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Diabetes Type II in Correlation to Non-Cancer and Cancer Diseases in 49 WHO Selected Countries (SC) on The Base of Age Standardized Death Rate (ASDR)

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ABSTRACT

Background: *Type 2 diabetes (2DM) represents one of most common diseases in the world and is the background for many other illnesses.*

Objective: *To determine the Age Standardized Death Rate (ASDR) of illnesses bound to the condition of 2DM.*

Material and Methods: *Among the 191 countries listed by WHO, the analysis was conducted in 49 countries (49 SC) with an approved registry. Eighteen among the most common illnesses, and 17 cancers were analyzed. ASDRs of 2000, 2010, and 2016 were correlated to 2DM.*

Results: *Despite the population increase (+19.7 %), in 2016 Vs 2000 a significant reduction was shown for all ASDRs, with the exception of Alzheimer and pancreatic cancer in 2000. Positive correlations with 2DM was found for iron deficiency anemia (IDA), sexually transmitted diseases (STD), hemorrhagic stroke, respiratory diseases, chronic kidney diseases, prostatic and cervix cancers.*

Negative correlations were shown for pancreatic, throat/bronchus/lung (TBL), brain, bladder, kidney and melanoma cancers. For all the other illnesses no correlation was found.

Conclusion: *In case of 2DM, the most of CVD were under control, a part from hemorrhagic stroke. IDA, STD, respiratory and chronic kidney diseases, prostatic and cervix cancer should be addressed more carefully, while 2DM and the relative therapies seems protective towards pancreatic, TBL, brain, bladder, kidney and melanoma cancers.*

Keywords

Diabetes type 2, Sexually transmitted diseases, Hemorrhagic stroke, Respiratory diseases, Chronic kidney disease, Prostatic cancer.

Introduction

Diabetes mellitus (2DM) accounts for the vast majority of people with diabetes around the world, in some countries up to the 95 % of prevalent cases [1], and was recognized to be the cause >1.6 million deaths in the world in 2016 [2], and the overall prevalence is predicted to be about 522 million by 2030 [3].

In general, after a diagnosis of 2DM, patients undertake therapy consisting mainly of life style modification (diet, physical training, smoking cessation) associated if necessary, to drugs aimed to reduce glucose levels, blood pressure and coagulation.

Frequently, the disease can be associated with organ damage and failure [4-6], and some authors have analyzed particular aspects such hypertension [7-9], retinopathy [10], and inflammatory markers [11]. In relation to the correlation between of 2DM and risk of cancers a consistent increase of liver, pancreas, and endometrium cancers were documented, with lower impact of

colorectal, breast and bladder cancers. The increases of kidney cancer and non-Hodgkin lymphoma were inconclusive, and lung cancer was not found to be associated with 2DM [12]. Other authors found similar data with a reduction of the risk of prostate cancer [13].

On the basis of some meta-analysis and epidemiological studies, an increased risk of breast, colon, and pancreatic cancers was shown with conflicting results for prostatic cancer [14]. In general, all these data were based on surveys conducted in a relatively limited number of countries giving only a partial overview of the problem. The aim of the present study was to analyze the correlation between 2DM and some of the most common illnesses and cancers on the base of ASDRs (Age Standardized Death rates x100000), limited to the years between 2000 and 2016 and available for those 49 countries considered reliable by WHO reliable in terms of data recording [15].

Material and Methods

Criteria of choice for the variables and time frame

ASDRs were used for all diseases (non cancer and cancer, Table 3) as listed in Global Health Estimates 2016 and published in 2018 [15]. The ASDRs were used because they free from bias related to the age.

However, they do not consider the number of people in the country, with the consequence that values in small countries (e.g, Bahamas- about 0.4 million inhabitants) have the same weight as for larger countries (e.g. USA- about 322 million inhabitants), which can create a bias in the average values of the 49 SC. However, despite the increase of the population, ASDRs remain significantly correlated in every country (Table 3).

For this reason, ASDRs values were considered sufficiently reliable despite the large differences among the countries in terms of population. For all the variables the values were concerning both genders, a part from prostatic cancer pertaining to males while breast, cervix, and ovarian cancers were relative to females only. Values of diabetes, IDA and chlamydia were also considered both for the entire population and for females only.

List of the 49 SC countries and criteria of choice of the countries

In total, the countries listed by WHO in terms of ASDRs were 191. However, the data of the present study were relative only to those 49 countries (selected countries or SC) considered by WHO "with high completeness and quality of cause-of-death assignment" that "may be compared and time series may be used for priority setting and policy evaluation" [15].

List of the countries

The following 49 SC countries were considered:
Armenia, Australia, Austria, Bahamas, Belgium, Brazil, Brunei, Canada, Chile, Croatia, Cuba, Czechia, Denmark, Estonia, Finland, France, Germany, Grenada, Guatemala, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Macedonia, Mauritius, Mexico, Moldova, Netherlands, New Zealand, Norway, Romania, Saint Vincent & Grenadinas, South Korea, Trinidad & Tobago, United Kingdom, USA, Uzbekistan.

Data collection

The values of ASDRs up to the fourth decimal place were taken from the WHO records [15]. Seventeen among the most common non cancer diseases and 17 cancers were analyzed in the years 2000, 2010, 2016 (Table 2). The Life expectancy (LE) for the year 2016 was taken from the Official Atlante De Agostini [16].

Statistical evaluation

The mean values ± SD were calculated for all the variables, and differences between the years were tested using the U Mann-Whitney test with a cut-off of $p < 0.05$.

In terms of correlations among variables, following a linear Pairwise Correlation analysis, the presence of some or more out outlier may compromise the r values. The impact of the outlier was minimized using the Robust fit [17] further adjusted following the method M of Huber [18].

The correlation calculated with the application of the two correction were arbitrarily considered significant only in case of $p < 0.01$, with a cut-off value of $r= 0.338$. The JMP14 Pro of SAS Institute were used for the analysis.

Results

The data concerning the modification of the population in the period between 2000 and 2016 are reported in Table 1.

The 49 SC represented between 19.4 % and 21.4 % of the world population. In the 191 countries between 2000 and 2016 the population increased by 21.4 %, while in the 49 SC the increase was only 11.8 %. The modifications of the ASDRs for the selected diseases and LE were reported in Table 2.

Year	Total population 10^6			Total population 10^6 males			Total population 10^6 females		
2000	6087.944			3063.097			3024.847		
2016	7391.064			3717.324			3673.749		
	Population males 10^6			Population females 10^6			Total population 10^6		
Year	142 countries	49 SC	% of total 49 SC	142 countries	49 SC	% of total 49 SC	142 countries	49 SC	% of total 49 SC
2000	2422.607	640.490	20.9	2362.244	662.603	21.9	4785.851	1303.093	21.4
2016	2997.634	719.690	19.2	2936.073	737.667	20.1	5933.707	1457.357	19.7

Table 1: Population of 191 countries compared to 49 SC relative to males and females in 2000 and 2016.

Diseases	GHE	Gender M/F	ASDRs values Mean ± SD			% 2016 Vs 2000
			2000	2010	2016	
Diabetes	800	M/F	25.29 ± 31.551	24.60 ± 34.173	23.41 ± 31017[a]	-7
Diabetes	800	F	24.99 ± 32.686	23.20 ± 33.466	21.12 ± 28.477	-15
Iron-deficiency anemia [IDA]	580	M/F	0.76 ± 1.261	0.67 ± 1.045	0.57 ± 0.857	-25
Iron-deficiency anemia [IDA]	580	F	0.69 ± 1.030	0.67 ± 0.984	0.57 ± 0.836	-17
Tuberculosis (TBC)	30	M/F	4.04 ± 6.339	2.17 ± 3.251	1.43 ± 2.172	-65
STD (sexually transmitted diseases) excluding HIV	40	M/F	0.17 ± 0.207	0.10 ± 0.126	0.08 ± 0.118	-53
Chlamydia	60	F	0.024 ± 0.0253	0.015 ± 0.0143	0.010 ± 0.0103	-58
HIV/AIDS	100	M/F	5.00 ± 15.801	3.30 ± 8.160	3.54 ± 9.373[a]	-29
Diarrheal diseases	110	M/F	2.36 ± 6.472	1.52 ± 3.072	1.32 ± 2.133	-44
Hepatitis	185	M/F	0.77 ± 0.948	0.44 ± 0.456	0.43 ± 0.316	-44
Respiratory infectious	380	M/F	25.42 ± 21.866	17.63 ± 13.744	16.55 ± 11.338	-35
Alzheimer	950	M/F	9.18 ± 8.25	12.80 ± 9.045	15.78 ± 11.193	+72
CVD	1100	M/F	270.3 ± 131.87	209.8 ± 129.18	179.2 ± 115.84	-34
Ischemic stroke	1141	M/F	42.27 ± 27.07	29.94 ± 22.188	23.99 ± 18.664	-51
Hemorrhagic stroke	1142	M/F	34.03 ± 21.692	23.92 ± 16.632	19.75 ± 14.088	-58
Respiratory diseases	1170	M/F	34.18 ± 19.531	26.04 ± 10.172	20.02 ± 9.350	-41
Digestive diseases	1210	M	32.61 ± 14.673	28.71 ± 13.373	25.481 ± 14.403[a]	-21
Peptic ulcer	1220	M/F	3.07 ± 2.199	1.95 ± 1.561	1.85 ± 1.472	-40
Acute glomerulonephritis	1271	M/F	0.05 ± 0.163	0.03 ± 0.074	0.03 ± 0,053	-40
Chronic kidney disease	1272	MF	3.31 ± 3.272	3.06 ± 2.673	2.78 ± 2.670[a]	-16
Cancers						
Mouth oropharynx	620	M/F	3.91 ± 2.051	3.65 ± 2.036	3.47 ± 1.843	-11
Stomach	640	M/F	11.22 ± 6.236	8.37 ± 4.818	7.29 ± 3.999	-35
Colorectal cancer	650	M/F	15.74 ± 5.933	14.57 ± 4.695	14.03 ± 4.599	-11
Liver	660	M/F	5.40 ± 3.386	5.42 ± 3.067	5.39 ± 2.670[a]	0
Pancreas	670	M/F	6.72 ± 1.975	7.20 ± 2.026	7.18 ± 2.124[b]	+7
TBL (trachea/bronchus/lung)	680	M/F	25.45 ± 10.158	24.11 ± 9.552	22.37 ± 8.538	-12
Melanoma	690	M/F	2.52 ± 1.215	2.64 ± 1.352	2.56 ± 1.185	+2
Breast	700	F	21.37 ± 7.065	18.52 ± 5.146	18.01 ± 5.937	-16
Cervix	710	F	6.50 ± 5.339	5.74 ± 5.359	5.09 ± 4.502	-22
Ovarian	730	F	6.10 ± 240	5.97 ± 2.163	5.50 ± 1.859	-11
Prostate	740	M	23.79 ± 16.114	22.53 ± 18.254	20.26 ± 15.547[a]	-15
Kidney	745	M/F	3.20 ± 1.667	2.96 ± 1.269	3.01 ± 1.314	-6
Bladder	750	M/F	3.41 ± 1.420	3.26 ± 1.350	3.05 ± 1.131	-11
Brain	751	M/F	4.20 ± 1.567	4.10 ± 1.452	4.06 ± 1.335[a]	-3
Thyroid cancer	754	M/F	0.56 ± 0.207	0.48 ± 0.156	0.48 ± 0,222	-14
Lymphoma	760	M/F	6.60 ± 2.515	5.79 ± 1.847	5.71 ± 1.700	-13
Leukemia	770	M/F	4.79 ± 1.036	4.36 ± 0.925	4.12 ± 0.941	-14
Life expectancy	years	M/F	74.89 ± 4.377	77.58 ± 4.115	79.16 ± 3.658	+5.7

Table 2: ASDRs of the different diseases divided by gender: mean values ± SD.
GHE (Global Heath Estimation code).
a = Mann-Whitney U test 2000 Vs 2016 $p > 0.05$, b = 2010 Vs 2016 $p < 0.05$.

In the period 2000 Vs 2016, in the 49 SC, LE increased by 2.7 years while the other variables showed very different trends. The average ASDR of 2DM for the total population was not significantly different (despite a - 7% decrease), while considering females only the reduction was more consistent (-15 %) and statistically significant.

Most of the common illnesses were significantly reduced, a part from Alzheimer which increased by 72 %. The averages reduction of HIV, diarrheal diseases, and chronic kidney diseases were not statistically significant due to the large variance. In relation to cancers, a statistically significant reduction was found for all cancers with the exception of liver, and brain cancers showing

almost identical ASDRs during the entire period. The only cancer with a significant increase was the pancreatic cancer (+ 7 %). The correlations between 2DM and all the diseases in 2000 and 2016 were reported in Table 3.

Disease	Gender	Years				
		2000	2016	2000 Vs 2016	Vs LE	
2DM	M/F	***1.0000***	***1.0000***	***0.922***	***-0.424***	
Iron-deficiency anemia [IDA]	M/F	***0.810***	***0.807***	***0.964***	-0.244	
Iron-deficiency anemia [IDA]	F	***0.351***	***0.761***	***0.872***	-0.126	
Tuberculosis (TBC)	M/F	0.051	0.159	***0.889***	***-0.585***	
STD (excluding HIV)	M/F	***0.338***	0.318	0.315	***-0.356***	
Chlamydia	F	***0.580***	0.093	***0.499***	-0.166	
HIV/AIDS	M/F	***0.624***	0.247	***0.976***	-0.249	
Diarrheal diseases	M/F	0.131	0.234	***0.949***	-0.185	
Hepatitis	M/F	0.108	0.174	***0.626***	-0.280	
Respiratory infections	M/F	0.164	***0.426***	***0.662***	***-0.478***	
Alzheimer	M/F	0.047	-0.293	***0.793***	***0.531***	
CVD	M/F	0.025	0.150	***0.929***	***-0.849***	
Ischemic stroke	M/F	0.018	0.097	***0.889***	***-0.699***	
Hemorrhagic stroke	M/F	0.234	***0.384***	***0.918***	***-0.793***	
Respiratory diseases)	M/F	0.234	***0.356***	***0.411***	-0.199	
Digestive diseases	M/F	0.174	0.216	***0.916***	-0.703	
Peptic ulcer	M/F	0.204	0.306	***0.679***	-0.633	
Acute glomerulonephritis	M/F	0.034	0.035	***0.938***	-0.164	
Chronic kidney disease	M/F	***0.633***	***0.356***	*0.905*	***-0.350***	
Cancers						
Mouth oropharynx	M/F	-0.008	-0.007	***0.806***	***-0.396***	0.033
Stomach	M/F	0.061	0.085	***0.907***	***-0.563***	0.042
Colorectal	M/F	-0.377	-0.226	***0.775***	0.117	-0.144
Liver	M/F	0.073	0.071	***0.794***	-0.273	0.075
Pancreas	M/F	***-0.466***	***-0.466***	*0.922*	***0.450***	***-0.403***
TBL (trachea/ bronchus/lung)	M/F	***-0.543***	***-0.537***	*0.941*	***0.381***	***-0.455***
Melanoma	M/F	-0.254	-0.337	***0.948***	0.243	-0.301
Breast	F	0.017	0.263	***0.740***	-0.198	***0.389***
Cervix	F	0.771	0.625	***0.976***	-0.686	0.761
Ovarian	F	-0.173	-0.041	***0.768***	0.086	0.055
Prostate (PCa)	M	***0.445***	***0.359***	***0.931***	-0.174	***0.537***
Kidney	M/F	***-0.484***	***-0.390***	***0.810***	0.186	***-0.391***
Bladder	M/F	***-0.520***	***-0.388***	***0.862***	0.207	***-0.365***
Brain	M/F	***-0.589***	***-0.508***	***0.852***	0.168	***-0.491***
Thyroid cancer	M/F	0.150	0.226	***0.631***	-0.159	0.239
Lymphoma	M/F	-0.071	-0.026	***0.854***	***0.366***	0.119
Leukemia	M/F	***-0.347***	-0.018	***0.723***	0.113	-0.016

Table 3: Correlations Vs 2DM: r values p <0.01 are reported in bold italics characters.

a = 2DM in 2000 and cancer in 2016.

In terms of interpretation, the negative correlations cannot consider 2DM as a protective condition, since they are also consistent with improvements due to the therapies undertaken after the diagnosis. Positive correlations indicate that, despite the therapy, still the disease should be addressed with more care in terms of prevention.

Correlations with LE

Considering the diseases in terms of LE, Alzheimer was the only disease positively correlated ($p < 0.01$), while all the others showed a significant inverse correlation ($p < 0.01$) or no correlation.

Correlations 2000 Vs 2016

All the correlations were statistically significant ($p < 0.01$): for some diseases they were less consistent than for others, in particular chlamydia and respiratory diseases. However, despite the population growth, it appeared quite a stable condition over the time.

Correlations in 2000 and 2016 Vs 2DM

In relation to diseases other than cancers, positive correlations were found for IDA (respectively for M/F and F separately), and chronic kidney diseases in all the periods considered. For STD, chlamydia, and HIV, the correlations were positive only in the year 2000, whereas for respiratory infections, respiratory diseases, and hemorrhagic stroke, the positive correlation was limited to 2016.

Diseases such as TBC, diarrheal diseases, hepatitis, Alzheimer, CVDs, ischemic stroke, digestive diseases, and acute glomerulonephritis were found to be not correlated. For cancers, a part of colorectal cancer, the correlations were similar in 2000 and 2016 and significantly negative for pancreas, TBL, cervix, prostate, kidney, bladder, and brain cancers. For melanoma the cut-off (negative correlation) was reached only in 2016.

Positive correlations were found for cervix cancer and prostatic cancer. Colorectal cancer and leukemia were negatively correlated in 2000 only, while no correlation was shown for breast cancer in any of the periods.

2DM as a cancer predictor

Prediction for cancers was estimated considering the correlations between the ASDRs in 2000 Vs 2016 which were not different from those previously determined in the years, with the exception of breast cancer showing a significant ($p < 0.01$) positive correlation, and behaving as a predictor.

Discussion

The aim of the present analysis was to give an overview about the relationship of 2DM with the most common illnesses. Criticism for the data available in the literature was not within the scope of this study, since all the studies were giving a contribution to the knowledge of the disease, no matter whether they concerned one or more countries. Data recorded in some studies and/or in some countries can be consistent for the period considered, however

they do not represent the entire picture of the 49 SC between 2000 and 2016.

The results of the present investigation have the limitation due to the differences between the 49 SC and the rest of the 142 countries in terms of population, ecological, environmental, demographic/social, and economic characteristics. In previous studies these differences have been already described [19,20].

In the 49 SC, particularly LE, gross domestic product (GDP), and particular matter (PM) were significantly higher, as was for those variables characteristic of more developed countries (cars, mobile phones, internet connections). This means that the results cannot be taken as a worldwide picture since the 49 SC represent only about 20 % of the total population. The choice of ASDRs as main variable can be a further limitation because each disease could be concomitant to other illnesses which may precipitate the death.

Furthermore, for chlamydia it was not possible to differentiate between *Chlamydia trachomatis* or *Chlamydia pneumoniae*, since no data were available, and chlamydia in males was not listed within the WHO records. In relation to cancers, there was no distinction about the different types in the same anatomical location, and some of them are more refractory to the therapy, therefore they are characterized by a lower survival time.

In a nut shell, this study has to be considered only as "the tip of the iceberg". Despite these limitations, some interesting observations can be drawn from this analysis.

General overview

In the period between 2000 and 2016 the LE increase in the world was estimated to be in 5.5 years [21], while in the 49 SC it was lower, accounting for 2.7 years only. The ASDRs of almost all non-cancer diseases were significantly reduced, a part from Alzheimer disease increasing by 72 %. The HIV and digestive diseases, despite an average reduction (respectively by 29 % and by 21 %), resulted in being not significantly modified due to a large variance among countries.

For what concern cancers, in the period 2000/2016, the ASDR of pancreatic cancer was increasing by about 7 %, whereas liver, brain, and prostate cancer were not significantly modified. For all the other cancers (mouth oropharynx, stomach, colorectal, TBL, melanoma, breast, cervix, ovarian, bladder, thyroid, lymphoma and leukemia) the ASDRs were significantly reduced.

The overall improvement of these illnesses may be due to many factors. At first, the therapies which usually prolong survival, together with the life style modifications, and increased prosperity which may have a consistent impact on ASDRs. Environmental modifications are also an important aspect, and the data of the 49 SC should be the object of further studies.

Diabetes and other diseases different from cancer

In terms of the relationship of 2DM with other common diseases, the data do not confirm the results of previous observations available in the literature. The comorbidity associated to 2DM was analyzed by some authors [4,22], reporting data about the risk of increase in almost all the diseases considered. Due to these discrepancies, the consistency of all the correlations will be analyzed for each of the listed diseases.

IDA

IDA is classically defined as hypochromic microcytic anemia, and still is by far the most common form of blood dyscrasia. However, sometimes it is very difficult to differentiate IDA from other types of anemia [23].

In the present analysis, the highest correlations with 2DM was found with IDA for both genders, and also separately considering the data on females. Some observations on this aspect were done by other authors in relation to anemia in general [24], not focusing specifically IDA, and supposing that most probably anemia was due to the chronic inflammatory process commonly documented in 2DM [25].

Erythrocytes are transporting hemoglobin -and indirectly iron- and are equipped with glucose receptors (GLUT1, 2 and 4) to collect glucose from the blood aimed to generate energy through the pentose phosphate cycle. These last characteristics mean they are sensible to the glucose concentration. However, these receptors can lose efficiency due to oxidative stress (OS) which is very common condition in the case of 2DM patients [26,27].

In case of 2DM, erythrocytes may change their structure, becoming smaller and twisted spontaneously around fibrin fibers. These changes seem to be caused by the iron overload, which increases the non-enzymatic fibrinogen polymerization [28]. The consequence is a compromised O2 transport/delivery together with shortening of life [29].

At the same time, in these patients the erythropoiesis is unable to compensate for shortened erythrocytes lifespan caused by the enhanced phagocytosis triggered by cytokine activated macrophages [30]. All these events justify the high correlation between 2DM and IDA.

The impact of IDA should be considered particularly important in the light of bacterial and viral infections- that will be analyzed separately- but also for some other diseases.

Tuberculosis

In the past, 2DM was considered a risk factor for tuberculosis [31], and the same was shown more recently in some developing country [32], or in some territories of developed countries also, where a clear correlation was documented [33]. However, in the context of the 49 SC no correlation was found with tuberculosis.

Chlamydia

Chlamydia, similar to tuberculosis is also a bacterial disease, and infection showed positive correlation with 2DM only in the

year 2000 (no correlation was shown in 2016). High titer of *C. pneumoniae* have been determined in the past, mainly in those patients suffering from severe 2DM and presenting retinopathy [34].

However, in a multiethnic study no association was documented [35] despite in vitro studies which concluded that *C. pneumoniae* has a negative impact on beta cell function and viability [36]. These data may confirm that some interference exists although not well defined. The disappearance of the correlation 2DM/Chlamydia in 2016 could be due to the improvement of the therapies of both diseases during this time.

HIV

HIV is a viral disease showing the same behavior as chlamydia, with a positive correlation in 2000 which was not confirmed in 2016. Some authors in the past concluded that the risk of developing diabetes in HIV infected patients was seen very high [37,38].

However, antiretroviral therapy (ART) was considered to be the most incriminating risk factor for 2DM, because it leads to insulin resistance and increased inflammatory status [39]. For these reasons, the use of insulin and oral antidiabetics was becoming part of the therapy, and this probably has an impact on the disappearance of the correlation in 2016.

Diarrheal diseases

Diarrheal diseases can be due mainly to bacterial and/or viral infections. They are part of the GI complication of diabetes, and up to 22 % of the cases can be due to the autonomic neuropathy causing abnormal motility and secretion of fluids in the colon [40]. Sometimes, the use of high amount of fibers in the diet - commonly suggested after the 2DM diagnosis - can be the prominent cause, and the adverse reaction due to hypoglycemic drugs also cannot be excluded.

Hepatitis

Hepatitis is a classical viral infection, not showing any correlation with 2DM. Hepatitis B and C can be present in 2DM, and some authors believe they are consistent as an additional metabolic complication [41]. Other authors showed that hepatitis C increases the risk of 2DM in relation to age, race (African Americans), and obesity condition [42].

STDs

In relation to STDs (with the exclusion of HIV), they are more linked to bacterial infections (e.g. gonorrhea), and positive correlation was shown in 2000 only, despite in 2016 was very close to the cut off. Despite some general public information, no studies seem to be available giving more detail on this aspect (chlamydia, as part of the STDs has been already discussed).

One mention should be made for candidosis (in particular for non albicans species *C. glabrata*), which is not listed among the STDs. Candidosis is very frequent in females in the case of 2DM, due to the increase of glucose in the vaginal secretion acting as a growth factor for candida [43]. In general, from the data concerning infections it seems that the interference of 2DM is not linked to the bacterial, viral or fungal origin although each strain may be differently affected.

Alzheimer

This was the only illness showing a consistent growth from 2000 to 2016. In the present analysis no correlation was found with the disease, indicating that 2DM is not negatively affecting the disease. Some common pathological processes between 2DM and Alzheimer have been described in the past showing a similar desensibilization of insulin receptor [44]. More recently, the overlapping mechanisms of diabetes with dementia were described, consisting of the common conditions of inflammation, OS, mitochondrial dysfunction, and brain insulin resistance [45].

Experimental studies have also shown that high glucose levels increase of the beta-amyloid production [46]. A pooled analysis of studies done in 10 different countries between 2011 and 2014 [47] showed a 60 % greater risk for the development of dementia compared to subjects without diabetes, with women being at higher risk than men for vascular dementia (19 % more).

Despite these observations, and the effect of 2DM on cognitive impairment [48], our data do not confirm these findings, which could mean that high brain glucose levels, in the late age, could be protective against Alzheimer's disease ASDR. Due to the high correlation between IDA and 2DM, one may not rule out that the combination of the two could be considered as protective and tentatively some hypotheses can be made. The brain is among the highest consumer of oxygen and glucose. In the case of IDA, the O2 availability will be lower, but at same time the gradient between micro-vessels and tissues will be also lower, reducing the amount of O2 availability and limiting the OS in the cerebral tissue.

At the same time, hypoxia increases the hypoxic cerebral gene expression aimed to increase the vasodilation through NO• (nitric oxide) release and supply more O2 [49]. However, NO• is a free radical, and in case of a high amount of O_2• (superoxide) because of the inflammation, an increase of OH• (hydroxyl radical) will take place generating a massive OS. In other terms, hypoxia will be the ground for OS depending upon the balance between O_2, O_2• (superoxide), NO•, and OH•. The pace maker of this equilibrium seems to be the inflammation. In the case of 2DM, the insulin resistance (and also the IGF-1 resistance) can be partially compensated by the high glucose levels in the brain, allowing improvement of neuronal activity, repairing mechanisms, and indirectly reducing the inflammatory process.

At the end, with the increase of aging, and in the case of high levels of brain glucose, the final balance instead of being negative becomes positive.

Cardiovascular diseases

CVDs are considered the major cause of death and disability among people affected by 2DM [50]. In a systematic analysis of

the literature, 2DM was confirming the high prevalence of CVDs including stroke, MI, angina, heart failure and atherosclerosis, accounting for approximately half of all the deaths in the period between 2007-2017 [51]. The data of 57 articles were analyzed, with about 4.5 million of 2DM patients and pertaining to at least 30 countries, with the conclusion that CVDs were affecting approximately 32% of the patients being the prominent cause of death. However, one issue was posed by the authors in that more accurate registry studies were needed to measure the global prevalence of CVDs.

In our analysis, CVDs and ischemic stroke were not found correlated with 2DM and the consequence is that this may open the issue of the differences among countries. Some author was proposing that an important aspect in defining the risk of CVDs can be represented by the epigenetic factors [52]. Life style, environment, and particularly the diet are determinant for the expression of the diseases, since these variables are driving the epigenetic expression.

In the present analysis, among the CVDs, the only disease emerging as significantly correlated with 2DM was the hemorrhagic stroke. Four elements at least should be addressed as important to trigger this last event:
the increase of vasoconstriction in cerebral vessels [53]; the endothelial damage caused by advanced glycation end products (AGEs); the tendency of 2DM to generate a condition of hypercoagulability and hypofibrinolysis which can generate thrombosis particularly in microvessels [54]; the hypertension, which is present in more than 50 % of patients with 2DM [55].

Finally, the use of anticoagulants/antiplatelet therapy is also an important element to be considered [56] due to the increase of bleeding which is a frequent side effect of these products. The hypothesis could be that thrombosis in some microvessels deviates the flow to the closest vessels, and the concomitant hypertension can break some of those with severe wall damage due to the glycation process resulting in bleeding. The occlusion of vessels with higher caliber (causing the ischemic stroke), due to the hypercoagulability status, although possible, seems to be a more rare event in 2DM.

Respiratory diseases

In our analysis, the correlation between respiratory diseases and 2DM was found to be significant in the year 2016 only and not in 2000, which may indicate that these events become more consistent with an increase in age.

In the literature, for some authors the link between 2DM and respiratory diseases was not completely clarified [57], while for others it was well documented and consisted of significantly higher risks for COPD (chronic obstructive pulmonary disease), asthma, and emphysema [58,59]. Dyspnea and chronic cough were also found more frequently in 2DM and were supposed to anticipate the lung ageing process [60].

Digestive diseases

In the present study no correlation was found between 2DM and digestive diseases, and it seems they do not compromise the survival, despite important for the quality of life.

Gastrointestinal (GI) symptoms occur more commonly in to 2DM than in the general population in the form of diarrhea, constipation, oesophageal dysfunction, anorectal disorders and gastroparesis, such that one or more of these symptoms are reported in up to 75 % of cases [61].

The autonomic neuropathy in GI innervation was considered responsible for these complications [62], because the inadequate glycemic control impairs GI motility especially in long-standing diabetes [63]. The loss of inhibitory intrinsic innervation in 2DM is most remarkable, together with microvessel dysfunction, direct cellular effect of hyperglycemia, OS, altered metabolism, change in nerve growth factors, and altered brain-GI tract interaction [64].

In 2DM, gastroparesis was shown in about 1 % of the cases [65] being the most common among the possible different causes (e.g. rheumatologic diseases, paraneoplastic disorders) [66]. The relationship between 2DM and irritable bowel syndrome (IBS) seems not to be sufficiently documented, and both can be considered as independent diseases.

The issue of indolepropionic acid -which is a microbiota produced metabolite- as protective of the β-cell function [67] opens to the possible modifications of GI function in relation to the microbiota. Microbiota can be influenced by the diet which is a common tool to control the disease, and many authors have addressed this aspect, discussing differences between normal subjects and 2DM patients [68,69] supposing that microbiota is an important mediator triggering many common diseases including 2DM.

A moderate dysbiosis and a decrease of some butyrate producing bacteria was shown in these patients [70] with a role in determining insulin resistance, lipid metabolism, appetite and some of the associated diseases such as metabolic syndrome [71]. Changes in the intestinal ecosystem may be the cause of inflammation, and the alteration of the short chain fatty acids production contributes to insulin resistance [72] and gut hormones production [73].

However, considering the complexity of microbiota which is a sort of "fingerprint" of the subjects, many more studies and a very large number of cases are needed to define its real correlation with 2DM.

Acute glomerulonephritis

This disease was considered in the present study as an example of bacterial infections, and no correlation was shown with 2DM in the time frame between 2000 and 2016.

Chronic kidney disease (CKDs)

The correlation between 2DM and CKDs was shown to be statistically significant in all the period considered, particularly in 2000 (r 0.633). CKDs arel a known complication of 2DM, that

occurs between 20% to 40% of the cases and requiring frequent renal replacement therapy (dialysis or transplantation). This prevalence is more consistent in subjects > 65 years old compared to younger people (respectively about 25 % and 50 %) [74,75].

Along with retinopathy and neuropathy, CKDs are defined as a microvascular complication [76] and in some countries account for nearly half of the end stage renal disease (ESRD) [77], despite that solid markers different from microalbuminuria are still needed [78]. The CKDs are characterized by anemia in nearly all patients and is defined as normocytic, normochromic, and hypoproliferative anemia due to the reduced production of erythropoietin (EPO) [79]. In this case, the combination with IDA should be considered as summative in determining the modification of ASRDs.

Cancers

The analysis of the correlations with the most forms of cancer is very complex, and it would be necessary to formulate hypotheses probably out of the authors' knowledge. One of the main reasons is that each cancer has many different typologies, and what could be true for one cancer may be not valid for another, despite belonging to the same anatomic region.

The last consensus analysis of diabetes and cancer indicates that some cancers develop more commonly in 2DM patients particularly in liver, pancreas and endometrium [12]. The same was for colorectal, breast, and bladder cancers although with a lower risk. Prostatic cancer seems to occur less often, while for kidney and non-Hodgkin lymphoma the data were inconclusive.

Some of the data, like the risk of cervix cancer, were confirmed in our analysis but not for other cancer. Prostatic cancer was found with a significant higher risk in 2DM, while for mouth oropharynx, stomach, liver, breast, thyroid, and lymphoma cancers no interference was shown. Conversely, for pancreatic, TBL, melanoma, kidney, bladder, and brain cancers a negative correlation was found, indicating a sort of protection.

Brain cancer was shown with a lower incidence in the case of hyperglycemia [80], and some previous observations was also underlining the reduction/noninterference of lung cancer [58]. This does not mean that 2DM should be considered preventive for these cancers, but indicates that the therapies undertaken to control the disease (e.g. life style modification, control of hypertension) may favorably reduce the risk.

Furthermore, those significant negative correlations in 2000 that disappeared in 2016, as for colorectal cancer and leukemia, may be due to the modifications of the environment, prosperity, and life style in the 49 SC over time. One interesting finding was concerning breast cancer, since 2DM appears as an early symptom comparing data of 2DM in 2000 and cancer in 2016.

Retinopathy and peripheral nervous diseases where not in the list of WHO data and they could not be considered, despite they are well known important consequences of 2DM with a very negative impact on the quality of life. One particular aspect should be focused upon concerning the OS. Most of the diseases analyzed in the present study are characterized by OS.

For some authors, sometimes the importance of OS measure is overestimated, particularly for CVDs which seemed not affected by modification of the OS markers [81]. However, it is important to measure also the antioxidant defense which can be modified by the diet and also by the therapy [82]. This measure is necessary to have a complete picture of the oxidative condition. Unfortunately, this is almost never accomplished and OS still remains an incomplete variable.

Conclusion

We tried to answer the question "how can doctors foresee the future of a patient once a diagnosis of 2DM is established?"
Diet, physical activity, smoking cessation, and therapies to control hypertension and coagulation are the common tools capable in reducing the ASDRs of 2DM and other concomitant illnesses. In particular, the ASDRs of CVDs has been improved substantially over time, but there are still issues that should be addressed more carefully, such as the hemorrhagic stroke.

Similarly, IDA, STD, respiratory infection, respiratory disease, and chronic kidney diseases seem not to be under appropriate control, while Alzheimer's disease can be taken out of the worries. Retinopathy and PNS (Peripheral Nervous System) impairment, which also worsen the quality of life, were unfortunately not listed in the WHO records and could not be considered.

In terms of cancer, the problem of prostatic cancer for males, and cervix or breast cancer for women should be addressed with care. For the breast cancer 2DM seems to be a significant predictor. For some cancers such as those affecting pancreas, TBL, melanoma, kidney, bladder, and brain it seems that the common therapies used to control 2DM and comorbidities are capable of reducing the ASDRs risk.

For mouth oropharynx, stomach, colorectal, liver, ovarian, thyroid, and lymphoma cancers, the risk is not significantly different when compared to non 2DM patients.

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References

1. Venkat Narayan KM, Zhang P, Kanaya AM, et al. Diabetes the pandemic and potential solutions. In Disease control priorities in developing countries 2 ed Washington DC, World Bank. 2006; 591-603.
2. World Health Organization. Diabetes. 2018.
3. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas global estimate of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94: 311-321.

4. Kondapally Seshasai S, Kaptoge, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. NEJM. 2011; 364: 829-841.
5. Boheme MWJ, Buechele G, Framkenhauser J, et al. Prevalence incidence and concomitant co-morbidities of type diabeted mellitus in South West Germany- a retrospective cohort and c SSase control study in clains data of a large statutory health insurance. BMC Public Health. 2015; 15: 855.
6. Dungan K, Harris E, Braithwaite SS, et al. Type 2 diabetes and concomitant illnesses in Contemporary Endocrinology Type 2 diabetes mellitus an evidence approach to practical management Humana Press.
7. Lastra G, Syed S, Romayne Kurukulasuriya, et al. Type 2 diabetes mellitus and hypertension an update Endocrinol Metab Clin North Am. 2014; 43: 103-122.
8. Fox CS. Cardiovascular diseases risk factor type 2 diabetes mellitus the Framingham Heart Study. Trends Cardiovasc Med. 2010; 20: 90-95.
9. Chen G, McAlister FA, Walker RL. Cardiovascular outcome in Framingham participants with diabetes the importance of blood pressure. Hypertension. 2011; 57: 891-897.
10. Hammes HP, Welp R, Kempe HP, et al. Risk factor for tetinopathy and DME in type 2 diabetes-results from German/ Austrian DVP database. PLOSone 2015; 10.
11. Danesh J, Erqou S, Walker M, et al. The Emergency Risk Factors Collaboration 2007 analysis of individual data on lipid inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular disease. Eur J Epidemiology. 2007; 22: 839-869.
12. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer a consensus report. Diabetes Care. 2010; 33: 1674-1685.
13. Pandey A, Forte V, Abdallah M, et al. Diabetes mellitus and risk of cancer. Min Edocr. 2011; 36: 187-209.
14. Cannata D, Fierz Y, Vijayakumar A, et al. Type 2 diabetes and cancer: what is the connection Mount Sinai J of Medicine. 2010; 77: 197-213.
15. Global Health Estimates 2016: death by Cause, Age, Sex, by Country and by Region 2000-2016. Geneva World Health Organization. 2018.
16. Atlante Geografico DE Agostini. Ed De Agostini Novara Italy. 2016.
17. Street J, Carroll RJ, Ruppert D. A note on computing Robust Regression estimates via iteratively reweighted least squares. The AM Statistician. 1988; 42: 152-154.
18. Huber PJ, Hoboken, NJ, John Wiley, et al. Robust statistics. 1981.
19. Cornelli U, Recchia M, Grossi E, et al. Life expectancy does not depend on classical ecological variables stochastic and non stochastic analysis. GFL J Pub Health Epidemiol. 2018; 1: 104.
20. Cornelli U, Belcaro G, Recchia M. The prostate cancer road map hypothesis in 49 countries from iron-deficiency anaemia IDA to death. Cancer Res Ther Oncol. 2019; 7: 204.
21. WHO. Global life expectancy up to 5.5 years since 2000. Agence France- Presse. 2019.
22. Li L, Cheng WY, Glicksberg BS, et al. Identification of type 2 diabetes subgroups through topological analysis of patient similarity. Sci Trans Med. 2015; 7: 311ra174.
23. Ganz T. Anemia and inflammation. NEJM. 2019; 381: 1148-1157.
24. Barbieri J, Caitano Fontela P, Roseli Winkelmann E, et al. Anemia in patients with type 2 diabetes mellitus 2015 in Anemia. 2015; 15.
25. Andrew M, Arredondo M. Ferritin levels and hepcidin mRNA expression in peripheral mononuclear cells from anemic type 2 diabetic patients. Biol Trace Element Res. 2012; 149: 1-4.
26. Bigagli E, Ludovici M. Circulating oxidative stress biomarkers in clinical studies on type 2 diabetes and its complications. Ox Med Cell Longevity. 2019; 17.
27. Mohanty JG, Nagababu E, Rifkind JM. Red blood cells oxidative stress impairs oxygen delivery and induces red blood cell aging. Front in Physiol. 2014; 5.
28. Buys AV, Van Rooy MJ, Soma P, et al. Changes in red blood cell membrane structure in type 2 diabetes: a scanning electron and atomic force microscopy study. Cardiov Diabetol. 2013; 12: 25.
29. Lipinski B, Pretorius E. Novel pathway of ironinduced blood coagulation implication for diabetes mellitus and its complications. Pol Arch Med Wewn. 2012; 122: 115-122.
30. Nemeth E, Ganz T. Anemia and inflammation. Hematol Oncol Clin North Am. 2014; 28: 671-681.
31. Root HE. The association of diabetes and tuberculosis. NEJM. 1934; 210: 1-13.
32. Alisjahbana B, Sahiratmadja E, Nelwan EJ, et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Cli Inf Dis. 2007; 45: 428-435.
33. Restrepo BI, Fisher-Hoch SP, Crespo JG, et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiol Infect. 2007; 135: 483-491.
34. Banaee T, K Revakhki RD, Abrishami M, et al. Higher titers of anti-chlamydia pneumoniae IgG in diabetic retinopathy a cross sectional study. Diab Metab Res Rev. 2015; 31: 168-174.
35. Lutsey PL, Pankow JS, Bertoni AG, et al. Serological evidence of infections and type 2 diabetes the multiethnic study of atherosclerosis. Diabet Med. 2009; 26: 149-152.
36. Rodriguez AR, Placentia-Villa G, Witt CM, et al. Chlamydia pneumoniae promotes dysfunction of pancreatic beta cells. Cell Immunol. 2015; 295: 83-91.
37. Hernandez- Romieu AC, Garg S, Rosemberg ES, et al. Is diabetes prevalence higher among HIV infected individuals compared to the general population Evidence from MMP and NHANES 2009-2010. BMJ Open Diabetes Res Care. 2017; 5: e000304.
38. Duncan AD, Goff LM, Peters BS. Type 2 diabetes prevalence and its factors in HIV a cross sectional study. PLOSone. 2018; 13: e0194199.
39. Noubissi EC, Katte JC, Sobngwi E. Diabetes and HIV. Cursuchar Diab Reports. 2018; 18: 125.
40. Wolosin JD, Edelman SV. Diabetes and the gastrointestinal

tract. Clin Diab. 2000; 18.
41. Hong YS, Chang Y, Ryu S, et al. Hepatitis B virus infection and diabetes mellitus a cohort study. Sci Rep. 2017; 7: 4606.
42. Metha SH, Brancati FI, Strathdee A, et al. Hepatitis C virus infection and incidence type 2 diabetes. Hepatology. 2003; 38: 50-56.
43. de Leon EM, Jacober SJ, Sobel JD, et al. Prevalence and risk factor for vaginal Candida colonization in women with type 1 and type 2 diabetes. BMC inf Dis. 2002; 2: 1.
44. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes. Brain Res Review. 2007; 56: 384-402.
45. Lee HJ, Seo HI, Cha HY, et al. Diabetes and Alzheimer's disease mechanism and nutritional aspects. Clin Nutr Res. 2018; 7: 229-240.
46. Yang Y, Wu Y, Zhang S, et al. High glucose promotes Aβ production inhibiting APP degradation. PLOSone. 2013; 8: e69824.
47. Chatterjee S, Peters SAE, Woodward MH, et al. Type 2 diabetes ans rik factor for dementia in women compared with men a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes care. 2016; 36: 300-307.
48. Palta P, Schneider ALC, Biessels GC, et al. Magnitude of cognitive dysfunction in adults with type 2 diabetes a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. J Int Neuropsychol. Soc. 2014; 20: 278-291.
49. Hare GMT. Anaemia and the brain. Curr Opin Anaestesiol. 2004; 17: 363-369.
50. International Diabetes Federation. Diabetes and cardiovascular disease. Brussels International Diabetes Federation. 2016; 1-144.
51. Eiarson TR, Acs A, Ludwig C, et al. Prevalence of cardiovascular in type 2 diabetes a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018; 17: 83.
52. Martin-Timón I, Sevillano-Collantes C, Segura-Galindo A, et a. Type 2 diabetes and cardiovascular disease have all the risk factors the same strength. World J Diabetes. 2104; 5: 444-470.
53. Syed AA, Reddy GR, Ghosh D, et al. Adenylyl cyclase 5-generated cAPM controls cerebral vascular reactivity during diabetic hyperglycemia. J Clin Invest. 2019; 129: 3150-3152.
54. Soares AL, de Oliveira Sousa M, Salles Moura Fernandes AP, et al. Hemostatic changes in patients with type 2 diabetes. Rev Bras Hematol Hemother. 2010; 32: 482-488.
55. Lastra G, Syed S, Kurukulasuriya LR, et al. Type 2 diabetes and hypertension an update. Endocrinol Metab Clin North Am. 2014; 43: 103-122.
56. Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with anticoagulant therapy. Stoke. 2014; 37: 256-262.
57. Visca D, Pignatti P, Spavenello A, et al. Relationsip between diabetes and respiratory diseases linical and therapeutic aspects. Pharmacol Res. 2018; 137: 230-235.
58. Ehrlich SF, Quesenberry CP, Van Den Eeden SK, et al. Patients diagnosed with diabetes are at increased risk for asthma chronic obstructive pulmonary disease pulmonary fibrosis and pneumonia but not lung cancer. Diab Care. 2010; 33: 55-60.
59. George C, Ducatman, Conway BN. Increased risk of respiratory diseases in adults with type 1 and type 2 diabetes. Diab Re Clin Pract. 2018; 142: 46-55.
60. De Santi F, Zoppini G, Locatelli F, et al. Type 2 diabetes is associated with and increase prevalence of respiratory symptoms as compared to the general population. BMC Pulm Med. 2017; 17: 101.
61. Bytzer P, Talley NJ, Leemon et, al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus a population-based survey of 15,000 adults. Arch Intern Med. 2001; 161: 1989-1996.
62. Reszczyńska M, Marczak-Karpina B. Dysfunction of the lower gastrointestinal tract as a complication of diabetes- a problematic issue in diabetic care. Clin Diabet. 2016; 5: 100-106.
63. Gatopoulou A, Papanas N, Maltezos E. Diabetic gastrointestinal autonomic neuropathy: current status and new achievements foe everyday clinical practice. Eur J Int Med. 2012; 23: 499-505.
64. Uranga-Ocio JA, Bastús-Díez S, Delcáder-Palacios D, et al. Enteric neuropathy associated to diabetes mellitus. Rev Esp Enferm Dig. 2015; 107: 366-377.
65. Bharucha AE. Epidemiology and natural history of gastroparesis. Gastroenterol Clin North Am. 2015; 44: 9-19.
66. Williams CS, Ferris CD. Diagnosis and treatment of chronic gastroparesis and chronic intestinal pseudo-obstruction. Gastroenterol Clin N Am. 2003; 32: 619-658.
67. de Mello VD, Paannen J, Lindström J, et al. Indoleproprionic acid and novel lipid metabolites are associated to the gut microbiome as a target for treatment of type 2 diabetes with lower risk of type 2 diabetes in the Finnish Diabetes prevention Study. Sci Reports. 2017; 7: 46337.
68. Larsen N, Vogensen FK, van den Berg FJW, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLOSone. 2010; 5: e9085.
69. Allin KH, Nielsen T, Pedersen O. Gut microbiota in patients with type 2 diabetes mellitus. Eur J Endocrinol. 2015; 172: R167-R177.
70. Qin J, Li Y, Cai Z, et al. A metagenome-Wide Association Study of gut microbiota in type 2 diabetes. Nature. 2012; 490: 55-60.
71. Aydin Ö, Nieuwdorp M, Gerdes V. The gut microbiome as a target for the treatment of type 2 diabetes. Curr Diab Rep. 2018; 18: 55.
72. Sircana A, Framarin L, Leone N, et al. Altered gut microbiota in type 2 diabetes just a coincidence. Curr Diab Rep. 2018; 18: 98.
73. Han JL, Lin HL. Intestinal microbiota and type 2 diabetes from mechanism insights to therapeutic perspective. WJG. 2014; 20: 17737-17745.
74. Geith O, Farouk N, Namoory N, et al. Diabetic kidney disease world wide difference of prevalence and risk factors. J Nephropharmacology. 2016; 5: 49-56.

75. Bramlage P, Lanzinger S, van Mark G, et al. Patient and disease characteristics of type-2 diabetes patients with or without chronic kideney disease an analysis of the German DPV and DIVE databases. Caridovasc DiabetologFroupy. 2019; 18: 33.
76. Anushka Patel, Stephen MacMahon, John Chalmers, et al. The ADVANCE Collaborative Group 2008. Intensive Blood Glucose Control and Vascular Outcomes in patients with type 2 diabetes. NEJM. 2008; 358: 2560-2572.
77. De Cosmo S, Viazzi D, Pacilli A, et al. Predictors of chronic kidney disease in type 2 diabetes. A longitudinal study from AMD Annals initiative. Medicine. 2016; 96: 27.
78. Kyriakos I. Diabetic nephropathy it is always there Assumptions, weaknesses and pitfalls in the diagnosis. Hormones. 2017; 16: 351.
79. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012; 23: 1631-1634.
80. Kitahara CM, Linet MS, Brenner AV, et al. Personal history of diabetes, genetic susceptibility to diabetes and risk of brain glioma a pooled analysis of observational studies. Cancer Epidemiol Biomarkers Prev. 2014; 23: 47-54.
81. Cournaud M, Burillo E, Saulnier PJ, et.al. Circulating concentrations of redox biomarkers do not improve the prediction od adverse cardiovascular events in patients with type 2 diabetes mellitus. J Am heart Association. 2018; 7: e00737.
82. Belcaro G, Cornelli U, Finco A. The carotid intima-media thickness modification following atorvastatin is bound to the modification of the oxidative balance. J Cardiovasc Pharm Ther. 2014; 19: 446-450.