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Changes in procoagulants track longitudinally with insulin resistance: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study

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Abstract

Aims—To examine the association between changes in procoagulants (fibrinogen factors VII and VIII and von Willebrand factor) and the risk of insulin resistance.

Methods—Using data from the Coronary Artery Risk Development in Young Adults study, we followed 2398 black and white adults without diabetes, aged 25–37 years at year 7, to year 20. Levels of fibrinogen factors VII and VIII and von Willebrand factor were divided in tertiles (low/middle/high) at years 7 and 20 and four groups reflecting changes were defined: ‘low’ (low at years 7 and 20), ‘stable’ (low/middle at years 7 and 20, but not both low at years 7 and 20), ‘high’ (high at year 7 and low/middle at year 20; or low/middle at year 7 and high at year 20) and ‘highest’ (high at years 7 and 20). Linear regression models were used to evaluate 13-year changes (year 20–year 7) in fibrinogen level and factors VII, VIII and von Willebrand change groups in relation to insulin resistance measures.

Results—Homeostasis model assessment of insulin resistance (year 20) and changes in log homeostasis model assessment of insulin resistance (year 20–year 7) were significantly associated with the 13-year increase in fibrinogen ($P < 0.001$). Compared with participants in the low group, those in the high group had significantly higher levels of homeostasis model assessment of insulin resistance (year 20) and changes in homeostasis model assessment of insulin resistance (year 20–year 7) for fibrinogen factor VII and von Willebrand factor ($P < 0.017$). No significant associations were observed between fibrinogen VIII and insulin resistance measures.

Conclusions—An increase in fibrinogen level and persistently high levels of factor VII and von Willebrand factor are significantly associated with increased risk of insulin resistance. These findings provide new insight into the mechanisms to explain the heightened risk for thrombosis in adults with insulin resistance/diabetes.

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Competing interests
None declared.

Introduction

Adults with pre-diabetes and diabetes have a heightened risk of thrombosis, but the mechanisms to explain these findings remain unknown [1]. Few potential factors have been purported to contribute to these associations, such as inflammation, obesity and lifestyle factors [2,3].

High levels of procoagulants, such as fibrinogen, factors VII and VIII and von Willebrand factor, have also been linked to glucose disorders [4–8]. While increased levels of fibrinogen have been associated with incident diabetes and insulin resistance in most of the studies, independent of obesity and lifestyle factors [4,5], the evidence is much poorer and controversial for the other procoagulants [6–8]. In addition, while some of the procoagulants have also pro-inflammatory effects (fibrinogen, factor VIII and von Willebrand factor) it remains unclear if their link with glucose disorders is mediated through inflammation.

In this report, we examined the association of procoagulant (fibrinogen, factors VII and VIII, and von Willebrand factor) progression and insulin resistance, as well as changes in insulin resistance, in a sample of young adults without diabetes. We further sought to determine whether this relation is independent of obesity and lifestyle factors, evaluated both at baseline and changes over time, and if it is mediated through inflammation.

Patients and methods

Study participants

Participants in this study were from the Coronary Artery Risk Development in Young Adults (CARDIA) study, an ongoing multi-centre prospective study including 5115 black and white adults aged 18–30 years at baseline (1985–1986), recruited from four urban areas in the USA [9]. Fibrinogen was measured for 2398 participants at year 7 (our baseline, 1992–1993) and year 20 (follow-up, 2005–2006). Procoagulant factors (fibrinogen VII, VIII and von Willebrand) were measured for 1033 eligible participants in two of four CARDIA sites at years 7 and 20. Pregnant women or participants with diabetes [defined as fasting glucose ≥7 mmol/l (126 mg/dl) or using glucose-lowering medication] were excluded.

Measurements

Baseline characteristics were either measured using a standardized protocol or collected by questionnaires [9]. BMI was computed from measured height and weight as weight (kg)/ height (m) ^{2}. Fasting glucose and insulin were measured using a chemistry analyser or radioimmunoassay, respectively.

Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR): fasting plasma insulin (μUI/l) × fasting plasma glucose (mmol/l)/22.5 [10]. Fibrinogen and C-reactive protein (CRP) were both measured using a BN II nephelometer (XXXX, XXXX, XXXX) in the same laboratory and the same standard protocols for the year-7 and year-20 examinations. Factors VII, VIII and von Willebrand were assayed using different media in each examination (citrate at year 7; EDTA at year 20).

Statistical analysis

Year 7 and year 20 participant characteristics were compared using *t*-test, χ^2-test, Fisher's exact test or Wilcoxon test, as appropriate. HOMA-IR and CRP values were log-transformed to normalize the distribution. Because different assay methods were used to measure factors VII, FVIII and von Willebrand at years 7 and 20, we categorized procoagulant change groups based on the tertiles of individual procoagulant factor at years 7

and 20: 'low' (persistently in the lowest tertile at years 7 and 20, referent), 'stable' (lowest or middle tertile at years 7 and 20, but not in the lowest tertile both at year 7 and year 20), 'high' (highest tertile at year 7 and lowest or middle tertile at year 20; or lowest or middle tertile at year 7 and highest tertile at year 20) and 'highest' (persistently in the highest tertile at years 7 and 20). Linear regression models were used to examine the longitudinal associations between changes in fibrinogen level (as continuous variables) or changes in factor VII, VIII or von Willebrand groups with HOMA-IR at year 20 and changes in HOMA-IR (year 20–year 7) in two models: model 1 [adjusted for age, sex, race, study centre, family history of diabetes, education, year 7 (HOMA-IR, procoagulant level, BMI, physical activity, smoking and alcohol use)]; and model 2 [adjusted for all variables in model 1 plus 13-year changes in (BMI, physical activity, smoking and alcohol use)]. We also assessed if any association was independent of inflammation by further adjusting for CRP in a separate model (model 2 + log CRP). When comparing differences in the adjusted means between procoagulant change groups, with the low group as the reference, a significance level of 0.017 was used for each comparison so that the overall level of significance was < 0.05 (Bonferoni inequality). All analyses were conducted with SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA).

Results

The mean age of the participants at year 7 was 32 years, 58% were white and 45% were men. As a group, the participants were overweight at year 7 and further gained weight over 13 years of follow-up. Cholesterol (total, LDL and HDL fractions) and triglycerides increased, the prevalence of smoking decreased and the physical activity was unchanged during the 13 years of follow-up. The mean procoagulant levels in these participants increased (Table 1).

After adjustment, we found a significant increase in mean year 20 HOMA-IR for every 1-SD increase in fibrinogen [β (SE) = 0.09 (0.01), $P < 0.001$ and 0.04 (0.01), $P < 0.001$ for models 1 and 2, respectively]. Clinically, this translates into a 10% in model 1 or 4% in model 2 increase in the risk of worsening insulin resistance at year 20, for each standard deviation (SD) increase in fibrinogen between year 7 and year 20.

Similar associations were observed for changes in HOMA-IR over 13 years in regard to changes in fibrinogen: β (SE) = 0.09 (0.01), $P < 0.001$ and 0.04 (0.01), $P < 0.001$, respectively, for models 1 and 2.

Table 2 shows the longitudinal association of changes in factors VII, VIII and von Willebrand groups with year 20 HOMA-IR and changes in HOMA-IR (year 20–year 7). Compared with participants in the low group, those in the highest group had significantly higher levels of HOMA-IR at year 20 and changes in HOMA-IR (year 20–year 7) for factors VII and von Willebrand. No significant pattern of association was observed between changes in factor VIII groups and HOMA-IR measures.

Lastly, when we assessed whether any observed association between procoagulant and insulin resistance measures is mediated through CRP by further adjusting for year 7 CRP level in a separate model (model 2 + log CRP), we found little or no attenuation of the associations (data not shown).

Discussion

Our results show that, among young adults without diabetes, increasing fibrinogen over time, as well as persistently high levels of factors VII and von Willebrand, are associated with increasing insulin resistance, independent of obesity, lifestyle factors and inflammation.

The strengths of our study lie in the large data set that includes young adults, mostly free of other co-morbidities, and in performing more sophisticated adjustment for covariates (we adjusted for BMI and lifestyle factors both at baseline and change over time) compared with prior reports. Another novelty of our study is that we found a significant association between procoagulant and insulin resistance after adjustment for CRP (as a surrogate marker of systemic inflammation). In addition, fibrinogen factor VIII (which is a pro-inflammatory and endothelial dysfunction biomarker) was not associated with increasing insulin resistance, while persistently high levels of fibrinogen factor VII (which is not an acute-phase reactant) were, suggesting that inflammation cannot solely explain this association. At the same time, we acknowledge that inflammation is a very complex process, and adjusting for CRP but not for other markers such as oxidative stress cannot completely exclude inflammation as a potential factor on the causal link.

These findings provide new insight into the mechanisms to explain the heightened risk for thrombosis in adults with insulin resistance/diabetes. Although our study did not have the power to detect a direct association between insulin resistance, higher procoagulant levels and thrombotic events (only 5.8% of our analytic cohort suffered from thrombotic events over 13 years, including nine heart attacks, 11 peripheral vascular disease events, 14 strokes and 26 deep vein thrombosis/pulmonary embolisms), the individuals who developed events were more likely to be in the high/highest change groups and have increased insulin resistance. Further studies should be designed to assess these associations and to investigate if therapeutic approaches targeted at reducing the levels of fibrinogen, factors VII and von Willebrand can reduce the incidence of thrombotic events in these subjects.

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What's new?

- New insight is provided into the mechanisms to explain the heightened risk for thrombosis in patients with insulin resistance/diabetes.
- Increasing fibrinogen and persistently high levels of fibrinogen factor VII and von Willebrand factor are associated with insulin resistance, independent of changes in lifestyle factors and obesity.
- The association between procoagulants and insulin resistance is not mediated through the inflammation.

Table 1

Characteristics of study participants at years 7 and 20

Variable	Baseline (year 7)	Year 20	*P*-value*
Age (years)	32.2 (3.6)		
African American race (%)	41.8		
Male gender (%)	45.2		
Highest education attained (years)	15.4 (2.5)		
Family history of diabetes (%)	28.6		
BMI (kg/m^2)	26.3 (5.7)	29.3 (7.2)	< 0.001
Current alcohol drinker (%)	54.6	55.4	0.560
Current smoker (%)	21.6	16.8	< 0.001
Physical activity (exercise unit), median (interquartile range)	277.5 (144.0–487.0)	276.0 (132.0–492.0)	0.451
Total cholesterol (mg/dl)	175.9 (33.1)	185.4 (34.4)	< 0.001
LDL cholesterol (mg/dl)	107.4 (31.2)	109.9 (31.5)	0.005
HDL cholesterol (mg/dl)	52.0 (13.5)	54.1 (16.5)	< 0.001
Triglycerides (mg/dl), median (interquartile range)	65.0 (46.0–80.4)	86.0 (62.0–131.0)	< 0.001
Fibrinogen (mg/dl)	330.3 (72.1)	403.0 (90.6)	< 0.001
C-reactive protein (μg/ml), median (interquartile range)	1.0 (0.4–2.8)	1.1 (0.5–3.0)	0.146
Factor VII (%)†, median (interquartile range)	75.0 (64.0–85.0)	109.5 (94.0–127.0)	< 0.001
Factor VIII (%)†, median (interquartile range)	94.0 (74.0–121.0)	144.0 (114.0–186.0)	< 0.001
Von Willebrand antigen (%)†, median (interquartile range)	98.0 (76.0–128.0)	137.0 (107.0–175.0)	< 0.001
Fasting glucose (μg/dl)	90.1 (7.7)	98.4 (20.8)	< 0.001
Log$_e$ (HOMA-IR)	0.9 (0.5)	1.1 (0.6)	< 0.001

Data shown are means (SD) unless stated otherwise.

**P*-value for comparison between year 7 and year 20.

†Data collected in an ancillary study included participants from two (Chicago, Minneapolis) of the four Coronary Artery Risk Development in Young Adults (CARDIA) study sites.

HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2

Longitudinal relationships between changes in procoagulant factors and HOMA-IR

	Changes in coagulation factor group											
	Factor VII, %				von Willebrand, %				Factor VIII, %			
	Low	Stable	High	Highest	Low	Stable	High	Highest	Low	Stable	High	Highest
	Year 20 $\log_e$ (HOMA-IR), mean (SE)											
Number	162	317	305	163	210	316	175	224	195	326	237	190
Model 1	0.84 (0.05)	0.95 (0.03)	1.07 (0.03)*	1.27 (0.05)*	0.92 (0.05)	0.99 (0.03)	1.04 (0.04)	1.17 (0.05)*	0.97 (0.05)	0.93 (0.03)	1.08 (0.04)	1.17 (0.05)
Model 2	0.92 (0.05)	0.97 (0.03)	1.03 (0.03)	1.20 (0.05)*	0.94 (0.04)	1.00 (0.03)	1.05 (0.04)	1.12 (0.04)*	0.99 (0.04)	0.94 (0.03)	1.08 (0.03)	1.15 (0.05)
	Δ $\log_e$ (HOMA-IR), mean (SE)											
Model 1	−0.07 (0.05)	0.03 (0.03)	0.15 (0.03)*	0.35 (0.05)*	−0.00 (0.05)	0.07 (0.03)	0.12 (0.04)	0.25 (0.05)*	0.05 (0.05)	0.01 (0.03)	0.16 (0.04)	0.25 (0.05)
Model 2	0.01 (0.05)	0.06 (0.03)	0.12 (0.03)	0.28 (0.05)*	0.02 (0.4)	0.08 (0.03)	0.13 (0.04)	0.20 (0.04)*	0.07 (0.04)	0.02 (0.03)	0.16 (0.03)	0.23 (0.05)

Data shown are mean $\log_e$ (HOMA-IR) or changes in $\log_e$ (HOMA-IR) in given procoagulant factor group.

*$P < 0.017$ compared with the referent group, low–low (Bonferroni adjustment for multiple comparisons).

Model 1: adjusted for age, sex, race, study centre, education, family history, year 7 (smoking, alcohol, physical activity, BMI) and year 7 (procoagulant levels and HOMA-IR). Model 2: model 1 + changes in covariates (smoking, alcohol, physical activity, BMI) (year 20–year 7).

HOMA-IR, homeostasis model assessment of insulin resistance.