Overall Quality of Care Predicts the Variability of Key Risk Factors for Complications in Type 2 Diabetes: An Observational, Longitudinal Retrospective Study

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OBJECTIVE

An association between variability in clinical parameters (HbA_{1c}, blood pressure, cholesterol, and uric acid) and risk of complications in type 2 diabetes has been reported. In this analysis, we investigated to what extent such variability is associated with overall quality of care.

RESEARCH DESIGN AND METHODS

The quality of care summary score (Q-score) represents a validated, overall quality of care indicator ranging between 0 and 40; the higher the score, the better the quality of care provided by the diabetes center. We identified patients with five or more measurements of clinical parameters after the assessment of the Q-score. Multiple linear regression analyses assessed the role of the Q-score in predicting the variability of the different parameters.

RESULTS

Overall, 273,888 patients were analyzed. The variability of all the parameters systematically increased with decreasing Q-score values. At multivariate linear regression analysis, compared with a Q-score >25, a score <15 was associated with a significantly larger variation in HbA_{1c}, blood pressure, uric acid, total cholesterol, and LDL cholesterol and a lower variation in HDL cholesterol. The analysis of standardized β coefficients show that the Q-score has a larger impact on the variability of HbA_{1c} (0.34; $P < 0.0001$), systolic blood pressure (0.21; $P < 0.0001$), total cholesterol (0.21; $P < 0.0001$), and LDL cholesterol (0.20; $P < 0.0001$).

CONCLUSIONS

The variability of risk factors for diabetic complications is associated with quality of care. Quality of care improvement initiatives should be targeted to increase the achievement of the recommended target while reducing such variability.

In Italy, a continuous improvement effort implemented by a network of diabetes clinics, i.e., AMD (Associazone Medici Diabetologi) Annals, has been in place since 2006 (1,2). After 8 years from the launch of the initiative, half of the diabetes clinics in Italy participated in the AMD-Annals initiative, caring for over one-sixth of all diagnosed patients. Process and intermediate outcome measures consistently improved, in parallel with a more intensive and appropriate use of pharmacologic treatments (3).

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Among the indicators included in AMD-Annals reports, a quality of care summary score (Q-score) is calculated. The Q-score has been developed and validated in two previous studies (4,5) and integrated in the AMD-Annals initiative since the 2009 edition (3). The score is based on a combination of process and outcome indicators relative to HbA_{1c}, blood pressure, LDL cholesterol, and microalbuminuria. The score ranges between 0 and 40, with a higher score indicating better quality of care (Fig. 1). In the two previous studies (4,5), the Q-score was closely related to long-term outcomes. In fact, the risk of developing a new cardiovascular event was 80% higher in patients with a score <15 and 20% higher in those with a score between 15 and 25, as compared with those with a score >25.

Recently, much attention has been paid to the possibility that a variability in time of blood glucose (HbA_{1c}, fasting, and postprandial hyperglycemia) (6), blood pressure (7), lipids (8,9), uric acid (10), and body weight (11) may be a risk factor for the development of complications in subjects with or without diabetes.

The mechanisms underlying these findings are, at the moment, largely speculative. It should be argued that when these factors vary over time, they could favor an increase in oxidative stress, either increasing the generation of free radicals (glucose, blood pressure, plasma cholesterol, and uric acid) (6,12,13) or decreasing the defense against them (HDL) (14).

The reasons for intraindividual variability in different clinical parameters are largely unknown. Nevertheless, such variability could reflect at least partially the quality/efficacy of treatments used. Following this hypothesis, the aim of the present analysis was to evaluate whether overall quality of care at baseline, as summarized by the Q-score, was able to predict the variability of HbA_{1c}, blood pressure, serum uric acid, and lipid profile in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This was an observational, longitudinal retrospective study. The data were derived from the AMD-Annals initiative, i.e., from electronic medical records of all patients attending 300 diabetes clinics between 2005 and 2011 (3). The database contains information on over 1,000,000 patients with type 2 diabetes with at least one visit during the years at the participating centers.

Data relative to the 1st year of observation for each patient were considered for the calculation of the Q-score (baseline). Baseline values of the different parameters were represented by the last value recorded during the 1st year of observation of each patient. Baseline descriptive variables included age, sex, duration of diabetes, smoking, weight, BMI, HbA_{1c}, blood pressure, serum uric acid, lipid profile, estimated glomerular filtration rate (eGFR; Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), albuminuria, diabetes treatment scheme, antihypertensive treatment, lipid-lowering treatment, and aspirin.

To ensure a robust estimate of variability, we identified those subjects having at least five measurements of HbA_{1c}, systolic and diastolic blood pressure, serum uric acid, total cholesterol, HDL cholesterol, LDL cholesterol, and/or triglycerides in the years after the baseline. The availability of a minimum of five measures for each parameter after the baseline in each patient was required in the selection procedure to ensure a robust estimate of variability (Fig. 2).

No patients were asked for input in the creation of this article. The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

Statistical Methods

Patients were grouped according to the Q-score values (<15, 15–25, and >25). Descriptive data are summarized as mean and SD for continuous variables and percentages for categorical variables and compared among the three groups through Kruskal-Wallis one-way ANOVA test.

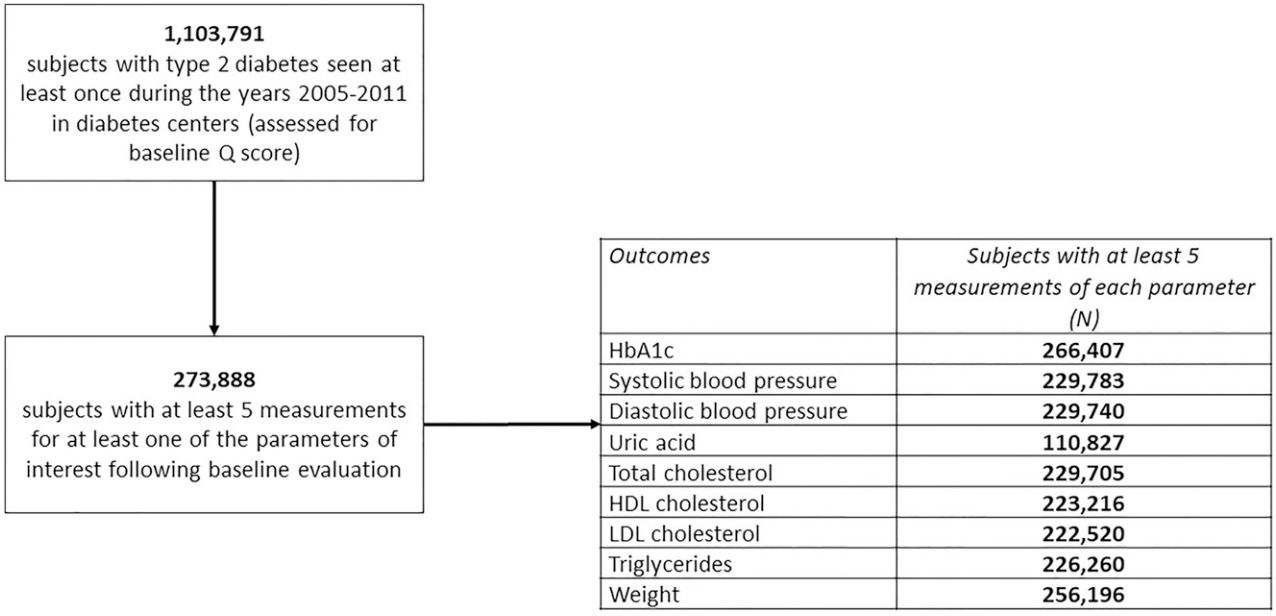
Variability of HbA_{1c}, systolic and diastolic blood pressure, uric acid, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides was expressed as the SD of the measures during the follow-up. Variability in the three groups was compared through Kruskal-Wallis one-way ANOVA test.

Multiple linear regression analyses were performed to evaluate the role of the Q-score in predicting the variability of the different parameters. Each measure of variability was tested as a dependent variable in a separate regression model adjusted for age, sex, and diabetes duration. Results of the linear regression models are expressed as β parameters along with their associated *P* value. To assess which measures of variability the Q-score had a greater effect on, standardized β coefficients were also calculated. Since greater variability can be associated with larger baseline values of the parameters of interest, additional

Quality of care indicator	Scoring
HbA_{1c} measurement <1/year	5
HbA_{1c} ≥8.0%	0
HbA_{1c} <8.0%	10
Blood pressure measurement <1/year	5
Blood pressure values ≥140/90 mmHg, irrespective of treatment	0
Blood pressure values <140/90 mmHg	10
Lipid profile measurement <1/year	5
LDL cholesterol ≥3.37 mmol/L (130 mg/dL) irrespective of treatment	0
LDL cholesterol <3.37 mmol/L (130 mg/dL)	10
Microalbuminuria (MA) measurement <1/year	5
Not treated with ACE-inhibitors despite the presence of MA	0
Treated with ACE-inhibitors in the presence of MA or MA absent	10
Score range	**0-40**

- ✓ Q score is based on a combination of process and outcome indicators relative to HbA1c, blood pressure, LDL-cholesterol and microalbuminuria.
- ✓ The score ranges between 0 and 40; the higher the score, the better the overall quality of care provided.
- ✓ Two previous studies (Nutr Metab Cardiovasc Dis 2008; 18:57–65; Diabetes Care 2011; 34:347–352) documented that the risk to develop a new cardiovascular event was 80% higher in patients with a score <15 and 20% higher in those with a score between 15 and 25, as compared to those with a score >25.
- ✓ Q score is an integral part of the AMD Annals indicators (Acta Diabetol 2015; 52:557-71).

Figure 1—The Q-score.



Outcomes	*Subjects with at least 5 measurements of each parameter (N)*
HbA1c	**266,407**
Systolic blood pressure	**229,783**
Diastolic blood pressure	**229,740**
Uric acid	**110,827**
Total cholesterol	**229,705**
HDL cholesterol	**223,216**
LDL cholesterol	**222,520**
Triglycerides	**226,260**
Weight	**256,196**

Figure 2—Study flow chart.

regression models were performed, including the baseline value of the parameter of interest in the model. Finally, to take the hierarchical nature of the data into account (patients clustered within centers), a multilevel model was also applied and the intracluster correlation (ICC) was calculated.

Tests were two sided, and a *P* value <0.05 was considered statistically significant. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Overall, 273,888 patients with type 2 diabetes cared for by 300 diabetes clinics were included in the cohort (Fig. 2). Baseline characteristics according to the three Q-score classes are reported in Table 1. A low Q-Score was associated with slightly older age, higher prevalence of female sex, longer diabetes duration, and poorer control of all the parameters investigated, with the only exception of GFR.

Patients were followed up for an average of 2.5 ± 0.9 years. Mean values and SDs of the different parameters of interest according to Q-score classes are reported in Table 2. The average value and the variability of all the parameters investigated systematically increased with decreasing Q-score values.

At multivariate linear regression analysis, the Q-score was an independent predictor of the variability of all the parameters considered (Table 3). In fact, compared with a Q-score >25, a score <15 was associated with a significantly larger variation in HbA_{1c}, blood pressure, uric acid, total cholesterol, and LDL cholesterol and a lower variation in HDL cholesterol. Furthermore, compared with a Q-score >25, also having a Q-score between 15 and 25 was associated with a significantly larger variation in HbA_{1c}, systolic blood pressure, uric acid, total cholesterol, and LDL cholesterol.

The analysis of standardized β coefficients show that the Q-score has a larger impact on the variability of HbA_{1c}, systolic blood pressure, total cholesterol, and LDL cholesterol (Table 3).

When baseline values of the parameters of interest were included as covariates in the multivariate models, standardized β coefficients decreased, but the association between poorer quality of care and higher variability remained highly statistically significant for all the parameters considered, with the only exception of triglycerides (Table 3). Finally, taking the clustered nature of the data into account did not substantially modify study results. All ICC values were largely <0.20, suggesting a modest center effect (Table 3).

CONCLUSIONS

Our data show that the higher the overall quality of care as expressed by the Q-score, the lower the variability in the key clinical parameters for diabetes care, i.e., HbA_{1c}, blood pressure, lipid profile, uric acid, and weight. These new data show that the variability in HbA_{1c} levels, systolic blood pressure levels, and total and LDL cholesterol levels is particularly influenced by a Q-score <15 and to a lesser extent by a Q-score between 15 and 25.

The interaction between glucose variability/blood pressure/lipids variability in favoring the appearance of diabetic complications, as well as the relationship between glucose variability and major outcomes, has been documented in an increasing number of studies in the recent years (6–11). Evidence linking glucose variability to adverse consequences in hospitalized people without diabetes is also available and noteworthy (6,15,16).

As previously mentioned, in terms of physio-pathological mechanisms, a huge body of experimental studies, both in vitro and in vivo, suggests that variability in glucose, blood pressure, and uric acid levels favors an increase in oxidative stress, increasing the generation of free radicals (6,12,13,17,18); other mechanisms as possible triggers of diabetes complications deserve consideration (19–22). On the other hand, in glucose-oscillating conditions, the intracellular antioxidant system seems to be less effective (23), and the protective antioxidant action of HDL cholesterol seems reduced if its levels are suboptimal

Table 1—Baseline patient characteristics according to Q-score classes

Characteristics	Q-score <15	Q-score 15–25	Q-score >25	*P* value
n (%)	32,868 (12.0)	211,506 (77.2)	29,514 (10.8)	
Age (years)	67.3 ± 10.1	67.0 ± 10.4	66.6 ± 10.4	<0.0001
Male sex (%)	50.4	54.6	57.4	<0.0001
Duration of diabetes (years)	11.9 ± 9.1	10.2 ± 8.9	9.3 ± 8.4	<0.0001
Smoking (%)	5.8	5.7	4.9	<0.0001
Weight (kg)	80.8 ± 16.2	79.5 ± 15.6	78.0 ± 14.8	<0.0001
BMI (kg/m^2)	30.2 ± 5.3	29.6 ± 5.1	28.9 ± 4.9	<0.0001
HbA_{1c} (%)	8.0 ± 1.4	7.3 ± 1.3	6.9 ± 1.0	<0.0001
HbA_{1c} (mmol/mol)	64 ± 15.3	56 ± 14.2	52 ± 10.9	<0.0001
Systolic blood pressure (mmHg)	143.8 ± 19.1	139.9 ± 18.7	133.7 ± 17.0	<0.0001
Diastolic blood pressure (mmHg)	80.5 ± 9.8	79.5 ± 9.6	77.5 ± 8.9	<0.0001
Uric acid (mg/dL)	5.3 ± 1.1	5.4 ± 1.0	5.4 ± 1.0	<0.0001
Total cholesterol (mg/dL)	193.2 ± 40.3	184.9 ± 38.1	177.2 ± 34.0	<0.0001
HDL cholesterol (mg/dL)	50.4 ± 13.4	50.2 ± 13.6	50.4 ± 13.8	0.006
LDL cholesterol (mg/dL)	115.4 ± 34.9	107.7 ± 32.8	101.1 ± 28.9	<0.0001
Triglycerides (mg/dL)	144.8 ± 94.7	140.9 ± 91.6	132.3 ± 76.6	<0.0001
eGFR (mL/min*1.73 m^2)	75.9 ± 20.4	75.6 ± 20.5	76.0 ± 20.0	0.002
Albuminuria (%)	38.3	34.3	29.2	<0.0001
Antihypertensive treatment (%)	47.3	43.1	41.6	<0.0001
ACE inhibitors and/or ARBs (%)	41.1	36.5	34.5	<0.0001
Lipid-lowering treatment (%)	32.1	29.3	31.7	<0.0001
Aspirin (%)	22.2	20.7	21.7	<0.0001
Diabetes treatment scheme (%)				
Diet	2.6	8.4	10.5	<0.0001
Oral agents	53.5	62.4	70.1	
Oral agents + insulin	24.8	14.4	8.4	
Insulin	19.0	14.8	11.0	

Data are expressed as percentage (%) or mean ± SD. ARB, angiotensin receptor blocker.

and unstable over time (14). These are the possible reasons why variability in these parameters can be considered the key pathogenic factor for diabetic complications and also a cardiovascular risk factor (24,25).

To the best of our knowledge, this is the first study assessing the relationship between quality of care and variability in risk factors for complications. It remains to be established by which mechanisms poor quality of care can increase the risk of variability in such a large array of different parameters. A low Q-score, which is mainly driven by the difficulty in reaching satisfactory HbA_{1c}, blood pressure, and lipid levels, can reflect poor patient compliance to medical recommendations, as well as clinical inertia, with a substantial delay in the intensification of treatment. These factors can be responsible for elevated baseline levels of the different parameters, as well as their intraindividual variability over time.

Table 2—Mean values and variability (SD) of clinical parameters during the follow-up by baseline Q-score classes

Parameters	Q-score <15	Q-score 15–25	Q-score >25	*P* value*
HbA_{1c} (%)	8.0 ± 0.7	7.4 ± 0.6	7.1 ± 0.5	<0.0001
HbA_{1c} (mmol/mol)	64 ± 7.7	57 ± 6.6	54 ± 5.5	<0.0001
Systolic blood pressure (mmHg)	141.6 ± 12.9	138.4 ± 12.2	133.9 ± 11.4	<0.0001
Diastolic blood pressure (mmHg)	78.8 ± 6.7	78.2 ± 6.4	76.8 ± 6.3	<0.0001
Uric acid (mg/dL)	5.5 ± 0.7	5.5 ± 0.7	5.4 ± 0.6	<0.0001
Total cholesterol (mg/dL)	184.3 ± 21.6	178.9 ± 19.9	173.7 ± 18.5	<0.0001
HDL cholesterol (mg/dL)	49.8 ± 5.1	49.8 ± 5.1	50.1 ± 5.1	0.003
LDL cholesterol (mg/dL)	107.0 ± 18.5	102.4 ± 17.1	98.0 ± 15.9	<0.0001
Triglycerides (mg/dL)	140.2 ± 34.9	137.7 ± 34.6	131.5 ± 32.9	<0.0001
Weight (kg)	80.7 ± 2.3	79.3 ± 2.2	77.6 ± 2.1	<0.0001

Data are mean ± SD. *Kruskal-Wallis one-way ANOVA.

In terms of implications for clinical practice, these findings suggest that variability in the clinical parameters can derive from poor quality of care or poor compliance with medical recommendations; therefore, any effort should be devoted to keeping the parameters constantly within ranges recommended by guidelines over time, with timely therapy intensification whenever needed. Our data also suggest the need to focus on stabilizing not only HbA_{1c} levels but all relevant parameters in order to reduce the risk of long-term complications.

Our study has limitations. First, information on medication adherence was not available. Adherence could at least partially explain the relationship between diabetes care quality and variability in risk factors. Second, the study population was selected based on the availability of at least five measurements during follow-up for each of the parameters of interest. In other words, the study population possibly represents a "compliant" patient group. Patients with low Q-scores (due to less than five measurements during follow-up, probably related to less or no measurements in the baseline year) had a higher chance of being excluded. Nevertheless, despite this limitation, a clear association between poorer quality of care and higher variability of the different parameters was clearly documented in our study. Third, we only evaluated glycemic variability in terms of HbA_{1c} variability despite the evidence that many patients with similar levels of HbA_{1c} may have very different degrees of glycemic variability, as measured by continuous glucose monitoring. Glycemic variability covers two predominant categories of measurements: short-term glycemic variability, represented by both within-day and between-day glycemic variability, and long-term glycemic variability, usually

Table 3—Association between baseline Q-score and variability of clinical parameters during the follow-up

	Q-score <15			Q-score 15–25		
Characteristics	β*	Standardized β*	*P* value	β*	Standardized β*	*P* value
Model A						
HbA_{1c}	0.16	0.34	<0.0001	0.07	0.16	<0.0001
Systolic blood pressure	13.72	0.21	<0.0001	0.71	0.11	<0.0001
Diastolic blood pressure	0.38	0.10	<0.0001	0.13	0.03	<0.0001
Uric acid	0.04	0.06	<0.0001	0.02	0.03	0.001
Total cholesterol	30.37	0.21	<0.0001	13.89	0.10	<0.0001
HDL cholesterol	−0.15	−0.04	<0.0001	−0.05	−0.01	0.04
LDL cholesterol	25.50	0.20	<0.0001	11.40	0.09	<0.0001
Triglycerides	29.12	0.07	<0.0001	20.57	0.05	<0.0001
Weight	0.18	0.09	<0.0001	0.08	0.04	<0.0001
Model B						
HbA_{1c}	0.05	0.10	<0.0001	0.02	0.05	<0.0001
Systolic blood pressure	0.81	0.13	<0.0001	0.38	0.06	<0.0001
Diastolic blood pressure	0.32	0.09	<0.0001	0.10	0.03	<0.0001
Uric acid	0.04	0.07	<0.0001	0.02	0.03	0.004
Total cholesterol	1.58	0.11	<0.0001	0.04	0.62	<0.0001
HDL cholesterol	−0.12	−0.03	0.0001	−0.02	−0.01	0.39
LDL cholesterol	1.31	0.10	<0.0001	0.49	0.04	<0.0001
Triglycerides	−0.45	−0.01	0.18	−0.25	−0.01	0.34
Weight	0.06	0.03	0.0002	0.01	0.01	0.35
Model C						
HbA_{1c} (ICC: 0.05)	0.06	0.12	<0.0001	0.02	0.05	<0.0001
Systolic blood pressure (ICC: 0.10)	0.80	0.13	<0.0001	0.40	0.06	<0.0001
Diastolic blood pressure (ICC: 0.11)	0.24	0.07	<0.0001	0.09	0.02	0.0001
Uric acid (ICC: 0.02)	0.05	0.09	<0.0001	0.02	0.04	<0.0001
Total cholesterol (ICC: 0.01)	1.84	0.13	<0.0001	0.79	0.05	<0.0001
HDL cholesterol (ICC: 0.04)	0.00	0.00	0.93	0.04	0.01	0.09
LDL cholesterol (ICC: 0.01)	1.56	0.12	<0.0001	0.66	0.05	<0.0001
Triglycerides (ICC: 0.00)	−0.47	−0.01	0.17	−0.18	0.00	0.50
Weight (ICC: 0.01)	0.05	0.03	0.001	0.01	0.01	0.06

The results are from multiple regression analyses. Model A was adjusted for age, sex, and diabetes duration; model B was adjusted for age, sex, diabetes duration, and baseline value of the single parameter; and model C was adjusted for age, sex, diabetes duration, baseline value of the single parameter, and clustering. *Reference class: Q-score >25.

involving HbA_{1c}. However, it should be noted that measures of short-term variability are impossible to obtain in very large numbers of patients with type 2 diabetes followed for a long period of time. For this reason, we focused on long-term glycemic variability, based on serial determinations of HbA_{1c} over a long period of time.

Finally, the results regarding the variability of the risk parameters were all highly statistically significant due to the high numbers of patients and measurements. Additional research is needed to explain the meaning of these levels of variability and their clinical relevance.

In conclusion, the AMD-Annals database documented for the first time that intraindividual variability in risk factors can be at least partially related to the quality of care provided by centers. These data suggest that parameter variability could represent additional quality indicators, in the light of the mounting body of evidence linking variability of risk factors to long-term diabetes complications.

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