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Modulation of Coronary Heart Disease Risk by Insulin Resistance in Subjects With Normal Glucose Tolerance or Prediabetes

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Abstract

Aims/hypothesis—This study is based on the hypothesis that: 1)coronary heart disease (CHD) risk is accentuated in the insulin resistant subset of persons with normal glucose tolerance (NGT) or prediabetes (PreDM); 2)the prevalence of insulin resistance, and associated abnormalities, is greater in subjects with PreDM; and 3)insulin resistance is the major contributor to increased CHD risk in these individuals.

Methods—A 75 g oral glucose challenge was used to classify volunteers as having NGT or PreDM. Steady-state plasma glucose (SSPG) concentrations during the insulin suppression test subdivided both groups into insulin sensitive (IS=SSPG <8.4 mmol/L) or resistant (IR=SSPG ≥8.4 mmol/L). Measurements were made of demographic characteristics, blood pressure, and lipid and lipoprotein concentrations, and comparisons made between the subgroups.

Results—Subjects with PreDM (n=127) were somewhat older, more likely to be non-Hispanic men, with increased adiposity than those with NGT (n=315). In addition, they had higher FPG concentrations, were insulin resistant (SSPG concentration; 11.4 vs. 7.2 mmol/L), with higher blood pressures, and a significantly more adverse CHD risk lipid profile ($p<0.001$). Twice as many subjects with PreDM were IR (72% vs. 35 %), and the CHD risk profile was significantly worse in the IR subgroups in those with either NGT or PreDM.

Conclusions/interpretation—CHD risk profile is significantly more adverse in subjects with PreDM as compared to individuals with NGT. However, glucose tolerance status is not the only determinant of CHD risk in nondiabetic individuals, and differences in degree of insulin resistance significantly modulate CHD risk in subjects with NGT or PreDM.

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Contribution Statement
D.A. helped to design the study, analyzed and interpreted the results, and wrote and edited the manuscript. G.M.R. designed the study and edited the manuscript. Both have given final approval of the version to be published.

Conflict of Interest
Danit Ariel and Gerald Reaven declare that they have no conflict of interest.

Statement of Human and Animal Rights
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent
Informed consent was obtained from all patients before being included in the study.

Keywords

Insulin resistance; Prediabetes; Normal glucose tolerance; Coronary heart disease; Insulin suppression test

Introduction

The American Diabetes Association (ADA) introduced the classification of prediabetes (PreDM) to recognize an "intermediate group of individuals whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal [1]." As defined by the ADA, PreDM is not a clinical entity in its own right, but identifies individuals at increased risk to develop diabetes as well as coronary heart (CHD). Although there appears to be general agreement that PreDM is a significant predictor of incident type 2 diabetes (T2DM), the relationship between PreDM and CHD is not so clear. For example, in 2009 the United States Preventive Services Task Force performed a systematic review in nondiabetic individuals and concluded that prior to the development of diabetes "no study consistently found that elevated fasting glucose level could predict CHD events [2]". Similarly, Sarwar, et al [3] published results of a population-based prospective study demonstrating that hazard ratios for CHD risk "were generally modest and nonsignificant across tenths of glucose values below 7.0 mmol/L." In contrast, the results of the Emerging Risk Factors Collaboration [4] analysis of 102 studies indicated that CHD risk was increased when fasting glucose concentration was ≥ 5.6 mmol/L. However, they concluded that in people "without history of diabetes, information about fasting blood glucose concentration or impaired fasting glucose did not significantly improve metrics of vascular disease prediction when added to information about several conventional risk factors." In that context, Onat, et al [5] indicated that although neither fasting nor postprandial glucose concentrations predicted CHD in men, impaired glucose tolerance was an independent predictor in women. Of interest in these studies was the observation that C-reactive protein concentrations predicted progression from PreDM to T2DM, but not development of CHD.

The present study is an attempt to extend these earlier observations, and is on the premise that the multiple "metrics of vascular disease prediction" referred to by the Emerging Risk Factors Collaboration [4] can be subsumed under the rubric of insulin resistance. There is evidence that insulin resistance is increased in prevalence in subjects with PreDM as compared to those with normal glucose tolerance (NGT), and this difference in insulin action is associated with a significantly more adverse CHD risk profile [6]. The overall goal of this study is to extend these observations. More specifically, the hypotheses to be tested are: 1) the CHD risk profile within either glucose tolerance group, NGT or PreDM, will be significantly more adverse in insulin resistant as compared to insulin sensitive individuals; and 2) a substantial majority of subjects with PreDM will be insulin resistant, helping to explain why the Emerging Risk Factors Collaboration [4] found that CHD was increased in individuals with PreDM. Finally, the postulated cardio-metabolic heterogeneity will serve as the basis for speculation that addresses the lack of consensus concerning the relationship between PreDM and CHD.

Methods

Study Population

This is a retrospective cross-sectional analysis of individuals who had previously participated in our research studies from 1990-1998; all had provided informed consent and all the study protocols were approved by Stanford's Institutional Review Board. Subjects were all in good general health, with no history of coronary artery, kidney, or liver disease. Subjects were selected for this analysis on the basis of their plasma glucose concentration during a 75-gram oral glucose tolerance test (OGTT). Using ADA criteria [1], volunteers were classified as having either NGT (fasting plasma glucose concentration <5.6 mmol/L and a 2-hour concentration <7.8 mmol/L, or PreDM (fasting plasma glucose concentration ≥5.6 and <7.0 mmol/L and/or a 2-hour value ≥7.8 and <11.1 mmol/L.)

Experimental Measurements

a) Demographic characteristics—Ethnicity was determined during a medical history. Weight was determined with individuals wearing light clothing and no shoes. Height was also measured without shoes, using a metallic metric tape. Body mass index (BMI) was calculated (kg/m^2).

b) Blood pressure—Blood pressure (BP) was measured using an automatic blood pressure recorder. Prior to BP measurements, subjects were seated quietly for five minutes in a chair with feet on the floor and arm supported at heart level. Using an appropriately sized cuff, three BP readings were taken at one-minute intervals and averaged.

c) Metabolic evaluation—All metabolic tests were performed at the General Clinical Research Center of Stanford Medical Center after an overnight fast. Glucose, lipid and lipoprotein concentrations were assayed in the core laboratory at Stanford University Medical Center by standardized methods approved by the Centers for Disease Control.

d) Glucose tolerance—Plasma glucose was measured before (fasting) and 30, 60, 12, and 180 min after ingestion of 75 grams of oral glucose [7].

e) Insulin action—Insulin-mediated glucose disposal was quantified with the modified version [8] of the insulin suppression test (IST) as introduced and validated by our research group [9-11]. Briefly, after an overnight fast, an intravenous catheter was placed in each of the subjects' arms. One arm was used for the administration of a 180-minute infusion of octreotide (0.27 μg per m^2/min), insulin (32 mU per m^2/min) and glucose (267 mg per m^2/min); the other arm was used for collecting blood samples. Blood was drawn at 10-minute intervals from 150 to 180 minutes of the infusion to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state insulin concentrations are similar in all subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, the higher the SSPG concentration, the more insulin resistant the individual. It should be noted that insulin-mediated glucose disposal as determined by the IST is closely correlated with those obtained with the euglycemic, hyperinsulinemic clamp technique [9,10].

Results of prospective studies had indicated that the most insulin resistant third of a normal, nondiabetic population was at increased risk of cardiovascular disease (CVD) [12,13]. In the current study, a SSPG concentration of 8.4 mmol/L was the value that separated the upper third from the lower two-thirds of individuals with NGT. Using this cut-point, the experimental population was classified as insulin resistant (IR; SSPG ≥ 8.4 mmol/L) or insulin sensitive (IS; SSPG < 8.4 mmol/L).

In addition, fasting plasma glucose and insulin concentrations were used to calculate surrogate estimates of insulin action (HOMA-IR) and insulin secretion (HOMA-β) as described by Matthews, et al [14].

Statistical methods

Data were analyzed using SAS (version 9.4; SAS Institute, Cary, NC), and values reported as mean ± SD or percent where applicable. Statistical differences between experimental groups were assessed by one-way ANOVA, followed by post hoc Tukey's studentized range test to adjust for multiple comparisons. For categorical variables, univariate analyses were performed using chi-squared tests. Statistical significance was defined as a p-value <0.05 and all testing was two-tailed.

Results

Table 1 compares CHD risk factors in subjects with NGT or PreDM, and demonstrates that individuals with NGT were somewhat younger, more likely to be women, of non-Hispanic race, with lower BMI values. By selection, fasting plasma glucose (FPG) and 2-hour glucose concentrations were higher in individuals with PreDM, associated with higher fasting plasma insulin (FPI) and 2-hour insulin concentrations. The PreDM population was more insulin resistant by direct measure of insulin-mediated glucose disposal (higher SSPG concentrations), as well as by surrogate [14,15] estimates (HOMA-IR, FPI) of insulin action. However, there was no difference in the surrogate estimate [14] of insulin secretion (HOMA-β) between the two groups. Subjects with PreDM also had higher blood pressures, and higher plasma triglyceride (TG), total and low-density lipoprotein cholesterol (TC and LDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C) concentrations. However, high-density lipoprotein cholesterol (HDL-C) concentrations were significantly lower in subjects with PreDM.

The impact of differences in insulin action in subjects with NGT is illustrated in the left columns of Table 2. By selection, approximately one-third of subjects with NGT were IR, and SSPG concentrations were increased approximately 2-fold in these individuals. Surrogate estimates of insulin resistance (HOMA-IR and FPI concentrations) were also significantly increased in NGT-IR persons, as was the estimate of insulin secretion (HOMA-β). The IR and IS subgroups of subjects with NGT were not different in terms of age, sex distribution, or racial background. However, every other measured variable was significantly different between IR and IS individuals, including both fasting and 2-hour post glucose load glucose concentrations, resulting in a CHD risk profile that was substantially more adverse in the NGT-IR group.

Results in the right panel of Table 2 indicate that approximately twice as many subjects with PreDM were classified as IR as compared to the NGT group, associated with a greater than 2-fold increase in SSPG concentration, higher HOMA-IR values, and higher FPI concentrations. Although FPG concentrations were not different, the 2-hour post-glucose challenge glucose concentration was significantly higher in PreDM-IR individuals. It should be noted that the plasma insulin concentration 2-hour after oral glucose was approximately twice as high in the PreDM-IR group, as was the HOMA-β value. Age, sex distribution, and racial background were not different in IR vs. IS persons with PreDM. However, with the exception of TC, LDL-C, and non-HDL-C, every other individual CHD risk factor was significantly more adverse in those who were IR.

Tables 1 and 2 have compared experimental groups on the basis of absolute values of CHD risk factors. In order to put the comparisons in a more clinical context, Table 3 compares the prevalence of “abnormal” CHD risk factors in the IR and IS subgroups of those with either NGT or PreDM based on Adult Treatment Panel III [16] and metabolic syndrome criteria [17]. These data indicate that not only are the mean values of CHD risk factors significantly more adverse in IR individuals (Table 2), IR individuals have an increased prevalence of “abnormal” CHD risk factors, whether they are NGT or PreDM.

Discussion

The results of this study appear to be consistent with observational findings [4] that CHD is increased in subjects with PreDM. To begin with, by definition, plasma glucose concentrations are higher in individuals meeting the criteria for PreDM [1] than in those with NGT. However, and relevant to the goals of this study, the findings in Table 1 demonstrate that in addition to higher glucose concentrations, subjects with PreDM were older, heavier, more insulin resistant (higher SSPG concentrations and HOMA-IR values), had higher blood pressures, and exhibited all of the dyslipidemic risk factors associated with insulin resistance [18].

In light of the adversity in the cardio-metabolic risk profiles of subjects with PreDM as compared to those with NGT (Table 1), it seems somewhat surprising that controversy continues to exist as to whether or not subjects with PreDM are at increased risk of CVD. In this context, the results in Tables 2 and 3 support both of the hypotheses that led to the initiation of this study, and in so doing provide a possible explanation for why this issue has not been resolved.

In terms of the first hypothesis, although there were no differences in the age, sex, or racial distribution of the IR vs. IS subgroups, essentially every other cardio-metabolic risk factor measured was significantly more adverse in the IR subgroups. Similarly, the results in Table 3, comparing the prevalence of conventional clinical abnormalities of blood pressure and lipid/lipoprotein concentrations, demonstrated that abnormalities in the IR subgroups in most cases were at least 2-fold greater, irrespective of being NGT or PreDM. Thus, the results in Table 2 clearly demonstrate that within either glucose tolerance group, NGT or PreDM, the cardio-metabolic risk profile was significantly worse in the IR as compared to IS subjects.

Turning to our second hypothesis, since the prevalence of IR and its associated cardio-metabolic risk in subjects with PreDM was increased approximately 3-fold (Table 2), it should not be surprising that the Emerging Risk Factors Collaboration concluded that subjects with PreDM were at increased risk for CHD [4]. Another way to view this issue is that inspection of Table 2 indicates that, with the exception of differences in glucose concentration, the cardio-metabolic profile appears reasonably comparable in the NGT-IR and PreDM-IS subgroups, representing one-third of the population. The dramatic differences in cardio-metabolic risk are between the two-thirds of the population with either NGT-IS or PreDM-IR, providing further support for our hypothesis that incident CHD will be greater in those with PreDM.

The findings in this study demonstrate that cardio-metabolic heterogeneity exists in nondiabetic individuals, and can help explain why CHD risk is increased in individuals with PreDM. However, this phenomenon can also serve as a possible explanation concerning the controversy as to the relationship between PreDM and CHD [2-4]. To put it most simply, differences in the relative prevalence of the four experimental subgroups shown in Table 2 will affect the incidence of CHD. For example, in a given population, the larger the NGT-IR subgroup and the smaller the PreDM-IR subgroup, the less likely that subjects with PreDM will be found to develop more CHD. Obviously, our data only serve as a “possible” explanation, but the speculation seems justified in terms of the enormous degree of cardio-metabolic heterogeneity our findings have documented in nondiabetic individuals.

Although not the goal of the study, the findings address at least two pathophysiological issues that seem worthy of commenting upon, and consideration of the plasma glucose response to the oral glucose challenge serves an introduction to both. Table 2 indicates that the 2-hour glucose concentration was significantly higher in both IR subgroups, associated with significantly greater insulin resistance (SSPG concentration, HOMA-IR, and FPI). The two estimates of insulin secretory function (HOMA-β and 2-hour insulin) were also significantly greater in the IR subgroups. Thus, it appears that the pancreatic β-cell in both the NGT and PreDM populations was able to increase insulin secretion in response to the insulin resistance, but these compensatory efforts were only partially successful as 2-hour plasma glucose concentration did increase.

The increase in 2-hour glucose concentrations in IR subjects also brings to the fore the uncertainty concerning the role of postprandial hyperglycemia as a significant CHD risk factor [18,19]. Our results do not help resolve this issue, but they do emphasize that, in addition to dysglycemia, the multiple CHD risk factors in PreDM-IR individuals include not only hypertension and dyslipidemia, but also inflammatory and procoagulant abnormalities related to insulin resistance [20]. Thus, given an inability to discern which of these multiple abnormalities in PreDM-IR subjects represents the *primary* reason why CHD is increased, it seems reasonable to subsume them under insulin resistance, the pathophysiological defect that unifies them.

The conclusions drawn from this study must be tempered for several reasons. To begin with, the data represent a new analysis of measurements made previously for other reasons. Secondly, the population is predominantly of European origin. Thirdly, the definition of

insulin resistance is somewhat arbitrary, as to a certain degree is the definition of preDM. However, experimental evidence from two prospective outcome studies support the criterion used to classify individuals as insulin resistant [12,13]. The decision to define PreDM by ADA criteria [1] for fasting plasma glucose concentration (≥5.6 <7.0 mmol/L) rather than the WHO definition [21] of ≥6.1 <7 mmol/L) was based on the results of the Emerging Risk Factor Collaboration [4] that the fasting glucose threshold at which incident CHD increased was ≥5.6 mmol/L. Finally, it must be emphasized that the findings are cross-sectional in nature, and provide evidence of CHD risk, not incident CHD. On the other hand, we are unaware of any previous study in which a direct measurement of insulin-mediated glucose disposal has been used to compare the CHD risk profile of apparently healthy, nondiabetic individuals with NGT or PreDM, subdivided into IR and IS subgroups. We hope that the evidence of metabolic heterogeneity in the CHD risk profile of subjects with PreDM will stimulate other investigators to evaluate the importance of insulin resistance, *per se*, as the link between PreDM and CHD outcome. In the context of population-based studies, since it is not possible to perform specific measurements of insulin action in such studies, in addition to using the surrogate estimates of insulin resistance that are now available [14,15], consideration should be given to exploring new and promising biomarkers of insulin resistance, e.g., microRNAs, [22,23] to identify this high risk population.

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Table 1

Comparison of cardiovascular risk factors in individuals with normal glucose tolerance (NGT) versus prediabetes (PreDM)

Variable	NGT (n= 315)	PreDM (n=127)	P value
Age (yrs)	46 ± 14	54 ± 10	<0.0001
Sex (% male)	43	55	0.03
Non-Hispanic White (%)	89	83	0.02
BMI (kg/m^2)	25.5 ± 4.1	28.6 ± 4.5	<0.0001
SSPG (mmol/l)	7.2 ± 3.7	11.4 ± 4.2	<0.0001
FPG (mmol/l)	4.8 ± 0.5	5.7 ± 0.5	<0.0001
2-hr glucose (mmol/l)	5.3 ± 1.2	7.6 ± 1.7	<0.0001
FPI (pmol/l)	70.3 ± 36.4	110.4 ± 65.7	<0.0001
2-hr insulin (pmol/l)	363.1 ± 308.6	704.8 ± 552.7	<0.0001
HOMA-IR	2.2 ± 1.2	4.1 ± 2.5	<0.0001
HOMA-ß	165.2 ± 159.6	153.5 ± 114.6	0.45
SBP (mmHg)	123 ± 18	139 ± 20	<0.0001
DBP (mmHg)	76 ± 11	84 ± 12	<0.0001
Triglyceride (mmol/l)	1.2 ± 0.7	1.8 ± 0.9	<0.0001
Total cholesterol (mmol/l)	4.8 ± 0.9	5.2 ± 0.9	<0.0001
LDL cholesterol (mmol/l)	2.9 ± 0.8	3.2 ± 0.8	<0.0001
HDL cholesterol (mmol/l)	1.34 ± 0.34	1.17 ± 0.28	<0.0001
Non-HDL cholesterol (mmol/l)	3.4 ± 0.9	4.1 ± 0.9	<0.0001

Variables are expressed as the mean ± standard deviation, or percent.

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, Homeostasis model assessment for insulin resistance; HOMA-ß, Homeostasis model assessment for beta-cell function; SBP, systolic blood pressure; SSPG, steady-state plasma glucose; 2-hr, 2 hour.

Table 2

Comparison of cardiovascular risk factors by insulin resistance status in individuals with normal glucose tolerance (NGT) and prediabetes (PreDM)

	NGT			preDM		
Variable	**Insulin Sensitive (n= 206; 65%)**	**Insulin Resistant (n=109; 35%)**	**P Value**	**Insulin Sensitive (n= 36; 28%)**	**Insulin Resistant (n= 91; 72%)**	**P Value**
Age (yrs)	46 ± 13	48 ± 14	0.14	53 ± 10	54 ± 10	0.47
Sex (% male)	42	46	0.54	67	51	0.10
Non-Hispanic White (%)	91	84	0.33	81	85	0.27
BMI (kg/m^2)	24.3 ± 3.6	27.6 ± 4.2	<0.0001	25.8 ± 3.4	29.7 ± 4.4	<0.0001
SSPG (mmol/L)	5.0 ± 1.8	11.5 ± 2.3	<0.0001	5.9 ± 1.5	13.7 ± 2.6	<0.0001
FPG (mmol/l)	4.7 ± 0.5	4.9 ± 0.4	0.0008	5.7 ± 0.4	5.7 ± 0.6	0.93
2-hr glucose (mmol/l)	5.1 ± 1.2	5.7 ± 1.1	<0.0001	6.6 ± 1.7	8.0 ± 1.6	<0.0001
FPI (pmol/l)	60.2 ± 29.7	89.4 ± 40.3	<0.0001	66.6 ± 42.1	127.8 ± 65.5	<0.0001
2-hr insulin (pmol/l)	260.8±160.4	556.4 ± 412.8	<0.0001	417.9 ± 593.4	818.4 ± 494.7	0.0002
HOMA-IR	1.8 ± 1.0	2.8 ± 1.3	<0.0001	2.5 ± 1.5	4.7 ± 2.5	<0.0001
HOMA-ß	147.1 ± 176.3	199.3 ± 115.0	0.006	87.2 ± 57.7	179.7 ± 121.0	<0.0001
SBP (mmHg)	120 ± 17	129 ± 19	<0.0001	131 ± 17	142 ± 21	<0.01
DBP (mmHg)	73 ± 17	81 ± 19	<0.0001	78 ± 12	86 ± 11	<0.001
TG (mmol/L)	1.0 ± 0.5	1.5 ± 0.8	<0.0001	1.3 ± 0.7	2.0 ± 0.9	<0.0001
TC (mmol/L)	4.7 ± 0.8	4.9 ± 0.9	0.02	5.2 ± 0.9	5.3 ± 0.9	0.64
LDL-C (mmol/L)	2.8 ± 0.7	3.0 ± 0.8	0.03	3.3 ± 0.9	3.2 ± 0.8	0.67
HDL-C (mmol/L)	1.40 ± 0.35	1.21 ± 0.29	<0.0001	1.30 ± 0.33	1.12 ± 0.24	<0.001
Non-HDL-C (mmol/L)	3.3 ± 0.8	3.7 ± 0.9	<0.0001	3.9 ± 1.0	4.2 ± 0.9	0.14

Variables are expressed as the mean ± standard deviation, or percent. BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, Homeostasis model assessment for insulin resistance; HOMA-ß, Homeostasis model assessment for beta-cell function; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; non-HDL-C, non-HDL cholesterol; SBP, systolic blood pressure; SSPG, steady-state plasma glucose; TC, total cholesterol; TG, triglyceride; 2-hr, 2-hour.

Table 3

Percentage of individuals with normal glucose tolerance (NGT) and prediabetes (preDM) who have abnormal CVD risk factors

Variable	NGT		preDM	
	Insulin Sensitive (n= 206)	Insulin Resistant (n=109)	Insulin Sensitive (n= 36)	Insulin Resistant (n= 91)
SBP ≥ 130 (mmHg)[a]	25	47	56	69
DBP ≥ 85 (mmHg)[a]	15	42	31	63
Triglyceride ≥ 1.7 (mmol/l)[a]	8	28	19	59
Total cholesterol ≥ 5.2 (mmol/l)[b]	23	39	44	55
LDL cholesterol ≥ 3.4 (mmol/l)[b]	18	33	39	40
HDL cholesterol M < 1.04, F < 1.30 (mmol/l)[a]	24	50	31	62

Variables are expressed as percent.

DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

[a] cut-points based on the metabolic syndrome criteria

[b] cut-points represent borderline-high levels as per ATP III