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STATE-OF-THE-ART REVIEW

State-of-the-Art Review on Diabetes Care in Italy

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Abstract

BACKGROUND Diabetes is a significant health problem in Italy as in other western countries.

OBJECTIVE To review available epidemiological data and the legislative framework for diabetes care in Italy.

METHODS Review of Italian Health Ministry's official documents and analysis of epidemiological data published by Italian Scientific Societies.

FINDINGS Diabetes affects more than 5% of the Italian population. The expenditures for the care of people with diabetes are about €10 billion ($US 11 billion) a year and are increasing over time. Italian law regulates the clinical care of people with diabetes and creates a clinical framework involving medical organizations, prevention programs, personnel training, and legal protection. The National Health Program is structured in essential levels of assistance that can be defined differently in the various regions. In 2013, the "National Diabetes Plan," defining priority areas for intervention, was approved and represents the main regulatory tool for the management of diabetes within the Italian National Health Service. In Italy, the status of diabetes care is being monitored using the data from 2 permanent observatories: the ARNO Observatory Diabetes and the Associazione Medici Diabetologi Annals.

CONCLUSIONS A comprehensive approach to diabetes is offered to all citizens, consonant with the constitutionally guaranteed right to health. However, this important effort translates into a relevant financial burden for the National Health Service.

KEY WORDS costs, diabetes, diabetes care, diabetic complications, Italy, legislative framework, prevalence

THE SCOPE OF THE PROBLEM

In Italy, diabetes affects more than 3.5 million people, about 5.5% of the general population.[1] In the last 20 years, the number of Italians with diabetes has increased by about 60%, from only 3.4% in 1993.[1-3] As a result of these epidemic proportions, the Italian Health Service estimates spending about €10 billion ($US 11 billion) yearly for direct and indirect costs related to diabetes care.[4] This relative increase in expenditure is, at least in part, due to the increase of the mean lifetime expectancy observed in Italy over the last decades. Current epidemiological data show that 1 person out of 3 affected by diabetes is older than 65, and of these, 1 out of 4 is older than 75 years of age.[2]

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ITALIAN NATIONAL HEALTH SERVICE AND DIABETES

The Italian National Health System (INHS) is strongly focused on pediatric care, the aging population, and the chronically ill, all contributing to a favorable effect on life expectancy in Italy. This is exemplified by a high quality of diabetes care, offered without cost to patients, and provided by dedicated specialists. The Italian Constitution ensures the "right to health" to every citizen. No one can be excluded from health care in Italy because of age, gender, creed, conduct, or income level. The Italian health care system may still be regarded as "fee for service" because the patient is a virtual payer as fees collected by the national and regional governments through the tax system represent the actual reimbursement.[5] However, the growing economic burden of universal coverage by the Italian government is a formidable problem.

The National Health Program is structured in LEAs (essential levels of assistance).[6] LEAs define all of the medical assistance modalities offered by the INHS offers to citizens, with or without partial contributions based on a patient's income. Each Italian region has the right to define these levels in different ways, but they must still adhere to a nominal set of medical assistance guidelines that remain free of charge. Foreign residents have full access to the medical assistance as well. For example, the financial responsibility for European citizens is the same as for the Italian people, whereas for the non-European citizens, the costs of assistance are regulated by specific agreements between the governments.

ORGANIZATION OF THE MEDICAL ASSISTANCE FOR DIABETES

The INHS promotes a comprehensive approach to diabetes[7] organized by assistance levels—type 1 diabetes (T1D) (pediatric and adult) and type 2 diabetes (T2D)—and offers 2 different options for outpatients: primary care and secondary/specialist care (limited to those patients requiring a higher level of care). Primary care is managed by general practitioners with the collaboration of diabetes specialists depending on the presence of complications, comorbidities, and therapeutic modalities. Specialist care is provided by structured diabetes units, usually in hospital centers, in which a team composed of different specialists (endocrinologists, nurses trained in the prevention and management of diabetic complications, nutritionists, podiatrists, and psychologists) provides integrated disease management.

The principal focus of these units is patients' education, prevention, and treatment of diabetic complications and associated conditions: diabetic foot complications, pregnancy and gestational diabetes, bariatric surgery for patients with diabetes and obesity, cardiovascular disease and metabolic syndrome, retinopathy, neuropathy, and nephropathy. In addition, lifestyle interventions incorporate psychological support and educational approaches to obesity and weight management, healthy eating patterns, medical nutrition therapy and carbohydrate counting, physical activity, and sensor augmented pump (SAP) therapy.

THE LAW 115/1987

Diabetes care in Italy follows dedicated rules,[7] which are outlined by the March 1987 law 115/87 titled "Measures for the Prevention and Treatment of Diabetes Mellitus"; this represented a relevant civil and medical achievement for people with diabetes in Italy. This law regulated the clinical care of people with diabetes and also created a framework for medical organizations, prevention programs, personnel training, and legal protection. In short, this law resulted from unwavering actions of volunteer associations that pressured the political system to recognize the need for a comprehensive management of this important chronic disease.

Today, the legislative framework for diabetes care in Italy is different. First of all, the INHS changed in 1996 when welfare was delegated by law 662/96 to various geographic regions. In addition, rules were modified for institutional accreditation of the facilities for diabetes (DL January 14, 1997), of staff training (National Health Plan for the Continuous Medical Education, the State-Regions Agreement of March 23, 2005) and, finally, the lobbying of the patients themselves (agreement of the LEA State-Regional Conference, November 8, 2001).

Thus, 26 years after the enactment of law 115/87, in 2013 the National Diabetes Plan (*Piano Nazionale Diabete;* PND) was approved and currently represents the basic regulatory tool that the scientific societies and patients' associations use for the management of diabetes within the INHS.[5] The PND was based on the analysis of the best scientific evidence and practices but was also influenced by the worldwide developments in these fields, including patient associations and scientific societies. Consequently, diabetes care was included in the priorities

of the Health National Program. The program organizes a network of services placing patients with diabetes at the center and coordinating the activities of all the health care professionals, from primary to secondary care, to provide the best possible assistance, prevent and treat complications, and ensure the best quality of life. Thus, the assistance system moves from "cure" to "care" and optimizes available resources. INHS safeguards the health of all citizens. Accordingly, states and regions allocate a conspicuous portion of public resources to develop and maintain services, activities, and interventions targeting patient behaviors.

The PND defines priority areas for intervention, which include the reduction of social and territorial inequalities, the essential levels of diabetes care, the continuous improvement of quality of care, the relevant objectives and fields of biomedical and health research, the requirements for education, the training and development of the professional staff involved, and the criteria and metrics to monitor the process and outcomes. Other important aspects are the centrality of the person with diabetes, defined as a resource and not a problem, the role of volunteers' associations of patients with diabetes as stakeholders of health and social needs, the integration among the various settings of care (eg, specialist-specialist and specialist-general practitioner), and the appropriate use of resources based on the Diagnostic Therapeutic Pathways (*Percorsi Diagnostici Terapeutici Assistenziali*).

The PND emphasizes the importance of a multidisciplinary and multiprofessional approach, with the active involvement of people with diabetes, to ensure better results in the treatment of the disease and the vital role of primary prevention to safeguard the sustainability of the health system.

DIABETES MONITORING

In Italy there are 2 permanent observatories for the monitoring of diabetes care: the ARNO Observatory Diabetes and the *Associazione Medici Diabetologi* (AMD) Annals.

The ARNO Observatory. The Arno Observatory, a partnership between the Italian Society of Diabetology and Inter University Consortium Arno Cineca, has been active for 20 years[2] and represents an informative patient-centered basis for clinic and organizational planning.[6] Arno analyses have been conducted on a population of 8,822,450 persons (ARNO Observatory), and of those, 548,735 were affected by diabetes in 2014 with a prevalence rate of 6.2%.[2] The resident population on January 1, 2010 was 60,626,442 people,[1] so the total number of people with diabetes in Italy at that time can be estimated to be around 3,800,000. The population with diabetes was identified through 3 sources: national pharmaceutical data, hospital discharge records (HDR), and fee exemptions as a result of diabetes. The data from the sale of pharmaceuticals identified the majority of cases (84%), whereas those from the HDR and fee exemptions identified 9% and 71% of the cases, respectively.

Two-thirds of patients with diabetes were older than 65, and 1 out of 4 was older than 80 years.[2] Less than 1% were younger than 20 years, and 3% were younger than 35.[2] The prevalence of diabetes was 6.1% in men and 5.5% in women, with a 10% difference that is consistent in all age groups >35 years.[2]

Currently, 67% of the patients are treated with oral hypoglycemic agents (OHA), 10% of them with a combination of insulin and OHA, and 11% with insulin alone.[2] Only 12% of the patients do not receive any pharmacological treatment.[2] Based on these treatment modalities, it is estimated that patients with T2D represent 91% of all those with diabetes. A conservative estimate of the frequency of T1D, based on the number of patients treated with insulin alone who are younger than 64 years, suggests a rate of around 4% of all those with diabetes. This estimate is obviously arbitrary, but also realistic because the percentage of Italian patients with T2D younger than 64 and treated with insulin seems negligible.

Costs of diabetes care. The direct cost of diabetes care in Italy is estimated around €9 billion ($US 10 billion). Adding the costs of the devices and the direct distribution of some drugs, the total expense reaches €10-€11 billion (about $US 14 billion). Reliable data about indirect costs of diabetes (lost earnings and working days, etc.) are still lacking.

In Italy, as in the United States, the cost of health care per person is 2.2 to 2.5 times higher for people with diabetes than for the general population, mainly because of the chronic complications, particularly cardiovascular.[2] The subdivision of the costs for drugs, hospital admissions, and services is roughly similar between Italy and United States. In Italy, hospitalization accounts for 57% of the costs (which is about 45% of total direct costs, as in United States).[2] In Italy, drugs account for 22%-25% of the costs (compared with 30% in the United States) and specialists, laboratory tests, and

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devices account for 10% of the costs[2] (whereas in the United States, it is 9% for medical consultation only). From 2006 to 2010, the increase in the total direct cost of diabetes for the INHS was approximately 20% (about €1.4 billion or $US 1.5 billion), and the projections for the future are not favorable.

The cost of insulin and OHA for diabetes care is maintained at around 22% of the total, but most of the expenses are due to drugs for the cardiovascular system, such as statins, with an increased cost of 40%-50% compared with that of people without diabetes.[2] Specifically, the cost of statins and other medications for dyslipidemia have increased by 115%.[2] Of note, the costs related to drugs for the cardiovascular system (including angiotensin converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARBs]) have increased due a widespread use in diabetic population, even though cost per person decreased because of the use of generics. The introduction in clinical practice of innovative drugs for diabetes will further increase the average costs for the population with diabetes. Using the most recent drugs (dipeptidyl peptidase [DPP] IV inhibitors, glucagon-like peptide [GLP] 1 receptor agonists [RA], and sodium-glucose cotransporter [SGLT] 2 inhibitors) will indeed increase the annual cost several fold for patients with T2D previously treated with metformin and sulfonylureas only.

Hospitalization. Among people with diabetes, there is a 62% increased rate of hospitalization and a 57% greater use of specialized units and wards.[2] The total average expenditure for diabetes care is equal to €2900 (about $US 3200) yearly per patient, of which 50% is due to hospitalization, 20% to drugs, and 21% to specialized units access.[2]

The more frequent diagnoses for hospital admission of patients with diabetes are heart failure and acute pulmonary edema.[2] Diabetes significantly impacts the cost and length of hospital stay with an average cost that is higher, for heart failure and acute pulmonary edema by 200% and 147%, respectively.[2] The difference in cost is relevant also for diagnoses related to kidney failure (+ 253%).[2] Finally, hepatobiliary and pancreatic malignancies are diagnosed more often in those with diabetes than in the general population (+222%).[2]

Indicators of quality of care. The analysis of data from various information sources makes it possible to define a few indicators of the quality of diabetes care and to assess the adherence with the best clinical practice. However, reaching optimal targets is still elusive. Of note, at least 1 hemoglobin A1c (A1C) measurement is performed each year by only 66% of people with diabetes, whereas the screening of diabetic nephropathy, the strongest predictor of cardiovascular risk in those with diabetes, is performed in less than one-third of cases.[2] These data are even less satisfactory among those who are identified only by means of registries indicating pharmaceutical prescriptions or fee exemptions.[2] Thus, probably only part of the Italian population with diabetes undergoes regular and appropriate checkups in diabetes centers.

At least one-fifth of patients with diabetes in Italy required 1 hospital admission per year, mainly because of cardiovascular problems.[2] In 2010, major or minor amputations in patients with diabetes accounted for 614 cases—a 5-fold increase when compared with those without diabetes.[2]

The AMD Annals. The AMD Annals[3] have been active since 2006 and, by means of digital patients' files, provide reliable data about the activity of the Italian diabetes care units. The AMD Annals highlight the gap between the standards of care and the actual assistance in Italy, measuring the effectiveness and efficiency of the system and providing a guide for the improvement of clinical governance. This process is obtained through the following steps:

1. Identification of a set of quality indicators
2. Identification of a "standard set" of information, to be collected during everyday practice for the construction of each indicator and performance measurement
3. Creation of a network of participating units, which are at odds with similar overseas initiatives generally set as "pay for performance"; the AMD Annals network is created on a voluntary basis and without any financial incentive; the participating diabetes care units are provided with a standard computerized database and are identified by a code number to ensure their anonymity; the centralized indicators use the AMD Annals as a benchmarking tool
4. Evaluation of the indicators at the local level, as provided by the software

The last analysis involved 550,000 participants with diabetes who were followed for 8 years in 320 diabetes units in all of the Italian regions.[3] This survey used indicators of process, of intermediate outcome, and of adherence to the guidelines for drug therapy (Table 1). The changes over the years in the quality of care were established through the Q score, developed as part of the study QuED,[8] and then applied in the QUASAR study.[9] The score is calculated based on data assessment during the last 12 months

Table 1. Data from the AMD Annals

Type	Indicators
Process (at least once in the year)	A1C
	Lipid profile
	Blood pressure
Renal function	
Foot assessment	
Fundus oculi examination	
Intermediate outcome	A1C: ≤7.0% or >8.0%
	Total cholesterol
	LDL cholesterol: <100 mg/dL or ≥130 mg/dL
	HDL cholesterol
	Triglycerides
	Blood pressure: <130/80 mmHg or ≥140/90 mmHg
	BMI: <27 kg/m^2 or ≥30 kg/m^2
	Glomerular filtration rate : <60 mL/min/1.73 m^2
	Micro-/macroalbuminuria
	Patients who smoke
Use, intensity, and appropriateness of drug treatment	OHA
	Use of insulin alone
	Use of insulin in combination with OHA
	Patients not treated with insulin despite A1C >9%
	Lipid-lowering agents
	Antihypertensive drugs

AMD, Associazione Medici Diabetologi; A1C, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index; OHA, oral hypoglycemic agents.

(including A1C, blood pressure, low-density lipoprotein [LDL] cholesterol, and microalbuminuria), adherence to targets, and appropriateness of treatment. As an index of increasing quality of care, the Q_score of each patient has a range between 0 and 40 and may be linked to the incidence of adverse cardiovascular events, such as angina, myocardial infarction, stroke, transient ischemic attack, revascularization procedures, lower limb complications, and mortality.

Patients with T1D. From 2004 to 2011, there was a decrease in the number of diabetes visits per year per patient with T1D from 2.9 to 2.7 (Table 2).[3] Note that the percentage of patients

Table 2. Data from Patients with T1D*

	2004	2005	2006	2007	2008	2009	2010	2011
N patients	13,456	14,141	16,910	20,385	23,108	25,037	26,918	28,804
Males (%)	54.9	54.8	55.1	55.2	54.6	54.5	54.6	54.5
Age (%)								
0-15	2.2	2.0	2.0	2.2	2.3	2.2	2.2	2.3
16-25	10.3	9.8	9.9	10.2	10.2	10.3	10.4	10.5
26-35	21.2	20.9	19.7	19.2	18.9	17.9	17.4	16.9
36-45	23.0	23.2	24.0	24.2	24.4	24.4	23.9	23.4
46-55	17.1	17.4	17.4	17.5	17.9	18.9	19.0	19.5
56-65	12.6	13.1	13.5	13.5	13.4	13.5	13.9	14.4
66-75	9.4	9.4	9.4	8.9	8.8	8.7	8.6	8.5
>75	4.2	4.2	4.1	4.2	4.1	4.2	4.4	4.6
First admissions (%)	8.2	8.1	9.0	9.4	7.7	7.2	8.1	7.6
Average number of visits	2.9	3.0	2.9	2.9	2.8	2.8	2.7	2.7

T1D, type 1 diabetes.
* Modified from Associazione Medici Diabetologi.[10]

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with T1D at target for the main parameters simultaneously decreased by about 12% compared with the 2007 values.[3] In addition, the number of patients with severely decompensated T1D decreased from 26.4% in 2004 to 19.6% in 2011.[3] The average A1C in this population was >8% and it was unchanged from 2007 to 2011 (8.1 ± 1.6 vs 8.1 ± 1.5).[3] During this observation period, the number of patients with optimal metabolic balance or severely decompensated disease decreased with a concomitant increase of patients with A1C between 7% and 8%.[3] This "shift towards the mean" may be due to an improvement in the global management of diabetes: A1C ranging between 7% and 8% is regarded as optimal metabolic balance in the elderly, and one-third of Italian patients with diabetes are older than 65 (and one-quarter older than 75).

Of note, patients with T1D who had constant monitoring of their lipid profile increased by 32% from 2004 to 2011.[3] Moreover, the number of patients with LDL-cholesterol below 100 mg/dL steadily increased to more than 40% of the participants in 2011, corresponding to a 35% increase from 2004.[3]

The use of insulin pump therapy for patients with T1D increased on an annual basis, as demonstrated by a recent observational study (IMITA) performed in Italy by units involved in this therapy.[11] Sensor-augmented insulin pump (SAP) therapy is currently in use and patients are trained for optimizing information provided by this device. Dedicated teams within specialized diabetes units manage SAP therapy. The Health Service System dispenses all the necessary instruments.

Diligent pregnancy planning is strongly recommended for patients with T1D in Italy, but often (about 50% of cases) pregnancies are associated with little preconception planning.[3] However, the Italian referral diabetic units have specific clinical programs for pregnancy planning. For these women, insulin pump or SAP therapy are usually proposed to optimize glucose control before and during pregnancy.

Patients with T2D. There is a steady increase in the prevalence of T2D in patients older than 70 years of age, though the proportion of younger patients with T2D is decreasing (Table 3).[3] A1C determination was routinely measured in > 90% of patients.[3] Patients with A1C < 7% increased by 12%, whereas patients with A1C > 8% decreased by 22%.[3] Several large clinical studies[12-14] have reconsidered the intensity of treatment for fragile patients with diabetes. Consequently, a slight increase in the mean level of A1C was observed in this subgroup.[3]

There was a significant increase in the use of metformin, a progressive but mild increase in the use of glinides and acarbose, a sharp drop in the use of glitazones, and a slow but progressive increase of GLP-1 RA and DDP-IV inhibitors.[3] A 36% increase in sulfonylurea use was somewhat surprising.[3] Insulin use increased by more than 60%, with a reduction of patients experiencing poor glycemic control independent of insulin use.[3] These conflicting data may be due

Table 3. Data from Patients with T2D*

	2004	2005	2006	2007	2008	2009	2010	2011
N patients	239,638	270,589	316,768	369,503	411,777	452,224	494,166	532,651
Males (%)	53.3	53.7	53.9	54.1	54.3	54.6	54.7	54.9
Age (%)								
0-35	1.4	1.3	1.2	1.1	1.0	0.9	0.9	0.8
36-45	3.8	3.6	3.6	3.5	3.4	3.2	3.1	3.0
46-55	12.4	11.8	11.2	11.0	10.9	10.6	10.3	10.0
56-65	28.4	27.7	27.3	27.0	26.3	25.6	25.6	25.4
66-75	34.0	34.6	34.6	34.5	34.8	34.7	34.1	33.4
76-85	18.0	18.9	19.8	20.3	20.6	21.5	22.3	23.2
>85	1.9	2.0	2.2	2.6	2.9	3.4	3.7	4.1
First admissions (%)	13.0	13.0	14.2	13.4	12.2	11.5	12.6	12.0
Mean control numbers								
Only diet	2.0	1.9	1.9	1.9	1.9	1.8	1.8	1.7
OHA	2.3	2.2	2.1	2.1	2.1	2.1	2.0	2.0
Insulin	2.6	2.6	2.6	2.5	2.5	2.5	2.4	2.4
Insulin + OHA	2.9	2.9	2.8	2.7	2.7	2.7	2.6	2.5

T2D, type 2 diabetes; OHA, oral hypoglycemic.
* Modified from Associazione Medici Diabetologi.[10]

to "therapeutic inertia" caused by an increasing demand for yet decreased number of specialists in INHS centers for diabetes care.[3]

From 2004 to 2011, there was an increased attention to the monitoring and treatment of LDL-cholesterol, aimed at achieving the established therapeutic goals, namely LDL-cholesterol < 100 mg/dL (70 mg/dL in patients with multiple cardiovascular risk factors),[15] with the intensified use of lipid-lowering drugs, particularly statins.[3] The modalities of the antihypertensive treatment improved as well from 2004 to 2011. Patients treated with a single drug increased from 32.2% in 2004 to 60.4% in 2011, and those with multiple therapies from 17.4% to 35.7%, respectively.[3] As a result, the percentage of patients with T2D who remained untreated despite documented hypertension decreased from 60.4% to 30.2%.[3] Since 2004, the use of all classes of antihypertensive drugs increased, especially for ARBs, diuretics, and beta blockers. Diabetic retinopathy increased by 45%, and a routine eye checkup is currently performed in 41.2% of the population with diabetes.[3] In contrast, routine monitoring for the prevention of diabetic foot remains unsatisfying and, even with a relative improvement of about 80% since 2004, this control is regularly performed in only 17.7% of patients.[3] The number of smokers and overweight patients remained unchanged, whereas the proportion of patients with obesity showed a relative increase of 14.6%.[3]

TREATMENT OF DIABETES IN ITALY

The Italian clinical practice guidelines, representing standards of care for diabetes management, were jointly released in 2014 by the Italian Society of Diabetology and the AMD.[15] This document was based on American Diabetes Association recommendations and a clinical evidence review performed by Italian experts. The first recommended step in the treatment of both T1D and T2D is lifestyle (dietary pattern and physical activity) changes. Patients with T1D and T2D should be taught about healthy eating, as well as medical nutrition therapy and carbohydrate counting, especially with complications and when insulin is used, respectively. Physical activity is prescribed as a "drug analogue" to all patients, according to their age, comorbidities, and therapeutic modalities. The drugs currently available for INHS prescription are summarized in Table 4.

The prevention of hypoglycemic events receives particular attention. At the referral diabetes units, patients with T1D can have continuous glucose monitoring to optimize their glucose balance while decreasing the risk of hypoglycemia. Continuous glucose monitoring may also be implemented in patients with insulin-treated T2D who are at risk of hypoglycemia.

The flow chart for the therapy of T2D, proposed by the 2014 Italian Standard of Care[15] (Fig. 1), recommends metformin as a second therapeutic step after lifestyle changes. As a third step—after lifestyle and metformin—each of the available OHA may be used as "first-to-add" without a specific indication. The endocrinologist should decide the most appropriate choice based on the individual patient characteristics and personal circumstances. In Italy, basal-bolus insulin therapy for persistently decompensated patients is prescribed with insulin analogues as detailed in Table 4. More and more, Italian endocrinologists use the algorithm proposed by the American Association of Clinical Endocrinologists.[16]

Table 4. Drugs Available for INHS Prescription in Italy

Class	Molecules
Biguanides	Metformin
Sulfonylureas	Glibenclamide, gliclazide, glimepiride, glipizide, gliquidone
Glinides	Repaglinide
Glitazones	Pioglitazone
α-glycosidase inhibitors	Acarbose
GLP-1 receptor agonists	Exenatide, exenatide LAR, liraglutide, lixisenatide
DPP-IV inhibitors	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin
SGLT-2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin
Regular, NPH, and premixed insulin	
Insulin analogues	Aspart, glulisine, lispro
Long-acting insulin analogues	Degludec, detemir, glargine, glargine 300, protamine lispro

INHS, Italian National Health Service; GLP-1, glucagon-like peptide 1; DPP-VI, dipeptidyl peptidase IV; SGLT-2, sodium-glucose cotransporter 2; NPH, neutral protamine Hagedorn.

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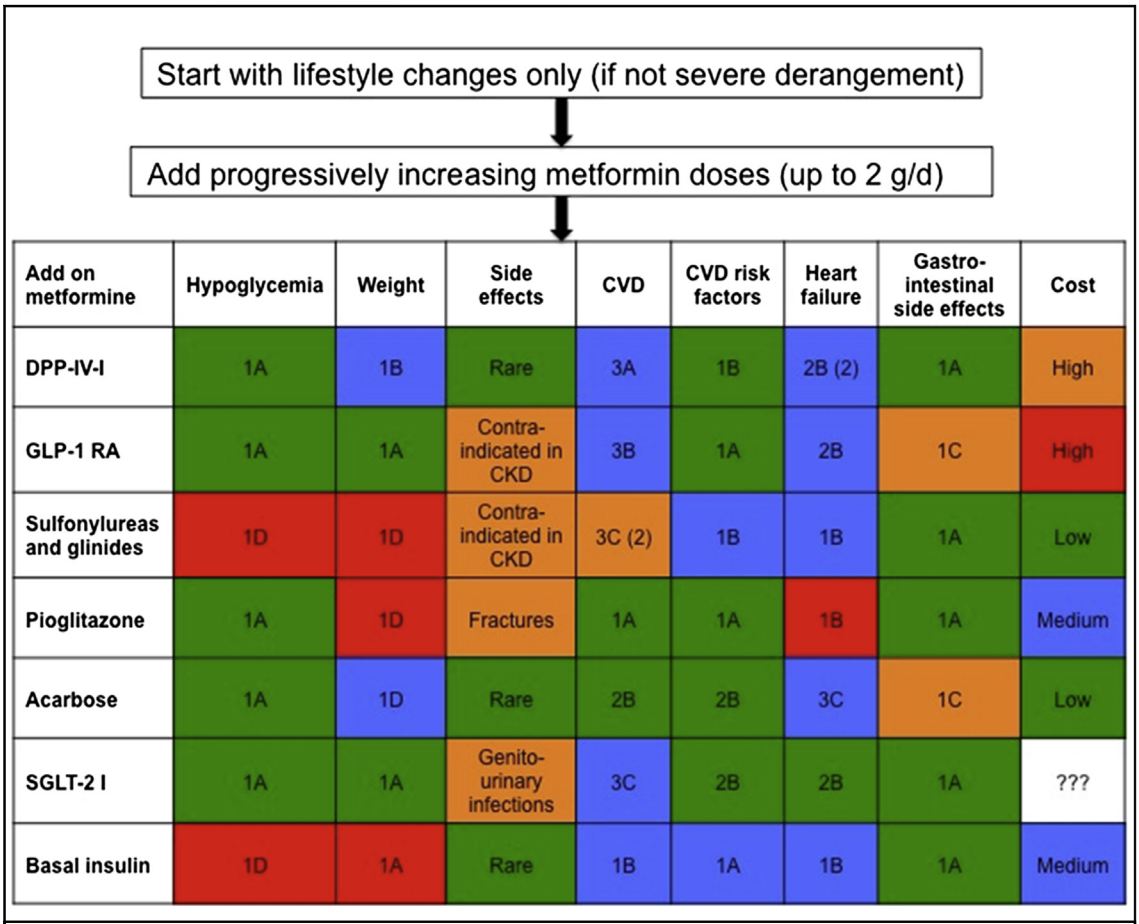
ACUTE COMPLICATIONS OF DIABETES

A study by the Italian National Institute of Health and the Department of Medical Sciences, University of Turin, found that the admissions for acute complications of diabetes in Italy from 2001 to 2010 were due to hypoglycemic coma, ketoacidosis, and hyperosmolar state. Admissions as a result of acute complications decreased by 51%, with a similar trend for men and women, for the various ages, and for the different regions.[17]

CHRONIC COMPLICATIONS OF DIABETES

Retinopathy. There are no national data available about the prevalence and incidence of legal blindness (residual vision not exceeding 1/20 in the best eye) in patients with diabetes, and there is no registry of patients with diabetic retinopathy (DR) in Italy. Epidemiological data suggest that at least 30% of the population with diabetes is suffering from DR and that every year about 1% of patients with diabetes suffers from severe eye complications.[18] In T1D and T2D, the main risk factors associated with an early onset and a rapid evolution of retinopathy are duration of diabetes, poor glycemic control, and presence of concomitant arterial hypertension.[15] The prevalence of DR is about 20% in patients diagnosed after age 30 and with a disease duration $>$ 5 years.[19,20] The prevalence rises to 40%-50% after 10 years and up to 90% after 20 years.[19,20]

In young patients with a prepubertal diagnosis of diabetes and <5 years of disease, the prevalence of DR is nearly negligible.[19,20] On the other hand, when diabetes is diagnosed after 30 years of age, the prevalence of retinopathy is about 20% after 5



Add on metformine	Hypoglycemia	Weight	Side effects	CVD	CVD risk factors	Heart failure	Gastro-intestinal side effects	Cost
DPP-IV-I	1A	1B	Rare	3A	1B	2B (2)	1A	High
GLP-1 RA	1A	1A	Contra-indicated in CKD	3B	1A	2B	1C	High
Sulfonylureas and glinides	1D	1D	Contra-indicated in CKD	3C (2)	1B	1B	1A	Low
Pioglitazone	1A	1D	Fractures	1A	1A	1B	1A	Medium
Acarbose	1A	1D	Rare	2B	2B	3C	1C	Low
SGLT-2 I	1A	1A	Genito-urinary infections	3C	2B	2B	1A	???
Basal insulin	1D	1A	Rare	1B	1A	1B	1A	Medium

Figure 1. Flow chart for the therapy of type 2 diabetes, proposed by the 2014 Italian Standard of Care. Color code: red, negative effect; orange, partially negative effect; green, positive effect; blue, neutral effect. Abbreviations in boxes point to evidence grade (1-6) and strength of recommendations (A-D). Modified from Associazione Medici Diabetologi.[15] Abbreviations: CVD, cardiovascular disease; DPP-VI, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter 2; RA, receptor agonist; I, inhibitor; CKD, chronic kidney disease.

years, 40%-50% after 10 years, and >90% after 20 years of disease.[18] The cumulative incidence of retinopathy during a 4-year observation period ranged from 34% to 59%, depending on the age of the patient and severity of disease.[18,21] As a whole, DR is responsible for 13% of cases of severe visual impairment in Italy.[18,21]

Nephropathy. Diabetes is still the leading cause of end-stage renal disease (ESRD), and the incidence of ESRD due to diabetes is rapidly increasing. In 2009, the incidence of new cases of ESRD caused by diabetes was 19.6% and was second only to hypertension (25.3%).[22] These data are in accordance with those of other western countries, in which the incidence of chronic kidney disease and ESRD are progressively decreasing in patients with T1D[23] while steadily increasing in patients with T2D.

Neuropathy. The prevalence of diabetic peripheral neuropathy (DPN) is estimated at approximately 30% (range: 13%-54%), both in patients with T1D and with T2D and shows a progressive increase with the age.[24] This wide range of prevalence is primarily due to varying diagnostic procedures and different definitions of neuropathy. However, the available data suggest that about 30% of patients suffering from diabetes for at least 15 years developed neuropathy, whereas 50% of them presented with neuropathy after 25 years.[24]

A multicenter Italian study on 8757 patients from 109 diabetes centers with T1D and T2D reported a 32.3% prevalence of DPN and confirmed that the prevalence and severity of this complication increased with age and duration of disease.[25] In Piedmont, a cohort of 379 patients with T1D had a 28.5% prevalence of DPN.[26] Finally, the SEARCH for Diabetes in Youth study demonstrated that DPN may be documented in young patients with a prevalence that is higher in T2D than T1D (25.7 vs 8.2%, respectively).[27]

Macrovascular Complications. In Italy, people with diabetes have an excess mortality of 30%-40% compared with those without diabetes.[28,29] The DAI study (Diabetes and Informatics study group, Italian Association of Diabetologists, and Italian National Institute of Health), a multicenter cohort study of 14,432 patients with T2D, investigated the prevalence and incidence of macrovascular complications (myocardial infarction, ischemic heart disease, cerebral thromboembolism, coronary artery bypass surgery, angioplasty, and amputation) and related cardiovascular risk factors.[30] This study was conducted on a representative, random sample of all patients with a diagnosis of diabetes at >39 years of age who were followed in the 157 participating services. At enrollment, 37% of patients had macrovascular complications.[30] About 29% of them had 1, 7% had 2, and less than 1% had 3 vascular complications.[30]

The incidence of stroke in this cohort was 2 to 3 times higher than that observed in nondiabetic populations.

The assessment of the incidence of coronary events (Table 5) found the following:

1. The incidence of coronary heart disease (CHD) in this cohort of patients with diabetes was lower than that reported in other studies.
2. The incidence of major coronary events was twice as high in men as in women and the ratio was lower than in the general population, confirming that the impact of diabetes on CHD events (either fatal or not) is stronger in women than in men;

Table 5. Cardiovascular Event Rate Standardized for Age

Events	Men (13,837 person-year)			Women (15,232 person-years)			*P*
	n	I	CI 95%	n	I	CI 95%	
CHD	241	15.7	13.1-18.2	318	17.6	14.9-20.3	.06
MI	164	10.3	8.3-12.3	88	4.7	3.3-6.1	**<.001**
Stroke	96	5.5	4.2-6.8	92	6.3	4.5-8.2	.12
Amputations	36	2.3	1.4-3.1	12	0.5	0.2-0.8	**<.001**
Fatal events	66	4.4	3.2-5.5	45	2.5	1.6-3.4	**<.01**
Revascularizations	51	3.5	2.4-4.7	38	1.8	1.2-2.5	.05
Major coronaric events*	208	13.1	10.9-15.4	114	5.8	4.3-7.2	**<.001**
All	571	35.7	32.0-39.4	524	29.8	26.2-33.4	**<.001**

CHD, coronary heart disease; I, incidence for 1000 person-years; CI, 95% confidence interval; CL 95%; MI, myocardial infarction.
Statistically significant difference between genders are in bold.
* Major coronaric events are myocardial infarction, revascularizations, and fatal CHD.
Modified from Istituto Superiore di Sanità.[30]

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3. The presence of microvascular complications was a major risk factor for macroangiopathic events, especially in women; and
4. The risk factors seem to be different for women and men, in that poor glycemic control and hypertension were predominant among men, whereas diabetic dyslipidemia (ie, elevated levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol) and microvascular complications were more prevalent in women; these results agree with previous data on the predictive role of glycemic control, hypertension, and dyslipidemia on the onset of CHD events.[31,32]

Men, but not women, with diabetes followed by specialized centers in Southern Italy demonstrated a lower risk of CHD than those in the Center-North regions.[30] This protective effect observed in Southern regions could be the result of a change in lifestyle and of an enhanced Mediterranean diet spontaneously adopted in this part of Italy.

GESTATIONAL DIABETES MELLITUS (GDM)

In Italy, gynecologists, general practitioners, and endocrinologists perform the screening for GDM with a 75 g oral glucose tolerance test based on international guidelines.[15] The GDM prevalence in Italy is increasing, as in the rest of world, with the mother's age at pregnancy, her weight, and the presence of concomitant risk factors.[33] Regional differences in the care of women with GDM are still present, but in the near future, the organization of regional referral units for insulin-treated GDM will likely reduce adverse events for both mother and child. Finally, the large prevalence of GDM in migrant women, with different cultures and languages, still needs an in-depth evaluation for an adequate care plan, both during pregnancy and afterward, because GDM is a risk factor for the development of T2D in the mother as well as the offspring.

CONCLUSIONS

PND is a patient-centered approach to diabetes care in Italy, consonant with the constitutionally guaranteed right to health for everybody. PND ensures continuity of care for patients and training for health care professionals. As a result, all stakeholders, including administrators and patients' organizations, participate in a multidisciplinary care model for diabetes.

Notwithstanding the increasing prevalence of diabetes in Italy, which is in line with other western countries, indicators of disease outcome are improving. Moreover, legal blindness, ESRD, and amputations related to diabetes are decreasing. These phenomena may be due to widespread protection and care for patients with diabetes provided by universal coverage. The implementation of the system, still far from perfect because of wide differences among autonomous regions, is progressively improving metabolic control and complication management. In aggregate, this reduces costs for the whole health care system in Italy, thereby ensuring some level of sustainability.

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