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Will undocumented migrants contribute to change epidemiology, presentation and pharmacologic treatment of diabetes in Western countries?

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ABSTRACT

Aims: Migrants from countries in which health and social conditions are unsatisfactory, and their offspring, are becoming a growing component of the western population. Available health data show that their morbidity is at least comparable to that of the host country population, with a significant contribution of chronic diseases as diabetes.

The possibility that diabetes shows different features in undocumented migrants is the hypothesis that we tried to investigate in this study.

Methods: We retrospectively analysed the data of 413 patients with type 2 diabetes mellitus (T2DM): 222 patients followed in a diabetes clinic at a University Hospital and 191 undocumented migrants cared for by a Charity in Milan, Italy.

Results: We found that the onset of the disease was earlier in migrants; they showed a significant lower body mass index (BMI) and had lower socioeconomic conditions. They had a worse glycaemic control. The pattern of complications was also different between the two groups, with cardiovascular complications more frequent in Italians.

Finally, also pharmacologic treatment differed significantly.

Conclusions: Age of onset, clinical manifestations and complications of T2DM in undocumented migrants and natives may show significant differences. This is important for both epidemiological and clinical reasons.

If these preliminary observations are confirmed by larger studies, we can conclude that undocumented migrants should be screened for T2DM earlier than natives, and that therapies should be tailored to the specific features of their disease.

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1. Introduction

The number of people leaving their homeland as either refugees or economic migrants is increasing. As a consequence, migrants, both documented and undocumented, represent a growing proportion of the population in many western countries. Thus, their health status begins to become an important issue for health services of the host countries. The so-called Healthy Migrant Effect (HME), if it exists upon arrival [1], tends to be lost with duration of residence, exposure to pollutants, and adherence to unhealthy life-styles [2–4]. Thus, when considering chronic non-communicable diseases (NCD), researchers have found that their prevalence in documented migrants is at least comparable to that of their native-born counterpart [5,6].

Diabetes has been the object of various studies in migrant populations. The results of these studies are occasionally slightly discordant, and this is possibly due, at least in part, to the great heterogeneity of ethnicities gathered under the definition of “migrants”. In spite of this, some interesting patterns seem to emerge. For example, diabetes shows a greater prevalence in migrants to both Northern and Southern Europe than in the local population [7,8]. These studies have also shown, in the migrant population, differences due to gender and ethnicity/country of birth. Furthermore, a recent Australian study has shown that diabetic patients born in North Africa, South East Europe and the Middle East, though residents in Australia, have a poorer prognosis than patients born in Australia [9].

When it comes to undocumented migrants, having reliable information on their health conditions becomes much more difficult. This is due to many factors, including the lack of specific databases, the difficulty for these people to cope at the same time with the need to get medical assistance and that of escaping controls, and their attitude toward frequent changes of residence for familiar and working reasons. In this situation, non-governmental organizations (NGOs), providing free medical help to these persons, could be a useful source of information when they keep electronic records of these patients. Indeed, we have already used this approach to demonstrate the importance of NCD among undocumented migrants [10]. Unfortunately, very few data are available at present on prevalence, clinical features and treatment of diabetes and its complications in this peculiar population. In any case, it would not be appropriate to refer to epidemiologic data of the country of origin, even if available, since this approach does not take into account the impact of migration itself and of the factors related to the host country. On this basis, we undertook this preliminary study, which through the evaluation of possible differences between undocumented migrants and natives with diabetes, could help to achieve a better classification of diabetic patients potentially useful for better treatment and prevention [11].

2. Patients and methods

2.1. Patients

The 413 patients included in this study were all diagnosed with T2DM and were subdivided into two groups. The first

group was made of all the foreign patients ($n = 191$) who in 2017 sought medical assistance at the diabetic outpatient clinic run by the “Fratelli di San Francesco” (FSF), one of the biggest charities based in Milan, which provides free medical help and medicines to undocumented migrants. This group included people coming from miscellaneous countries, grouped into 5 macro areas (Asia: 82 patients, Eastern Europe: 22, Northern Africa: 26, Sub-Saharan Africa: 20, Latin America: 41), but given its small size and the preliminary character of this study, was considered as a whole. The second group was made of a comparable number of Italian patients ($n = 222$) randomly selected among those attending a diabetic outpatient clinic at San Gerardo Hospital (SGH) in Monza during the same period. All patients satisfied the criteria accepted in epidemiological studies for defining the diagnosis of diabetes [12]. The complications defined in a recent NICE guideline were taken into consideration [13]. They were derived from the medical records in both clinics.

Data were retrieved from the medical records by two independent investigators in SGH and FSF. Clinical data regarded family history of diabetes, age at diagnosis, body mass index (BMI), unhealthy lifestyles (smoking and alcohol consumption), glycated haemoglobin (HbA1c), glycosuria and ketonuria, complications, use of antidiabetic agents, use of drugs for concomitant cardiovascular diseases. In addition, for each patient the Q-score was computed: this is an indicator of how satisfactory the quality of care is in diabetic patients; it has also been shown to be a good predictor of cardiovascular risk [14]. Information was missing for most of the socio-demographic variables that we intended to collect, with the exception of ethnic origin, Socio Economic Status (SES) and education. SES was determined on the basis of the gross individual income in the period of the study as compared to the mean gross individual income in Lombardy in the same period ($\approx 24,000$ €), as available at www.comuni-italiani.it/03/statistiche/. SES was considered low for a gross individual income $< 20,000$ €, mid between 20,000 and 30,000 €, and high if $> 30,000$ €. For education we used the following grading: low = primary school, mid-low = secondary school, high = University. Also for the latter two items information was sometimes unavailable. All data were organised into a single database.

2.2. Statistical methods

SAS software was used to process data and fit statistical models (SAS Institute Inc. 2008. SAS/STAT[®] 9.2 User’s Guide. Cary, NC: SAS Institute Inc.).

Mean \pm standard error of continuous variables (e.g. BMI and Q-score) was computed separately for migrants and Italian born patients, and the difference between the two groups was reported with its 95% confidence limits. As for binary variables (e.g. presence of glycosuria and occurrence of cardiovascular events), asymptotic standard errors of proportions were computed according to Vollset [15], and 95% exact confidence limits of the difference between groups were computed according to Clopper and Pearson [16].

To give a global picture of the interrelationships between socioeconomic and health characteristics of Italian born and migrant diabetic patients, we resorted to Multiple Corre-

Table 1 – Clinical and socio-economic data.

	Natives	Migrants	Migrants vs natives (95% conf. limits)
Age (years) ^a	222, 59.2 ± 0.62	190, 51.3 ± 0.67	−7.9 (−9.71, −6.11) ^c
Age at diagnosis (years) ^a	221, 48.1 ± 0.68	160, 43.7 ± 0.80	−4.3 (−6.40, −2.28) ^c
Duration of diabetes (years) ^a	221, 11.2 ± 0.50	160, 7.2 ± 0.59	−4.0 (−5.49, −2.47) ^c
Hospitalisation for diabetes (%) ^{b,d}	222, 13.5 ± 0.8	184, 17.9 ± 2.8	+4.4 (+6.8, +2.6) ^c
Family history of diabetes ^b	216, 79.6 ± 2.7	168, 44.1 ± 3.8	−36.6 (−44.8, −26.7) ^c
Q-score ^a	220, 29.1 ± 0.56	188, 24.5 ± 0.60	−4.6 (−6.20, −2.99) ^c
BMI (kg/m ²) ^a	221, 30.9 ± 0.39	164, 27.1 ± 0.45	−3.7 (−4.89, −2.54) ^c
Low Socio Economic Status (%) ^{a,b}	213, 20.2 ± 2.75	112, 75.0 ± 4.09	+54.8 (+44.5, +64.1) ^c
Unhealthy life styles ^b	222, 33.3 ± 3.2	186, 27.4 ± 3.3	−5.9 (−15.6, +3.8)
Glycated haemoglobin (% of total Hgb) ^a	222, 7.09 ± 0.10	128, 9.00 ± 0.13	+1.9 (+1.59, +2.23) ^c
Glycosuria (%) ^b	220, 25.9 ± 3.0	170, 44.7 ± 3.8	+18.8 (+8.8, +28.5) ^c
Ketonuria (%) ^b	220, 1.4 ± 0.8	167, 6.0 ± 1.8	+4.6 (−5.4, +14.6)
Cardiovascular disease (%) ^b	222, 41.0 ± 3.3	180, 6.7 ± 1.9	−34.3 (−43.3, −24.8) ^c
Cardiovascular events (%) ^b	222, 20.7 ± 2.7	183, 6.6 ± 1.8	−14.2 (−23.7, −4.4) ^c
Cardiovascular risk factors (%) ^{b,e}	222, 92.8 ± 1.7	186, 75.3 ± 3.2	−17.5 (−27.0, −7.8) ^c
Nephropathy (%) ^b	222, 5.9 ± 1.6	180, 11.1 ± 2.3	+5.3 (−4.6, +15.0)
Retinopathy (%) ^b	222, 19.4 ± 2.6	181, 18.8 ± 2.9	−0.6 (−10.4, +9.2)
Neuropathy (%) ^b	222, 9.0 ± 1.9	181, 5.5 ± 1.7	−3.5 (−13.2, +6.3)
Ulcers (%) ^d	222, 2.2 ± 1.0	181, 2.2 ± 1.1	−0.0 (−9.8, +9.7)
Hepatitis C virus (%) ^b	77, 92.2 ± 3.1	25, 80.0 ± 8.0	−12.2 (−34.1, +10.1)

^a n, Mean ± standard error, difference “migrants vs natives” (95% confidence limits).

^b n, Prevalence (%) of the condition ± asymptotic standard error, difference “migrants vs natives” (95% exact confidence limits ²).

^c Statistically significant difference “migrants vs natives” (p < 0.05).

^d Percentage of patients having at least one hospital admission for diabetes-related problems.

^e Hypertension, obesity, dyslipidaemia, smoking.

spondence Analysis (MCA) [17]. This multivariate technique represents a multiple contingency table as a table whose n rows are the profiles of the characteristics (e.g. socioeconomic status, educational level, health conditions) of the subjects included into the analysis, and whose K columns ($K = \sum_j^m k_j$) are the categories of the m variables (k_j categories for the jth variable) used to describe the characteristics of the subjects. From a geometrical viewpoint, subject profiles can be plotted as points in the space on whose K axes the categories are reported, whereas each category is a point in the space on whose n axes the subjects are reported. The points are scattered in a (K–m) dimensional space, according to a *chi-square* metric, which is used to define the similarities between row or column profiles. The MCA aims to determine those planes on which the projections of this cloud of points provide a synthetic but not distorted image of the multidimensional structure of the cloud of points with little loss of information. These planes are identified by the first two main dimensions that are the axes of maximum dispersion (or *inertia*) of the cloud. In addition, some variables may be treated by MCA as illustrative variables, i.e. variables that do not contribute to determine the shape of the multivariate structure of data, but whose position on the graph allows us to see how they are related to the structure, in our case to show how different are the characteristics of Italian born and migrant patients.

2.3. Ethics

The design of the study was submitted to the local ethics committee; since the study is only observational, it was not given an authorization protocol number.

All data were completely and permanently anonymized.

All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The authors declare no conflicts of interest.

3. Results

Table 1 compares the clinical and socio-economic conditions of foreign and Italian born diabetic patients. It should be noted that while sex distribution results almost comparable (male patients were 69.8% among natives and 63.9% among migrants), migrants are younger by nearly 8 years and were diagnosed earlier by about 4 years; as a consequence, in migrants the duration of diabetes was shorter by 4 years. Migrants show lower BMI and occurrence of positive family history. As many as 3 patients out of 4 were of low Socio Economic Status among migrants, but only 1 patient out of 5 among natives.

Glycaemic control is much less satisfactory in foreign-born patients, as demonstrated by higher values of HbA1c. Glycosuria is more frequent in migrants, and a comparable difference is observed also for ketonuria.

Unhealthy life styles are slightly less frequent among migrants, mainly cigarette smoking. Foreign and Italian born patients show different patterns of diabetes complications. The presence of cardiovascular diseases and events, as well as the exposure to cardiovascular risk factors, is by far higher among natives, whereas kidney impairment is more frequent among migrants though this difference is not statistically significant. However, in consideration of its clinical and economic

Table 2 – Drug therapy.

	Natives	Migrants	Migrants vs natives (95% conf. limits)
3 or more anti-diabetic drugs ^a	222, 37.8 ± 3.2	191, 12.6 ± 2.4	−25.3 (−34.4, −15.7) ^b
Fast acting insulin ^a	222, 18.9 ± 2.6	191, 22.5 ± 3.0	+3.6 (−6.1, +13.2)
Long acting insulin ^a	222, 46.8 ± 3.3	191, 33.0 ± 3.4	−13.9 (−23.3, −4.2) ^b
Oral hypoglycaemic drugs ^a	222, 84.2 ± 2.4	191, 75.9 ± 3.1	−8.3 (−17.9, +1.4)
3 or more drugs for concomitant diseases (%) ^a	222, 69.4 ± 3.1	191, 20.9 ± 2.9	−48.4 (−56.5, −39.6) ^b
Anti-thrombotic drugs ^a	222, 32.4 ± 3.1	191, 12.0 ± 2.3	−20.4 (−29.7, −10.8) ^b
Drugs for cardiovascular diseases ^a	222, 14.0 ± 2.3	191, 1.6 ± 2.3	−12.4 (−21.9, −2.7) ^b
Anti-hypertensive drugs ^a	222, 68.0 ± 3.1	191, 39.3 ± 3.5	−28.7 (−37.8, −19.3) ^b
Anti-dyslipidemic drugs ^a	222, 71.2 ± 3.0	191, 17.8 ± 2.8	−53.4 (−61.2, −44.8) ^b

^a n, Percent of subjects prescribed with drugs ± asymptotic standard error, difference “migrants vs natives” (95% exact confidence limits).

^b Statistically significant difference “migrants vs natives” ($p < 0.05$).

impact, renal involvement has been kept in statistical analysis.

The two groups do not appear to differ in the prevalence of ocular and neurologic complications, and skin ulcers, especially “diabetic foot”. Only 35% of Italian born patients and 13% of migrants were tested for hepatitis C virus, and most of them were found to be positive. Since the worldwide prevalence of hepatitis C is <3%, it is very likely that in both clinics only patients suspected to be infected have been tested. For this reason hepatitis C data were not further considered.

A large number of differences emerged between foreign and Italian born patients in the treatment of diabetes and co-morbidities (Table 2). In general, treatment of diabetes was mainly based on oral anti-diabetics (prescribed to 80.4% of patients) and insulin (fast acting and long acting, prescribed to 41.4% of patients). Only 12.6% of migrants were given 3 or more antidiabetic agents, compared to 37.8% of Italian born patients. Pioglitazone, GLP1-agonists and DPP-4 inhibitors were marginally used. GLP1-agonists and the newer sodium-glucose cotransporter (SGLT) 2 inhibitors (ATC code A10BK) were used in 21 of the 222 Italian born patients (9.5%), and in none of the 192 migrants. Long acting insulin was prescribed more frequently to Italian born patients (46.8% vs 33.0%). Treatment of co-pathologies was also different between the two groups: Italian born patients were much more likely to use 3 or more drugs for concomitant diseases, the wider differences regarding anti-dyslipidemic (71.2% vs 17.8%) and anti-hypertensive drugs (68.0% vs 39.3%).

MCA was carried out on 23 variables totalling 58 categories: i.e. all variables in Table 1 (with the exception of those variables that were not significantly different between the two groups of patients) and Table 2, and also education level. Ethnic groups and sex were included in the analysis as illustrative variables. The results of this analysis are summarised in Fig. 1a–c, where the categories of the variables related to socio-demographic structure (Fig. 1a), diabetes (Fig. 1b) and cardiovascular diseases (Fig. 1c) are plotted on the plane of the first two factorial axes (F1, F2), accounting for 72% + 14% = 86% of the total variability.

Fig. 1a shows that migrants are located in the upper right quadrant of plane (F1, F2), which is characterised by lower SES and younger age, whereas Italian born patients are located in the lower left quadrant, which is characterised by better socio-economic status, higher education level, and older age. A large part of the variability of F1 is accounted for by SES (5.8%),

education level (12.8%) and age (8.4%). It is worth noting that among migrants the patients coming from East Europe and Latin America display a slightly better SES than those coming from Sub-Saharan and North-East Africa (on the rightmost portion of Fig. 1a).

Fig. 1b shows that in migrants diabetes is characterised by earlier diagnosis (suggesting earlier onset of diabetes), lower Q-score, higher number of hospitalisations, larger use of fast acting insulin and oral antidiabetic drugs. On the other hand, Italian born patients are characterised by later diagnosis, higher Q-score, less hospitalisations, as well as by lower values of HbA1c, lower prevalence of glycosuria, negative family history (in migrants the information on these three variables is often missing). Variables related to antidiabetic drug consumption account for a large portion of the variability of F2: number of prescribed drugs (6.1%), fast acting insulin (14.9%), long acting insulin (20.8%), oral antidiabetic drugs (5.3%), but only a negligible portion of the variability of F1 (3.2% on the whole).

Fig. 1c shows that the presence of cardiovascular concomitant diseases and the occurrence of cardiovascular events is more frequent in Italian born patients (left) than in migrants (right). Consequently, also the use of medicines for the cardiovascular system is higher among Italian born patients. Variables related to cardiovascular conditions account for a large part of the variability of F1: cardiovascular disease (6.5%), cardiovascular risk factors (4.3%), number of prescribed drugs (10.5%), anti-thrombotic (4.1%), anti-hypertensive (5.9%), anti-dyslipidemic (9.3%) drugs.

4. Discussion

Among chronic non-communicable diseases, T2DM is the fastest growing all over the world [18]. It differs from type 1 diabetes in which auto-antibodies can be detected, though some T2DM patients may also show the presence of auto-antibodies, e.g. to glutamate decarboxylase (GADA) [19]. Many factors play a role in the epidemiology and clinical manifestations of this disease. Among them ethnicity and socio-economic conditions seem to be quite relevant [20,21].

Since the population of undocumented migrants is rapidly growing in western countries and is likely to exceed 4% of the total population [20], its contribution to epidemiology and clinical picture of diabetes deserves to be considered. However,

the role of many confounding factors has always to be kept in mind. The most important could be the reduced possibility to access regular medical care, a multi-causal phenomenon known to happen for diabetic patients more in general [22]. Our study, which to our knowledge is the first study comparing both clinical characteristics and disparities in treatment between diabetic undocumented migrants and diabetic Italian citizens, gives a preliminary insight into this situation although the number of migrants we could enrol is rather limited.

The first finding is that Italians have a significantly longer history of diabetes and this does not appear to be due to their older age, since the age at diagnosis was significantly lower in migrants. This is even more remarkable if we consider that both welfare conditions in the countries of origin of our undocumented migrant and difficulties in accessing health services in Italy could delay the diagnosis of diabetes. Also, this finding is keeping with the observation that the age of onset of both type 1 and type 2 diabetes is very low in certain populations [23]. The possible role of other confounding factors has to be considered, among which urbanization could be relevant, but this does not seem to be the case with our patients. Indeed, Italian patients live in Milan metropolitan area, just as undocumented migrants; and urbanization, both in EU and in countries of origin, seems more related to prevalence than to incidence of diabetes. Finally, the increased prevalence of diabetes associated with living in urban areas appears to be a consequence of an increased prevalence of obesity and metabolic syndrome [24], the latter being more frequently seen in more affluent patients [23]. This does not seem to be the case with our undocumented patients, who have a by far lower socioeconomic status than Italians and are less obese. Apart from obesity, principally deriving from unhealthy eating habits, we could gather information on smoking and alcohol consumption, but not on other lifestyles potentially relevant in the onset and presentation of diabetes, as physical activity and education level [24]. Indeed, the latter was a variable which we tried to collect, but the high number of missing data in migrants has made this information rather incomplete.

As easily predictable, glycaemic control was worse in undocumented migrants, as reflected by higher levels of HbA1c and of glycosuria, the latter being certainly due to the disease itself and not to treatment, since no patient in the migrant group was on SGLT-2 inhibitors.

The prevalence of complications was also different between the two groups, an observation that can only partially be explained by the fact that natives were better compensated. As a matter of fact, complications were not more frequent in migrants, but affected different organs. On one hand cardiovascular complications occurred significantly more often in Italian patients, on the other, migrants showed a higher prevalence of renal involvement, though this did not reach statistical significance. Many researchers have reported a different prevalence, age of onset and clinical course of complications in non-European diabetic patients, especially in Asian and Asian descent subjects [25–27]. The different in the prevalence of complications observed in our study cannot simply be explained by the older age of Italian patients, since they had higher cardiovascular but lower renal com-

plications. For cardiovascular complications, Okrainek et al. demonstrated that there is a lower risk in migrants, with the exclusion of those more recently arrived, with no previous education, and not married [28]. Also the shorter duration of disease in migrants of our study could be an important factor, because it has been demonstrated that, in the absence of other risk factors, a diabetes duration of less than 10 years is associated with a lower risk of cardiovascular complications [29]. Thus, the different prevalence of complications in our two groups of patients cannot simply be ascribed to ethnic diversity, but should be explained taking into account many interplaying factors.

The differences in pharmacological treatment observed in the two groups were not unexpected: migrants are less treated for both diabetes and co-pathologies. This fact has been already described accurately in documented migrants [30], but is for the first time documented by our study in a diabetic population of undocumented migrants. In any case, a few considerations are worth to be made. The lower use of drugs acting on the cardiovascular system appears to be related to the low prevalence of cardiovascular diseases in migrants, while the increased amount of oral anti-diabetics in migrants is likely to reflect a larger availability of these medicines for charities taking care of these patients. The use of insulin is more puzzling: if refrigeration at home can be a problem for many undocumented migrants, it is not clear while they use less long-acting insulin but the same quantity of fast-acting insulin. Finally the fact that Italians are treated with more drugs for concomitant diseases could reflect either a higher co-morbidity in this group or a better care and follow-up of these patients. The latter seems to be the case, if one considers their significantly higher Q-score.

We are aware that our study has some limitations.

First, since data come from two diabetes clinics, their activities might not be fully comparable. For example laboratory tests can be prescribed more easily to Italian patients; their results can prompt changes in therapy and/or diet and therefore have an impact on the clinical picture of the disease.

Second, the same complication definitions were used in both clinics, and complications were ascertained in both cases from patient's clinical notes. In spite of this, it is possible that linguistic problems or lack of personal medical documentation has led to some imprecisions.

Third, the two groups have been randomly selected and they had comparable sex distributions, but migrants happened to be younger than Italians. However, this reflects the demographic features of the undocumented migrants who are usually younger than natives.

However, drawing some conclusions from these considerations we can suggest that, according to the classification of Ahlqvist et al. [11], our undocumented migrants could fit into their first two groups: Severe Autoimmune Diabetes (SAID) and Severe Insulin Deficient Diabetes (SIDD). At present this remains only an hypothesis since we lack important data, as GADA, but some features are highly suggestive: early onset, unsatisfactory metabolic control, lower BMI, lower risk of cardiovascular complications, presence of ketoacidosis. These are two severe form of diabetes.

This consideration has to be located against the background of increasing migratory fluxes worldwide and high

prevalence of diabetes in migrants not only to Europe, but all over the world [31–33]. As a consequence, it is possible to speculate that we can witness some modifications in both epidemiology and clinical manifestations of diabetes in a short time. A better knowledge of diabetes in documented and undocumented migrant could be of great help in designing more global health strategies.

Conflict of interest

The authors state that they have no conflict of interest.

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7. Authors' contributions

All authors were involved in the design of the study and discussion of the results. SM provided statistical analysis; AIP, DC and SG collected the data of Italian diabetics and SB and AR those of Migrants. AS and NM contributed to all drafts of the manuscripts. GF and SGC supervised the study and wrote the final manuscript.

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