HbA_{1c}, Insulin Resistance, and β-Cell Function in Relation to Cognitive Function in Type 2 Diabetes: The CAROLINA Cognition Substudy

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Cognitive dysfunction is increasingly recognized as a complication of type 2 diabetes. There is a growing evidence for etiologic roles of glycemia and insulin resistance, although important questions remain (1,2). Elevated levels of glycosylated hemoglobin (HbA_{1c}) appear to be related to worse cognition, but there are indications that the same holds true for lower HbA_{1c} levels, possibly because intensive glycemic control increases the risk of hypoglycemia (1). Previous studies relating HbA_{1c} to cognition did not sufficiently address this possible nonlinear relationship. Regarding insulin resistance, it has been postulated that disturbances in cerebral insulin signaling might negatively affect cognition (2). Indeed, in individuals without type 2 diabetes, both hyperinsulinemia and insulin resistance have been related to poorer cognitive performance and dementia (2). However, a comprehensive understanding of the interrelationship between markers of insulin homeostasis and cognition in type 2 diabetes is still lacking (1). Finally, there may be interindividual differences in susceptibility for developing cognitive dysfunction, where factors such as age and sex could modify the relations between glycemia, insulin resistance, and cognition. We therefore investigated, in a large cohort of patients with type 2 diabetes, how HbA_{1c} and indices of insulin resistance and β-cell function relate to cognitive function, specifically addressing potential nonlinear associations and the influence of age and sex.

We studied participants of the cognition substudy of the CAROLINA (CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes) trial (NCT01243424). CAROLINA is a randomized, active comparator, double-blind study of 6,041 patients with relatively early type 2 diabetes, where the primary purpose is to evaluate the cardiovascular safety and efficacy of the dipeptidyl peptidase 4 inhibitor linagliptin versus the sulfonylurea glimepiride. The CAROLINA Cognition substudy investigates if linagliptin is superior to glimepiride in the prevention of accelerated cognitive decline (3). In brief, the Mini-Mental State Examination (MMSE), a test of global cognitive function, and the Trail Making Test and Verbal Fluency Test combined into one composite score for an attention and executive functioning score were conducted at baseline, after 160 weeks of treatment, and at study end (3). Baseline scores were used for the present analyses. Insulin resistance was assessed with the HOMA2 of insulin resistance (HOMA2-IR). Indices of β-cell function were proinsulin, C-peptide, the proinsulin-to-C-peptide ratio, and the HOMA2 of β-cell function (HOMA2-β). The relationships between HbA_{1c} and indices of insulin resistance and β-cell function and the cognitive measures, adjusted for confounders (age, sex, education, and race, and for HbA_{1c}, use of glinide or sulfonylurea), were assessed with ANCOVA; we also examined analyses stratified by HbA_{1c} (by median value), age (≥70 years, <70 years), and sex (women, men). Nonlinear associations were addressed by adding a quadratic term of the mean-centered

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Table 1—β-Coefficients (95% CIs) for the relationship between HbA_{1c} and indices of insulin resistance and β-cell function and MMSE

			Age (years)†			Sex‡		
	N	All	<70	≥70	*P* for interaction	Men	Women	*P* for interaction
HbA_{1c} (%)	4,335	−0.02 (−0.14, 0.10)	0.00 (−0.13, 0.14)	−0.05 (−0.30, 0.19)	0.73	0.02 (−0.12, 0.17)	−0.07 (−0.28, 0.15)	0.31
Median split								
<7.1%	2,148	0.50 (0.09, 0.90)*	0.21 (−0.25, 0.66)	1.06 (0.29, 1.83)*	0.06	0.36 (−0.12, 0.83)	0.65 (−0.06, 1.37)	0.36
≥7.1%	2,187	−0.27 (−0.49, −0.04)*	−0.07 (−0.32, 0.19)	−0.70 (−1.15, −0.25)*	0.01*	−0.11 (−0.37, 0.15)	−0.51 (−0.91, −0.11)*	0.04*
Only patients without use of sulfonylurea or glinide								
β-Cell function								
C-peptide (nmol/L)	2,027	0.06 (−0.20, 0.32)	0.05 (−0.25, 0.35)	0.01 (−0.51, 0.53)	0.87	−0.08 (−0.36, 0.21)	0.39 (−0.16, 0.93)	0.19
Proinsulin (qmol/L)	2,232	−0.003 (−0.006, −0.001)*	−0.002 (−0.005, 0.001)	−0.007 (−0.015, 0.001)	0.30	−0.002 (−0.005, 0.001)	−0.006 (−0.012, 0.001)	0.31
Proinsulin–to–C-peptide ratio	2,011	−0.051 (−0.082, −0.021)*	−0.045 (−0.077, −0.012)*	−0.054 (−0.126, 0.018)	0.96	−0.021 (−0.053, 0.012)	−0.114 (−0.176, −0.052)*	0.01*
HOMA2-β	2,026	0.0006 (−0.0037, 0.0024)	−0.0010 (−0.0043, 0.0024)	−0.0008 (−0.0074, 0.0057)	0.98	−0.0011 (−0.0044, 0.0021)	0.0004 (−0.0058, 0.0067)	0.54
Insulin resistance								
HOMA2-IR	2,026	0.0119 (−0.0859, 0.1096)	0.0101 (−0.1011, 0.1212)	−0.0085 (−0.2085, 0.1915)	0.84	−0.0407 (−0.1444, 0.0630)	0.1432 (−0.0626, 0.3491)	0.18

Estimates for all patients are obtained from an ANCOVA with factors of sex and race (for HbA_{1c}, also use of sulfonylurea or glinide) and covariates of age, years of formal education, and baseline value of interest. Estimates within subgroup HbA_{1c} (<7.1%, ≥7.1%) are obtained from an ANCOVA using the same model within the HbA_{1c} subgroup. *$P < 0.05$. †For the subgroup age (<70, ≥70 years), the same models without covariate age were run. ‡For the subgroup sex, the same models without factor sex were run. Interaction *P* values are taken from models as above with the additional subgroup term (subgroup age or sex, respectively) and interaction term (subgroup age × baseline value of interest or sex × baseline variable of interest, respectively).

variable to the ANCOVA model. Potential confounding and mediating factors were added stepwise to the model to investigate any relationship further. Relationships between indices of insulin resistance and β-cell function and the cognitive measures were only examined in patients not using sulfonylurea or glinide.

This analysis involves 4,335 patients with type 2 diabetes (60.7% male; mean [SD] age 64.7 [9.4] years, diabetes duration 7.8 [6.2] years, HbA_{1c} 7.1 [0.6]% [55 (6) mmol/mol], MMSE score 28.0 [2.5]). The association between HbA_{1c} and MMSE was nonlinear ($P < 0.001$) and proved to be bell shaped. An analysis by median split (HbA_{1c} <7.1, ≥7.1% [<54, ≥54 mmol/mol]) revealed that both low and high HbA_{1c} levels were associated with worse performance (Table 1), independent of use of sulfonylurea or glinide, estimated glomerular filtration rate, duration of diabetes, depression, cardiovascular risk factors, macrovascular disease, microvascular complications, and diabetic foot. A significant age–HbA_{1c} interaction ($P = 0.01$) was observed, where data suggested that associations between both high and low HbA_{1c} levels and worse MMSE scores were most prominent in patients ≥70 years. A significant sex–HbA_{1c} interaction ($P = 0.04$) was also found in patients with HbA_{1c} levels ≥7.1% (54 mmol/mol), where data suggested a more prominent relationship between high HbA_{1c} and poor performance in women (Table 1). Negative linear associations were found between both proinsulin and the proinsulin–to–C-peptide ratio and the MMSE, independent of HbA_{1c}, HOMA2-IR, estimated glomerular filtration rate, duration of diabetes, depression, cardiovascular risk factors, macrovascular disease, microvascular complications, and diabetic foot. For the proinsulin–to–C-peptide ratio, a significant interaction with sex ($P = 0.01$) was observed. For other insulin-related measures (Table 1) and for the attention and executive functioning score (data on file), no significant (linear or nonlinear) associations were observed.

This large cross-sectional study in patients with type 2 diabetes shows a bell-shaped association between HbA_{1c} and cognitive function, with modifying effects of age and sex, with those over the age of 70 years and women being

more vulnerable. Although a causal relationship between HbA_{1c} and cognitive function cannot be inferred by these cross-sectional observations, they add to an emerging literature indicating that in older individuals, particularly, both tight and loose glycemic control may adversely affect cognition (1). This issue clearly needs further investigation. The lack of association between cognitive performance and C-peptide and the HOMA2 indices are congruent with recent studies in patients with type 2 diabetes (4). The negative linear association between elevated proinsulin and cognitive function could involve a direct effect of proinsulin on cardiovascular risk (5). Another explanation for this finding could be that proinsulin and the proinsulin–to–C-peptide ratio are more suitable markers of β-cell function in people with type 2 diabetes, particularly because proinsulin secreted by the β-cells increases further as diabetes progresses, whereas C-peptide and insulin levels decrease when β-cells get exhausted.

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