.0763
Age	0.8354	0.2316	13.0075	2.3056	1.464-3.630	.0003
BMI	0.6087	0.3210	3.5954	1.8381	0.980-3.448	.0579
Gender	−0.1732	0.5882	0.0866	0.8410	0.265-2.665	.7685
ln TG	1.0354	0.4045	6.5525	2.8163	1.275-6.223	.0105
Age	0.9248	0.2322	15.8570	2.5213	1.516-4.193	.0001
BMI	0.6657	0.3126	4.5358	1.9459	1.054-3.591	.0332
Gender	−0.7960	0.6379	1.5572	0.4511	0.129-1.575	.2121
HDL	−0.0617	0.0879	0.4923	0.9402	0.791-1.117	.4829
Age	0.8970	0.2286	15.3940	2.4523	1.567-3.838	.0001
BMI	0.7441	0.3134	5.6381	2.1045	1.139-3.890	.0176
Gender	−0.3741	0.6109	0.3749	0.6879	0.208-2.278	.5403
LDL	0.1410	0.0451	9.6687	1.1514	1.054-1.258	.0019
Age	0.8553	0.2372	13.0049	2.3520	1.478-3.744	.0003
BMI	0.7300	0.3156	5.3810	2.0750	1.118-3.852	.0204
Gender	−0.4541	0.5949	0.5826	0.6350	0.198-2.035	.4453
MAP	0.4913	0.1904	6.6595	1.6344	1.125-2.374	.0099
Age	0.6786	0.2397	8.0108	1.9710	1.232-1.281	.0046
BMI	0.5696	0.3246	3.0780	1.7675	0.936-3.339	.0794
Gender	−0.3911	0.5908	0.4381	0.6763	0.212-2.153	.5081
Smoking level						
1	0.3332	1.0979	0.0921	1.3954	0.162-12.002	.7616
2	1.0441	0.7193	2.1074	2.8410	0.694-11.634	.1466
3	0.4920	0.7097	0.4805	1.6355	0.433-6.183	.4882
4	1.6360	0.6785	5.8133	5.1347	1.278-20.635	.0159
5	2.4648	0.9122	7.3018	11.7617	1.968-70.296	.0069
Age	1.0855	0.2572	17.8191	2.9611	1.789-4.902	.0000
BMI	0.8448	0.3197	6.9844	2.3275	1.244-4.355	.0882
Gender	−0.6051	0.6290	0.9254	0.5460	0.159-1.873	.3361

NOTE. The reference category is nonsmokers. Smoking level: 1, 1-4 cigarettes per day; 2, 5-9; 3, 10-19; 4, 20-29; 5, >30. Age interval, 10 years; MAP interval, 10 mm Hg; BMI interval, 5 kg/m^2; LDL interval, 10 mg/dL; HDL interval, 5 mg/dL; ln TG interval, 1 ln unit. See Table 3 for abbreviations.

Table 5. Multiple Logistic Regression Analysis of the Effect of Each Variable on the Development of Diabetes + IGT

Variable	β Coefficient	SE	Wald χ^2	OR	95% CI	$P(\chi^2)$
Glucose 2 h	0.2838	0.0681	17.3710	1.3281	1.162-1.518	.0000
Age	0 2539	0.2744	0.8559	1.2890	0.753-2.207	.3549
BMI	0.4715	0.3079	2.3454	1 6024	0.876-2.930	0.1257
Gender	−0.6339	0.5501	1.3280	0.5305	0.180-1.559	.2492
ln TG	1.1783	0.4261	7.6453	3.2488	1.409-7.489	.0057
Age	0.4362	0.2616	2.7819	1.5469	0.926-2.583	.0953
BMI	0.7485	0.2979	6.3134	2.1137	1.179-3.790	.0120
Gender	−1.3457	0.6008	5.0175	0.2604	0.080-0.845	.0251
HDL	−0.1220	0.0932	1.7148	0.8851	0.737-1.063	.1904
Age	0 4314	0.2564	2.8298	1.5393	0.931-2.545	.0925
BMI	0.8182	0.2962	7.6304	2.2665	1 268-4.050	.0057
Gender	−0.9304	0.5572	2.7882	0.3944	0.132-1.176	.0950
LDL	0.0397	0.0498	0.6207	1.0405	0.944-1.147	.4308
Age	0.3852	0.2594	2.2047	1.4699	0.884-2.444	.1376
BMI	0.8473	0.2947	8.2807	2.3334	1.310-4.157	.0040
Gender	−0.7448	0.5332	1.9510	0.4748	0.167-1.350	.1625
MAP	0.4783	0.1997	5.7336	1.6133	1.091-2.886	.0166
Age	0.2080	0.2683	0.6013	1.2313	0.728-2.083	.4381
BMI	0.6481	0 3091	4.3959	1.9118	1.043-3.504	.0360
Gender	−0.8588	0.5352	2.5744	0.4237	0.148-1.209	.1086

NOTE. Age interval, 10 years; MAP interval, 10 mm Hg; BMI interval, 5 kg/m^2; LDL interval, 10 mg/dL; HDL interval, 5 mg/dL; ln TG interval, 1 ln unit; glucose 2 h interval, 10 mg/dL. See Table 3 for abbreviations.

emia served as a marker to identify individuals who developed CHD, these data should not be interpreted to mean that hyperinsulinemia is the cause of CHD. Firstly, identification of hyperinsulinemia as a risk factor for CHD is not meant to demean the importance of smoking or high LDL cholesterol. Furthermore, given all of the CHD risk factors associated with insulin resistance and compensatory hyperinsulinemia, it would be impossible at this time to discern which of these factors is most responsible for the link between insulin resistance and CHD. For example, it is clear from Table 4 that the differences in both blood pressure and plasma TG observed in 1981 also predicted the development of CHD. One way to differentiate between the impact of CHD risk factors is to include them all in a model and perform multiple regression analysis. Although such an approach is conventionally used, we do not believe it can provide useful information in this situation. The dangers of multivariate analysis in determining the "independent" effect of highly correlated CHD risk factors have been emphasized in the debate as to whether hypertriglyceridemia should be considered a risk factor for CHD.[32] We believe this to be even more true in the current context. There are multiple risk factors for CHD present in insulin-resistant individuals (Table 2). Since these variables are highly intercorrelated, including them together in a multiple regression analysis makes it difficult to determine the contribution of each variable in the multiple regression. A statistical approach that can be used to examine the partial correlation between the dependent variable and each of the independent variables is the r statistic. Using this approach, none of the variables are independently related to CHD. On the other hand, this does not mean that they do not play a role in the development of CHD. Furthermore, it is also possible that we did not even measure the most crucial determinant of CHD at the time of the original study in 1981.

Thus, we believe that the most important insight derived from this study is the fact that the presence of hyperinsulinemia in 1981, as a surrogate measure of insulin resistance and its associated abnormalities, identified a group of individuals who developed glucose intolerance, hypertension, and CHD at an increased rate. Consequently, it seems reasonable to suggest that efforts to identify individuals at high risk for CHD and to treat these individuals can no longer ignore the powerful predictive role of the multiple components of syndrome X.

ACKNOWLEDGMENT

We are indebted to the Fondo di Solidarietà Riccardo Barilla for its cooperation, without which this study would not have been possible.

REFERENCES

1. Zavaroni I, Bonora E, Pagliara M, et al: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance N Engl J Med 320:702-706, 1989

2. Fuller JH, Shipley MJ, Rose G, et al: Coronary-heart-disease risk and impaired glucose tolerance: The Whitehall Study. Lancet 1:1373-1376, 1980

3. Vaccaro O, Ruth KJ, Stamler J: Relationship of postload plasma glucose to mortality with 19-yr follow-up. Diabetes Care 13:1328-1334, 1992

4. Pyorala K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. Diabetes Care 2:131-141, 1979

5. Després J-P, Lamarche B, Mauriège P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 334·952-957, 1996

6. Kannel WB: Importance of hypertension as a major risk factor in cardiovascular disease, in Genest J, Koiw E, Kuchel O (eds): Hypertension: Physiopathology and Treatment. New York, NY, McGraw-Hill, 1977, pp 888-910

7. Carlson LA, Böttiger LE, Ahfeldt P-E: Risk factors for myocardial

infarction in the Stockholm Prospective Study: A 14 year follow-up focusing on the role of plasma triglycerides and cholesterol. Acta Med Scand 206:351-360, 1979

8. Castelli WP, Doyle JT, Gordon T, et al: HDL cholesterol and other lipids in coronary heart disease. Circulation 55:767-772, 1977

9. Miller NE, Thelle DS, Forde OH, et al: The Tromso Heart Study: High-density lipoprotein and coronary artery disease. A prospective case-control study. Lancet 1:965-968, 1978

10. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

11. Ferrannini E, Haffner SM, Mitchell BD, et al: Hyperinsulinaemia: The key feature of a cardiovascular and metabolic syndrome. Diabetologia 3:416-422, 1991

12. Landin K, Tengvory L, Smith U: Elevated fibrinogen and plasminogen activator (PAI-1) in hypertension are related to metabolic risk factors for cardiovascular disease. J Intern Med 227:273-278, 1990

13. Haffner SM, Stern MP, Hazuda HP, et al: Cardiovascular risk factors in confirmed prediabetic individuals: Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 263:2893-2898, 1990

14. Reaven GM, Chen Y-DI, Jeppesen J, et al: Insulin resistance and hyperinsulinemia in individuals with small, dense, low density lipoprotein particles. J Clin Invest 92:141-146, 1993

15. Juhan-Vague I, Alessi MC, Vague P: Increased plasma plasminogen activator inhibitor 1 levels. A possible link between insulin resistance and atherothrombosis. Diabetologia 34:457-462, 1991

16. Jeppesen J, Hollenbeck CB, Zhou M-Y, et al: Relation between insulin resistance, hyperinsulinemia, postheparin plasma lipoprotein lipase activity, and postprandial lipemia. Arterioscler Thromb Vasc Biol 15:320-324, 1995

17. Saltin B, Grimby G: Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. Circulation 38:1104-1115, 1968

18. Kadish AH, Litle RL, Sterberg JC: A new and rapid method for determination of glucose by measurement of rate of oxygen consumption. Clin Chem 14:116-131, 1968

19. Hales CN, Randle PJ: Immunoassay of insulin with insulin antibody precipitate. Biochem J 88:137-146, 1963

20. Bergmeyer HU (ed): Methods of Enzymatic Analysis. New York, NY, Academic, 1974, pp 1831-1835

21. Allain CC, Poon LS, Richmond W, et al: Enzymatic determination of total serum cholesterol. Clin Chem 20:470-475, 1974

22. Blackburn H: Classification of the electrocardiogram for population studies: Minnesota code. J Electrocardiol 2:305-310, 1969

23. Lopes-Virella HF, Stone P, Ellis S, et al: Cholesterol determination in high-density lipoproteins separated by three different methods. Clin Chem 23:882-884, 1977

24. Facchini F, Chen Y-DI, Hollenbeck C, et al: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 266:3008-3011, 1991

25. Facchini FS, Riccardo A, Stoohs A, et al: Enhanced sympathetic nervous system activity—The link between insulin resistance, hyperinsulinemia, and heart rate. Am J Hypertens 9:1013-1017, 1996

26. Lillioja S, Mott DM, Spraul M, et al: Insulin resistance and insulin secretory dysfunction as precursors of non–insulin-dependent diabetes mellitus. N Engl J Med 329:1988-1992, 1993

27. Warram JH, Martin BC, Krolewski AS, et al: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of the diabetic parents. Ann Intern Med 113:909-915, 1990

28. Sicree RA, Zimmet PZ, King HOM, et al: Plasma insulin response among Nauruans: Prediction of deterioration in glucose tolerance over 6 yr. Diabetes 36:179-186, 1987

29. Haffner SM, Stern MP, Mitchell BD, et al: Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. Diabetes 39:283-288, 1990

30. Skarfors ET, Lithell HO, Selinus I: Risk factors for the development of hypertension: A 10-year longitudinal study in middle-aged men. J Hypertens 9:217-223, 1991

31. Lissner L, Bengtsson C, Lapidus L, et al: Fasting insulin in relation to subsequent blood pressure changes and hypertension in women. Hypertension 20:797-801, 1992

32. Austin MA: Plasma triglyceride and coronary heart disease. Arterioscler Thromb 11:2-14, 1991