The METABOLIC Study: Multidimensional assessment of health and functional status in older patients with type 2 diabetes taking oral antidiabetic treatment

S. Maggi\textsuperscript{a,1}, M. Noale\textsuperscript{a,*,1}, A. Pilotto\textsuperscript{b}, A. Tiengo\textsuperscript{c}, P. Cavallo Perin\textsuperscript{d}, G. Crepaldi\textsuperscript{a}, for the Metabolic Working Group

\textsuperscript{a} CNSR - Institute of Neuroscience, Aging Branch, via Giustiniani 2, 35128 Padua, Italy
\textsuperscript{b} Geriatric Department, Health Unit 16, Padua, Italy
\textsuperscript{c} Department of Medicine, University of Padua, Padua, Italy
\textsuperscript{d} Diabetology Unit, University of Turin, Turin, Italy

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Abstract

\textit{Aim.} – The objective of the METABOLIC Study was to evaluate overall health status, with particular focus on assessment of functional status of older patients taking oral antidiabetic drug (OAD) treatment.

\textit{Methods.} – The study included 1342 type 2 diabetes patients aged ≥ 65 years treated with OADs, with or without insulin, who had been referred to outpatient clinics across Italy. Information on diabetes (duration, medications taken during the last 3 months, hypoglycaemic events and diabetic complications) was collected by questionnaire, and the patients’ overall health status was assessed using a multidimensional prognostic index.

\textit{Results.} – The sample recruited (mean age: 73.3 ± 5.5 years) had a mean duration of diabetes of 11.3 ± 8.2 years. Half were taking sulphonylureas alone or together with other medications, 9.7% were taking insulin in combination with other OADs, almost 30% were using biguanides and 6.2% were taking dipeptidyl peptidase-4 (DPP-4) inhibitors. Also, 12% of patients reported hypoglycaemic events, 90% of whom were taking insulin or sulphonylureas. In addition, 81% of the participants were completely independent in their activities of daily living, while 19% were mildly, moderately or severely disabled. Age, female gender, hypoglycaemic events, neuropathy and low diastolic blood pressure were the main variables associated with disability.

\textit{Conclusion.} – Disability is common in older diabetic patients and some associated factors, such as hypoglycaemia and low diastolic blood pressure, have been identified. Also identified was malnutrition as a specific factor associated with hypoglycaemic events independent of the use of insulin and sulphonylureas.

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\textit{Keywords:} Type 2 diabetes; Older patients; Functional limitations; Hypoglycaemia; METABOLIC Study

Résumé

Étude METABOLIC : une évaluation multidimensionnelle de l’état de santé et de capacités fonctionnelles des patients âgés atteints de diabète de type 2, en traitement antidiabétique oral.

L’objectif de l’étude. – METABOLIC est l’évaluation de l’état de santé global des patients âgés atteints de diabète de type 2, en traitement antidiabétique oral, avec une attention particulière pour l’évaluation de capacités fonctionnelles.

Méthodes. – L’étude comprend 1342 patients diabétiques de type 2 âgés de 65 ans ou plus, en traitement antidiabétique oral, avec ou sans insulin, en se référant aux centres antidiabétiques en Italie. Informations sur le diabète (durée, médicaments au cours des trois mois précédents, les événements hypoglycémiques, et les complications diabétiques) ont été recueillies dans un questionnaire. L’état de santé générale des patients a été évalué par l’indicateur MPI (Multidimensional Prognostic Index).

* Corresponding author. Tel.: +39 049 8218899; fax: +39 049 8211818.
E-mail address: marianna.noale@in.cnr.it (M. Noale).
\textsuperscript{1} The authors contributed equally to the study.
1. Introduction

Type 2 diabetes (T2D) is a chronic degenerative disease, and a major health and social concern in Italy as well as in other industrialized countries. The severe micro- and macrovascular complications associated with diabetes are well known, whereas the impact of the disease and its complications on physical disability are not as well understood. According to the literature, more than 50% of older diabetic patients are referred for physical functional impairment compared with approximately 2% of their peers [1-4].

Preventing the complications of T2D is based on interventions to modify or remove avoidable risk factors and to achieve good blood glucose levels with the help of pharmacological therapy. Treatment in older patients is particularly difficult due to polypharmacy and the co-morbidities such patients characteristically have. Particularly important variables in therapeutic algorithms appear to be the prevention of adverse events related to body weight changes and hypoglycaemic episodes, which are important in older patients because of the attendant risk of falls and, consequently, fractures [5,6]. Medication compliance in the aged is also negatively influenced by the onset of side-effects such as weight gain and hypoglycaemic episodes.

The aim of the METABOLIC Study was to assess overall health status with a particular focus on functional impairment in activities of daily living (ADL) in T2D patients aged ≥ 65 years taking oral antidiabetic drugs (OADs), with or without insulin, and attending outpatients diabetes centres.

2. Methods

A total of 1342 outpatients were recruited by consecutive enrollment at 57 diabetes centres scattered throughout Italy between September 2010 and October 2011. Inclusion criteria, as defined by the study protocol, were aged ≥ 65 years, treatment with OADs (the same drug over the past 3 months), the capacity to understand the study protocol and aims, and a signed consent form. Patients using insulin therapy only were not included in the study.

The primary endpoint of the study was to evaluate the prevalence of physical disability in ADL. Secondary endpoints included the evaluation of global health status and analysis of the OADs used by these patients.

The sample size was based on the primary endpoint of evaluating the prevalence rates of disability in ADL in older T2D patients. Daniel’s formula was used [7] with d (accuracy) = 5%. Based on data from the Italian Longitudinal Study on Aging (ILSA) [4] for the prevalence of disability in ADL among elderly diabetic patients and a possible 10% dropout rate, a sample size of 422 was calculated. For this reason, 57 outpatients diabetes centres were requested to identify 10–15 patients each by consecutive enrollment. Over the period of consideration, the investigators were able to recruit 1342 T2D patients, all of whom were included in the analyses.

The study was carried out in accordance with the guidelines for observational studies on drugs (Italian Medicines Agency [AIFA] announcement on March 20, 2008; Official Publication of new laws [Gazzetta Ufficiale] n. 76, March 31, 2008). The study protocol had the approval of the ethics committee of each participating centre. All study participants were asked to sign an informed consent form in which they agreed to adhere to the study requirements.

2.1. The METABOLIC questionnaire

The METABOLIC questionnaire, administered by diabetologists, collected data on the patients’ social history (living status, formal and informal healthcare), medical history of diabetes (duration, medications taken during the preceding 3 months), hypoglycaemic events over the past 3 months and drug therapy (excluding antidiabetic medications). Assessment of the overall health status using a Multidimensional Prognostic Index (MPI) [8], including evaluation of autonomy in ADL [9], instrumental ADL [10], cognitive status (Short Portable Mental Status Questionnaire, SPMSQ) [11], risk of pressure ulcers [12], co-morbidities (Cumulative Illness Rating Scale, CIRS) [13] and nutritional status (Mini Nutritional Assessment, MNA) [14], was also carried out. The MPI was used because it has been extensively adopted in geriatrics as a set of validated reliable scales for the assessment of health and functional status of older patients [15-21]. Blood pressure and heart rate were measured at the end of the interview.

Diabetes complications (coronary, cerebrovascular, peripheral arteriopathy, nephropathy, retinopathy, neuropathy) and haematocchemical determinations (within the previous 6 months) were taken from clinical records and recorded on the
questionnaire form by the diabetologists. Blood samples were collected from each patient 11 days (mean) prior to completing the METABOLIC questionnaire.

Two training meetings for the investigators were organized to describe the METABOLIC study and its objectives, the questionnaire and the Web platform used for data collection. During the data-collecting period, a support service (telephone, e-mail) was activated at the CNR Aging Branch to answer any questions or problems that might be raised.

2.2. Statistical analysis

The prevalence rate of physical disability was assessed using the ADL scale, and patients were classified according to the presence and severity of their physical disability [4] as: completely independent (by all six items); having mild disability (by two items); and having moderate/severe disability (by three or more items). The differential distribution of the characteristics measured by the questionnaire was assessed using the χ² or Fisher’s exact test for categorical variables (alpha = 0.05, two-tailed). Quantitative variables were compared using generalized linear models (GLMs) with Bonferroni adjustment after verifying homoscedasticity (Levene’s test; in the event of heteroscedasticity, Welch’s analysis of variance [ANOVA] was applied) or with the non-parametric Kruskal-Wallis test.

Logistic regression models were defined in relation to disability in ADL (mild or moderate/severe vs. complete autonomy). The variables considered in the models included demographic and clinical characteristics (gender, age, systolic and diastolic blood pressure), anthropometric evaluation (body mass index [BMI]), diabetes characteristics (duration, hypoglycaemic events within the previous 3 months, complications, haematocotoxic parameters) and geriatric evaluations (cognitive status, lifestyle, nutritional status, co-morbidities). The identification of variables associated with disability in ADL was conducted by first considering univariate logistic regression. Any significant variable with P ≤ 0.25 was introduced into a multivariate model to select associated factors, using a stepwise selection method. Odds ratios (ORs) and corresponding 95% confidence intervals (CI) were calculated for each significant variable. The final logistic model was adjusted for clusters of diabetes centres identified by cluster analysis as comparable centres in terms of proportions of subjects with disability. A logistic model was constructed following the same statistical procedure to identify factors associated with hypoglycaemic events.

The analyses were carried out using SAS version 9.2 software (SAS Institute, Cary, NC, USA).

3. Results

General characteristics of the study patients are presented in Table 1. Overall, 81% were completely autonomous in ADL (by all six questionnaire items), 15.4% had mild disability (by two aspects of daily living) and 3.6% had moderate or severe disability (by three or more ADL). The differences between age groups and gender were significant, with women and older subjects being more disabled (P < 0.0001). A significant association was found between disability in ADL and the occurrence of hypoglycaemic episodes or hospitalization because of hypoglycaemic events in the previous 3 months, which were also more frequent in those with mild or moderate/severe disability compared with totally independent subjects (P < 0.0001 for both). All diabetic complications were significantly associated with physical disability (P < 0.0001 for all): the prevalence of each complication looked at was higher among patients with moderate/severe disability than among those with mild disability or complete independence.

Mean values from the haematocotoxic examinations are shown in Table 2, and the distribution of MPI scales is presented in Table 3.

Of all the patients enrolled, 9.7% were treated with insulin in combination with other drugs, 50.1% with sulphonylureas, 32% with biguanides, 6.2% with DPP-4 inhibitors (alone or in combination with other drugs) and 2% with thiazolidinediones, alpha-glucosidase inhibitors or other combinations of OADs.

Results of a logistic regression model using disability (mild or moderate/severe vs. completely independent) as a dependent variable, and all variables that were significantly associated in the univariate analysis as predictive variables, are presented in Table 4. The diabetic patient with disability of any degree in ADL was typically older and female, and had experienced hypoglycaemic events in the last 3 months and neuropathy. Higher diastolic pressure appeared to have a protective effect.

Of the 161 participants reporting at least one hypoglycaemic event in the 3 months prior to the interview, 29 (18.0%) reported needing assistance; nearly 90% of the hypoglycaemic events were reported by patients treated with insulin (together with other drugs) or sulphonylureas. Hypoglycaemic events were also reported by 14 patients taking only biguanides, by three patients taking DPP-4 inhibitors along with other drugs and by one patient taking alpha-glucosidase inhibitors. Factors associated with hypoglycaemic events in the logistic regression model were insulin and sulphonylureas (OR: 8.82, 95% CI: 4.47–17.40; P < 0.0001 and OR: 4.79, 95% CI: 2.70–8.49; P = 0.0168, respectively), diabetes duration in years (OR: 1.04, 95% CI: 1.02–1.06; P = 0.0002) and MNA score (OR: 0.85, 95% CI: 0.80–0.90; P ≤ 0.0001).

4. Discussion

The prevalence of diabetes is rising worldwide, and is expected to increase from its present level of 150 million to 225 million by the end of the decade and up to as many as 300 million by 2025. The greatest absolute increase in the number of cases is being seen among older individuals, in whom the prevalence rate is about 15% [22]. A major concern is the fact that, in addition to the traditional major complications, diabetes in the aged now appears to be associated to a significant increase in physical disability.

Our present multicentre study has found that, in a cohort of free-dwelling older diabetic patients treated with OADs, the prevalence of physical disability is reportedly around 20%. The level of disability is usually assessed by self-reported information on difficulties in mobility, walking and other common ADL
or by physical performance tests (PPTs). For example, Gregg et al. [1] analyzed data from the US Third National Health and Nutrition Examination Survey (NHANES III) in 3475 women and 3113 men aged 60 years or more and found that, among those with diabetes, 32% and 15%, respectively, reported some physical inability compared with 14% and 8%, respectively, among non-diabetics. Moreover, diabetes-related disability was reflected in several PPTs involving walking speed and balance.
Table 2
Hematochemical determinations. Metabolic study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall sample</th>
<th>ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Median</td>
</tr>
<tr>
<td>Glycemia, mg/dl</td>
<td>138.49 ± 35.44</td>
<td>134.0</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.03 ± 0.74</td>
<td>0.90</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>176.6 ± 35.9</td>
<td>176.0</td>
</tr>
<tr>
<td>Cholesterol HDL, mg/dl</td>
<td>49.90 ± 12.94</td>
<td>48.0</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>130.30 ± 63.6</td>
<td>117.0</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.2 ± 1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

ADL: activities of daily living.

Table 3
Components of the Multidimensional Prognostic Index (MPI). Metabolic study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Mean±SD</th>
<th>ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Median</td>
</tr>
<tr>
<td>N. autonomous ADL (range 0–6)</td>
<td>5.7 ± 0.8</td>
<td>6.0</td>
</tr>
<tr>
<td>N. autonomous IADL (range 0–8)</td>
<td>7.1 ± 1.7</td>
<td>8.0</td>
</tr>
<tr>
<td>N. errors SPMSQ (range 0–10)</td>
<td>3.3 ± 3.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Exton-Smith Score (range 5–20)</td>
<td>19.1 ± 1.6</td>
<td>20.0</td>
</tr>
<tr>
<td>CIRS Severity index</td>
<td>1.5 ± 0.3</td>
<td>1.4</td>
</tr>
<tr>
<td>CIRS Comorbidity index</td>
<td>1.8 ± 1.7</td>
<td>2.0</td>
</tr>
<tr>
<td>MNA score (range 0–30 points)</td>
<td>25.3 ± 2.7</td>
<td>26.0</td>
</tr>
<tr>
<td>Score on the MNA (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 17, malnourished</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>17–23.5 risk of malnourishment</td>
<td>20.4</td>
<td>14.9</td>
</tr>
<tr>
<td>≥ 24 well-nourished</td>
<td>78.5</td>
<td>84.8</td>
</tr>
</tbody>
</table>

* Welch’s ANOVA.

In the large prospective study of osteoporotic fractures (SOF), more than 8000 women aged ≥ 65 years were enrolled, and their yearly incidence of disability in several tasks (such as walking, doing heavy housework and preparing meals) was twofold higher in those with vs. without diabetes. The association persisted even after adjusting for potential confounders and co-morbidities [23]. Volpato et al. [3] conducted a 3-year longitudinal study of a random sample of 729 physically impaired women aged 65+ years and found that those with diabetes had an 80% higher risk of mobility disability compared with those

Table 4
Variables associated with disability in activities of daily living (ADL). Metabolic study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Slight, moderate, severe disability vs. independence in ADL (n = 1253)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate model</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>2.19</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.10</td>
</tr>
<tr>
<td>Hypoglycemic events</td>
<td>2.72</td>
</tr>
<tr>
<td>Complications, neuropathy</td>
<td>3.79</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>0.97</td>
</tr>
</tbody>
</table>

* Stepwise selection on variables associated with the outcome with P ≤ 0.25 in the univariate models.
without diabetes. In an Italian cohort of 5632 individuals aged 65–84 years participating in the ILSA, the prevalence rate of diabetes of about 13% in both men and women. A significantly higher prevalence rate of disability was found among diabetic individuals compared with other participants, with the risk of being unable to perform any physical test being two to three times higher compared with non-diabetic subjects in both men and women with diabetes [4].

The pathophysiological mechanisms linking diabetes and physical disability are multifactorial. Interestingly, an inverse relationship was found between diastolic blood pressure and disability that was independent of other diseases and diabetes complications. Such findings in older individuals are not novel. Although a low diastolic blood pressure is generally regarded as a favourable sign, this may not apply to older patients in whom it could compromise coronary blood flow, and so increase the risk of coronary heart disease, or simply be a marker of poor health [24]. Other studies have also suggested an association between lower blood pressure and the development of cognitive impairment [25,26], which could lead to a general state of frailty and disability. In addition, low diastolic blood pressure has been reported to be an independent predictor of mortality [27].

In fact, physical and cognitive disorders may be responsible for the association of low diastolic blood pressure and disability as previously reported, although our present results also suggest a potentially direct relationship between low diastolic blood pressure and disability in older diabetic patients, independent of co-morbidities and complications. Further studies are required to confirm these novel findings.

The present study has also found that hypoglycaemic events and neuropathy are associated to disability most probably through the increased risk of falls. Indeed, older people with diabetes are at increased risk for injurious falls [28], and the possible risk factors for injurious falls in older diabetics include hypoglycaemia, peripheral neuropathy, visual impairment and polypharmacy [2,23]. Falls by older adults are associated with high rates of morbidity, mortality and functional decline [29]. For this reason, the guidelines for falls prevention in older patients with diabetes recommend that they should be screened for their risk for falls and that ways to prevent their falling should be sought.

The extent to which the frequency of iatrogenic hypoglycaemia in T2D patients is a function of the specific glucose-lowering drug used or the stage of disease is not entirely clear. Is the greater frequency of hypoglycaemic events in patients treated with insulin the result of its greater glucose-lowering potency (given in sufficient doses) and its pharmacokinetic imperfections, or is it because patients who require insulin have more advanced insulin-deficient T2D with the associated compromised glucose counterregulation? Our study has found that insulin and sulphonylureas are indeed associated with hypoglycaemic events independent of other major risk factors, such as age, duration and complications of diabetes, and nutritional status. Patients taking other OADs, however, could also experience hypoglycaemia because of different factors, such as malnutrition and unhealthy eating habits, which are commonly seen in older individuals. In fact, the MNA was a significant and independent factor associated with hypoglycaemic events.

The present study has several limitations. First, potential selection biases could have affected our sample population. It is possible that patients with more severe forms of diabetes requiring more complex medical treatment and those experiencing diabetes-related complications may have been more likely to be referred to our study centres, while older patients with less severe forms of diabetes may have been referred to geriatric outpatients centres or simply to their general practitioners. This may have led to the selection of more disabled patients and, therefore, to an overestimation of disability in our diabetic population. However, the contrary is also possible in that the oldest and more severely disabled patients may not have been able to attend a diabetic centre for a visit. This would then result in the selection of a less-disabled sample and, ultimately, to an underestimation of disability in our diabetic population. Also, the hypoglycaemic events were self-reported by the patients and no blood determinations were available to confirm them.

Also excluded from our sample population were patients using treatment with insulin alone. Although they generally constitute a smaller percentage among older patients, they might be at higher risk of disability due to the longer duration and greater severity of their diabetes. Furthermore, some of the conditions that our clinical investigators classified as ‘complications’ could have been co-morbid disorders, given the high prevalence of multiple chronic conditions in older patients. Finally, the SPMSQ was used for cognitive assessment in our sample as it is considered a valid instrument for overall screening of cognitive function, but it is not sensitive enough to detect differences in mild cognitive impairment across groups. This might explain why no association was found with hypoglycaemic events, which are otherwise considered an independent risk factor of cognitive decline.

On the other hand, our study has several strengths. The large number of participants and a sampling strategy based on consecutive enrollment favour the representativeness of our sample. Moreover, the availability of clinical records guaranteed the validity of the data collected.

In conclusion, our study has demonstrated that disability is commonly seen in older T2D patients and has identified some preventable risk factors, such as hypoglycaemia and low diastolic blood pressure. Our results have also identified malnutrition as a specific factor associated with hypoglycaemic events and independent of the use of insulin and sulphonylureas. We recommend that these findings now be taken into consideration in the management and treatment of older diabetic patients.

The METABOLIC Study Working Group

Andrea Corsi, Aglioloro Alberto (Sampierdarena, GE); Allochis Gabriele (Novara); Aricò Concetta Nadia (Belluno); Balbo Marcella (Alessandria); Marangoni Alberto, Balzano Sara (Bassano del Grappa, VI); Battisti Basilio (Rieti); Testa Ivano, Brandoni Gabriele (Ancona); Bruno Alberto, Degiovanni Mariella (Torino); Buzzetti Raffaella, Foffi Chiara (Latina); Calatola Pasqualino (Salerno); Cantarella Santi Antonio
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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