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ORIGINAL RESEARCH

Economic Impact of COVID-19 Lockdown on Italian NHS: Focus on Diabetes Mellitus

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Background: In Italy, the adoption of a total lockdown has generated almost total suspension of outpatient visits except for emergencies. Even after lockdown, the pandemic fear created additional barriers to access the health services. The aim of our study is to evaluate the economic impact of the lockdown for COVID-19 on public health in Italy, focusing on its effects on diabetic population.

Materials and Methods: We analyzed the impact of the lockdown on excess mortality and morbidity in the Italian diabetic population during 2020. The analysis was divided into several steps: a quantification of specialist visit reduction, the calculation of excess mortality in the diabetic population, the economic evaluation of the slowdown in the use of innovative diabetic therapies. Furthermore, the impact of the lockdown on the reduction of procedures and follow-up visits in diabetic population was evaluated. The overall impact of the pandemic and lockdown effects on costs and quality of life was then calculated.

Results: During 2020, a drop of 28% in patient access has been observed. Diabetic patients recorded a twice higher mortality value compared to general population (20.4% vs 10.2%). The analysis of market data revealed a slowdown in consumption of new antidiabetic therapies (−14%, 27% vs 41%). We estimated an expense of €26.6 million for NHS and a loss of 257 utilities in diabetic population due to the missed benefits related to slowdown in innovative antidiabetic drugs use and non-optimal follow-up and control of diabetes complications. In simulation scenarios, we also estimated an overall expenditure ranging from €38.7 to 94.0 million and a loss of 294–836 utilities.

Conclusion: Diabetic population paid a high tribute to pandemic and lockdown, both in terms of number of deaths and burden of diabetic complications, together with an overall deterioration of quality of life.

Keywords: COVID-19, diabetes type II, diabetic complications, quality of life, economic impact

Introduction

COVID-19, an acute respiratory syndrome with immunological implications, due to SARS-CoV2, has been the first worldwide sanitary emergency after globalization, and Italy was the first country to face the pandemic after China.[1] During 2020, Italy reported about 2.1 million cases and 75,891 deaths. In a context of general uncertainty, governments adopted different approaches to reduce the number of deaths from COVID-19 disease. The Chinese response to the COVID-19 emergency has shown that quarantine, social distancing, and isolation of infected populations can contain the epidemic. Many European countries have so implemented exceptional interventions, such as case isolation, quarantine of suspected and confirmed cases, closure of schools and universities,

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banning of public events and mass gathering situations, compulsory face mask use, up to widescale social distancing, including local and national lockdowns. Among all the countries that activated lockdown measures, Italy has implemented the longest and most restrictive ones; on the other hand, Sweden has not implemented it at all, and other countries, such as the USA and Switzerland, only recommended home isolation and adopted, with different modality and terms, social distancing measures. Despite the duration and extent of lockdown, Italy showed a greater number of deaths per million of inhabitants than those expressed by other countries despite curves of distribution and percentage of population involved were very similar.[2,3] Difference in local diffusion of the disease was probably due to regional HLA alleles correlation with the clinical severity of the disease and other factors, such as the presence of cross immunity versus other coronaviruses.[4–6] AB0 blood type and hypertension could have also influenced the mortality rate among COVID-19 patients.[7,8] The above suggests that factors other than social distancing also contributed to determine the differences in the spread of the disease.

Moreover, even after lockdown, the pandemic has created additional barriers to access health services: constraints on reservations, access quotas, delay of previous programmed interventions, telephone consultancy and so on. Furthermore, particularly during the second wave in the autumn, the pressure exerted by the media induced avoidance of care due to concern over contracting the virus.

The first and unequivocal consequence of the lockdown was the collapse of GDP all over the world, and this happened proportionally to the duration and the extent of the adoption of the restrictive measures.[9] During 2020 Italy showed the most remarkable decline in GDP: −8.9% versus the −6.8% reported by European countries, the −2.2% of Switzerland, and the −3.5% of the USA. This will have a negative impact on the ability to finance the National Health System (NHS) in the coming years.[9] Second, but not less important, consequence of lockdown was the almost total suspension of outpatients visits except for emergencies sent by the few General Practitioners still active during the pandemic. This situation lasted a little over a quarter, but the restart was obviously gradual and the recall of missed visits (mainly by telephone) necessarily approximate, due to the concomitant presence of existing bookings. This led to the loss of a semester of expert care for all patients, diabetic ones included, as well as a decrease in scheduled visits during the following months due to the fear of contagion. The main assessment of the health impact of COVID-19 is the computation of deaths. According to WHO guidelines, a COVID-19 death is defined as a fatal event resulting from a clinically compatible illness in a confirmed COVID-19 case, unless there is a clear alternative cause of death (eg, trauma, stroke, acute myocardial infarction). Furthermore, there should be no period of full recovery between illness and death.[10] Multiple measures are commonly used to assess the proportion of infected individuals with fatal outcomes. Infection fatality ratio (IFR), which estimates the proportion of deaths among all infected individuals, is unlikely to provide a clear picture of fatal events related to COVID-19, since it assumes an accurate count of all infected subjects. However, it is well known that this point represents a main issue in COVID-19, due to the large number of patients asymptomatic or presenting mild symptoms, as well as the limited testing capacity.[11,12] Therefore, case fatality ratio (CFR), estimating the proportion of deaths among identified confirmed cases, is often used to measure COVID-19 deaths in scientific reports, even if this calculation has some limitations in an ongoing epidemic. By performing an age standardization of CFR the differences across countries were reduced. However, Italy had the highest CFR (3.9%), while Switzerland became the best-performing country (1.2%), same as Germany (1.3%) and United States (1.3%).[13] Considering the huge number of asymptomatic subjects, mortality rate, often expressed as deaths per one million population, can be a useful tool to weigh the impact of COVID-19 in the different Countries. Latest available data from WHO (31st December 2020) report a wide range of cumulative deaths due to COVID-19 per one million population (Table 1). Irrespective of the different measures applied by the governments, mortality rate has been more relevant in Italy: around 55% higher than Germany and Sweden, and more than double than Switzerland and USA (Table 1). This evidence seriously questions the validity of social measures such as lockdown and makes it interesting to investigate the economic and public health consequences of such measures. The aim of our study is to evaluate the economic impact of the lockdown for COVID-19 on public health in Italy, focusing on its effects on the diabetic population.

Epidemiological Background

Diabetes is one of the leading causes of morbidity and mortality throughout the world, accounting for about 4.2 million deaths among 20–79-year-old adults worldwide. Diabetes is estimated to contribute to 11.3% of the deaths globally and confers a two-fold excess risk of vascular outcomes (coronary heart disease, ischemic stroke, and vascular deaths), independently of other

Table 1 COVID-19 and Mortality Rate

	Cumulative Cases	Cumulative Cases/1 Million Population	Cumulative Deaths	Cumulative Deaths/1 Million Population	Mortality Rate
Italy	2,107,166	34,877	74,159	1227	3.52%
Germany	1,745,518	20,800	34,182	407	1.96%
Sweden	437,379	43,173	8727	861	1.99%
Switzerland	452,296	52,070	7645	880	1.69%
USA	20,445,654	61,588	354,215	1067	1.73%

Data available from World Health Organization on 31 December 2020.

known risk factors.[14] During 2016 in Italy, among a diabetic population exceeding 3.2 million, were reported 22,441 deaths as primary cause and 74,022 as secondary one (63% associated with cardiovascular diseases including hypertension) with a standardized mortality rate of 28.4 for 100,000.[15–17] On average, a diabetic patient has access to two visits per year, besides an evaluation of retina status; screening of diabetic foot, macrovascular complications (Doppler of carotid arteries) and ECG are also performed every 2 years.

During 2020 Italy had 75,891 deaths for COVID-19, with an average age of 81 years. Diabetic accounted for 29.3% of the total deaths for COVID-19.[18] Whereas in our country, diabetic patients usually cover about 25% of hospital admissions and less than 6% of the population. The number of diabetic patients' dead with COVID-19 amounted then to about 22,236, whereas the number of diabetic patients' dead for diabetes during 2018 was 21,328.[19] On the contrary, even if it is not yet possible to know how many deaths can be attributed to diabetes during 2020, we can guess that, as well as for other chronic diseases, many deaths attributed to COVID-19 masked de facto deaths due to diabetes.

Lockdown Policies

Following the outburst of COVID-19 epidemic the word "lockdown" became of very large use to describe public policies restricting freedoms (of certain activities or movement) with the aim to contain the spread of the virus. Behind the word lockdown there have been very different kinds of policies adopted by the governments, both in terms of duration and results achieved, which also influenced the possibility and/or disposition of diabetic patients to attend the programmed visits. By comparing policies adopted by Switzerland and Italy during the first wave of COVID-19 pandemic, it is possible to see significant differences such as a shorter closure of schools (61 days for Switzerland vs 107 for Italy), a shorter closure of bars, restaurants and shops excluding those defined as essential (56 days for Switzerland vs 69 for Italy); moreover, Switzerland presented no limitation to the movement of people and no obligation to wear masks even indoor shops excluding restaurants. It is therefore appropriate to assess what impact the more severe Italian policies have had and whether the viral dynamics have been modified by the policies adopted. Epidemic data from March, April, May, and June were looked at to find an answer. Considering that March and April represented the peak of spread of the epidemic in spring 2020 and in the months in which the measures were fully implemented, the average of the two is considered to measure the subsequent decline in the infection. Considering the average number of cases recorded between March and April, in Italy 3348 positive tests per day (55.47 per million inhabitants) were reported, in Switzerland in the same period 557 positive tests per day (64.99 per million inhabitants) were recorded. Compared to the first analysis period considered, in Italy in May there was a decline of 73.5%, further reduced by 92.5% in June, as for Switzerland, the reduction was 92.6% in May and 95.0% in June. The above reported data are self-explanatory in indicating that the stricter measures adopted in Italy for a longer period, particularly the 69-days total lockdown and the penalization of students who were kept away from schools for an extended period, did not have any visible impact on the dynamic of the epidemic. In confirmation of this, an assessment of the effectiveness of non-pharmaceutical intervention to mitigate the spread of the pandemic highlighted that increase healthcare workforce, closure of educational institutions, small gathering cancellation, educate and actively communicate with the public represented the four most effective intervention whereas national lockdown only came in nineteenth place.[20] Moreover, in Italy at the end of the third quarter the carry-over annual Gross Domestic

Product (GDP) growth for 2020 is equal to –8.9% (ISTAT 2021), whereas for Switzerland, GDP at the end of the third quarter is reported at –2%, referring to the pre-crisis level at the end of 2019.[21] This difference is totally due to the different policies adopted to limit pandemic spread. Finally, a recent cost-benefit analysis of the lockdown in UK demonstrated that even with the lowest estimate for lockdown costs incurred was 40% higher than highest benefits from avoiding the worst mortality case scenario at full life expectancy tariff, so that, also considering the results of vaccinations in reducing the number of hospitalizations and deaths, a fast easing of all kinds of restrictions should be enacted.[22,23]

Objective

This study aims to analyze the relationship between chronicity and pandemic management, highlighting the clinical and economic effects on the diabetic population. A multifocal analysis was conducted to show the impact of the pandemic and its management on excess mortality in the diabetic population. It was also observed a reduced access for follow-up visits and treatments in chronic patients with a decline in clinical benefits due to slowdowned prescription of the most innovative antidiabetic therapies and related consequences on costs associated with diabetic complications and worsening quality of life. The impact of suboptimal follow-up and control of micro- and macro-vascular complications in the diabetic population in Italy during lockdown was assessed. The analysis aimed to assess the economic outcomes associated with potentially avoidable diabetic complications during 2020 with increased use of drugs capable of reducing the risk of cardio-nephro-metabolic complications and to express the consequences in terms of loss of quality of life. Attention was focused on cardiovascular complications, of great importance in this population, and the implications in macular degeneration disease and diabetic foot were also considered. Amputation in patients with diabetic foot was chosen as an indicator of suboptimal management of the disease, unequivocally linked to diabetes. For these complications, it was decided to estimate the increase in costs due to non-optimal management during the lockdown and the consequences on the worsening of the quality of life.

Methods

The analysis was conducted with the aid of an analytical support developed in MS Excel® and was divided into several steps. First step: quantification of the reduction in access to specialist diabetic visits during the last year based on real-world data from the Liguria region. Second step: calculation of excess mortality in the diabetic population during 2020. Third step: economic evaluation of the slowdown in the use of innovative diabetic therapies carried out considering the diabetic complications estimated for the year 2020, potentially avoidable if these drugs were used more, as well as the assessment of these effects in terms of quality of life. For the base case scenario, in 2020 a linear trend observed in the year 2019 was assumed. Furthermore, the impact of the lockdown on the reduction of procedures and follow-up visits, important for the prognosis of diabetic patients with cardiovascular problems, and of patients with macular degeneration was evaluated. Finally, data concerning the growth of diabetic foot amputations during the year 2020 and the related consequences on economic aspects and quality of life were analyzed, as an example of negative outcome of the suboptimal management of patients with diabetes during lockdown. Data accessed is freely available, and no review and approval were required for this research by an institutional review board or ethics committee.

Reduction of Access to Specialist Diabetic Visits

The impact of the pandemic on the reduction of access to diabetic specialist visits was estimated based on the data, relating to our Genoa health facility (about 560,000 inhabitants) and 20,457 diabetic patients (corresponding to active patients in our health register referring to the last 2 years). Commonly, all active patients receive a specialist evaluation at least once a year. Starting from this observation, the variations for the year 2020 have been calculated.

Excess Mortality in the Diabetic Population

The analysis provided for the comparison between the general mortality in Italy in the year 2020 vs 2019[2,19]; subsequently, the number of deaths due to COVID-19 in diabetic patients in the year 2020 was compared with deaths due to diabetes in 2018 (data last year available),[19] to highlight 2020 excess mortality in the diabetic population compared to the general one. In addition to the excess mortality in the overall diabetic population, the detail referred to the excess cardiovascular mortality in this population was analyzed with reference to a German study.[24] In this study, the impact of the

lockdown period in central Germany on overall and cardiovascular deaths was estimated, reporting a significant increase in cardiovascular and cardiac mortality during the COVID-19-related lockdown.[24] In comparison to the reference non-pandemic period in 2019, despite a non-significant increase in all-cause mortality, cardiovascular and cardiac mortality increased significantly, the last one by 11.8% (IRR 1.12, 95%-CI 1.05–1.19; p<0.001). During the same period, this study also detected a drop in cardiac catheterization procedures.

Economic Evaluation of the Slowdown in the Use of Innovative Antidiabetic Therapies

Consumption data about the main antidiabetic therapies administered in Italy have been extracted based on market data relating to the last 3 years.[25] In detail, the variations in the use of sulfonylureas, glinides (repaglinide), SGLT2 inhibitors (SGLT2i), GLP1 receptor agonist (GLP1ra), combination of biguanide (metformin) and sulfonylurea and combination of biguanide (metformin) and SGLT2 inhibitors (SGLT2i) were then evaluated. The first categories represent old therapies, associated with a higher risk of complications, the others correspond to therapies recently introduced into therapy and characterized by a more positive safety profile, as reported in literature.[26–31] Starting from market data, the analysis observed the trend of consumption during 2020, comparing it with that of the previous 2 years identifying potential effects on prescriptions related to the lockdown. For drug consumption were used market data for the 3-year period 2018–2020; however, for the year 2020, data available up to October reported to the year were used, assuming a linear consumption trend. On the basis of annual consumption data and assuming the use of one pack per month per patient, the target population of diabetic subjects who could have received the new therapies was obtained. The analysis envisaged associating the effects of these consumption data, deviating from what was expected, to the onset of diabetic complications. Then, the economic evaluation of these effects was conducted and the results in terms of quality of life were estimated. The economic model, based on a one-year time mark, has been developed referring to Italian NHS and data have been inputted by reference to the scientific literature, using Italian evaluation of costs whenever possible and referring to internationally acknowledged data when it was not possible otherwise.

The events analyzed were ischemic heart disease (IHD), stroke, hospitalization for heart failure (HHF), end stage renal disease (ESRD), severe and moderate hypoglycemia. Adopting the NHS perspective, the base case scenario of the analysis considered direct cost data. However, to extend the impact of diabetes complications to a social perspective, we also developed simulation scenarios including indirect costs. The economic valorization was conducted by attributing to each type of treatment the respective events frequency of occurrence based on literature sources. Data concerning the effect of hypoglycemic therapies on cardio-nephro-metabolic risk have been extrapolated from recent studies cited above.[27,31] Risk values (hazard ratio, HR) for ischemic heart disease (IHD), stroke, hospitalization for heart failure (HHF), end stage renal disease (ESRD) and hypoglycemic events associated with the consumption of treatments in analysis have been considered. To estimate the hypoglycemia cost we have referred to the incidence of hypoglycemic events reported in international literature for patients with type 2 diabetes.[32,33] We have considered only severe and moderate hypoglycemia events, not including mild ones because of their negligible economic impact. We have inputted direct mean costs of severe hypoglycemic events referring to an Italian study,[34] whereas for moderate ones we have adopted a large Swedish study.[32] EQ-5D scores for diabetes-related comorbidities were drawn from international literature.[35] Event rates in diabetic population and cost per event are shown in Table 2.

Table 2 shows the risk of IHD, stroke, HHF, ESRD, hypoglycemia occurrence, respectively, for sulfonylureas, glinides, combination of biguanide and sulfonylurea, combination of biguanide and SGLT2 inhibitors, GLP1 agonist, SGLT2 inhibitors, highlighting the different impact of therapies on events over a year.

The total cost per patient was then calculated for each therapy, considering the cost associated with the management of diabetes-related complications. Based on the consumption of innovative therapies in 2020, down from the trend, the number of events that could have been avoided, if the 2019 trend had been followed, was calculated. Applying this information to the target population of this analysis, identified in the share of diabetic patients who could have been treated in 2020 with innovative drugs in case of linear growth in consumption, the total number of avoidable events and the related potentially obtainable savings, as well as the potential benefits in terms of quality of life, were obtained. It was therefore highlighted how the

Table 2 Event Rate in the Diabetic Population by Type of Treatment and Cost per Event

	IHD	Stroke	HHF	ESRD	Hypoglycemic Event	
					Moderate	Severe
Rates in diabetic population	**0.97%**	**0.59%**	**0.51%**	**0.054%**	**22%***	**1.16%***
Drugs class	**HR**					
Sulfonylureas-glinides	1.35	1.28	1.47	1	1	1
GLP1 agonists	0.91	0.65	0.65	1	0.32	0.16
SGLT2 inhibitors	1.18	0.56	0.54	0.74	0.32	0.00
Event costs						
Direct cost per event	€15,949	€10,237	€11,000	€32,000	€335	€19,110
Indirect cost per event	€9775	€6274	€6742	€6650	€45	€1110

Note: *Related to treatment with sulfonylurea.
Abbreviations: IHD, ischemic heart disease; HHF, hospitalization for heart failure; ESRD, end stage renal disease; SGLT2i, sodium/glucose cotransporter-2 inhibitors; GLP1 agonists, glucagon-like peptide 1 receptor agonists.

use of different therapeutic regimens can significantly influence the clinical profile of the patient with relative impact on the costs borne by the NHS due to the onset of complications, as well as determining a worse quality of life for the patient. In addition, a simulation scenario was developed in which the impact of a double growth in the use of innovative therapies in the year 2020 compared to that observed in 2019 was analyzed, considered a condition that could have occurred in the absence of the pandemic. Starting from the base case, hypothesizing the effects of linear consumption growth in 2020 compared to 2019, three simulation scenarios were then developed: the first one assessed the impact of adding indirect costs to the base case scenario, the second one assessed the impact of a double growth trend compared to 2019 considering only direct costs, and the third one considered double growth trend and added indirect costs to direct ones.

Effects of Reduced Hospital and Follow-Up Procedures in Patients at Cardiovascular Risk, at Risk for Macular Degeneration and with Diabetic Foot

Furthermore, our study aimed to evaluate the potential effects of reducing hospital procedures relevant for the prognosis of the diabetic patients with cardiovascular problems and degenerative and vascular pathologies of the macula during lockdown. Specifically, the effects of reduction, respectively of cardiac catheterization procedures and intra-vitreous injections with vascular endothelial growth factor (VEGF) inhibitors were evaluated. To develop the analysis, literature studies were used certifying the reduction of the procedures of interest during the lockdown. About the cardiovascular aspects, a German study, already mentioned above, reported a reduction of 44.6% in catheterization procedures for chronic coronary syndrome and 18.6% for acute coronary syndrome.[24] Considering the epidemiology relating to chronic and acute coronary syndrome in the diabetic population, the target population was estimated. The percentage reduction in catheterization procedures taken from the German study was then applied to this population to derive the number of unmanaged events and estimate the potential damage in terms of worsening quality of life and costs due to the development of heart failure. Regarding the reduction in the number of eye examinations as well as of the programmed intravitreal treatments an Italian study was adopted for the analysis.[36] This study reviewed the charts of all patients who had a visit at a medical retina referral center during the Italian quarantine (from 9 March 2020 to 3 May 2020), number and characteristics of these data were compared with data from the same period in 2019 (from 9 March 2019 to 3 May 2019). Compared to the reference period in the previous year, a reduction of 60% in diabetes patients' visits was observed, as well as a 59.6% decrease in intravitreal treatments.[36] These results are aligned with those of other international studies.[37] In addition, a Chinese study showed that interruption of anti-VEGF treatments exposes patients at significative risk for severe adverse visual sequelae.[38] A USA team recently demonstrated that patients who missed a visit for intravitreal injection lost more vision than

patients who completed the scheduled visits (no visit −5.024 ±1.88, canceled visit: −1.633 ±0.65, completed visits 0.373 ±0.50; p = 0.0028) so that a delay in care of even only 5.34 weeks resulted in vision loss (Italian lockdown lasted 9.857 weeks).[39] The population of diabetic subjects treated in Italy with intravitreal injection was estimated, starting from the fact that about 30% of the total intravitreal injections are administered to diabetic patients by an average of eight injections per year.[40] The economic impact related to the reduction of treatment for these patients was then estimated. Based on literature evidence reporting an increase in diabetic foot problems and, specifically, amputation during the COVID-19 pandemic in a local setting (Hospital of University of Campania "Luigi Vanvitelli" Naples, Italy),[41] an analysis was conducted to estimate the effects on this outcome at a national level, valuing the economic consequences and losses in terms of quality of life. The hospital admission rate for lower limb amputation in diabetic patients for the year 2019 was used as a pre-pandemic reference,[42] and then compared to the data of Campania Region extended at national level. This figure was associated with the cost for hospital access according to the national tariff and the impact of amputation in terms of quality of life reported in the literature.[35,43]

Furthermore, a simulation scenario was developed to evaluate the potential prolonged effects of the condition that occurred during the lockdown assuming the maintenance of the limitations, due to the contingent access to hospitals or the fear of patients, for a period of 30, 45 or 60 days after the end of lockdown.

Results

Visits and Prescriptions

During 2020 a severe drop in patient access has been observed. Analyzing the period ranging from March 9 (data of the start of global lockdown in Italy) to the end of December 2020, we observed that out of 20,491 patients treated in ASL 3 clinics in Genoa only 14,819 came to visit at least once. Between May and September, we worked to recover 5672 visits missed during the lockdown, partially with patients in presence, and through phone calls when the patient could not, or preferred not to come in person. So, considering that we performed 2438 phone visits, we globally missed 5672 visits in presence (−28%), reduced to 3234 (−16%) including the phone calls (Table 3).

Table 3 Drop in Diabetic Patient Visits Observed in 2020

Data on Diabetic Patients and Visits	N	Δ%
Diabetic patients treated	20,491	
Patients who came to visit (9 March ; 31 December 2020)	14,819	
Missed visits	5672	−28
Phone visits	2438	
Controlled patients	17,257	
Uncontrolled patients	3234	−16

However, the relevance of a phone visit is not comparable to the visit with the patient physically present, considering that during a phone visit it is almost impossible to provide radical changes in therapy. Moreover, the number of accesses to our clinics for a first evaluation during 2020 decreased of 59.8% vs the previous year. A drop of more than 25% in access to specialist evaluation of diabetic patients during 2020 is also not far from the truth if applied to the national contest, being our structure one of the few which performed a global recall of the patients who missed the visit during the lockdown period. To confirm this, we compared our data with the national projection prepared by our scientific association, AMD (Associazione Medici Diabetologi) which estimates a decrease of 22.5% in accesses for visits, both first visits and follow up, corresponding to 666,781 out of the 2,962,978 performed in Italy during 2019 (data AMD, presented at the web meeting "AMD 'incontra' la Direzione Generale Prevenzione del Ministero della Salute" 22nd October 2020). These are the results of a comparative analysis of information gathered from the activity of over 2000 member association in 2019 and 2020 related to specialist visits in subjects with diabetes. The analysis was aimed at highlighting the effects of the restrictive measures imposed by the COVID-19 emergency on the trend of first visits and checkups. For 2020, a 90% reduction in visits during the three months lockdown was assumed for the analysis, based on the findings of the survey on 15 sample specialist centers. In support of all the above data a recent study upon the impact of the COVID-19 outbreak on the propension to cancel forecasted medical appointments of Italian patients with pre-existing medical conditions demonstrated an association between post-traumatic stress symptoms and the tendency to cancel medical appointments, because of

the stress of the sudden change to everyday life induced by the lockdown.[44] The reduction in accesses also determined the interruption of preventive education (usually carried out in groups), as well as early diagnosis and treatment of diabetic complications. At this point we must wonder whether this drop may have determined any health consequences for the diabetic population. The first point to be evaluated: the high rate of diabetic patients' deaths for COVID-19 should have implied the need to program even tighter controls rather than shut down the accesses for all the visits already scheduled. Many studies already published in the first pandemic phase showed the importance of a good metabolic control for a favorable outcome of the infection.[45–51] Moreover, a recent published study on the impact of the lockdown on diabetic patients in Saudi Arabia showed a reduction in the compliance level of diabetic patients toward their disease.[52] As regards the excess mortality recorded during 2020, our analysis highlighted the penalization suffered by the diabetic population. Compared to the general population, in fact, diabetic patients recorded a 2 times higher mortality value (excess mortality 20.4% vs 10.2%). But if this aspect is difficult to be translated in social and economic parameters, not the same is for the advantages for public health deriving from the progressive shifting operated by diabetologist from old to new therapies during the last years. It is universally recognized that diabetic patients die mainly for cardiovascular diseases, and during the last years it has been demonstrated that drugs such as SGLT2 inhibitors (SGLT2i) and GLP1 receptor agonists (GLP1ra) can significantly modify this outcome, even in a very short timeline. The treatment with SGLT2i can indeed reduce major cardiovascular events (MACE) with a rate between 20 and 30%,[26,53,54] depending on the duration of the diabetes and the type of MACE, whereas the treatment with GLP1ra can reduce MACE for almost the same amount, ranging from −4% to −39%,[26,55,56] while the treatment with old therapies such as sulphonylureas can increase the incidence of MACE.[57] During the years preceding pandemic there was a clear trend which showed a progressive increase in the use of these new drugs in diabetic population treatment; this trend has progressed at a lower rate during 2020, because of the reduction of access of diabetic patients to the specialist clinic (Table 4).

This even though at the end of October 2020 the number of patients treated with SGLT2i and GLP1ra amounted still to 70% of the number of patients still treated with sulphonyureas.[25] Considering that the percentage of reduction in starting the new therapies (−14%, 27% vs 41%) is consistent with the number of missed outpatient visits during 2020 (−16%, calculating the visits with the presence of the patient) we estimated the number of patients which could have been treated at best in Italy if there had not been a total lockdown and the aftermath of fear that led to a low propensity to access visits. We therefore estimated that in 2020, if a linear trend in the use of new antidiabetic therapies had been maintained, 1197 events (respectively due to stroke, IHD, HHF, ESRD, severe hypoglycemia) and 8089 moderate hypoglycemic events, for a total of 9286 event, could have been avoided while saving more than €11.1 million for NHS and increasing quality of life equal to 173 utilities, by considering the target population of 53,927 potentially treatable diabetic patients (Table 5). We can also expect that further data showing an increase in number and severity of diabetic related pathologies newly detected will be published during next few months: more MACE, higher

Table 4 Trend of Use of the Antidiabetic Therapies Analyzed (2018–2020)

Drugs Class	2018	2019			2020		
	N	N	ΔN	Δ%	N	ΔN	%
Sulfonylureas	6,387,487	5,811,077	−576,410	−9	5,430,978	−380,099	−7
Glinides	2,206,394	1,884,195	−322,199	−15	1,684,707	−199,488	−11
Biguanide/Sulfonylureas combination	2,182,087	1,680,186	−501,901	−23	1,355,278	−324,908	−19
Total group	**10,775,968**	**9,375,458**	**− 1,400,510**	**−13**	**8,470,963**	**−904**	**−10**
Biguanide/SGLT2 inhibitors combination	726,915	1,030,221	303,307	42	1,245,296	215,075	21
GLP1 agonists	1,096,438	1,600,708	504,270	46	2,141,305	540,597	34
SGLT2 inhibitors	1,510,969	2,054,283	543,314	36	2,556,221	501,938	24
Total group	**3,334,322**	**4,685,213**	**1,350,891**	**41**	**5,942,822**	**1,257,610**	**27**

Abbreviations: SGLT2i, sodium/glucose cotransporter-2 inhibitors; GLP1 agonists, glucagon-like peptide 1 receptor agonists

Table 5 Effects of Slowdown in the Use of Innovative Antidiabetic Therapies

Events	2020		Δ		
	Real	Simulation	Events	Costs	Utilities
Stroke	407	188	219	€2,239,488	−13
IHD	706	566	140	€2,229,910	−7
HHF	404	159	245	€2,693,626	−12
ESRD	29	24	5	€154,984	0
Severe hypoglycemia	626	37	589	€1,124,881	−28
Moderate hypoglycemia	11,864	3775	8089	€2,709,832	−113
Total	**14,036**	**4750**	**9286**	**€11,152,721**	**−173**

Abbreviations: IHD, ischemic heart disease; HHF, hospitalization for heart failure; ESRD, end stage renal disease.

impairment in ejection fraction, more severe hypoglycemic events, worsening of diabetic macular degeneration, more hospitalizations for severe diabetic foot ulcerations and gangrene, as well as the potential effects of these on mortality.

Cardiovascular Mortality and Complications

Regarding cardiovascular mortality and events during the lockdown period, applying the evidence reported in international literature to the Italian contest linked to the effects of lockdown to the cardiac and cardiovascular mortality and reduction of cardiac catheterization procedures, we have estimated an excess of 261 deaths in diabetic population and a reduction of 2984 catheterizations in patients with chronic coronary syndrome and of 1265 in patients with acute coronary syndrome. Assuming for this last group of patients one hospitalization for heart failure in the following year, due to inappropriate management of the disease, an additional cost increase of more than €13.9 million with a reduction of 63 utilities in the following year was calculated (Table 6). In this contest it is important to note that an Italian multicentre, observational, nationwide survey which focused on 1 week period during the COVID-19 outbreak in Italy (12–19 March) detected a 48.4% reduction in admissions for acute myocardial infarction (AMI) compared to the equivalent week in 2019 ($p < 0.001$).[58] A similar reduction in hospitalizations was also registered for heart failure (HF): 46.8% reduction, 95% CI 39.5–55.3; $p = 0.005$). This dramatic reduction in the number of hospitalizations for AMI will also mean an increase of future mortality for AMI as well as the number of patients with post-AMI HF. In fact, to reduce the progression to HF in a patient with AMI it is important to perform at the soonest a reperfusion, by

Table 6 Effects of Reducing Hospital Procedures and Follow-Up Visits in Diabetic Patients at Risk

Events	2019	2020	Δ		
			Events	Cost	Utilities
Cardiovascular mortality	11,730	11,991	261		
Cardiac catherization procedures	35,494	32,509	−2984		
Acute coronary sindrome Heart failiure Deaths due to heart failure	35,494	34,229	−1265 1265 190	€13,911,423	−63
Injections for diabetic macular edema	11,250	10,420	−830	€185,902	
Amputations in patients with diabetic foot	496	714	218	€1,321,806	−21
Total				**€15,419,131**	**−84**

thrombolysis or by primary percutaneous coronary intervention; time to reperfusion, up to 2 hours, is important for survival as well as for recovery of left ventricular function.[59,60] To quantify future deaths a study on the relationship between time to treatment and mortality as a continuous function was performed and it was therefore highlighted that the risk of 1-year mortality is increased by 7.5% for each 30-minute delay, jumping at 360 minutes from about 3% to over 10% ($p < 0.001$).[61] Moreover, a ten year follow up study published in 2003 showed a sustained benefit for the early treatment,[62] and is demonstrated that long term survival rates directly correlate with B-type natriuretic peptide concentrations (and hence with HF) with a 1600-days death rate ranging from −5% to −35% depending on the severity of HF.[59] By applying this information to our analysis, we estimated a further excess (estimated in the year after lockdown) of 190 deaths for heart failure mortality due to suboptimal management of cardiopathic patients in the diabetic population in the year following the AMI (Table 6). Similarly, to what has been observed in the cardiovascular field, patients with macular degeneration have also been hit by the effects of the pandemic. Our analysis has estimated that that due to a reduction of about 60% of intravitreal injections for diabetic patients, corresponding to 830 missed injections, has generated an increase in expenditure equal to €185,902, conservatively assuming daily hospital access for diabetic macular edema in target population (Table 6). Finally, it is of interest to consider the effects of lockdown on diabetic foot management. In fact, among the first elements to be detected since the lockdown, was a higher incidence of gangrene as a complication of recently detected and poorly treated foot ulcers, as shown by the document published by the Vanvitelli University of Naples which shows a significant increase in the prevalence of gangrene and amputations among diabetic patients admitted to hospital during the lockdown period (from March 9th to May 18th).[41] The prevalence detected in 2020 group compared to 2019 group was 64% vs 29% ($p = 0.009$), + 120, 7%, for gangrene, and 60% vs 18% ($p = 0.001$), + 233%, for patients requiring amputation. The cause of this sharp increase detected during the lockdown period can be referred to the sudden interruption of foot and lower limb care, so determining a delay in diagnosis and treatment.[63] We can then also consider the results of a population study performed in Piedmont, Italy, which reported, over a population of about 4,400,000 inhabitants and 250,000 individuals with diabetes, a 5-year incidence of hospitalization for diabetic foot without amputations of 1762 per 100,000 patients, of 324 per 100,000 for hospitalization with major amputations, and of 343 per 100,000 for hospitalization with minor amputations.[64] Moreover, in Italy, from 2001 to 2010, the standardized discharge rate for amputation in the hospitalized diabetic population increased from 12 to 13.3 per 100,000,[65] and the last rate available, referred to 2019, has settled on 13.56.[42] Considering only this last as more affordable datum, and applying the above reported rates detected by the group of Vanvitelli University to it, we can deduce that during the lockdown of last spring we probably had an increase of 233% of hospitalizations for amputation, with an estimated excess of 31.64 cases per 100,000 in the period. This, applied to the Italian diabetic population, amounts to more than 218 amputation in excess of the average during the previous year considered. We have calculated that this corresponds to an increase in costs of more than €1.3 million with a reduction of 21 utilities (Table 6). This not counting the patients who did not attend visits, for fear of COVID-19, during the following period. Overall, this analysis scenario estimated a cost increase for the NHS of more than €15.4 million and a loss of 84 utilities because of a worse management of patients during the lockdown.

Simulation Results

In the analysis of the lockdown effects on the slowdown in innovative antidiabetic therapies use, the addition of indirect costs to direct ones would have resulted in potential savings equal to €16,594,987.

Potential benefits deriving from adopting the new therapies under normal conditions without any special anti-pandemic policy have been studied. The results show a realistic double growth trend compared to 2019, with a reduction of 4696 severe events (respectively due to stroke, IHD, HHF, ESRD, severe hypoglycemia) and 31,735 moderate hypoglycemic events, for a total of 36,431 events. This outcome thereby would imply a saving of more than €43.8 million and an improvement in the quality of life equal to 679 utilities. Finally, it was calculated that adding indirect costs to this scenario would have resulted in a saving of €65.1 million. Figure 1 shows the results of the simulation considering three simulation scenarios developed from the base case: (simulation 1) impact of adding indirect costs to the base case scenario (simulation 2) impact of a double growth trend compared to 2019

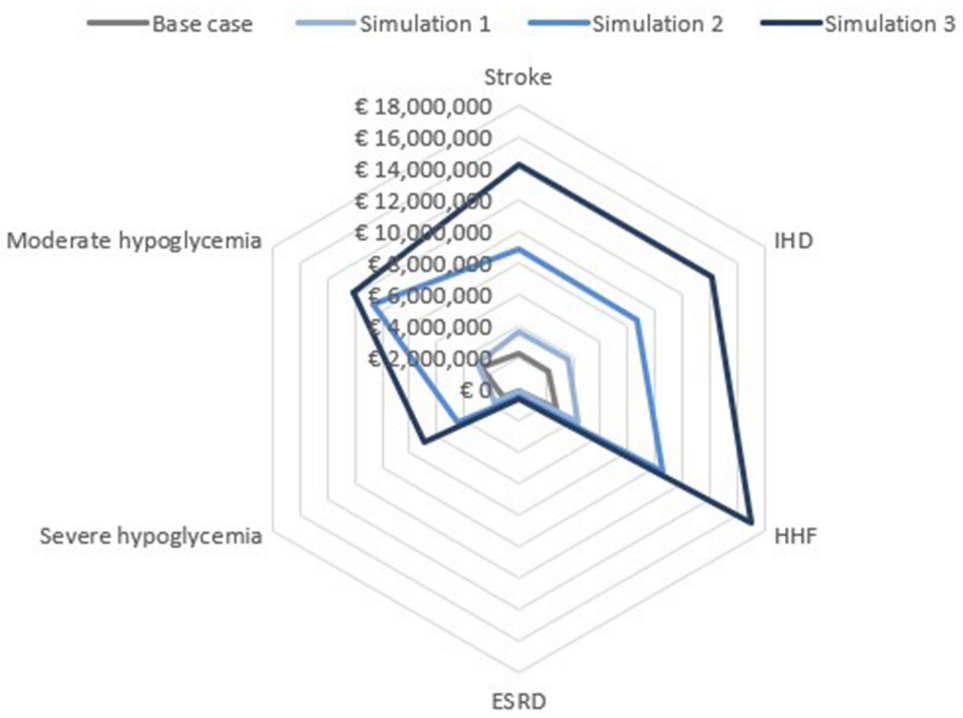

Figure 1 Simulation scenario results: analysis of the lockdown effects on the slowdown in innovative antidiabetic therapies use.
Notes: Base case: linear growth of innovative antidiabetic therapies consumption in 2020 compared to 2019 (direct costs); Simulation 1: linear growth of innovative antidiabetic therapies consumption used in 2020 compared to 2019 (direct costs + indirect costs); Simulation 2: double growth of innovative antidiabetic therapies consumption in 2020 compared to 2019 (direct costs); Simulation 3: double growth of innovative antidiabetic therapies consumption in 2020 compared to 2019 (direct costs + indirect costs).

considering only direct costs (simulation 3) that considered double growth trend and added indirect costs to direct ones. The detailed charts for individual scenarios are available as Supplementary Material, (Figure 1A–D).

Moreover, Figure 2 shows the results of the simulation scenario developed to evaluate the prolonged effects of the condition occurred during the lockdown assuming the maintenance of the limitations, due to the contingent

Figure 2 Simulation scenario results: potential prolonged effects of restriction, simulation scenario 30, 45 and 60 days.

access to hospitals or the fear of patients, for a period of 30 days (simulation 1), 45 days (simulation 2) or 60 days (simulation 3) after the end of lockdown. Figure 2 shows how health costs increase and patients' quality of life decreases as days increase.

The missed benefits linked to the possibility of using more innovative antidiabetic drugs in 2020 and the damage caused by a non-optimal follow-up and control of micro- and macro-vascular complications in the diabetic population in Italy during the lockdown involved an estimated expenditure of €26.6 million for NHS and a loss of 257 utilities in diabetic population (Figure 3). Considering the results of the simulation scenarios, this expense could also be higher, ranging from a minimum of €38.7 million and a loss of 294 utilities to a maximum of about €94.0 million and a loss of 836 utilities, assuming to extend our simulation trend to the whole of 2020 (Figure 3).

Discussion

Focusing on diabetic patients, this population paid a double fee to the pandemic. First, the excess in mortality for COVID-19: 29.3% of the total deaths, comparing both of them to general population and to hospitalized patients (only 6% of the population and 20–25% of hospitalized patients suffer from diabetes). Indeed, compared to the general population, diabetic patients recorded a two times higher mortality value (excess mortality 20.4% vs 10.2%). Second, the excess of mortality, mainly for major cardiovascular events, due to the delay when not by the removal from the care of the NHS both during the lockdown and the subsequent uncertainty period, logistical and organizational obstacles, and fear. The delay in visits and consequent interventions also determined an increase in peripheral amputations, as well as decreased eye examinations and ophthalmological treatments with subsequent reduced vision.

The missed or delayed cardiological intervention for AMI will also induce an increase in 2021 of cardiovascular mortality as well as a major severity of residual FE impairment among diabetic patients, which in turn will lead to a further increase in mortality in the years to come.

Last but not least, about 20% drop in accesses for specialist visits during 2020 has induced a slowdown in the transition to the new therapies capable of reducing the future incidence of MACE, de facto delaying for a year the clinical, epidemiological, and social health gains deriving from this important change in therapeutic mentality adopted a few years ago. Potential benefits deriving from adopting the new therapies under normal conditions without any special anti-pandemic policy have been studied and simulation scenarios developed. The results of our study showed that if the slowdown in the use of new therapies had not occurred, in 2020 an expense of over €11.1 million for the NHS and a loss of 173 utilities would have been avoided. Furthermore, assuming a realistic double growth trend compared to 2019, the benefits would increase, making it possible to save more than €43.8 million and an improvement in the quality of life equal to 679 utilities, which would rise to €65.1 million, if indirect costs were also considered. On the other hand, the

Figure 3 Summary of results: base case and simulation scenarios.

analysis estimated a cost increase for the NHS of more than €15.4 million and a loss of 84 utilities due to a suboptimal follow-up and control of micro- and macro-vascular complications in the diabetic population in Italy during lockdown. The simulation analysis also estimated a higher cost if the continuation of the conditions occurring during the lockdown were considered for a minimum period of 30 days to a maximum of 60 days, resulting in an expense of respectively €22.1 million and €28.9 million. Considering overall the missed benefits linked to the possibility of using more innovative antidiabetic drugs in 2020 and the damage caused by a non-optimal follow-up and control of micro- and macro-vascular complications in the diabetic population in Italy during the lockdown, we estimated an expense of €26.6 million for NHS and a loss of 257 utilities in diabetic population. The simulation scenarios also assessed the impact of adding indirect costs. It assumed that the results deriving from missed doubling in prescription of innovative drugs in 2020 and from extended restrictions beyond the duration of the lockdown determine an overall expenditure ranging from a minimum of €38.7 million and a loss of 294 utilities to a maximum of €94.0 million and a loss of 836 utilities.

As with all modelling analyses, this study is subject to limitation. In the absence of a specific data pool to use, some key assumptions have been applied to extrapolate clinical trial data from studies. It should be specified that where data input for Italy has not been available, reliable international sources have been considered. The effects of the conditions that occurred during the lockdown were drawn from the relevant studies available at the time of the analysis and it is desirable that future studies conducted in Italy confirm the hypotheses of the consequences also in the long term and that evidence is disseminated on the outcomes of the pandemic in the diabetic population in Italy. While the use of market data may seem a limitation because there was no information from real-world studies, it has been the most reliable tool to grasp what really happened during 2020. Based on our knowledge, this article is the first in Italy that has studied the effects of the policies adopted to manage pandemic on the diabetic patient, considering epidemiological, clinical, and economic implications. On the other hand, various publications are available reporting the effects of COVID-19 and lockdown measures on general morbidity and mortality and in specific classes of patients at risk, and the number of publications reporting the long-term effects is expected to increase in the coming months.[66–68]

Conclusion

In summary, the total lockdown policy as well as the subsequent recommendations to defer non-urgent visits and medical procedures during the following months, all this enhanced by the fear of contagion induced by the media, led to a restrictive attitude in exploiting the potential of our highly developed healthcare system. Not to mention that diabetes, representing 3.4% of the total deaths in Italy,[19] is only one of the many chronic diseases which have been impaired by restrictive measures such as lockdown.

What could have been done otherwise? Not easy to say, but since March 6, 2020, a comment by Dr Anderson from the Imperial College of London prophetically reported:

> Governments will not be able to minimize both deaths from coronavirus disease 2019 (COVID-19) and the economic impact of viral spread. Keeping mortality as low as possible will be the highest priority for individuals; hence governments must put in place measures to ameliorate the inevitable economic downturn.[69]

In the cited paper, the authors suggest that given the sharp increase of mortality immediately detected for the oldest people as well as for the patients presenting several underlying comorbidities, targeted social distancing for these groups could have been the most effective way to reduce morbidity and concomitant mortality. For those who remember G.B. Shaw's play "The Doctor's Dilemma", this could represent the final starting point for reflection.

Disclaimer

All medical authors belonging to ASL3 Genoa actively managed a COVID-19 Unit during the first wave of the pandemic.

Disclosure

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