FPG and HbA_{1c} are independent risk factors for microvascular but not macrovascular complications in newly diagnosed type 2 diabetes

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Background and Aims: Individuals with HbA_{1c} values higher than expected for their fasting plasma glucose (FPG) are said to be at higher risk of complications than those with the same FPG but lower HbA_{1c}. We used data from the UK Prospective Diabetes Study (UKPDS) to determine whether HbA_{1c} and FPG are associated independently with incident microvascular and macrovascular complications in type 2 diabetes and used the haemoglobin glycation index (HGI) to summarise HbA_{1c} variation relative to FPG.
Materials and Methods: Of 5,102 UKPDS participants there were 3,538 with the required data. Microvascular events were defined as the first to occur of: retinopathy requiring photocoagulation; vitreous haemorrhage; or fatal or non-fatal renal failure. Macrovascular events were defined as the first to occur of: fatal or non-fatal myocardial infarction; fatal or non-fatal stroke; non-fatal ischaemic heart disease; or sudden death. Cox models were fitted for 313 microvascular and 766 macrovascular events observed during median 9.3 and 9.7 years follow-up, respectively. Potential confounders included in all models were post-dietary run-in values for age, sex, ethnicity, HDL and LDL cholesterol, triglycerides, systolic blood pressure and albuminuria (urine albumin ≥ 50 mg/l) and smoking status at time of diagnosis. FPG and HbA_{1c} were used in the first analysis as baseline values and in the second analysis as time-dependent variables (updated mean). HGI was calculated as actual HbA_{1c} minus the HbA_{1c} predicted from a linear regression equation fitted to baseline FPG.
Results: For microvascular complications, baseline FPG but not baseline HbA_{1c} was a predictor whereas updated mean HbA_{1c} and updated mean FPG were both independent predictors after adjustment for possible confounders (Table). For macrovascular complications, after adjustment for possible confounders, baseline FPG but not baseline HbA_{1c} was a predictor but only updated mean HbA_{1c} was a predictor. Median (1^{st}, 3^{rd} quartile) HGI was -0.069% (-0.75, 0.59) at baseline, 0.014% (-0.63, 0.72) at year 3, 0.27% (-0.38, 1.06) at year 6 and 0.47% (-0.18, 1.34) at year 9, showing that HbA_{1c} varies by more than 1% for individuals at the same FPG.
Conclusion: FPG and HbA_{1c} make independent contributions to predicting the risk of microvascular disease suggesting a role for the HGI, which measures disparity between HbA_{1c} and FPG as measures of glycaemia, in the management of type 2 diabetes. Updated mean HbA_{1c} is a strong independent predictor of macrovascular disease.

Relation between diabetic complications and FPG and HbA1c adjusted for other confounders at baseline

	Microvascular complications					
	Baseline FPG, HbA_{1c}			**Updated mean FPG, HbA_{1c}**		
Variables	**Hazard ratio**	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**P-value**
FPG (per mmol/L)	1.17	(1.12, 1.22)	<.0001	1.16	(1.09, 1.24)	<.0001
HbA_{1c} (per %)	1.06	(0.98, 1.15)	0.17	1.30	(1.16, 1.44)	<.0001
	Macrovascular complications					
	Baseline FPG, HbA_{1c}			**Updated mean FPG, HbA_{1c}**		
Variables	**Hazard ratio**	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**P-value**
FPG (per mmol/L)	1.06	(1.02, 1.10)	0.0035	1.04	(0.99, 1.09)	0.15
HbA_{1c} (per %)	0.97	(0.91, 1.03)	0.32	1.12	(1.03, 1.21)	0.0056