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REVIEW

Diabetes in migrants and ethnic minorities in a changing World

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Abstract

On a worldwide scale, the total number of migrants exceeds 200 million and is not expected to reduce, fuelled by the economic crisis, terrorism and wars, generating increasing clinical and administrative problems to National Health Systems. Chronic non-communicable diseases (NCD), and specifically diabetes, are on the front-line, due to the high number of cases at risk, duration and cost of diseases, and availability of effective measures of prevention and treatment. We reviewed the documents of International Agencies on migration and performed a PubMed search of existing literature, focusing on the differences in the prevalence of diabetes between migrants and native people, the prevalence of NCD in migrants *vs* rates in the countries of origin, diabetes convergence, risk of diabetes progression and standard of care in migrants. Even in universalistic healthcare systems, differences in socioeconomic status and barriers generated by the present culture of biomedicine make high-risk ethnic minorities under-treated and not protected against inequalities. Underutilization of drugs and primary care services in specific ethnic groups are far from being money-saving, and might produce higher hospitalization rates due to disease progression and complications. Efforts should be made to favor screening and treatment programs, to adapt education programs to specific cultures, and to develop community partnerships.

Key words: Migrants; Ethnic minorities; Diabetes; Health Systems; Non communicable diseases; Genetics; Socioeconomic development; Social determinants

Core tip: At global level the phenomenon of migration of people is not expected to slow down in the next years, generating a multitude of clinical problems and economic

cost for the National Health System. The increasing burden of chronic diseases, particularly diabetes, in migrant minority populations is today a major public health challenge for several countries, mainly in Europe, fuelled by the economic crisis, inequalities, terrorism and wars. Even in a universalistic healthcare system, differences in socioeconomic status and barriers generated by the present culture of biomedicine might make high-risk ethnic minorities under-treated and not protected against inequalities. Our objective is to pinpoint the problems arising in the prevention and treatment of diabetes on a worldwide scale, aiming to give support to healthcare systems in the provision of effective interventions.

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INTRODUCTION

Migration, migrants and Health Systems

Migration is an ancient phenomenon, dating back to the time of our African ancestors and occurring on a variety of levels (intercontinental, intra-continental, and interregional)[1].

Several factors contribute to migration. At the beginning of the 19th century, migrants were mostly farmers, farmhands, workmen and refugees but lately, people belonging to the educated and well-off class have started to migrate towards developed countries because of the industrial globalization and the availability of grater opportunities in open-market economies, favored by the Internet revolution[2]. These two sets of factors, "push factors" in native countries (food shortage, wars, civil wars, terrorism) and "pull factors" in host countries (economic booming, job opportunities, well-being) remain the basis of migration.

Massive immigration has generated a series of clinical-administrative problems to National Health Systems throughout the world, and also to universalistic systems. This is mainly the case with the so-called chronic non-communicable diseases (NCD), particularly diabetes, due to the very high number of cases at risk[3], the long duration of treatment, the very high cost of complications[4], as well as the availability of effective preventive and therapeutic measures expected to alleviate the burden of disease[5].

We reviewed the documents of International Agencies on migration and performed a PubMed search of existing literature, using the terms "diabetes" and "migrants". This manuscript is aimed at pinpointing the problems arising in the worldwide prevention and treatment of diabetes, with specific reference to countries where they have been more extensively investigated, as a support to healthcare systems in the provision of effective interventions.

A global view of migration

On a worldwide scale, the total number of economic migrants exceeds 200 million, not considering asylum-seeking refugees. Albeit slowed down in the recent phase of recession, the flow will keep on in Europe and in Asia too, where China will become the main pole of attraction of the migration scenario[2]. Only about 10%-15% of migrants from all over the world are in an irregular situation: most of them have entered in a legal way but remain more long-term than their authorized residence[6].

As of January 2014, the number of migrants for economic reasons in the 28 countries of the European Union (EU) totals 19.6 million, representing 3.9% of the population (Figure 1). In absolute terms, the largest numbers are found in Germany (7.0 million persons), the United Kingdom (5.0 million), Italy (4.9 million), Spain (4.7 million) and France (4.2 million), collectively representing 76% of the total. Besides, according to estimates, there is an unknown number of undocumented migrants, accounting for a huge proportion of the population (up to 4%)[7]. The total number is expected to increase dramatically in the near future, due to massive migration of asylum-seekers refugees from conflict areas in Middle East and Northern Africa. A few EU countries are facing for the first time the problem of immigration and multi-ethnic population. Migrants have long been a negligible problem in Italy. In 1991, for the first time the number of migrants exceeded 1% of the total Italian population. Later, the number doubled in ten years to reach 7.5% by the end of 2010[8].

Migration to the United States has also been increasing since 1945 with the current immigrant population estimated at 38.5 million or 12% of the total population[9] (Figure 1). Large waves of immigration occurred over the past 20 years[10]; by 2050, nearly 1 in 5 United States residents is expected to be an immigrant, compared with 1 in 8 in 2005[11].

Since 1945, more than 7 million people have also settled in Australia. The 2011 Census reported that over one in four of Australian 22-million people were born overseas. Most of them were born in New Zealand (16.2%), the United Kingdom (13.6%), India (10.9%), China (10.0%) and South Africa (4.6%) (Figure 1). Pacific Islanders (Samoans and Tongans) represent another large component of immigration[12].

The complexity of migration remains a fundamental problem. Most statistics on migration are based on concepts that are not representative of a good deal of the dynamics of today migration flows. It is nearly impossible to have the exact numbers of short-term movements and status, as well as to assess properly the extent of undocumented migration that exploded around and across the Mediterranean Sea.

Problems in the study of chronic NCD in migrants

Different data sources may be used to describe the outbreak of NCDs in relation to indicators of migration or ethnicity, as country of birth, self-identified ethnicity, as well as more specific features (language and religious affiliation)[13-15]. The essence of ethnicity implies same origins

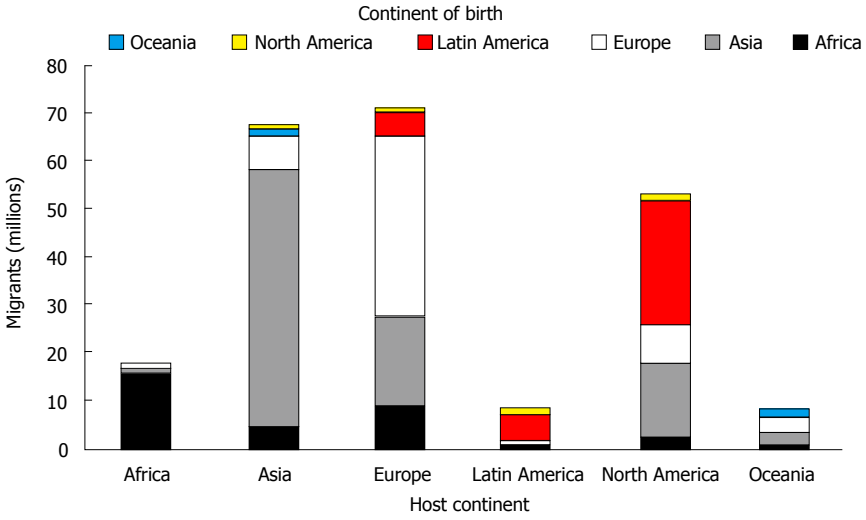

Figure 1 Worldwide numbers of migrants (over 200 million) in relation to continent of birth and host continent. Note that most migration occurred intra-continentally. Massive inter-continental migration is recorded from Africa, Asia and Latin America to Europe, as well as from Asia and Latin America to North America, with virtually no migrants to Africa and Latin America and from Oceania.

or social environment, definite culture and customs, and a common language or religious heritage[16,17], but proxy measures are difficult to define. Country of birth is a crude method, which becomes a vague measure as time since migration goes on[15,18]. Nationality or citizenship represent critical indexes as immigrants may have nationality and citizenship of the host country, but yet belong to ethnic groups with different lifestyle habits, religion and culture. Without an overall agreement concerning both the definition of ethnicity and of being a migrant, it is difficult to set the reasons behind the prevalence of NCDs or diabetes. The relation between migration status and disease may be affected by genes, exposure in pre-migration life to poverty, precarious health and sanitary conditions, eating habits, infections, rooted cultural customs retained in adulthood, exposures in post-migration life, as well as quality of health care and access to health services in countries of destination (Figure 2).

Diabetes prevalence in migrants vs native populations

Europe: With a few exceptions, prevalence, incidence and mortality rates for diabetes are much higher in migrants than in native people[2,19-22]. In the Netherlands, diabetes is more common (by a factor of 2) among the main groups of immigrants, *i.e.*, those born in Turkey, Morocco, Suriname or the Antilles. Even larger differences are observed in diabetes-related mortality, with rates 3 and 4 times higher among migrant men and women, respectively, compared to the indigenous population. Surinamese migrants have the highest prevalence and mortality rates[23], which are most likely due to the higher incidence, although differences in case-fatality rates may also exist.

In the United Kingdom, the prevalence of diabetes mellitus among migrants of South Asian origin (Afghanistan, Bhutan, Maldives, Nepal and Sri Lanka) is around 20%, *i.e.*, nearly five times higher than the local European population. Furthermore, age at onset of diabetes is 5-10-year earlier and chronic complications are more common amongst migrant populations[24]. In Italy, the prevalence of diabetes in migrants is definitely lower than in the general population, but only 15% of migrants are less than 50, *vs* 43.1% of the Italian population[25]. When adjusted for age and sex in a case-control study, the overall risk of diabetes in migrants was 1.55 (95%CI: 1.50-1.60)[26]. Notably, the risk varies among ethnic groups; the likelihood of being treated with a glucose-lowering drug is four-fold higher in people from Egypt and the Indian subcontinent, whereas it is halved in migrants from former Eastern socialist countries, in keeping with diabetes prevalence in their countries of origin[13]. Also in African migrants to France diabetes develops earlier compared to those staying their country of birth[27].

A 20-year longitudinal follow-up of first generation migrants residing in the United Kingdom reports an incidence of type 2 diabetes almost 3 times higher in the Indian Asian population and more than twice in the African Caribbeans, compared with the European controls. Notably, in the female population the increased likelihood of having diabetes was attributed to baseline insulin resistance and abdominal adiposity, not in men[28]. The Healthy Life in an Urban Setting (HELIUS) study, started in 2011, aimed at assessing the factors contributing to the occurrence of diseases, including NCD, cardiovascular diseases and mental disorders, in association with ethnic differences, in a cohort of about 60000 Amsterdam residents representative of 5 migrant groups as well as native residents[29]. Patients with diabetes coming from Asia, Middle East and Sub-Saharan Africa if compared to Western populations are at particularly higher risk of microvascular complications, *i.e.*, diabetic retinopathy, nephropathy and peripheral neuropathy[30]. It is also the case in ethnic minorities of the same regions settled in Western countries; *e.g.*, in the United Kingdom minority ethnic communities with type 2 diabetes, compared to white Europeans, are more likely to develop ocular complications, including sight-threatening retinopathy and maculopathy[31].

In seven European countries diabetes mortality of 30 migrant groups was much higher than in native residents (almost 90% higher for the male population and 120% higher for the female population)[32]. An English follow-

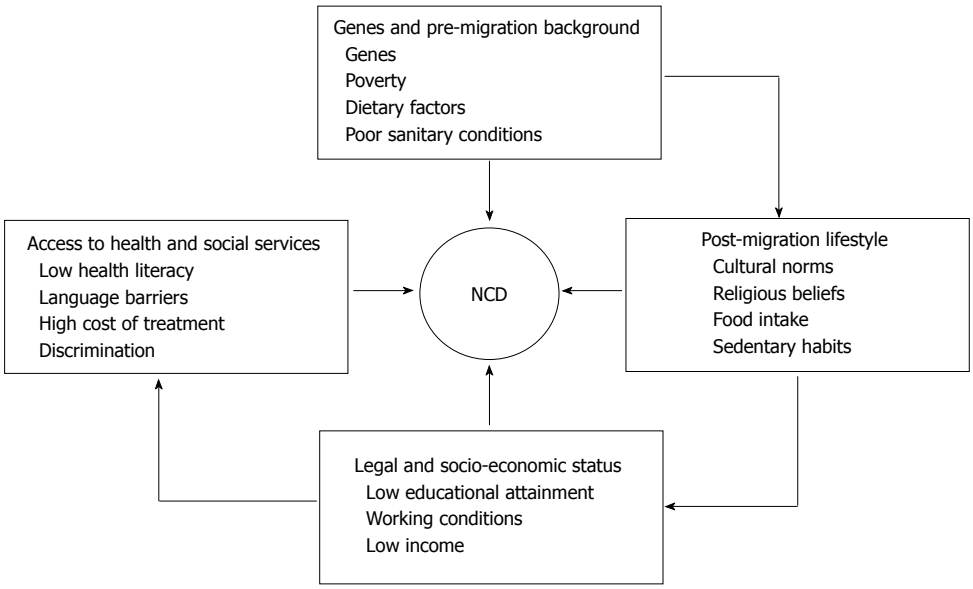

Figure 2 Factors associated with non-communicable diseases in migrants. A complex interaction between genetic, cultural and socio-economic factors is the basis for the development of NCDs, variably associated in different ethnic groups. NCD: Non-communicable diseases.

up study reported higher diabetes mortality rates in patients from South Asia compared to European patients, particularly among the young population[33]. Similar observations have been made amongst Asian Indian migrants[34].

These differences might be ascribed to a genetic background. Nevertheless, the few studies considering socio-economic factors and quality of diabetes care show a reduction of the role of ethnic differences in complication rates. Therefore, complications among ethnic minority groups with diabetes might also be driven by failure to achieve treatment goals and/or lower screening rates and preventive measures[31].

United States: In 9 regions of birth, covering a hundred countries, representing 16 million United States immigrants, overweight/obesity and diabetes prevalence were regularly estimated and compared from 1997 to 2005. Most of migrants were born in Mexico (48%), followed in order of decreasing number by migrants from all Asian regions (almost 20%), Europe, South America, Africa, the Middle East, and Russia. Among United States immigrants, a substantial heterogeneity is noted, by region of birth, in the prevalence of both diabetes and overweight, with diabetes rates stretching from 3.1% in Europe to 10.0% in the Indian subcontinent[35]. Migrants from South America, generally considered as Hispanic ethnicity, have lower diabetes and overweight prevalence than migrants from Mexico, Central America, and the Caribbean Islands; *i.e*., gathering individuals by ethnicity may conceal important differences in the prevalence of the disease.

Blacks (without any distinction for immigrant status) have higher rates of diabetes compared with whites[36]. The difference is likely to stem from the increased insulin resistance of black people at adiposity levels similar to whites[37], particularly in African migrant men, not in women. Black women have twice the obesity prevalence of white women[38], and a prospective incidence study on ethnicity and diabetes in middle-aged adults, African American men and, to a lesser extent, women had a considerably higher incidence of type 2 diabetes compared with white people. The elevated incidence and prevalence of diabetes is thus explained by modifiable risk factors such as adiposity[39].

The three largest Asian-American, native Hawaiian, Pacific Islander subgroups [people of Chinese (3.3 million), South Asian (2.8 million), or Filipino (2.6 million) ancestry] are all at increased risk to develop diabetes[40]. In general, their risk is higher relative to non-Hispanic whites, but lower than that of African Americans and Latinos[41,42]. Although data are limited[43], diabetes prevalence is more than doubled among Pacific Islanders (18.3%) *vs* with white participants (7.3%), and significantly higher than among other Asian subgroups, confirming that continental data must be disaggregated on a national scale[42]. Ethnicity-specific risks of microvascular complications (retinopathy) have also been demonstrated[44].

Australia: For all migrant groups, the odds of type 2 diabetes *vs* native residents are higher, after adjusting for age and across all socio-economic strata[45]. In the Fremantle Diabetes Study, the prevalence in Asians and the general population was similar, but the Asian patients were younger, less obese and less likely to be hypertensive. Nonetheless, they had a higher prevalence of retinopathy. During an 18-year follow-up, Asian ethnicity was independently protective against cardiovascular death, not all-cause mortality[46]. According to the Melbourne Collaborative Cohort Study[47], the baseline prevalence and the cumulative incidence of type 2 diabetes were more

than three-fold higher in migrants born in Greece or Italy than in individuals born in Australia[48]. These findings are consistent with the higher prevalence showed by Australian cross-sectional studies[49,50].

Higher BMI in the migrants was responsible for almost one-half the excess relative risk in incidence, whereas other risk factors for diabetes, including the waist-to-hip ratio, and diet, had little impact on the remaining excess relative risk. However, there is no evidence for a specific genetic susceptibility to diabetes in Italian migrants[51]. Health care is universally available in Australia and generally of good standard. Thus, the risk of excess mortality in migrants because of different chances of access to treatment and standard of care is minimized. The poorer outcome of migrant people with diabetes remains a priority study area, subject to continuous scrutiny[52].

Prevalence of NCD in migrants vs rates in the countries of origin

When the prevalence of diabetes in migrants is compared with that in the country of origin, the general characteristics, the prevalence of obesity, as well as the general degree of socioeconomic development, as measured by the gross domestic product[32], should always be considered. The lower the socio-economic status in the country of origin, the higher the risk to become obese. For example, in a study investigating on Ghanaian migrants in the Netherlands, people living in Amsterdam compared to those living in rural Ghana[53], were 10 times more likely to be overweight, and overweight represents a risk factor for the development of diabetes. This explains why among migrants from low-income countries compared to locally born European populations, diabetes mortality rates are more than 200% higher, in comparison to a 100% higher rates for migrants from middle-income countries[32]. In view of these considerations the high diabetes mortality of migrants seems to be associated to the movement from a poverty-ridden rural area, in early life, to an obesogenic urban environment in later life, with a few exceptions.

According to previous researches Asian Indians who moved to the United States have worse metabolic profiles when compared to their counterparts still living in India[54]. Contrary to that, the CARRS and MASALA Studies[55] reported a higher diabetes prevalence in indian people living in India than their homologous who have migrated to the United States, even with Asian Indians living in India having lower BMI and lower waist circumference values than their counterparts who have migrated to the United States. Surprisingly, both the overall and the age specific prevalence of prediabetes resulted lower in Asian Indians living in India than in Asian Indians minorities who moved to the United States; the explication could be linked to a more rapid conversion, through the natural history of the disease, in people living in India. Furthermore, the prevalence of type 2 diabetes in Asian Indians living in the United States was still significantly higher than that of the general United States population[41,55,56], despite the fact that the general United States population has, compared to Asian Indians, an overall higher BMI. Therefore it could be probable that India finds itself in an early stage of the diabetes epidemic; thus most susceptible subjects develop it the earliest[57].

Having regard to the current phase of rapid economic and nutritional changes over the Indian continent[58,59], these aspects could increase the risk in Asian Indians both in India and abroad. It is also likely that Asian Indians who have migrated to the United States have adopted healthier lifestyle habits, both in food choices and physical exercise, reducing their risk of type 2 diabetes occurrence[60], thereby altering the relation existing in this population between migration and NCD risk.

Another way of analyzing the role of country of origin is to compare migrants who come from the same country, now living in different countries. From January 2012, a multicenter cross-sectional study is evaluating differences in lifestyle, epigenetics and biochemistry that increase the risk of type 2 diabetes and obesity among homogenous sub-Saharan African participants (*i.e.*, Ghanaians) aged > 25 years living in rural and urban Ghana, the Netherlands, Germany and the United Kingdom[61].

Genetic factors should anyway be considered to dictate the prevalence of NCD in migrants, as compared to the native populations. Genetic studies have confirmed a role of the ethnic background in the higher prevalence of diabetes in South Asian people[62-64] and in the higher rates of hypertension among West African migrants[65,66], whereas the obesogenic environment of the country of immigration makes the difference between NCD prevalence in migrants *vs* the corresponding prevalence in the country of origin.

Disease convergence

In the long-term, diabetes risk in migrants is expected to converge towards the levels of the locally born populations. This relates to the "healthy migrant" effect, *i.e.*, migration is expected to be a selective process favoring healthy individuals, resulting in low occurrence of diseases among migrants in the first period after their arrival in the host countries[67]. As an example, in 2013, the median age of the national population in the EU-28 was 43 years, while the median age of non-nationals living in the EU was 35 years. This protective effect is also present with other NCDs[46], but as time goes by the relative advantage of migrants over locally born subjects could reduce.

Convergence can be also predicted due to the fact that migrants generally integrate over time into the society, and its customs, of their host country[68]. As migrants adopt the same habits being exposed to the same environmental risk factors as indigenous people, albeit gradually and slowly[69-71], their epidemiological profiles may move ever closer to those of locally born

subjects[68]. "Period" studies (comparing different time periods)[70,72,73] and "cohort" studies (comparing cohorts of migrants differing in terms of acculturation)[69] supported the convergence hypothesis: The risk of cancer resulted more similar to that of the indigenous populations among people with a longer period of migration, *i.e.*, among the second generation, and, within the first generation, among people who had migrated during infancy. However, convergence takes a lot of time, more than 20 years in some studies[74].

Another theory explains lower mortality in migrants by "the salmon bias" hypothesis, reflecting the trend of sick migrants returning back to their home country before death; in most settings, this does not fully explain the paradox[67,75,76], and it is possible that inaccurate counting of mortality among migrants minority groups lead to an underestimation bias[77].

Diabetes risk, disease progression and diabetes care in migrants

Predisposition to develop insulin resistance and truncal obesity, the exposure to a particular intrauterine environment and even the biological imprinting all push in the same direction enhancing the risk of diabetes[78], as well as its progression, in migrant populations, frequently fuelled by differences in standard of care. Many migrants in non-Western countries have risen in conditions of poverty and their bodies have been "programmed" to tackle hunger and starvation. The result is that later in life, when exposed to the obesogenic environment of the country of immigration (high-fat diet and sedentary lifestyle), they are particularly prone to stock energy reserves and thereby gain weight[2,53]. A cross-sectional study in a large cohort of migrants from the Philippines to the city of Rome recorded abdominal obesity in 52.5% and a high prevalence of undiagnosed type 2 diabetes and hypertension[79]. Years of residence in Italy showed a significant direct correlation with the degree of changes in food intake ($P = 0.001$) and weight gain ($P < 0.001$), suggesting a direct impact of lifestyle.

Also the so-called social determinants of health may be involved (*i.e.*, low socio-economic status, separation from family, anti-migrant feelings in the host community, traditional beliefs influencing the health-seeking behavior, the lack of legislation to ensure migrants' access to health and social services, effective policies to protect migrants' labor rights and welfare). This is mainly the case with insurance-type health care systems, but poor access to health services is also demonstrated in health care systems that are essentially built on a principle of equity and equality. Integration of migrant population into the receiving healthcare system is becoming a key issue in developed countries who receive a large number of migrants each year. Independently of the healthcare system, several reports have shown that migrants are undertreated compared with the native population[80,81]. This is probably related to a lower-than-needed attendance of migrants to primary care or preventive health services, due to personal barriers (job and time constraints) or socio-cultural conditions, not only to specific defects in the healthcare system[82,83]. In native Dutch and in various groups of immigrants aged 55 and older, the use of prescribed drugs was explained by Andersen's behavioral model[84], based on three individual factors of health care use: (1) need (self-rated chronic conditions); (2) enabling conditions (educational level, standardized household income); and (3) predisposing factors (Dutch language proficiency, modern attitudes on family care, male-female roles, family values, religion)[85]. Differences in the verbal interaction of Dutch GPs with immigrant *vs* Dutch patients have been demonstrated by video recording: Consultations with immigrant patients were over 2 min shorter, with major differences in verbal interaction and less empathy[82]. In diabetes, language proficiency and modern attitudes on male-female roles have been associated with utilization of diabetes drugs, especially in Turkish[86] and Moroccan elderly patients[85], where inequalities might be amplified by behavioral components (smoking, inactivity, alcohol consumption)[87,88].

Leisure time physical activity is definitely lower in migrants[89-91], but the amount of calories spent at work, because of more common manual labor, might be considerably higher[64]. An Australian study reported a higher relative risk of smoking and alcohol use[92], and lower adherence to recommendation for healthy diet is also frequently described. A systematic review from the United Kingdom, on a migrant South Asian population, reported that all South Asian groups were found to have a more sedentary lifestyle than their European counterparts[93]. However, the high variability and the large proportion of different migrant minorities moving across the world make it difficult to draw any conclusions.

Inequalities in migrant health care are not limited to diabetes groups. In a Swiss cohort of forced, asylum seekers migrants, lower scores for physical examinations and breast and colon cancer screening have been reported, despite universal healthcare coverage[94]. In a Swedish population-based follow-up concerning drugs given to patients after acute myocardial infarction, no major differences were observed in relation to socio-economic status[95]. However, among immigrants from outside the EU countries there was a 20%-30% reduced prescription of drugs recommended by Swedish guidelines (aspirin, beta-blockers, cholesterol-lowering drugs and ACE inhibitors). Also in this case, ethnicity may make the difference; in ethnic German migrants from the former Soviet Union to Germany only minor differences in drug utilization pattern were recorded, compared with native Germans[96]. In this case, however, much similar habits and traditions might help canceling the differences. Far from being money-saving for the Health Systems, underutilization of drugs and primary care services in specific ethnic groups is expected to produce a larger-than-needed use of emergency services and hospitalization rates due to disease progression and complications, which might translate into higher costs[97,98].

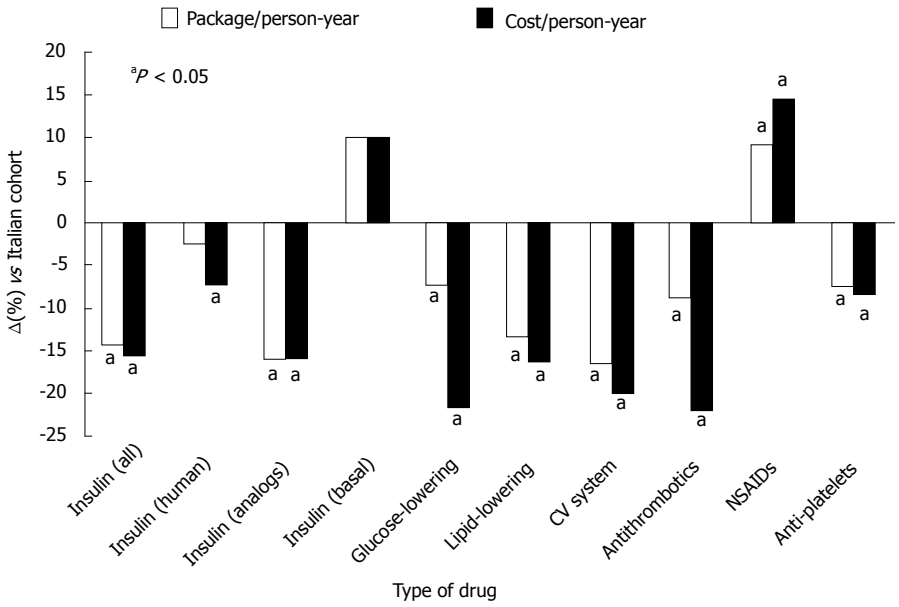

Figure 3 Differences in drug use and overall pharmacologic cost of diabetes in migrants, compared with native Italians. Both drug use and total costs were lower in migrants, with a different use of insulin and oral hypoglycemic agents. Non-steroidal anti-inflammatory drug use was higher, possibly as a consequence of more common traumas and manual work.

Data from the ARNO database: Drug use and the direct costs of drug-treated diabetes among migrants and Italian citizens has been extensively investigated on the basis of 2010 prescriptions in the population-based multiregional ARNO Observatory, a database containing the prescriptions and hospital admissions of a population of about 10 million Italian residents, living in 30 Health districts scattered throughout the country[99]. According to Italian rules, a diagnosis of diabetes grants free access to drugs, diagnostic procedures and hospitalization to persons residents in Italy, independently of their citizenship. All drug prescription data or hospital admission records contain a code including the date and place of birth. For people born outside Italy, the city code is replaced by the country code, thus permitting univocal identification of people born outside Italy.

Based on the above criteria, in the nested ARNO population of over 8 million people first and second-generation migrants were classified according to country of birth and citizenship. All patients who had at least one prescription of anti-diabetic medication, either oral agents or insulin (Anatomical Therapeutic Chemical Classification System, code A10A and A10B, respectively) during 2010 were considered as affected by diabetes. The odds of migrants of being diagnosed with diabetes compared to Italians were tested using a case-control study design, with one migrant matched for major confounders (age, sex and place of residence) to one Italian subject. Finally, migrants with diabetes were individually matched for confounders to Italians with diabetes to compare prescriptions, hospitalization rates, use of services and direct costs for the National Health System.

Migrants with diabetes were 15-year younger than native Italians. Both glucose-lowering and non-glucose-lowering drugs were underused in migrants with diabetes, with the notable exception of a few drugs (*i.e.*, non-steroidal anti-inflammatory agents), whose excess use might be related to more intense manual and traumatic work (Figure 3). Migrants had a different pattern of glucose-lowering treatment, with 44% higher prescriptions of oral drugs and 19% lower prescriptions of insulin and a different insulin pattern[26,100]. Also lipid-lowering drugs and antithrombotic drugs were 15%-20% underused in migrants. The total cost was 27% lower in migrants, due to a lower cost of drugs (29%), hospital admission (27%) and health services (22%)[26].

Notably, hospitalization rates due to diabetes per se were 60% more common in migrants *vs* native Italians of the ARNO observatory[26]. This might represent the consequence of under-treatment, also considering that hospital length-of-stay was longer in migrants. Contrary to that, a report from the London School of Economics found that hospital stay among the immigrant population was significantly shorter in Europe after adjusting for age, case mix and disease severity, suggesting unequal treatment for equal needs[101]. A cross-sectional analysis of health service use among elderly immigrants and native populations of 11 European countries recorded a migrants' overutilization of hospital stay and consultations in several countries, not in Italy, due to difficulties in the integration of migrants because of very recent immigration and cultural reasons[102]. No data are available on the attendance of migrants to emergency departments not followed by hospital admission, a procedure not traced by the Italian Health System. Emergency services might be overused, fuelled by socio-economic inequalities[103], to provide immediate care to less complicated conditions.

CONCLUSION

The growing burden of chronic diseases, specifically diabetes, in migrant and ethnic minorities represents a serious public health challenge for many European countries, also fuelled by the economic crisis, social inequalities, terrorism and wars. Migrant flow is not expected to slow down in the next few years, and it will generate an increasing economic cost for the National

Health System. The same is true for United States, where African and Mexican Americans may experience higher rates of diabetes prevalence, which will translate into different and increasing costs.

High-risk migrant minorities may remain undertreated and unprotected also in a universalistic healthcare system[104]. Poorer socioeconomic status and barriers generated by the present culture of biomedicine might make the difference on patients' side, but inequalities might also stem from physicians' side, with a different approach by both primary care physicians and specialists[105]. Efforts should be made to favor visits to general practitioners/diabetologists and attendance to screening and treatment programs, to adapt education programs to specific cultures[106], to cope with misbeliefs[107], and to develop community partnerships.

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MINIREVIEWS

Role of diabetes in heart rhythm disorders

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Abstract

The incidence of diabetes mellitus (DM) is increasing rapidly. DM is the leading cause of cardiovascular diseases, which can lead to varied cardiovascular complications by aggravated atherosclerosis in large arteries and coronary atherosclerosis, thereby grows the risk for macro and microangiopathy such as myocardial infarction, stroke, limb loss and retinopathy. Moreover diabetes is one of the strongest and independent risk factor for cardiovascular morbidity and mortality, which associated frequently rhythm disorders such as atrial fibrillation (AF) and ventricular arrhythmias (VA). The present article provides a concise overview of the association between DM and rhythm disorders such as AF and VA with underlying pathophysiological mechanisms.

Key words: Atrial fibrillation; Diabetes mellitus; Cardiovascular complications; Pathophysiological mechanisms; Ventricular arrhythmias

Core tip: The incidence of diabetes mellitus (DM) is increasing rapidly. DM is the leading cause of cardiovascular diseases. Atrial fibrillation (AF) and ventricular arrhythmias (VA) are most common form of arrhythmias, which lead to cardiovascular complications and mortality in patients with DM. The present article provides a concise overview of the association between DM and rhythm disorders such as AF and VA with underlying pathophysiological mechanisms.

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INTRODUCTION

Diabetes mellitus (DM) is recognized as a major cardiovascular (CV) risk factor and its close relationship

with cardiovascular morbidity and mortality is well established[1]. Although coronary artery disease and related cardiac events are the most documented diabetic cardiovascular effects, cardiac electrical system is also an important target for diabetic damage. In Framingham heart study, DM is established as an independent risk factor for atrial fibrillation (AF) after 38 years of follow-up[2]. A recent meta-analyses published by Huxley *et al*[3] revealed that patients with DM had a 40% greater risk of developing AF compared to patients without. On the other hand, there has been growing evidence about the relationship between hypoglycaemic episodes and ventricular rhythm disorders for the recent years[4,5]. The relationship between DM and arrhythmic disorders is not fully understood yet and there is a growing population of DM patients everyday. This relationship is expected to become more of an issue in the near future. Here we would like to present a brief overview on this relationship especially for AF and ventricular arrhythmias.

Diabetes and AF

AF is the most common arrhythmia in clinical practice resulting in major cardiovascular morbidity and mortality[6]. Earlier The Framingham Study and recently a study from Movahed *et al*[7] clearly established that DM is a powerful and independent risk factor for the development of AF. This close relationship between AF and DM raises the question for pathophysiological basis for this entity. Although there is no single and easy answer for this question, both electrical and anatomical remodelling seems to be important keys of these complex pathophysiological changes.

Extensive fibrosis in the atrial tissue is the anatomical hallmark of AF with a role in both starting and perpetuation of the arrhythmia and as the fibrosis expands it is more likely that paroxysmal AF transforms into permanent or anti arrhythmic resistant type[8,9]. Kato *et al*[10] showed that DM related atrial fibrosis has a potential role in starting AF in diabetic rat models. Exaggerated systemic and tissue level oxidative stress seems to be the key element in atrial fibrosis related to DM. Dudley *et al*[11] evaluated the superoxide anyone levels in a pig atrial model. The study compared the levels of superoxide in left atrial appendage between the sinus rhythm group and atrial rapid pacing (ARP) group. Results showed that in the ARP group left atrial superoxide anion levels were almost three times higher than the control group. Another study from Anderson *et al*[12] showed that mitochondrial oxidative stress is increased in diabetic human atrial tissue. These studies may show that despite increased levels of systemic oxidative stress in DM, there may be a production of reactive oxygen species *via* mitochondrial pathway specifically at the atrial tissue level.

Non-enzymatic glycosylation of proteins and the end products of this pathway (Advanced Glycation End products; AGEs) interact with their receptors (RAGE) and upregulate the connective tissue growth factor (CGTF)[13]. This system (AGERAGE) may start or contribute to atrial fibrosis in diabetic patients *via* stimulation of connective tissue growth factor in the atrial myocardium[14].

Dysfunction in the autonomic innervation and control of cardiovascular system is defined in diabetic patients[15]. It seems that autonomic imbalance in favour of sympathetic system, which might have a role in the onset of AF. Otake *et al*[16] previously documented that excessive sympathetic stimulation in streptozocin induced diabetic rats increases the incidence of AF compared to control group. Further electrophysiological studies in the diabetic rat atrium revealed shortened atrial effective refractory period (AERP) and increased dispersion of AERP. Another clinical study suggested that reduced heart rate recovery in type 2 DM patients with preserved ejection fraction is associated with increase in the incidence of AF[17]. These clinical and laboratory studies imply that autonomic dysfunction has a role in the pathogenesis of AF in DM patients.

Atrial electrical structure is also affected in diabetic patients. Shortened AERP increased dispersion of AERD and intra atrial conduction time, which are the key elements of atrial electrical remodeling[16,18]. Chao *et al*[19] analyzed the detailed three-dimensional electro anatomic mapping of 228 patients who has DM or abnormal glucose metabolism (AGM) and underwent AF ablation for the first time. Results showed that biatrial voltage measurements in DM and AGM group were significantly lower than control group. Furthermore these patients also had increased recurrence rate of AF in the follow up period. Acar *et al*[20] has shown in their published study, that patients with DM had significantly increased inter and intra atrial electro mechanic delay with impaired diastolic functions comparing to control group. On the other hand, it has been shown that there is a specific change in cell to cell integration in DM patients. In a streptozocin induced diabetic rat model study, connexin 43 expression was significantly higher than connexin 40 in diabetic rat atria, which may sign that connexin 43 expression is upregulated in diabetics as a gap junction protein[21].

Conversely, there are some other data suggesting that fluctuations in the blood glucose level rather than the long-term hyperglycemic environment is related to increase in the incidence of AF in diabetic patients[22]. Saito *et al*[23] showed that glucose fluctuations increase the incidence of AF in streptozocin induced diabetic rat models. Huxley *et al*[24] failed to show any correlation between fasting glucose, insulin levels, HbA1c levels measurements and AF onset in patients without diabetes. Another clinical study from Fatemi *et al*[25] prospectively evaluated the affect of intense glycemic control on incidence of AF in diabetic patients. Interestingly, they failed to present any association between incident AF and intense therapy comparing to standard therapy group. However, their choice of periodic electrocardiographic testing instead of event recorders might alter the results in terms of missing the paroxysmal AF episodes occurring any time besides the office control.

There are no randomized data specifically addressing the effect of DM in other supraventricular arrhythmias,

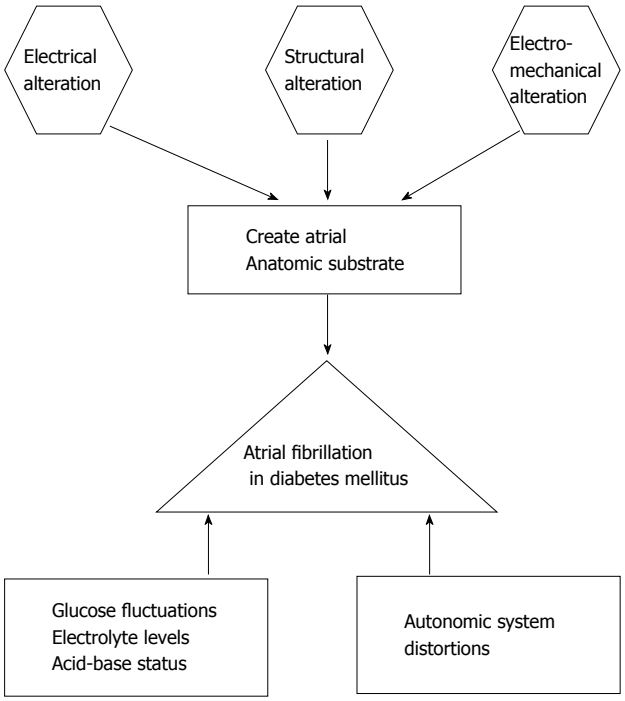

Figure 1 Potential pathophsiological mechanisms of atrial fibrillation in patients with diabetes mellitus.

but there are case reports discussing whether acute changes in metabolic profile during ketoacidosis episodes might trigger arrhythmias such as supraventricular tachycardia[26].

Overall, DM seems to be acting a pivotal role in generation and maintenance of AF in diabetic patients. Specific structural, electrical and electromechanically alterations in diabetic heart might create an anatomic substrate for the development of AF. On the other hand, acute hypo or hyperglycemia changes in electrolyte levels or acid-base status and autonomic system distortions may be a trigger mechanism for the arrhythmia (Figure 1). It is clear that there are still dark spots about the relationship between AF and DM that warrants further studies.

Diabetes and ventricular arrhythmias

Cardiovascular diseases (CVD) are the leading cause of death in diabetics and DM is almost a synonym for atherosclerosis and coronary artery disease. High incidence and extent of atherosclerotic heart disease in diabetics leads to high incidence of ventricular arrhythmias (VA) and sudden cardiac death (SCD) inevitably[27-29]. Although this close relationship between VA, SCDs and DM is mostly based on the extent of coronary artery disease among diabetics, non-coronary atherosclerotic processes like autonomic neuropathy, microvascular disease, ventricular structural and electrical changes may partly play a role in this phenomenon[30].

A ventricular repolarization anomaly, which is reflected by QTc interval prolongation, is associated with high risk of VA. There are several studies showing, marked QTc prolongation in diabetic patients[31]. Another strong predictor of VA, microvolt T wave alternans (TWA) measurement, has been studied in type 2 diabetic patients without known CVD, considering the glycemic status in each patient (which is reflected by HbA1c levels)[32]. In this small study, the frequencies of atypical TWA patients were significantly higher than the control group. In the diabetic patient group, patients with atypical TWA measurements had significantly elevated HbA1c levels, which is concluded as every 1% rise in HbA1c levels is linked with 13 fold higher risk of having atypical TWA and suboptimal glycemic control is linked with higher risk of spontaneous VA independent of QTc interval duration. These results from the studies are signing an electrical instability of diabetic myocardium, which creates a potential substrate for ventricular arrhythmias independent from the scarred myocardium areas from previous ischemic cardiac damages. On the other hand, autonomic neuropathy of diabetes results in an unbalanced sympathetic stimulation on myocardium, which may further contribute to this electrical instability and predispose to lethal arrhythmias[33]. In this context, cardiac sensory neuropathy of diabetics is another important issue that causes VA and sudden death indirectly *via* silent ischemia[34].

As DM creates a vulnerable myocardium for arrhythmias, it seems to be involved in the triggering mechanism for these arrhythmias too. A study from Chen-Scarabelli *et al*[35] investigated if there is a relationship between HbA1c levels and risk of VA in patients with implantable cardioverter defibrillators retrospectively. The study included 141 patients with DM and 195 patients without DM. A significant association between HbA1c levels of 8%-10% and spontaneous VA incidence in diabetic patients was observed, rather than the diabetic condition and independent from QT prolongation, stating that suboptimal glycemic control and persistent hyperglycemia is related with higher risk of spontaneous VA. On the other hand, in another randomized prospective study, link between hypoglycemic episodes and VA in patients with type 2 DM and documented CVD is investigated[4]. In this study, there were 30 patients treated either with insulin and/or sulfonylureas (SU) and there was an age matched control group of 12 patients treated with anti hyperglycemic agents with low risk of hypoglycemia. There were high incidence of hypoglycemia and silent VA in the insulin and/or SU group comparing to control subjects. A study from Pistrosch *et al*[5] further analyzed effects of hypoglycemia as a trigger for VA in larger patient cohort with type 2 DM revealed that hypoglycemia might be able to trigger VA and interestingly a tiroid stimulating hormone level in the low-normal range, which indicates subclinical hypertiroidism, is indepently associated with occurrence of VA. Although these two studies provide no casual relationship between hypoglycemia and VA in diabetic patients, it may be postulated that hypoglycemia may be triggering VA either with sympathetic overstimulation or QT prolongation[36].

Interestingly, another study investigating the association between diabetes and VA in patients with severe

heart failure revealed a negative independent relationship with diabetes and VA in this patient group. Moreover, the authors concluded that DM might have a protective effect for the occurrence of VA in the setting of decompensated heart failure[37].

In summary, DM might play a critical role in creating a vulnerable substrate and/or as a trigger for VA besides the expected risk based on the high extent and incidence of coronary artery disease. Conversely, there is clinical data that claims DM has a protector effect for VA at least in certain group of patients. Unfortunately, there is not enough randomized large-scale data in the literature to suggest a definite relationship and clear pathophysiological mechanisms for this entity.

CONCLUSION

AF and VA are most common form of arrhythmias, which lead to cardiovascular complications and mortality in patients with DM. Although, there are an evidence based risk factors for an arrhythmogenic substrate that may be specifically related to diabetes, such as heterogeneities in atrial and ventricular repolarization, the extend of myocardial damage, scar formation, autonomic system distortion, glucose fluctuations as well as structural and electrical alterations, the causal pathophysiological and electrophysiological mechanisms are warranted in further studies.

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