Basal-State Hyperinsulinemia in Healthy Normoglycemic Adults Is Predictive of Type 2 Diabetes Over a 24-Year Follow-Up

A preliminary report

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OBJECTIVE — We examined the predictive value of hyperinsulinemia in the basal state on the 24-year progression from normoglycemia to dysglycemia.

RESEARCH DESIGN AND METHODS — A sample of 515 normoglycemic men and women were studied again after 24 years for glycemic status.

RESULTS — Half of the participants developed dysglycemia: 11.1% progressed to impaired fasting glucose (IFG), 9.9% to impaired glucose tolerance (IGT), 4.5% to both IFG and IGT, and another 24.3% to type 2 diabetes. Elevated levels of overnight fasting (basal) insulin, triglycerides, BMI ≥27 kg/m^2, fasting blood glucose, blood pressure, North African or Yemenite background, and male sex each favored conversion to dysglycemia after 24 years. In multiple ordered logistic regression analysis, the most significant predictor of progression to dysglycemia was hyperinsulinemia (upper quintile), after adjusting for BMI, ethnic origin, sex, age, smoking, physical activity, blood pressure, and triglycerides.

CONCLUSIONS — Basal hyperinsulinemia in normoglycemic adults constitutes an independent risk factor for developing dysglycemia over 24 years.

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This study examined hyperinsulinemia in the basal state as an independent factor associated with the 24-year progression to dysglycemia (impaired fasting glucose [IFG]/impaired glucose tolerance [IGT] or type 2 diabetes) in normoglycemic ethnically diverse adult men and women.

In the 1980s, Modan et al. (1,2), following the analysis of baseline information of the present cohort, proposed that hyperinsulinemia, reflecting peripheral insulin resistance, is linked to hypertension, obesity, dyslipidemia, and glucose intolerance, a cluster termed "metabolic syndrome" by Reaven (3). Insulin resistance has since been assigned a central place in the metabolic disturbances associated with obesity and type 2 diabetes. We previously reviewed the evidence for the possible role of hyperinsulinemia, especially in the basal state, in sustaining, expanding, or initiating insulin resistance (4).

RESEARCH DESIGN AND METHODS

— The current analysis covers 515 survivors of a longitudinal study to which a 2-h oral glucose tolerance test was done 24 years earlier and at follow-up, when mean age was 70.4 ± 7.0 years. Study population, sampling, and laboratory procedures were previously described (1,5). The study was approved by the institutional review board of the Sheba Medical Center. All subjects gave written informed consent.

Hyperinsulinemia in the basal state was defined as fasting insulin levels at baseline in the upper quintile (Q5) of the study sample. The group reported here (followed up with in 2000–2005) were all "normoglycemic" in 1980, based on fasting plasma glucose ≤110 mg/dl and 2-h plasma glucose <140 mg/dl. The potassium ferricyanide method used in 1980 overestimates glucose values by ~9% (6). Thus, the 110 cutoff of 1980 is approximately equal to the 100 cutoff used at follow-up. "Dysglycemia" was based on a follow-up oral glucose tolerance test and/or fasting glucose or if a subject reported using hypoglycemic medications. Baseline differences, between the normoglycemic and dysglycemic groups at follow-up, were tested using the χ^2 test for categorical variables and the one-way ANOVA for continuous variables. Adjusted multiple ordered logistic regression models with dummy variables for ethnicity explored predictors for IFG/IGT and diabetes.

RESULTS

— Over the 24 years of the study, half of the cohort maintained normal glucose tolerance (n = 259; 50.3%). The other half progressed to dysglycemia, evenly divided between those in the intermediate categories (designated IFG = 11.1%; IGT = 9.9%; IFG plus IGT = 4.5%) and those who fulfilled criteria for type 2 diabetes (n = 125; 24.3%). Dysglycemia was more common in men than in women (56.0 vs. 43.4%, respectively; P = 0.01). Ethnicity also contributed; participants originally from North Africa and Yemen were more likely to develop dysglycemia than those from Europe or America (60.5 vs. 44.4%, respectively; P = 0.002). Higher values of basal insu-

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Table 1—*Multiple ordered logistic regression model to predict progression to IFG/IGT or type 2 diabetes in a 24-year follow-up*

Predictor	Reference category	Predictor [prevalence (%)]	Odds ratio (IFG/IGT)	95% CI (IFG/IGT)	Odds ratio (type 2 diabetes)	95% CI (type 2 diabetes)
Fasting insulin Q5	Q1–Q4	103 (20)	1.67	0.94–2.95	1.98	1.13–3.48
BMI ≤27 kg/m^2	<27 kg/m^2	125 (24.3)	1.33	0.77–2.27	1.86	1.10–3.14
Ethnic origin	Europe/America	216 (41.9)†	1.0	—	1.0	—
Yemen		96 (18.6)	1.58	0.83–2.99	1.84	1.0–3.41
Middle East		127 (24.7)	1.11	0.62–1.98	0.64	0.34–1.18
North Africa		76 (14.8)	2.65	1.38–5.11	1.51	0.75–3.04
Fasting blood glucose, Q5	Q1–Q4	103 (20)	1.99	1.10–3.61	1.67	0.90–3.09
Male sex	Female	259 (50.3)	1.40	0.88–2.23	1.47	0.91–2.37
Blood pressure ≥130/85 mmHg	<130/85 mmHg	157 (30.5)	1.57	0.96–2.58	1.49	0.91–2.46
Triglycerides ≥150 mg/dl	<150 mg/dl	124 (24.1)	0.93	0.53–1.63	1.67	0.99–2.82
Sedentary‡	Physically active	215 (41.7)	1.49	0.94–2.36	1.11	0.69–1.78
Ever smoked	Never smoked	202 (39.2)	1.03	0.64–1.67	1.22	0.75–1.97
Age	10-year increments	—	0.75	0.54–1.06	0.84	0.60–1.18

*IFG/IGT = IFG or IGT or IFG + IGT. Q, quintile. †Prevalence of European/American in the sample. ‡Physical activity level at follow-up was used as a proxy for the level of physical activity at baseline: Subjects who reported doing no leisure-time physical activity during follow-up were categorized as "sedentary" and those who reported practicing any type of any duration of intentional physical activity were categorized as "physically active."

lin, triglycerides, BMI, and blood pressure at baseline, as well as higher values of fasting glucose, were each predictive of dysglycemia 24 years later.

In the logistic regression analysis, the most significant predictor for progression to type 2 diabetes was hyperinsulinemia in the basal state (upper quintile, Q5), while fasting glucose was the strongest predictor for IFG/IGT. BMI ≥27 kg/m^2 was a statistically significant predictor of diabetes only, after adjusting for sex, age, ethnicity, smoking, physical activity, blood pressure, and triglycerides (Table 1).

CONCLUSIONS — The present study is a late installment of results of a large survey, inaugurated in the early 1980s, that called attention to links between hyperinsulinemia, insulin resistance, dysglycemia, hypertension, obesity, and hyperlipidemia (1,2). Basal insulin was the strongest predictor for progression to type 2 diabetes over 24 years. Whereas ethnicity and higher values of basal insulin, triglycerides, BMI, blood pressure, fasting glucose, and male sex were each predictive of dysglycemia 24 years later, in the multiple regression model, the most statistically significant risk factor was basal insulin, reinforcing its importance as a chief component and perhaps a dominant factor in the development of type 2 diabetes.

Possible shortcomings of our study include remoteness of the outcome assessment from the baseline measurement causing inadequate information on medications, lifestyle changes, and time of onset of dysglycemia. Survival bias may affect the estimated links between basal hyperinsulinemia and dysglycemia, most likely attenuating them. A single baseline measurement of BMI has probably increased the magnitude of the association between obesity and the outcome of dysglycemia.

Our study has several strengths: the definition of normoglycemia was based on both fasting and 2-h postload glucose values, leaving our sample unconfounded by dysglycemia at baseline. The long follow-up period of 24 years, as well as the advanced age of subjects at follow-up, allowed us to report actual rates of dysglycemia. Finally, our cohort is of a well-chosen sample randomly selected from a national population registry, representative of the population with an equal number of men and women.

In our cohort, association between fasting plasma glucose and basal plasma insulin was weak with a correlation coefficient of 0.1 but was still statistically significant ($P = 0.02$), likely because of the large sample size. This suggests that, in this group of normoglycemic subjects, in the basal state, the absolute glucose value has a limited effect on basal insulin level. We conclude that in subjects with normoglycemia, basal insulin in the upper quintile confers an increased risk for the development of glucose dysmetabolism. We suggest that in "normal" subjects, fasting glucose and basal insulin are markers of different pathways to an overlapping group of disease processes.

Marked hyperinsulinemia is a common characteristic of several ethnic groups with a high prevalence of diabetes, including Mexican Americans (7), Pacific Islanders (8), Native Americans (9), and African Americans (10), even at an early age (10–14). Identifying individuals whose glucose tolerance will most likely progress over the years to dysglycemia would be of great public health benefit. Thus, a basal insulin measurement may turn out to be a useful adjunct in at-risk individuals with normal or near-normal glycemia. We provide here long-term epidemiological evidence that hyperinsulinemia in the basal state may relate to the root cause of type 2 diabetes. The increasing prevalence of hyperinsulinemia, particularly among groups such as young adults and non-Hispanic white women (15), in light of our findings, is alarming.

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of the concepts included today in the "metabolic syndrome."

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