Factors Related to Glycemic Control in IDDM and Insulin-Treated NIDDM Patients in Current Practice

A comparison of care policies

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OBJECTIVE — To evaluate, under routine conditions, the relation between different diabetes care policies and glycemic control through a by-center analysis procedure aimed at reducing some drawbacks of cross-sectional data.

RESEARCH DESIGN AND METHODS — A survey on insulin-treated diabetes care management (IDDM and NIDDM) involved 16 Italian randomly selected diabetes outpatient clinics. A total of 2,142 representative patients were investigated. The standardized HbA_{1c} average value of each center was related, by regression models, to some indicators of center care policy (average number of injections, average BMI, proportion of cases with recent fundus oculi examinations, or frequent visits) as well as to patients' average social levels (employment type). Homogeneity in patient admission criteria is assumed among the investigated centers as a basic condition for the procedure validity. Some known imbalances were controlled for both design and analysis.

RESULTS — HbA_{1c} showed a univariate inverse relation with daily number of injections in IDDM ($P = 0.0009$, $r^2 = 0.56$) but not in NIDDM ($P = 0.33$). It was inversely related to both fundus examination (IDDM $P = 0.04$; NIDDM $P = 0.099$) and qualified employment (IDDM $P = 0.06$; NIDDM $P = 0.026$). A stepwise regression analysis left in the model insulin injections ($P = 0.0002$) in IDDM (total $r^2 = 0.68$) and qualified employment ($P = 0.016$) and fundus examination ($P = 0.14$) in NIDDM (total $r^2 = 0.53$), after controlling for age, sex, disease duration, insulin therapy starting delay, and insulin dose per kilogram.

CONCLUSIONS — These results suggest that the confirmed benefits of a multiple-injection regimen in IDDM cannot be simply extrapolated to NIDDM, where patients' awareness and medical attention to complications proved to be the most important factors in current practice.

The care of diabetes is often provided by specialized outpatient clinics all over the world. The recent Diabetes Control and Complications Trial (1) has shown the fundamental role of an optimal glycemic control obtained through an "intensive" insulin therapy in preventing complications in IDDM patients. Glycemic control has also been found to be associated with both micro- and macrovascular complications in NIDDM patients (2–4); however, in these subjects it is still not clear whether intensive insulin therapy represents the best choice to achieve optimal blood glucose control. For all of these reasons, there has been heightened interest in organizational and economic aspects in diabetes care all over the world, especially concerning glycemic control and its implications for health care policy (5–13). At present, a major concern in diabetes management is predicting the effect of implementing new care policies in current practice. In this regard, intervention trials are very informative, but they usually impose artificial conditions that are difficult to meet in practice. On the other hand, observational studies have limitations in the interpretation of their results because of the lack of information about the temporal events relationship. The procedure used here, based on by-group rather than by-subject analyses, can substantially reduce the basic drawback of cross-sectional studies.

This type of analysis can be applied in observational multicenter studies when patients' characteristics are basically homogeneous among the different areas and when there are some differences in disease management.

In Italy, most of the insulin-treated patients are taken in care by a large network of outpatient diabetes clinics. Despite numerous suggestions and guidelines from different scientific societies, a homogeneous strategy is not in practice for the management of diabetes among these centers. This, then, is an ideal situation for evaluating the association between specific therapeutic strategies and patients' average glycemic control.

More specifically, the aim of this study was to evaluate whether, in the usual diabetes care setting, an intensive insulin treatment is associated with improved blood glucose control in both IDDM and NIDDM patients. This is particularly relevant in NIDDM given the lack of reliable evidence on this aspect. An additional aim of this study was to identify other factors related to diabetes care and/or to the patient's social condition that might contribute to improve blood glucose control.

RESEARCH DESIGN AND METHODS

— This study is part of a large two-step project aimed at describing health and care characteristics of both

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Received for publication 26 March 1997 and accepted in revised form 18 July 1997.

Table 1—*Characteristics of the IDDM study population*

Investigated variables	Total population Mean ± SD	Total population % (*n*)	Centers' range (means or %)
Age (years)	35.8 ± 13.2	—	31.6–43.4
Men	—	58.8 (336)	—
Standardized HbA_{1c} (%)	7.9 ± 1.7	—	6.2–9.5
Disease duration (years)	14.8 ± 11.1	—	8.6–20.2
Insulin per kilogram (IU/kg)	0.63 ± 0.23	—	0.52–0.73
BMI (kg/m^2)	24.1 ± 3.2	—	22.8–24.9
Insulin injections/day (*n*)	3.0 ± 0.8	—	0.1–3.5
Intensive therapy (%)	—	74.8 (427)	15.6–100
Visits/year (*n*)	6.1 ± 4.2	—	3.7–10.9
More than six visits/year (%)	—	31.9 (179)	0–71.4
Fundus examination (%)	—	73.6 (422)	31.3–100
Qualified employment (%)	—	39.0 (198)	13.9–61.9

n = 533.

IDDM and insulin-treated NIDDM patients cared for by Italian diabetes outpatient clinics. This project involved 20 outpatient diabetes clinics randomly selected from all of those in Italy (14). The present study refers to the data collected from the first step of the survey. According to the study protocol, each center had to list, in a prenumbered form, all insulin-treated patients who had attended it at least once in the first semester of 1993. All patients who went on insulin therapy <1 year before this study, who were aged <13 years, or who were pregnant were excluded. One center left the study just after the patient selection phase due to personnel problems.

Clinical record-based information on patient characteristics, type of therapy, diabetes management, and glycemic control was requested for 200 cases/center selected by simple randomization. These data were collected through a standard questionnaire.

To standardize the HbA_{1c} values and perform a quality-control assessment, variability and repeatability of the HbA_{1c} determinations were evaluated among the centers' laboratories. The 19 center-related laboratories were tested twice through single-blind measurements in duplicate of standard blood samples from three subjects each time (one nondiabetic subject and two diabetic subjects—one in good control and one in poor control). These measurements were used to set up laboratory-specific calibration curves for standardizing single patients' responses. Three centers were excluded, one for inconsistency between the laboratory results at the two time points (significant difference between the two calibration curves, $P = 0.0046$) and two because of the large proportion (>80%) of cases with missing values for HbA_{1c} in the clinical records. This study finally involved 16 diabetes outpatient clinics for a total of 2,921 investigated patients (91% of the randomly selected ones). Of those clinics, two underwent only one of the two quality-control tests, and another showed a comparatively higher laboratory intra-assay variability (variation coefficient of 7.5% vs. 1.2%–3.7%). All the analyses have been repeated after exclusion of these centers.

All patients diagnosed at <35 years of age and treated with insulin therapy within 2 years of diagnosis were classified as IDDM patients; others were classified as NIDDM.

To improve homogeneity among the different centers, all the analyses were carried out by type of diabetes after excluding patients aged >79 years. Patients with end-stage renal failure, cirrhosis, or cancer were also excluded from the analyses.

Therefore, of 2,921 involved patients, 385 were excluded because of end-stage renal failure, cirrhosis, cancer, or age >79 years. Finally, a total of 573 IDDM and 1,963 NIDDM cases were studied. HbA_{1c} was available in the clinical records for 533 IDDM (93%) and 1,609 (82%) NIDDM patients.

For both types of diabetes, each center was characterized in terms of its average value of standardized HbA_{1c}, average values of the investigated parameters related to diabetes management strategies (number daily injections of insulin per patient, BMI, proportion of patients reporting more than 6 visits/year, and complications examinations), and patients' average social level (proportion of patients with present or preretirement qualified employment). These observed differences in management strategies were related to the average glycemic control through a "by-group" analysis. The rationale of this procedure is the same as an analogous multilevel analysis used in school performance evaluation (15).

The relationship between HbA_{1c} and the putative glycemic control–related factors was evaluated by univariate and stepwise multiple regression analyses (REG procedure of SAS 6.10 software) and weighted for the center number of available cases with HbA_{1c} measurement. Univariate significant ($P < 0.10$) variables as well as age, sex, disease duration, and insulin dose per kilogram have been considered in the stepwise model, as explanatory variables, for both types of diabetes. For NIDDM, the time elapsed between diagnosis and the beginning of insulin therapy was also taken into account to improve center homogeneity.

RESULTS — According to the procedure employed in this study for each parameter measured, the average value was calculated in every center, and each center was thereafter considered as an individual unit for subsequent analysis.

Tables 1 and 2 list all the parameters evaluated in this study according to the type of diabetes; for each of them, the average value for the population and the range of the means calculated within each center are also included.

Table 3 shows the weighted univariate relationship between HbA_{1c} and the investigated parameters according to type of diabetes. For IDDM, the average level of HbA_{1c} for each center was inversely related to the center's average number of daily injections of insulin per patient ($P = 0.0009$, $r^2 = 0.56$) and to the proportion of cases investigated for retinal complications during the previous year ($P = 0.04$). In addition, frequency of visits, the other variable related to medical attention to complications, was inversely, if not significantly, associated. Proportion of patients with qualified employment was almost significantly associated ($P = 0.059$). The NIDDM picture was somewhat different, with the number of injections not reaching statistical significance despite the larger sample size of this type of diabetes, and with only a nearly significant association with fundus examination ($P = 0.099$). Instead, qualified employment was significantly associated ($P = 0.026$).

Table 2—*Characteristics of the NIDDM study population*

Investigated variables	Total population Mean ± SD	Total population % (*n*)	Centers' range (means or %)
Age (years)	64.0 ± 9.9	—	60.3–66.5
Men (%)	—	44.2 (868)	34.7–63.2
Standardized HbA_{1c} (%)	8.2 ± 1.7	—	5.9–9.5
Disease duration (years)	15.2 ± 8.4	—	12.5–18.3
Disease duration at insulin start (years)	9.5 ± 7.9	—	6.4–13.3
Insulin per kilogram (IU/kg)	0.47 ± 0.24	—	0.41–0.62
BMI (kg/m^2)	27.6 ± 4.6	—	25.7–29.3
Insulin injections per day (*n*)	2.2 ± 0.9	—	1.8–2.7
Intensive therapy (%)	—	40.2 (785)	5.9–68.9
Visits/year (*n*)	5.7 ± 3.3	—	3.3–9.6
More than six visits/year (%)	—	31.0 (594)	2.5–76.5
Fundus examination (%)	—	41.3 (1,152)	13.9–98.6
Qualified employment (%)	—	15.5 (272)	3.1–35.1

$n = 1,963$.

The stepwise multiple regression analysis also took into account age, sex, disease duration, and insulin dose per kilogram for both types of diabetes, as well as time elapsed between diagnosis and insulin therapy for NIDDM, even if they did not show any significant association with average HbA_{1c} levels in the by-center univariate analyses. Number of insulin injections also has been considered in the multiple model for NIDDM, in spite of the nonsignificant univariate result. As reported in Table 4, the average number of insulin injections remained significantly associated with glycemic control ($P = 0.0002$) as well as insulin dose per kilogram, in IDDM. This model explained 68% of the centers' variability, with number of insulin injections accounting for most of it (partial $r^2 = 0.55$). NIDDM patients showed a significant independent association with qualified employment ($P = 0.016$), which alone explained 31% of the centers' variability. The final model also included fundus examination ($P = 0.10$) and disease duration ($P = 0.12$), explaining 53% of the total variance. Insulin injections forced into the model accounted for only 6.8% of the centers' variability without a significant improvement to the model. Time elapsed between diagnosis and insulin therapy did not enter the model ($P = 0.86$ at the univariate analysis).

As insulin dose per kilogram showed a significant univariate direct association to both HbA_{1c} and number of insulin injections (in a by-subject, but not by-center, analysis), we carried out a further stepwise analysis not including insulin dose per kilogram among the explanatory variables: the NIDDM model produced identical results, whereas for IDDM, the selected variables were again number of insulin injections ($P = 0.0009$; partial $r^2 = 0.56$) but with qualified employment ($P = 0.04$; partial $r^2 = 0.12$) instead of insulin dose per kilogram.

The analyses carried out on the subset of the 13 centers with a more rigorous evaluation of HbA_{1c} precision did not change these results.

To further control for possible heterogeneity of IDDM patients among the investigated centers, as suggested by the disease duration variation (Table 1), the same analyses have been repeated on a subset of 12 centers with average disease duration ranging from 12.5 to 17.5 years. Results were identical to those of the full 16-center model.

CONCLUSIONS — In current practice, the evaluation of the health impact of research findings is rather complex and is normally based on longitudinal study results. This paper suggests that, for this purpose, cross-sectional data may also be used.

In fact, the by-group analysis procedure used aims at reducing some of the known drawbacks of these studies by considering average results of intervention policies operating in different areas, rather than single patients' characteristics. Validity of such a procedure depends on *1*) a sort of patient homogeneity among the different areas under study (as in random patient allocation in randomized controlled trials) and 2) some stable differences in the general policy of intervention of these areas (as in different treatments in randomized controlled trials). These differences among centers do not need to be substantial: systematic differences may derive from a different general philosophy of care among centers or simply from different approaches of single doctors. Patient homogeneity requires that both the disease and the disease-related environments are similar in the different geographical

Table 3—*Univariate regression analyses between the investigated variables and the center average HbA_{1c} levels, according to type of diabetes*

Variables	IDDM β	IDDM SE	IDDM *P*	IDDM r^2	NIDDM β	NIDDM SE	NIDDM *P*	NIDDM r^2
Insulin therapy prescription								
Average number of insulin injections per day	−1.69	0.40	0.0009	0.56	−0.50	0.49	0.33	0.07
Time elapsed between diagnosis and insulin	—	—	—	—	−0.01	0.09	0.86	0.002
Medical attention to complications								
Proportion of patients with more than six visits/year	−0.009	0.007	0.22	0.11	−0.002	0.006	0.78	0.006
Proportion of patients with fundus examination	−0.01	0.006	0.04	0.27	−0.009	0.005	0.099	0.18
Patient characteristics								
Proportion of patients with qualified employment	−0.02	0.01	0.059	0.23	−0.06	0.02	0.026	0.31
Average BMI	—	—	—	—	0.07	0.14	0.61	0.02

Average BMI was investigated only for NIDDM patients.

Table 4—*Stepwise multiple regression analyses between the investigated variables and the center average HbA_{1c} levels, according to type of diabetes*

Variables left in the model	β	SE	*P*	Partial r^2	Total r^2
IDDM					0.68
Average number of insulin injections per day	−1.85	0.34	0.0002	0.55	
Insulin dose per kilogram	4.32	1.87	0.038	0.13	
NIDDM					0.53
Proportion of patients with fundus examination	−0.007	0.004	0.14	0.10	
Proportion of patients with qualified employment	−0.07	0.02	0.016	0.31	
Disease duration	−0.17	0.09	0.078	0.12	

Independent variables were insulin injections, fundus examination, qualified employment, age, sex, disease duration, insulin dose per kilogram for both types of diabetes, and time elapsed between diagnosis and beginning of insulin therapy for NIDDM.

areas, as should be the operating criteria for the diabetes outpatient clinics' admissions. As regards diabetes, all these conditions seem to be generally verified in Italy, where the great majority of patients (especially the insulin-treated ones) attend specialized centers (16,17). In addition, the comparisons can also be controlled for known imbalances among the different subsets of patients through multivariable or stratified analyses.

Considering that in Italy, the average glycemic control is quite different even in centers specifically devoted to the care of the disease, our application shows that treating patients with intensive insulin therapy (high number of injections) is the most relevant factor for improving glycemic control in IDDM, since it explains more than half of the average HbA_{1c} variability among centers. In NIDDM, in contrast, the number of insulin injections is not associated with the degree of blood glucose control in either univariate or multivariable analyses. This indicates that the strong influence of intensive therapy on glycemic control demonstrated in IDDM patients by the Diabetes Control and Complications Trial (1) and confirmed by our results may not be simply extrapolated to NIDDM patients. Despite a due caution in the interpretation of NIDDM data, a different effect of intensive insulin treatment in blood glucose control in the two types of diabetes is supported by the fact that in these centers, the same doctors take care of both IDDM and NIDDM patients. Our results are supported by a recent report on changes in the medical management of glycemia (18), which shows a very mild glycated hemoglobin decrease in older-onset diabetic patients despite an increasing trend in the use of both insulin therapy and multiple-injections regimens over a 10-year period. According to these results, a randomized trial on insulin administration regimen in NIDDM patients (19) showed a comparable glycemic control improvement among groups treated with a two-injection scheme or a combination of glibenclamide and only one injection.

The most important predictor of good blood glucose control in NIDDM patients is qualified employment. This represents an indicator of social level that could affect glycemic control by generally healthy behavior (20). This result would support the basic role of patient education in NIDDM management (21–25).

As a final remark, we can see that the variation in glycemic control explained by the variables included in the regression models is rather relevant, despite the complexity of the problem. A limitation of our conclusions is that they are confined to the evaluation of an intermediate metabolic endpoint like HbA_{1c}, which, however, has been proved to be highly associated with the diabetes-related clinical endpoints in both IDDM (1) and NIDDM patients (2–4). Indeed, for NIDDM, no conclusive data are yet available on the net benefit of the different therapeutic strategies, especially concerning macrovascular complications (26).

In general, these results highlight the feasibility of taking advantage even of small variations in established care policies of sub-areas as a way to identify relevant determinants of a given endpoint. They also suggest the possible impact of some variations in current practice. These results can be obtained by a methodology that has almost the same validity as an intervention study, albeit being less expensive and time consuming and more respectful of the general conditions of the usual setting of diabetes care.

The results of this study could represent the starting point for planning intervention trials with a more realistic approach to define the hypothesis to be tested.

Acknowledgments— We are indebted to Eli Lilly S.p.A. Italia for its financial and organizational support.

APPENDIX

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