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Impact of differences in glucose tolerance on the prevalence of a negative insulinogenic index☆

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ABSTRACT

Objective: To determine the prevalence of a negative insulinogenic index (change in plasma insulin/change in plasma glucose from 0 to 30 min) from an oral glucose tolerance test according to glucose tolerance category.
Materials and Methods: Data from the San Antonio Heart Study (n = 2494), Japanese American Community Diabetes Study (JACDS; n = 594) and Genetics of NIDDM Study (n = 1519) were examined. Glucose tolerance was defined by ADA criteria.
Results: In the combined cohort, the prevalence of a negative insulinogenic index was significantly higher in diabetes 20/616 (3.2%) compared to normal glucose tolerance 43/2667 (1.6%) ($p<0.05$). Longitudinally, in the JACDS cohort, the prevalence did not change from baseline (3/594; 0.5%) to 5 (4/505; 0.7%) and 10 years (8/426; 1.9%) ($p = 0.9$) and no subject had a repeat negative insulinogenic index.
Conclusions: A negative insulinogenic index occurs at a low prevalence across glucose tolerance categories although more often in diabetes, but without recurrence over time.

1. Introduction

The insulinogenic index (change in insulin/change in glucose from 0 to 30 min) derived from an oral glucose tolerance test (OGTT) has been found to correlate with corresponding indices of the early insulin response to changes in glucose derived from the intravenous glucose tolerance test (IVGTT) (Tura, Kautzky-Willer, & Pacini 2006). It has been utilized as a measure of β-cell function in different populations (Haffner, Miettinen, Gaskill, & Stern 1995; Hanson et al. 2000; Phillips, Clark, Hales, & Osmond 1994) and instituted in large multicenter epidemiological and clinical trials (Kahn et al. 2011). Its correlation with more sophisticated measures of insulin secretion has been examined and is considered a reasonable surrogate, particularly in epidemiological investigations where more complex and time-consuming measurements are impractical (Hanson et al. 2000).

The mathematical calculation of this index comes with some inherent problems, such as when it is negative due to either a 30 min decrement in the insulin or glucose value from baseline, when it is positive as the result of both these measures being negative, or when there is no change in glucose from baseline to 30 min, resulting in a denominator of zero. The frequency of such occurrences across different degrees of glucose tolerance, whether they recur in the same individual over time and whether such is dependent on glucose tolerance is essentially unknown and could clearly impact the outcome of studies. Thus, in order to better understand the potential impact of negative glucose and/or insulin values in the calculation of the insulinogenic index, we assessed the frequency of such occurrences in single and repeated measurements and their association with glucose tolerance.

2. Materials and methods

2.1. Study populations

Subjects were from the San Antonio Heart Study (SAHS, n = 2494) (Han et al. 2002), the Genetics of Non-Insulin Dependent Diabetes study

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Table 1
Baseline characteristics of the San Antonio Heart Study (SAHS), Genetics of NIDDM (GENNID) Study and Japanese American Community Diabetes Study (JACDS) cohorts and the combined cohort.

	SAHS	GENNID	JACDS	Combined cohort
	(n = 2494)	(n = 1519)	(n = 594)	(n = 4607)
Age (y)	42.9 ± 0.22	51.5 ± 0.41	56.2 (22.9)[a]	47.1 ± 0.20
Female (%)	56.1	61.0	47.8	56.7
Body mass index (kg/m^2)	27.9 ± 0.11	29.4 ± 0.16	24.3 ± 0.14	27.9 ± 0.09
Fasting plasma glucose (mM)	5.00 ± 0.027	5.77 ± 0.039	5.48 ± 0.051	5.31 ± 0.021
30-min plasma glucose (mM)	8.15 ± 0.050	9.18 ± 0.060	9.61 ± 0.095	8.68 ± 0.037
2-h plasma glucose (mM)	6.44 ± 0.067	9.21 ± 0.096	8.28 ± 0.139	7.59 ± 0.055
Fasting plasma insulin (pM)	59.4 (66.0)	56.9 (58.6)	72.0 (48.0)	60.8 (61.9)
30-min plasma insulin (pM)	471 (454)	326 (322)	411 (318)	413 (396)
Insulinogenic index (pM/mM)	141 (165)	83 (100)	85 (93)	111 (136)
Glucose Tolerance				
NGT (%)	76.5	33.0	43.1	57.9
IFG (%)	4.9	8.5	10.4	6.8
IGT (%)	9.1	19.3	20.4	13.9
IFG + IGT (%)	2.8	14.5	13.1	8.0
DM (%)	6.6	24.6	13.0	13.4

Data are expressed as mean ± SEM for age, BMI and glucose, and as median (interquartile ranges) for insulin and insulinogenic index.
Insulinogenic index = increment insulin 0–30 min/increment glucose 0–30 min.
[a] Age for the JACDS cohort is expressed as median (interquartile range) as the distribution was not normal since two generations were studied.

(GENNID, n = 1519) (Raffel et al. 1996) and the Japanese American Community Diabetes Study (JACDS, n = 594 of whom 503 and 422 had repeat studies 5 and 10 years later) (Boyko, Leonetti, Bergstrom, Newell-Morris, & Fujimoto 1995). Subjects taking glucose-lowering agents or with missing demographic or OGTT data were excluded.

Local institutional review boards approved the studies and all subjects gave written informed consent.

2.2. Study procedure and calculations

After a 10–12 h overnight fast, a 75-g OGTT was performed (Fujimoto et al. 1987; Raffel et al. 1996; Stern, Gaskill, Hazuda, Gardner, & Haffner 1983). Basal samples were drawn in duplicate in all three studies. Normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG + IGT and diabetes were based on American Diabetes Association criteria (Genuth et al. 2003).

The insulinogenic index was calculated as the ratio of the change in insulin and glucose responses from 0 to 30 min. A ratio <0 was defined as a negative insulinogenic index. A positive index as a result of the combination of negative glucose and insulin values was also identified.

2.3. Assays

Radioimmunoassays were used to measure insulin in the three different cohorts as previously described for SAHS (Haffner, Stern, Hazuda, Pugh, & Patterson 1986; Han et al. 2002), GENNID (Raffel et al. 1996) and JACDS (Boyko et al. 1995). The intra-assay coefficients of variation for these assays were 6.5%, <9% and 5%, respectively. Plasma glucose was measured using the hexokinase method in SAHS and GENNID, which had intra-assay coefficients of variations of 2.9% and <2%, respectively. The glucose oxidase enzymatic method was used in the JACDS, and had an intra-assay coefficient of variation of 1.6%.

2.4. Statistical methods

Statistical analysis was performed using SPSS version 15 (SPSS Inc., Chicago, ILL). Data are expressed as mean ± SEM, unless they were not normally distributed in which case they are presented as median and interquartile ranges. Comparison of baseline characteristics among groups was performed by ANOVA, Kruskal–Wallis or Mann–Whitney U tests. The proportion of subjects in each study cohort with a negative insulinogenic index was calculated with exact 95% confidence intervals. To test whether these proportions differed across study cohorts, the Fisher's exact test with Bonferroni correction for multiple comparisons was used. A general linear model for repeated measures with Greenhouse–Geisser correction was performed to test within-subject effects over the three time points in the JACDS cohort at which repeated measurements were made (0, 5, and 10 years). A two-sided $p<0.05$ was considered significant.

3. Results

Baseline characteristics for the SAHS, GENNID and JACDS cohorts as well as all subjects combined are listed in Table 1. The proportion of subjects who were female differed across the three studies ($p<0.05$). SAHS subjects were younger ($p<0.001$) than GENNID and JACDS subjects, while JACDS subjects were leaner than those in the other two cohorts ($p<0.001$). The prevalence of a negative insulinogenic index ranged from 0% to 9.1% across glucose tolerance categories (Table 2). The prevalence in the SAHS cohort was 0.024 (CI 0.019–0.031), greater than that in the GENNID of 0.009 (CI 0.0045–0.14105) ($p<0.01$) and JACDS cohorts of 0.005 (CI 0.001–0.013) ($p<0.05$), independent of glucose tolerance and age. When all three cohorts were combined (baseline only for JACDS), the prevalence of a negative insulinogenic index was 1.6% (76/4607) and was higher in diabetes than NGT (3.2% vs. 1.6%, $p<0.05$; Table 2). Of note, one subject with diabetes in the SAHS cohort and one with IFG + IGT in the GENNID cohort had double negative values, resulting in a positive insulinogenic index; one subject with IFG in the GENNID cohort had no change in glucose from baseline to 30 min resulting in a denominator of zero, therefore the insulinogenic index could not be calculated. Exclusion of these three subjects did not change the results.

Table 2
Prevalence of a negative insulinogenic index for each glucose tolerance category in the combined cohort, the San Antonio Heart Study (SAHS), Genetics of NIDDM (GENNID) Study and Japanese American Community Diabetes Study (JACDS) cohorts at baseline.

	NGT	IFG	IGT	IFG + IGT	DM
Combined cohort	1.6% (2667)	2.9% (314)	0.5% (642)	0.3% (368)	3.2% (616)
SAHS	1.9% (1909)	4.0% (123)	0.9% (228)	1.4% (69)	9.1% (165)
GENNID	0.8% (502)	2.3% (129)	0.3% (293)	0.0% (221)	1.3% (374)
JACDS	0.8% (256)	1.7% (62)	0.0% (121)	0.0% (78)	0.0% (77)

Data in parentheses are the n within each category.