# A1C Is Associated With Intima-Media Thickness in Individuals With Normal Glucose Tolerance

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**OBJECTIVE** — One-hour glucose during an oral glucose tolerance test (OGTT) was recently proposed as a valuable marker to identify individuals with normal glucose tolerance (NGT) and increased intima-media thickness (IMT). However, central markers of glycemic control were not considered. The aim of this study was to identify which marker of glycemic control is most informative with respect to the variation of IMT in individuals with NGT.

**RESEARCH DESIGN AND METHODS** — Cardiovascular risk factors, glucose metabolism (OGTT), and IMT were determined in 1,219 nondiabetic individuals (851 women, 368 men; 558 with NGT).

**RESULTS** — One-hour glucose and A1C levels were significantly correlated to carotid IMT in individuals with NGT, whereas fasting and 2-h glucose levels were not informative. Only A1C was associated with IMT independent of other confounders, whereas 1-h glucose was not informative. Comparable results were found in the total cohort, including individuals with IFG and IGT.

**CONCLUSIONS** — A1C was the most informative glycemic marker with respect to IMT in individuals with NGT.

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Recent studies aimed to describe markers of glycemic control predicting diabetes risk or increased intima media thickness (IMT) in individuals with normal glucose tolerance (NGT) (1–3). Remarkably, 1-h glucose was independently associated with diabetes risk and cross-sectionally with IMT. However, established markers of glycemic control such as A1C were partially not considered (3). Thus, it is unclear whether 1-h glucose, which requires an oral glucose tolerance test (OGTT), is more informative than A1C. Finally, the value of 1-h glucose in individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) is unclear, although a cardiovascular risk marker should work in individuals with NGT, IFG, or IGT.

## RESEARCH DESIGN AND METHODS

— A total of 1,219 nondiabetic individuals (851 women, 368 men) of the MeSy BePo study (Metabolic Syndrome Berlin Potsdam) were analyzed. Details of phenotyping were described previously (4). Mean age of the cohort was 51 ± 0.4 years, BMI 28.8 ± 0.1 kg/m$^2$, waist 94 ± 0.4 cm, and systolic and diastolic blood pressure 123 ± 0.4 and 77 ± 0.3 mmHg, respectively. A total of 126 individuals were smoking. Glucose metabolism was categorized according to American Diabetes Association criteria by one 75-g OGTT. There were 558 participants who had NGT, 409 had IFG, 78 had IGT, and 174 had IFG and IGT. Mean fasting glucose was 89 ± 0.3 mg/dl (NGT: 83 ± 0.2 mg/dl, IFG: 96 ± 0.3 mg/dl, IGT: 83 ± 0.5 mg/dl, IFG + IGT: 98 ± 0.4 mg/dl), 1-h glucose was 162 ± 1 mg/dl (NGT: 144 ± 1 mg/dl, IFG: 165 ± 2 mg/dl, IGT: 175 ± 1 mg/dl, IFG + IGT: 200 ± 3 mg/dl), 2-h glucose was 121 ± 0.7 mg/dl (NGT: 108 ± 1 mg/dl, IFG: 115 ± 1 mg/dl, IGT: 154 ± 1 mg/dl, IFG + IGT: 159 ± 1 mg/dl), and A1C was 5.3 ± 0.01% (NGT: 5.2 ± 0.02%, IFG: 5.4 ± 0.02%, IGT: 5.4 ± 0.04%, IFG + IGT: 5.5 ± 0.03%).

IMT was measured at both carotid arteries. Patients were examined in the supine position with the head tilted backwards using a high-resolution ultrasound (Kretz Voluson 730; Kretz Technik, Marl, Germany). Carotid arterial IMT was measured at the posterior wall of the common carotid artery ($IMT_{ACC}$) and the bulbus ($IMT_{Bulbus}$) at three different positions. Mean values of those measurements were calculated. $IMT_{Total}$ was calculated as the mean value of $IMT_{ACC}$ and $IMT_{Bulbus}$. Mean $IMT_{ACC}$ was 0.632 ± 0.004 mm (NGT: 0.619 ± 0.006 mm, IFG: 0.634 ± 0.007 mm, IGT: 0.661 ± 0.017 mm, IFG + IGT: 0.655 ± 0.011 mm), $IMT_{Bulbus}$ 0.729 ± 0.005 mm (NGT: 0.710 ± 0.007 mm, IFG: 0.732 ± 0.008 mm, IGT: 0.765 ± 0.024 mm, IFG + IGT: 0.766 ± 0.013 mm), and $IMT_{Total}$ 0.679 ± 0.004 mm (NGT: 0.664 ± 0.006 mm, IFG: 0.681 ± 0.007 mm, IGT: 0.711 ± 0.018 mm, IFG + IGT: 0.707 ± 0.010 mm).

The experimental protocol of the study was approved by the institutional review board, and all subjects gave written informed consent.

After sampling in ETDA tubes, blood was immediately chilled on ice, centrifuged, and aliquots were immediately frozen at −80°C. Blood samples were analyzed for glucose, insulin, cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and creatinine by standard methods. A1C was measured by high-performance liquid chromatography (Menarini, Italy).

Statistical calculations were performed using SPSS 17.0 (SPSS, Chicago, IL). Skewed data were transformed by natural logarithm. Pearson correlations were calculated to analyze crude relations. Multivariate linear regression models were

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**Table 1 —*Multivariate linear regression models for $IMT_{ACC}$, $IMT_{Bulbus}$, and $IMT_{Total}$ in individuals with NGT, respectively***

| | Correlation | Standardized β | Correlation × standardized β × 100 (%) | *P* |
|---|---|---|---|---|
| $IMT_{ACC}$ | | | | |
| A1C | 0.313 | 0.139 | 4.4 | 0.002 |
| 1-h glucose | 0.022 | 0.129 | — | 0.62 |
| $IMT_{Bulbus}$ | | | | |
| A1C | 0.238 | 0.041 | — | 0.35 |
| 1-h glucose | 0.149 | 0.013 | — | 0.76 |
| $IMT_{Total}$ | | | | |
| A1C | 0.288 | 0.09 | 2.6 | 0.037 |
| 1-h glucose | 0.153 | 0.013 | — | 0.753 |

Results for A1C or 1-h glucose (after adjustment for age, sex, smoking, waist, HDL/total cholesterol ratio, and systolic blood pressure, respectively) are presented. The multiplicative term (correlation × standardized β × 100) explains the variation of IMT explained by the respective parameter in percent.

calculated to identify independent relations between potential risk factors and variation of IMT. An α-error <5% was considered to be statistically significant.

**RESULTS** — The 1-h glucose correlated moderately with IMT in individuals with NGT ($IMT_{ACC}$: $r = 0.136$, $P = 0.002$; $IMT_{Bulbus}$: $r = 0.172$, $P < 0.001$; $IMT_{Total}$: $r = 0.166$, $P < 0.001$). A stronger correlation was found between A1C and IMT in this group with NGT ($IMT_{ACC}$: $r = 0.310$, $P < 0.001$; $IMT_{Bulbus}$: $r = 0.238$, $P < 0.001$; $IMT_{Total}$: $r = 0.286$, $P < 0.001$). No relation was found between IMT and fasting glucose, 2-h glucose, or fasting insulin. Multivariate analysis within individuals with NGT revealed that only A1C was independently associated with IMT after adjustment for age, sex, waist, smoking, systolic blood pressure, and HDL/total cholesterol. A1C contributed 4.4% to the variation of IMT. In contrast, 1-h glucose was not further informative (Table 1).

Comparable results were found in the total cohort, which also included individuals with IFG and IGT. Correlations within the crude analysis were comparable to the results in individuals with NGT (data not shown). Again, only A1C was independently associated with $IMT_{ACC}$ and $IMT_{Total}$ ($P = 0.005$ and 0.032, respectively), although only a rather small proportion (2.3%) of the IMT variation was explained. The 1-h glucose was not independently associated with IMT. Additional risk markers, which were significantly associated with IMT, were age, systolic blood pressure, smoking, and the HDL/total cholesterol ratio, depending on the model calculated. In total, the investigated risk markers explained up to 26% of the variation of IMT. None of the correlations were indicative for a threshold in the relation between IMT and 1-h glucose or A1C.

**CONCLUSIONS** — Numerous studies suggested that individuals with diabetes or IGT have an increased cardiovascular risk (5,6). The relation between markers of glucose metabolism and IMT in individuals with NGT is less clear. Recently, 1-h glucose was associated with increased IMT (3). The authors proposed a cutoff value for 1-h glucose of 155 mg/dl, which was suggested to be of additive information to identify individuals with NGT and increased IMT. The results of the study presented here do not support those findings. Although the crude analysis revealed moderate correlations between 1-h glucose and IMT, this relation was not confirmed after adjustment for established cardiovascular risk factors. However, A1C was more strongly correlated to IMT than 1-h glucose and was the only marker that was independently associated with IMT in individuals with NGT. Nevertheless, the informative value of A1C was also limited by explaining only ~4% of the variation of IMT. Therefore, even A1C is not helpful in the identification of individuals with NGT and increased IMT. In previous reports, some risk factors were more strongly correlated to $IMT_{ACC}$, whereas others related stronger to $IMT_{Bulbus}$ (7). Interestingly, crude correlation between A1C and $IMT_{ACC}$ tended to be stronger than that with $IMT_{Bulbus}$. In some contrast, 1-h glucose was slightly more strongly related to $IMT_{Bulbus}$. However, whether this observation has physiological relevance is unclear, and our study was not designed to address this topic.

We conclude that A1C was the most informative glycemic marker with respect to IMT in individuals with NGT. In general, this independent relation of A1C to IMT suggests that glycemic control might have a pathophysiological relevance in the development of atherosclerosis, even in individuals with NGT.

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**References**

1. Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA, Groop L. Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. Diabetes Care 2009; 32:281–286
2. Abdul-Ghani MA, Abdul-Ghani T, Ali N, DeFronzo RA. One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. Diabetes Care 2008;31:1650–1655
3. Succurro E, Marini MA, Arturi F, Grembiale A, Lugara M, Andreozzi F, Sciacqua A, Lauro R, Hribal ML, Perticone F, Sesti G. Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. Atherosclerosis 2009;207:245–249
4. Fischer A, Fisher E, Möhlig M, Schulze M, Hoffmann K, Weickert MO, Schueler R, Osterhoff M, Pfeiffer AF, Boeing H, Spranger J. KCNJ11 E23K affects diabetes risk and is associated with the disposition index: results of two independent German cohorts. Diabetes Care 2008;31:87–89
5. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233–240
6. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397–405
7. Mackinnon AD, Jerrard-Dunne P, Sitzer M, Buehler A, von Kegler S, Markus HS. Rates and determinants of site-specific progression of carotid artery intima-media thickness: the carotid atherosclerosis progression study. Stroke 2004;35:2150–2154