HbA1c is associated with intima media thickness in individuals with normal glucose tolerance

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Introduction: 1h-glucose during an oral glucose tolerance test (oGTT) was recently proposed as a valuable marker to identify normal glucose tolerant individuals (NGT) with increased intima media thickness (IMT). However, central markers of glycemic control were not considered, thus it is still unclear, 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 1219 non-diabetic individuals (f=851, m=368; 558 NGT).

Results: 1h-glucose and HbA1c were significantly correlated to carotid IMT in individuals with NGT, while fasting and 2h-glucose were not informative. Only HbA1c was associated with IMT independent of other confounders, while 1h-glucose was not informative. Comparable results were found in the total cohort including individuals with IFG and IGT.

Conclusions: HbA1c was the most informative glycemic marker with respect to IMT in individuals with NGT.
Recent studies aimed to describe markers of glycemic control predicting diabetes risk or increased IMT in individuals with normal glucose tolerance (NGT) (1-3). Remarkably, 1h-glucose was independently associated with diabetes risk and cross-sectionally with IMT. However, established markers of glycemic control such as HbA1c were partially not considered (3). Thus, it is unclear whether 1h-glucose, which requires an oGTT, is more informative than HbA1c. Finally, the value of 1h-glucose in individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) is unclear, although a cardiovascular risk marker should work in persons with NGT, IFG or IGT.

RESEARCH DESIGN AND METHODS: 1219 non-diabetic individuals (f=851, m=368) of the MeSy Bepo study (Metabolic Syndrom 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, waist 94±0.4cm, systolic and diastolic blood pressure 123±0.4 and 77±0.3mmHg, respectively. 126 individuals were smoking. Glucose metabolism was categorized according to ADA criteria by one 75g oGTT. 558 participants had NGT, 409 IFG, 78 IGT and 174 had IFG and IGT. Mean fasting glucose was 89±0.3mg/dl (NGT: 83±0.2mg/dl, IFG: 96±0.3mg/dl, IGT: 83±0.5mg/dl, IFG+IGT: 98±0.4mg/dl), 1 hour glucose 162±1mg/dl (NGT: 144±1mg/dl, IFG: 165±2mg/dl, IGT: 175±1mg/dl, IFG+IGT: 200±3mg/dl), 2 hour glucose was 121±0.7mg/dl (NGT: 108±1mg/dl, IFG: 115±1mg/dl, IGT: 154±1mg/dl, IFG+IGT: 159±1mg/dl) and HbA1c 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 AG, 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±0.004mm (NGT: 0.619±0.006mm, IFG: 0.634±0.007mm, IGT: 0.661±0.017mm, IFG+IGT: 0.655±0.011mm), IMT_Bulbus 0.729±0.005mm (NGT: 0.710±0.007mm, IFG: 0.732±0.008mm, IGT: 0.765±0.024mm, IFG+IGT: 0.766±0.013mm) and IMT_Total 0.679±0.004mm (NGT: 0.664±0.006mm, IFG: 0.681±0.007mm, IGT: 0.711±0.018mm, IFG+IGT: 0.707±0.010mm).

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 (TG) and creatinine by standard methods. HbA1c was measured by HPLC (Menarini, Italy).

Statistical calculations were performed using SPSS 17.0 (Chicago, USA). Skewed data were transformed by natural logarithm. Pearson correlations were calculated to analyse crude relations. Multivariate linear regression models were calculated to identify independent relations between potential risk factors and variation of IMT. An alpha-error below 5% was considered to be statistically significant.

RESULTS: 1h-glucose correlated moderately with IMT in individuals with NGT (IMT_ACC:
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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 HbA1c 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, 2h-glucose or fasting insulin. Multivariate analysis within individuals with NGT revealed that only HbA1c was independently associated with IMT after adjustment for age, sex, waist, smoking, systolic blood pressure and HDL/Total Cholesterol. HbA1c contributed 4.4% to the variation of IMT. In contrast, 1h-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 HbA1c was independently associated with IMT after adjustment for age, sex, waist, smoking, systolic blood pressure and HDL/Total Cholesterol. HbA1c contributed 4.4% to the variation of IMT. In contrast, 1h-glucose was not further informative (Table 1).

CONCLUSIONS:
Numerous studies suggested that individuals with diabetes mellitus 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 1h-glucose was associated with increased IMT (3). The authors proposed a cut-off value for 1h-glucose of 155mg/dl, which was suggested to be of additive information to identify individuals with NGT and increased IMT. The results of the here presented study do not support those findings. While the crude analysis revealed moderate correlations between 1h-glucose and IMT, this relation was not confirmed after adjustment for established cardiovascular risk factors. However, HbA1c was stronger correlated to IMT than 1h-glucose and was the only markers which was independently associated with IMT in individuals with NGT. Nevertheless the informative value of HbA1c was also limited by explaining only about 4% of the variation of IMT. Therefore even HbA1c 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, while others related stronger to IMT_Bulbus (7). Interestingly crude correlation between HbA1c and IMT_ACC tended to be stronger than that with IMT_Bulbus. In some contrast, 1h-glucose was slightly stronger 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 HbA1c was the most informative glycemic marker with respect to IMT in individuals with NGT. In general this independent relation of HbA1c to IMT suggests that glycemic control might have a pathophysiological relevance in the development of atherosclerosis even in individuals with NGT.

ACKNOWLEDGMENT
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REFERENCES
Table 1: Multivariate linear regression models for IMT$_{\text{ACC}}$, Bulbus and Total in persons with NGT, respectively. Results for HbA1c or 1h-glucose (after adjustment for age, sex, smoking, waist, HDL/Total cholesterol ratio and systolic blood pressure, respectively) are presented. The multiplicative term (Correlation x Standardized $\beta$ x100) explains the variation of IMT explained by the respective parameter in percent.

<table>
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<tr>
<th>Parameter</th>
<th>Correlation</th>
<th>Standardized $\beta$</th>
<th>Correlation x Standardized $\beta$ x100 (%)</th>
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