Compensatory Hyperinsulinemia is a Hidden Risk Factor for Type 2 Diabetes: CARDIA 30-year Follow Up

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INTRODUCTION

Compensatory Hyperinsulinemia (CH):
the pancreatic response to early insulin resistance (IR)

- beta-cell insulin secretion is intact and adaptive
- glucose and lipids remain *within normal limits*
- does not meet criteria for prediabetes or metabolic syndrome; *eludes screening for diabetes risk*
- prevalent in U.S. populations, especially teenagers (see poster by Bradley *et al.*)
- part of a syndrome that includes CH, inflammation, pro-coagulation and hypoxia

Healthy Balanced Metabolism	Compensatory Hyperinsulinemia Syndrome	Metabolic Syndrome/ Prediabetes	Type 2 Diabetes Mellitus
	⊢ Hyperinsulinemia →		
		⊢ Hyperglycemia & Dyslipidemia →	

Research Question

Does CH early in life increase the risk for future diabetes?

Hypothesis:
Compensatory hyperinsulinemia is an independent risk factor for type 2 diabetes.

Specific Aim:
Estimate the risk of incident diabetes in young adults with CH, relative to those with low fasting insulin.

Experimental Approach

- retrospective analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) study cohort
- inclusion criterion: all CARDIA participants; exclusion criteria: hyperglycemia, hypertriglyceridemia, low HDL-C, pregnancy, not-fasting or diabetes at baseline;
- 3,507 participants, ages 18-30 years at baseline, with 30-year mean follow up
- CH cutpoint: top tertile of fasting insulin (9.9 microIU/mL)
- analysis: Cox proportional hazard regression
- primary outcome: time to incident type 2 diabetes
- effect size: hazard ratio (HR), 95% confidence limits (CI)

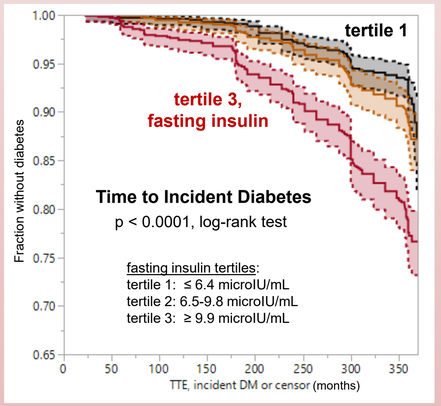
RESULTS

Table 1: Study participants at baseline (n=3,507)

Baseline characteristics	Reference Group (RG)[a]	CH group[a]
age	25.2 (3.5)	24.2 (3.8)[b]
sex, % female	48.0%	55.3%
race, % Black	46.3%	63.4%
BMI, kg/m^2	22.3 (3.2)	24.5 (5.0)[b]
family history of diabetes	12.5%	15.2%
fitness treadmill duration, sec	631 (177)	551 (179)[b]
fasting glucose, mg/dL	80.0 (7.2)	82.9 (7.2)[b]
fasting TG, mg/dL	58.7 (22.9)	66.1 (26.2)[b]
HDL-C, mg/dL	58.6 (11.8)	56.6 (10.8)[b]
systolic BP, mm Hg	109.5 (10.7)	112.0 (10.3)[b]
diastolic BP, mm Hg	68.0 (9.1)	69.6 (9.2)[b]
fasting insulin, microIU/mL[c]	6.4 (1.9)	15.4 (7.5)
HOMA2 %S[c]	161.6 (58.9)	67.3 (17.7)
HOMA2 %B[c]	97.2 (26.7)	162.1 (51.0)

[a]mean (s.d.); [b]p<0.0001 v. RG; [c]used in, or related to, CH definition

Fig. 1 Kaplan-Meier curves by fasting insulin tertiles



Cox Proportional Hazard Regression, Model 1:

Hazard Ratios (95% CI):
3.3 (2.5, 4.3), tertile 3 vs. 1, p<0.0001
2.3 (1.8, 3.0), tertile 3 vs. 2, p<0.0001
1.4 (1.0, 1.9), tertile 2 vs. 1, p=0.0269

Compensatory hyperinsulinemia: 3.3-fold ↑ in diabetes risk (unadjusted)

RESULTS

Cox Model 2, adjusted for ADA risk factors

Baseline Predictor Variables	HR (95% CI), Incident Diabetes	p-value
CH, insulin, tertile 3 vs. 1	**2.1 (1.6, 2.8)**	**< 0.0001**
race, black vs. non-black	2.1 (1.6, 2.7)	< 0.0001
family history of diabetes	1.9 (1.5, 2.5)	< 0.0001
overweight/obese	1.9 (1.5, 2.4)	< 0.0001
poor physical fitness	1.8 (1.3, 2.5)	0.0007
sex, male	1.1 (0.9, 1.5)	0.3251 (NS)
hypertension, >=140/90 or meds	1.2 (0.7, 2.0)	0.4415 (NS)
age category, 25-30 vs. 18-24	1.1 (0.9, 1.4)	0.4371 (NS)

ADA risk factors: Table 2.3, Standards of Medical Care in Diabetes, *Diabetes Care*, Jan 2021

Cox Model 3: Model 2 plus glucose and TG/HDL

Baseline Predictor Variables	HR (95% CI), Incident Diabetes	p-value
CH, fasting insulin tertile 3 vs. 1	**1.8 (1.3, 2.4)**	**0.0002**
race, black vs. non-black	2.3 (1.8, 3.0)	< 0.0001
family history of diabetes	1.9 (1.5, 2.5)	< 0.0001
overweight/obese	1.8 (1.4, 2.3)	< 0.0001
poor physical fitness	1.8 (1.3, 2.5)	0.0010
fasting glucose, 84-99 vs. <=78	1.7 (1.3, 2.2)	0.0004
fasting TG/HDL	1.3 (0.9, 1.7)	0.1819
sex, male	1.0 (0.8, 1.4)	0.7435 (NS)
hypertension. >=140/90 or meds	1.2 (0.7, 1.9)	0.5900 (NS)
age category, 25-30 v. 18-24	1.1 (0.9, 1.4)	0.2696 (NS)

Cox Model 4: Model 3 plus cotinine, uric acid/creatinine, WBC

Baseline Predictor Variables	Hazard Ratio, Incident Diabetes	p-value
CH, fasting insulin tertile 3 vs. 1	**1.8 (1.3, 2.5)**	**0.0002**
race, black vs. non-black	2.6 (2.0, 3.4)	< 0.0001
family history of diabetes	1.9 (1.4, 2.4)	< 0.0001
uric acid/creatinine, tertile 3 vs. 1	1.8 (1.4, 2.5)	< 0.0001
overweight/obese	1.7 (1.4, 2.2)	< 0.0001
poor physical fitness	1.7 (1.2, 2.4)	0.0029
fasting glucose, 84-99 vs. <=78	1.7 (1.3, 2.2)	0.0005
WBC count, tertile 3 vs. 1	1.5 (1.1, 2.0)	0.0095
serum cotinine, nicotine use	1.3 (1.0, 1.7)	0.0241
age category, 25-30 vs. 18-24	1.2 (0.9, 1.5)	0.2106 (NS)
fasting TG/HDL, tertile 3 vs. 1	1.1 (0.8, 1.5)	0.1819 (NS)
hypertension, >=140/90 or meds	1.0 (0.6, 1.7)	0.9009 (NS)
sex, male	0.9 (0.7, 1.2)	0.5843 (NS)

RESULTS

Cox Model 5: Model 4 with *insulin/BMI interaction*

Baseline Predictor Variables	HR (95% CI), Incident Diabetes	p-value
CH & obese	**3.3 (2.1, 5.0)**	**<0.0001**
CH & non-obese	**1.9 (1.4, 2.7)**	**<0.0001**
race, black vs. non-black	2.6 (2.0, 3.5)	<0.0001
family history of diabetes	1.8 (1.4, 2.4)	<0.0001
uric acid/creatinine, tertile 3 vs. 1	1.9 (1.4, 2.5)	<0.0001
poor physical fitness	1.8 (1.3, 2.5)	0.0007
fasting glucose, 84-99 vs. <=78 mg/dL	1.7 (1.3, 2.3)	0.0002
WBC count, tertile 3 vs. 1	1.5 (1.1, 2.0)	0.0075
serum cotinine, >=15 ng/mL	1.3 (1.0, 1.6)	0.0549 (NS)
age category, 25-30 vs. 18-24	1.2 (0.9, 1.5)	0.1522 (NS)
fasting TG/HDL, tertile 3 vs. 1	1.1 (0.8, 1.5)	0.5244 (NS)
hypertension, >=140/90 or meds	1.1 (0.6, 1.8)	0.8276 (NS)
sex, male	1.0 (0.8, 1.3)	0.9949 (NS)

Summary of Cox Models and CH Hazard Ratios

Model Number	HR (CI), Incident Diabetes	p-value	Baseline Predictor Variables
1	**3.3 (2.5, 4.3)**	< 0.0001	insulin tertiles only
2	**2.1 (1.6, 2.8)**	< 0.0001	Model 1 plus ADA risk factors
3	**1.8 (1.3, 2.4)**	0.0002	Model 2 plus fasting glucose, TG/HDL
4	**1.8 (1.3, 2.5)**	0.0002	Model 3 plus uric acid, WBC, cotinine
5	**3.3 (2.1, 5.0)**	<0.0001	Model 4 with insulin/BMI interaction: **CH & obese**
5	**1.9 (1.4, 2.7)**	<0.0001	Model 4 with insulin/BMI interaction: **CH & non-obese**

SUMMARY & CONCLUSIONS

Compensatory hyperinsulinemia:

- **an independent risk factor for future diabetes among young adults in CARDIA**
- **for obese individuals, CH at baseline *tripled* the risk for future diabetes**
- **for non-obese individuals, CH at baseline *doubled* the risk for future diabetes**
- **CH evades conventional screening for diabetes risk – new strategies are needed to detect this early, hidden condition**

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