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REVIEW

Diabetes Care in Venezuela

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Abstract

BACKGROUND The incidence of type 2 diabetes (T2D) and its economic burden have increased in Venezuela, posing difficult challenges in a country already in great turmoil.

OBJECTIVES The aim of this study was to review the prevalence, causes, prevention, management, health policies, and challenges for successful management of diabetes and its complications in Venezuela.

METHODS A comprehensive literature review spanning 1960 to 2015 was performed. Literature not indexed also was reviewed. The weighted prevalence of diabetes and prediabetes was estimated from published regional and subnational population-based studies. Diabetes care strategies were analyzed.

FINDINGS In Venezuela, the weighted prevalence of diabetes was 7.7% and prediabetes was 11.2%. Diabetes was the fifth leading cause of death (7.1%) in 2012 with the mortality rate increasing 7% per year from 1990 to 2012. In 2012, cardiovascular disease and diabetes together were the leading cause of disability-adjusted life years.T2D drivers are genetic, epigenetic, and lifestyle, including unhealthy dietary patterns and physical inactivity. Obesity, insulin resistance, and metabolic syndrome are present at lower cutoffs for body mass index, homeostatic model assessment, and visceral or ectopic fat, respectively. Institutional programs for early detection and/or prevention of T2D have not been established. Most patients with diabetes (~87%) are cared for in public facilities in a fragmented health system. Local clinical practice guidelines are available, but implementation is suboptimal and supporting information is limited.

CONCLUSIONS Strategies to improve diabetes care in Venezuela include enhancing resources, reducing costs, improving education, implementing screening (using Latin America Finnish Diabetes Risk Score), promoting diabetes care units, avoiding insulin levels as diagnostic tool, correct use of oral glucose tolerance testing and metformin as first-line T2D treatment, and reducing health system fragmentation. Use of the Venezuelan adaptation of the transcultural Diabetes Nutrition Algorithm for lifestyle recommendations and the Latin American Diabetes Association guidelines for pharmacologic interventions can assist primary care physicians in diabetes management.

KEY WORDS diabetes, diabetes care, management, prediabetes, Venezuela

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INTRODUCTION

Nutritional transition has promulgated adverse nutritional and lifestyle habits in Venezuela and other Latin American countries, clearly contributing to the incidence of noncommunicable diseases, especially obesity and diabetes.[1] Diabetes was the fifth leading cause of death in Venezuela in 2012, with a prevalence rate of 6.6% in Barquisimeto, a western Venezuelan city.[2] Considering the burden imposed by diabetes and the costs for its control, prevention, and treatment represents clear challenges for the health system. Unfortunately, the care of patients with diabetes in Venezuela is provided by a fragmented health system and prevention programs are not at all structured. This fragmentation of Venezuelan health systems is characterized by restricted access, poor technical quality, inefficient use of resources, and low user satisfaction.[3]

The Bolivarian Republic of Venezuela is a country with an estimated population in 2013 of 30,405,000 inhabitants,[4] a life expectancy at birth of 76 years,[5] and 8 geographic regions: capital, central, western, northeastern, Guayana, Andes, Zulia, and the Llanos (Plains).[4] Each region has peculiarities regarding geography, climate, urban/rural proportion, income, food availability, and eating patterns. Moreover, the Venezuelan population has unique epidemiologic, cultural, physiological, ethnic, nutritional, pathologic, and lifestyle characteristics, as well as a political, economic, and social environment that is distinct and mostly unstable. All of these factors can influence the prevalence, prevention, and treatment of diabetes and its complications. The aim of this study was to review the status of the prevalence, causes, prevention, management, health policies, and challenges for successful management of diabetes and its complications in Venezuela. The results can provide useful information for authorities to implement effective actions in diabetes care that decrease complication rates and disease burden.

METHODS

A comprehensive literature review spanning 1960 to 2015 was performed, using "diabetes" and "Venezuela" as keywords. Abstracts and full papers (either in English or Spanish) from the identified references were collected and screened by the authors for inclusion in this review. From the 1454 references identified in databases used (PUBMED [149], OVID [1004], ScIELO [57], Revencyt [4], and LILACS [240]), 68 met inclusion criteria for providing information about diabetes in Venezuela, specifically prevalence, morbidity/mortality, causes/drivers, pathophysiology, associated cardiometabolic risk factors, prevention, management, complications, costs, national programs, and health policies. Literature not indexed, such as white papers, government publications, conference proceedings, and other gray literature was selected and included if considered appropriate. The literature review was complemented by direct personal communications and contacts with national and provincial health authorities of Venezuela in an attempt to include unpublished evidence and policies to enhance completeness.

A national population survey to investigate the prevalence of diabetes and prediabetes has not been performed in Venezuela.[6] From the present review, the prevalence of diabetes and prediabetes was estimated taking into account published regional and subnational studies. A weighted prevalence analysis was conducted based on the number of participants included in each study. In other words, the prevalence was adjusted to reflect importance by value or proportion of individuals included in every study. Prevalence studies in children and adolescents, with unclear or poor methodology, without population-based sampling, or involving patients attending a local health center were excluded.

RESULTS

Causes and Factors Associated with Diabetes in Venezuela

Genetic and epigenetic factors. T2D is the archetype of a complex disease, with genetic and environmental determinants. In Venezuelan individuals, family history of T2D in males with or without obesity is associated with a decrease in insulin secretion, expressed as lower Homeostasis model assessment (HOMA) β-cell values, highlighting the role of genetic susceptibility.[7] Multiple genes conferring T2D risk were initially identified using candidate gene and linkage-based studies, more recently by genome-wide association studies.[8] To date, the transcription factor 7-like 2 (*TCF7L2*) gene is the T2D risk locus with the largest effect size per risk allele and the most replicated across studies.[9] In Venezuela, a recent study demonstrated that individuals harboring a CT genotype and carriers of the allele T of *TCF7L2 rs*7903146 single nucleotide polymorphism, have a higher T2D risk (odds ratio, 2.9 and 2.3, respectively).[10] Furthermore, an association has been demonstrated between the Gly482Ser polymorphism of the peroxisome

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proliferator-activated receptor-γ, coactivator 1α (*PGC-1α*) gene and an increase of cardiovascular risk in T2D patients from Zulia state, Venezuela.[11] Also, an apparent association between the G/A uncoupling protein (*UCP*)-3 genotype with hyperglycemia, hypertension, and increased adiposity has been observed in both sexes in Venezuela.[12]

Epigenetic explain the variation in gene expression in response to changes in environmental conditions. This includes any process that alters gene activity without changing the DNA sequence, leading to a rapid but reversible modification of DNA or chromatin that can be transmitted to daughter cells.[13] In Latin America, regional and ethnic variations in epigenetic processes might explain diversity in T2D prevalence. A previous study demonstrated that low birth weight is associated with an increased risk for developing obesity, metabolic syndrome (MetS), and T2D.[14] It has been proposed that fetal programming in pregnant women with deficient nutrition and/or an increased frequency of subclinical infection and preeclampsia can generate an increased likelihood of a low birth weight child with a higher risk for subsequently developing insulin resistance and a low degree of inflammation.[15] Interestingly, low birth weight is common in Venezuela ranging between 7.7% and 14.3% of all births, depending on race.[16] This ethnic disparity may be based on socioeconomic differences, but it has been well established that children with low birth weight have decreased β-cell mass, nephrons, hepatocytes, and muscle fibers.[17] Therefore, one can speculate that the development of T2D results from an interaction between the fetal and extrauterine nutritional environment with a robust genetic component.

Environmental and lifestyle factors. An unhealthy dietary pattern with physical inactivity increases the risk for diabetes via weight gain and obesity. In Venezuela, 2 studies involving 3422 adults reported that the weighted prevalence of physical inactivity was 68%[18,19] Similarly, in another study of 1399 adolescents, only 17.3% of boys and 7.5% of girls performed ≥60 minutes of physical activity per day ≥5 days per week.[20] Many factors can limit physical activity, but in Venezuela, considering that violent deaths were the leading cause of mortality in men aged 20 to 59 years in 2006 (36.5%) and 2009 (38.2%),[6] it is not surprising that the high crime rate is a major limiting factor to be considered when plans to increase physical activity are proposed.

Nutritional analysis of the typical intake and average requirement of the population found that the Venezuelan diet is unbalanced and unvaried. The Venezuelan dietary pattern is primarily composed of empanadas (fried corn cake stuffed with cheese, beans, or meat), coffee, beef, chicken, pasta, rice, bread, bananas, arepas (corn flour cake), margarine, juices, and sodas. This dietary pattern is characterized by a high intake of calories, complex carbohydrates, saturated fat sources, protein, sodium, cholesterol, sodas, and sugar, with a low intake of fruits, vegetables, fiber sources, and fish.[21] Between 2003 and 2010, the apparent consumption of foods recorded a slight increase in the consumption of legumes (8%) and fruits (12%); this benefit was probably counteracted by the decrease in the intake of vegetables (−20%) and fish (−28%), particularly fresh fish (−43%).[22] Other studies have reported a low consumption of fruits and vegetables using food intake frequency questionnaires.[23]

Caloric intake of the Venezuelan population increased by 27% between 1998 (2202 kcal/d) and 2009 (2790 kcal/d) to exceed the minimum caloric intake recommended by the Food and Agriculture Organization of the United Nations (2700 kcal). Nevertheless, the quality of food intake was still inadequate[22] and this increased caloric intake was associated with the increasing prevalence rates of obesity and T2D in Venezuela. Also, there is decreased production of healthy food with subsequent scarcity; this is coupled with subsidies for less-expensive, less-healthy foods that represent major sources of starch and saturated fat in the Venezuelan diet. This dynamic effect of addressing undernutrition and food insecurity with increased food availability exposes the hazards of injudicious provision of unhealthy foods that ultimately create an adverse dietary pattern and increased risk for chronic diseases.

Obesity is an independent risk factor of cardiovascular disease (CVD) and plays a crucial role in the development of diabetes.[24] Although no data from longitudinal studies or periodic national surveys are available, estimates of international agencies have suggested that the prevalence of obesity in Venezuela has tripled from 1980 (∼10%) to 2009 (∼30%).[25] Detecting obesity is important, considering that obese individuals with normal glucose tolerance may have an 80% decrease in insulin secretion.[26] It has been suggested that body mass index (BMI) may underestimate the actual proportion of Venezuelans with obesity. An evaluation of 1375 individuals aged ≥18 years reported that a BMI cutoff of ≥30 kg/m^2 misses 21% of people

with excess adiposity determined by bioelectrical impedance analysis. The best BMI cutoff to categorize obesity in Venezuela was 27.5 kg/m^2, with a sensitivity of 89.3% (95% confidence interval, 87-91) and a specificity of 85.4% (95% confidence interval, 81-89).[27] Similar results have been found in 750 Venezuelan individuals from a sample of the general population.[28] Therefore, it should be noted that in Venezuela, many people who are truly obese might be categorized as nonobese. This shortcoming can be addressed using a recently proposed complications-centric definition of obesity (eg, diabetes as an obesity-related complication) in people with BMI $\geq$25 kg/m^2.[29] This methodology also regards obesity as an adiposity-based chronic disease and proposes formal assessment of anthropometric measurements, including BMI adjusted for ethnicity, to identify individuals with increased adipose tissue that increases cardiometabolic risk, as well as the exploration of glucose homeostasis status when available.[29]

Pathophysiological peculiarities of diabetes in the Venezuelan population. The majority of individuals with obesity progressively develop dysglycemia with features of insulin resistance and β-cell dysfunction. This biological continuum from excess adiposity to T2D is complicated and intricate. As previously mentioned, male normoglycemic individuals from Zulia with a family history of diabetes showed lower insulin secretion to compensate insulin resistance regardless of weight, verified by a lower disposition index.[7] This finding suggests that β-cell dysfunction and impaired insulin secretion precede the appearance of T2D. In Venezuelan individuals with obesity, inflammatory events occur without insulin resistance[30] and are an important determinant of multiorgan cardiometabolic dysfunction increasing the risk for obesity-associated T2D.[31] In Latin Americans with obesity, inflammation occurs at lower body fat levels.[13,32] In fact, waist circumference cutoff points associated with the MetS are lower in the Venezuelan population compared with aggregate white data.[33,34] Additionally, less epicardial (ectopic) adipose tissue predicts MetS in individuals from Ciudad Bolívar (Guayana) and Mérida (Andeans) compared with data reported in whites.[35] Recently, a study with 2026 adults from Maracaibo, Venezuela, demonstrated a cutoff point of 2.00 for an updated HOMA (HOMA2-IR), which is lower than that reported in other populations.[36] Taken together, these data suggest that Venezuelans develop insulin resistance and accumulation of visceral fat earlier than other populations.

Epidemiology of Diabetes in Venezuela

Prevalence of diabetes in Venezuela. The International Diabetes Federation (IDF) reported that the number of people with diabetes in the world for 2013 was 382 million, and this figure will increase by 2030, particularly in developing countries.[37] The first studies published in Venezuela reported variable diabetes prevalence rates: 6% in 1963, 2.6% in 1972, 3.7% in 1978, and 4.4% in 1997.[38] However, the methodology of these studies was heterogeneous; for instance, in one of the studies, the diabetes prevalence rate was estimated based on glycosuria alone.[38] Moreover, data from the IDF,[39] published by the Latin American Diabetes Association (ALAD),[40] reported a prevalence of diabetes in Venezuela of 10.4%. According to the IDF Atlas of Diabetes,[39] age- and sex-specific global estimates of diabetes prevalence were based on 133 studies from 91 countries. However, only 37 studies were national surveys, and in those countries that did not have their own study, data from other countries were incorporated. The selection of the surrogate country was based on ethnic, socioeconomic, and other population similarities, as well as geographic proximity. Hence, it was reported that the adjusted prevalence rate of diabetes in Venezuela was 5.9%, but in fact, this was actually based on 2010 information from Brazilian studies.[41]

Three years later, a prevalence rate for diabetes in Venezuela of 6.6% was reported.[37] This corresponded to a value obtained for Barquisimeto in the CARMELA (Cardiovascular Risk Factor Multiple Evaluation in Latin America) study comparing prevalence rates of diabetes and other cardiovascular risk factors in 7 cities in Latin America.[2] According to the World Health Organization, the prevalence of elevated fasting plasma glucose (FPG) in individuals >25 years in 2008 in Venezuela was 11.1% in men and 10.9% women.[6] However, these data are uncertain point estimates with ranges standardized by age and without national population studies from 2000 to 2010.[6]

Prevalence rates in the literature for prediabetes and diabetes in Venezuela are summarized in Tables 1 and 2. The weighted prevalence of diabetes was 7.7% and prediabetes was 11.2%. These values should be used until results of a national study are available. The prevalence of other cardiometabolic risk factors (obesity, dyslipidemias, hypertension, MetS, and physical inactivity) in Venezuela has been reviewed.[21] EVESCAM (Cardio-metabolic Health Venezuelan Study) is the first and currently ongoing national population survey in Venezuela to

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Table 1. Prevalence of Diabetes in Venezuela by Regions*

Region	State	Population	n	Year	Prevalence Rates (%)			Author
					Men	Women	Total	
Capital	Capital district	Junquito Parish	321	2006	NR	NR	6.7	De Oliveria et al.[42]
	Vargas	Catia Parish	210	2006	NR	NR	9.5	Brajkovich et al.[43]
	Miranda	Sucre Municipality	471	2006	NR	NR	8.0	Brajkovich et al.[44]
Central	Carabobo	Valencia City	100	2008	20.0	6.3	9.0	Ruiz-Fernández et al.[45]
	Lara	Barquisimeto City	1848	2009	5.6	6.3	6.0	Escobedo et al.[2]
		Palavecino Municipality	337	2006	10.4	11.4	11.0	Nieto-Martínez et al.[46]
Andes	Mérida	Rangel Municipality (Paramo)	140	2006	11.8	6.7	8.6	Nieto-Martínez et al.[46]
		Ejido Parish	272	2010	15.8	14.6	14.9	Nieto-Martínez et al.[46]
Zulia	Zulia	Zulia State	3108	2005	7.8	7.4	NR	Florez et al.[19]

NR, not reported.
* Number of participants: 6807; weighted diabetes prevalence: 7.7%; 2015 estimates of patients with diabetes: 1,494,059. Municipality represents a political-territorial division that is divided into parishes.

examine the prevalence of diabetes and cardiometabolic risk factors, as well as their relationships with lifestyle.[47]

Mortality and diabetes DALYs in Venezuela. Diabetes-related morbidity in Venezuela has been rising since 1990, when the incidence was 91.7 per 100,000 inhabitants, reaching 338.6 in 1999-2001.[48] This increase significantly affected the health system, with >110,000 primary care consultations per year.[48] The fatality rate due to diabetes was much higher in the population >24 years (10%) compared with those who were younger (0.6%).[48] Additionally, diabetes was the fifth leading cause of death in Venezuela, accounting for 7.1% of global deaths in 2012.[49] The mortality rate due to diabetes rose 250% from 1990 to 2012 with a 7% increase per year (Fig. 1).[38,49] The overall incidence of diabetes deaths was similar between sexes; however, it is higher in men before age 75 and women after age 75 (Fig. 2).[49] In 2010, diabetes ranked ninth in years of life lost (YLL) with 134,000 years, an increase of 73% compared with 1990 when it ranked 11th.[49] Disability-adjusted life years (DALYs) are the sum of YLL due to premature mortality and years of healthy life lost due to disability (YLD). In 2012, CVD and diabetes were the leading causes of DALYs in Venezuela.[50,51]

Management of Diabetes in Venezuela—Prevention Strategies

Detection of individuals at risk for diabetes. T2D is undiagnosed in >45% of the Central and South American adult population.[52] Detecting people with diabetes or prediabetes is paramount, particularly in light of the success of lifestyle changes and pharmacotherapy on prevention, T2D management, and complication prevention.[53-55] The FINDRISC (Finnish Diabetes Risk Score) is one of the most efficient and often used screening tools to detect new cases of T2D.[56] However, the

Table 2. Prevalence of Prediabetes in Venezuela by Regions*

Region	State	Population	n	Year	Prevalence Rates (%)			Author
					Men	Women	Total	
Capital	Vargas	Catia Parish	210	2006	NR	NR	9.0	Brajkovich et al.[43]
	Miranda	Sucre Municipality	472	2006	NR	NR	10.0	Brajkovich et al.[44]
Central	Lara	Palavecino Municipality	337	2006	19.8	14.0	15.8	Nieto-Martínez et al.[46]
		Baquisimeto City	1848	2009	NR	NR	1.0	Escobedo et al.[2]
Andes	Mérida	Rangel Municipality (Paramo)	140	2006	23.5	15.7	18.6	Nieto-Martínez et al.[46]
		Ejido Parish	272	2010	7.0	3.7	4.5	Nieto-Martínez et al.[46]
	Zulia	Zulia State	3108	2005	19.6	14.9	NR	Florez et al.[19]

NR, not reported.
* Number of participants: 6,387; weighted prediabetes prevalence: 11.2%; 2015 estimates of patients with prediabetes: 2,165,464. Municipality represents a political-territorial division that is divided into parishes.

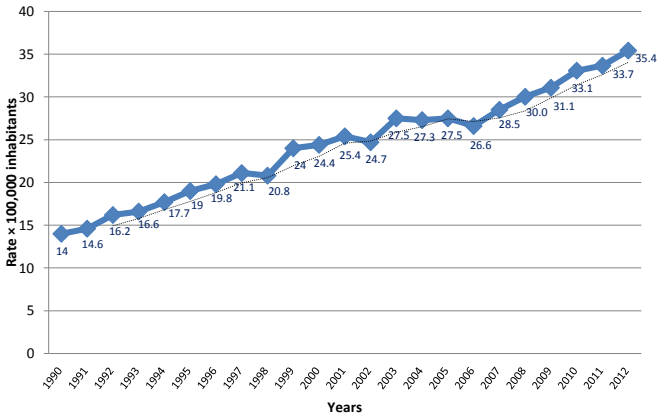

Figure 1. Diabetes mortality rate in Venezuela between 1990 and 2012. Data source: MPPS mortality yearbooks, 1990-2012. Adapted from reference 49.

FINDRISC needs to be validated in populations other than the Finnish population upon which it is based to determine its performance attributes (eg, sensitivity and specificity). Several Latin American countries have initiated validation studies and currently use the FINDRISC to detect people at high risk for glucose metabolism disorders.[57]

FINDRISC includes anthropometric (including waist circumference), metabolic, and lifestyle factors that predict T2D. By replacing the original cutoff point of waist circumference with the Latin American cutoff point in a Colombian (Bogota) or Venezuelan (Barquisimeto) clinical setting, the modified FINDRISC score demonstrated a similar performance to identify impaired glucose regulation in men and a better discrimination power in women compared with the original FINDRISC. [58] In Barquisimeto, a cutoff score >14 points had the best sensitivity-to-specificity ratio to screen individuals of both sexes and detect those with impaired glucose regulation who would be eligible for blood glucose testing.[58] Recently, a lower cutoff for screening (>10 points) was proposed in a population-based sample of 521 individuals recruited in EVESCAM.[59] Considering these data, it has been recommended that the modified FINDRISC for Latin America be used to define individuals requiring an oral glucose tolerance test (OGTT) to diagnose prediabetes or occult T2D.[21] The recommendation of validating and applying the Latin America FINDRISC for screening has been recently endorsed by a group of Latin American experts (López-Jaramillo P, Nieto-Martínez RE, Aure-Fariñez G, et al. Identificación y manejo de la Prediabetes: perspectiva Latinoamérica. Unpublished data).

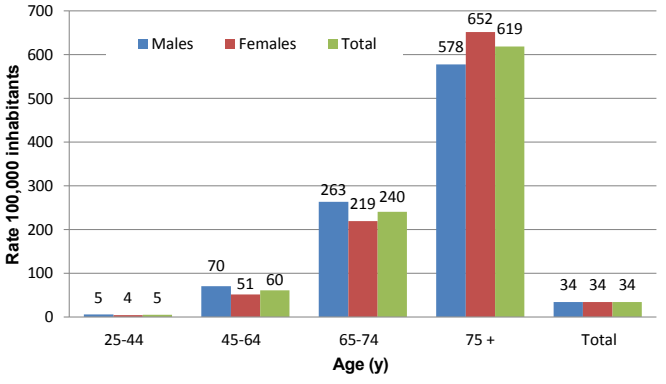

Figure 2. Diabetes mortality rates by sex and age groups in Venezuela. Data source: MPPS mortality yearbooks, 2010-2012. Adapted from reference 49.

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In Venezuela, institutional screening programs for early detection of T2D have not been established. Self-assessment websites have been proposed to alert the public about the risk for developing T2D. The Spanish Foundation of Diabetes proposed a web-based Spanish version of the e-FINDRISC.[60] During the first year, nearly 6000 e-FINDRISC screenings (23%) were completed for Latin American people, including 6.8% of these from Venezuela.[57] The e-FINDRISC detected 20.8% of individuals as high risk for developing T2D.[57]

Intervention strategies for diabetes prevention. Clinical trials demonstrate that lifestyle changes can prevent diabetes, but implementing lifestyle change in real life is a tremendous challenge. Two local interventions in primary care settings from Venezuela and Colombia based on the guidelines of the Diabetes Prevention Program (DPP) study in the United States have been tested.[57] In the health system of Maracaibo, Venezuela, this study evaluated 140 Latino individuals with prediabetes (63.6% women, age 48.1 ± 11.8 years, and BMI 32.1 ± 5.5 kg/m^2) who were assigned to receive either standard of care (SC group; n = 70) or lifestyle intervention (LI group; n = 70) for 2 years.[61] Ideal cardiovascular health behaviors (nonsmoking, achieving normal weight, engaging in adequate physical activity, and maintaining a healthy diet) and health factors (total cholesterol <200 mg/dL, blood pressure <120/80 mm Hg, and FPG <100 mg/dL) were evaluated at baseline and every 6 months.[61] The American Heart Association global cardiovascular health score assigning 1 point to each ideal behavior and factor (for a maximum of 7 points) and 0 points for poor status to each behavior and factor was calculated.[57] The cardiovascular score at baseline was 3.9 ± 0.1 (84.3% in SC and 88.6% in LI had poor to intermediate cardiovascular scores).[61] Larger improvements in the cardiovascular scores from baseline were obtained in the LI versus SC (2.0 ± 0.9 versus 0.8 ± 0.6; $P < 0.0001$) groups at 24 months of intervention.[57] At study end, only 4.3% of LI and 47.1% of SC participants had poor to intermediate cardiovascular scores ($P < 0.01$).[61] This study concluded that the implementation of DPP-based lifestyle intervention leads to moderate improvements in overall cardiovascular health among Latinos with prediabetes in Venezuela.[61]

Laboratory methods. Biochemical tests (eg, FPG, OGTT, and hemoglobin A1c [A1C]) are recommended as tools to assess glucose homeostasis and diagnose prediabetes and diabetes, but are not always available or reliable. For instance, in Venezuela, the OGTT is often done after a breakfast high in carbohydrates and not with a standardized 75 g of anhydrous glucose.[21] A1C has been recommended in combination with plasma glucose determinations for the diagnosis of diabetes. In Venezuela, it is possible that not all laboratories have an A1C test that is properly standardized. There are various patient factors that compromise the A1C interpretation, such as hemolytic anemia, structural hemoglobinopathies and thalasemia syndromes, uremia, hyperbilirubinemia, hypertriglyceridemia, chronic alcoholism, and vitamin C ingestion.[62]

Recently, a study evaluating the effects of diabetes definitions on diabetes prevalence from a pooled analysis of 96 population-based studies with 331,288 participants, including 2 subnational Venezuelan studies (5 populations), reported that an FPG-based diagnosis represented a balanced strategy (based on reliability, accessibility, and performance) and reduces any underestimation of diabetes prevalence.[63]

Treatment of Diabetes in Venezuela

Current treatment of diabetes in Venezuela. Diabetes management in Venezuela has been part of the IDMPS (International Diabetes Management Practices Study), an observational survey to collect, analyze, and disseminate data in a standardized manner from patients with diabetes in developing countries.[64] The research design included 5 waves, each consisting of a 2-week cross-sectional and a 9-month longitudinal survey, separated by 3-month intervals. In Venezuela, the results of wave 4 have been reported and involved 295 patients with diabetes (n = 97 with T1D [58.8% females] and n = 198 with T2D [55.3% females]).[64] Patients with T2D were older, heavier, and engaged in less frequent self-monitoring of blood glucose compared with patients with T1D.[64] Regarding control of cardiometabolic factors, only 8% of patients with T1D and 4.3% of patients with T2D attained all 3 recommended targets (blood pressure <130/80 mm Hg, low-density lipoprotein cholesterol <100 mg/dL, and A1C <7.0%).[64]

Diabetes treatment modalities in Venezuela are provided in Table 3. All of the patients with T1D were treated with insulin, most interestingly 15.5% in combination with oral glucose–lowering drugs (OGLD; 60% on metformin), and basal plus bolus was the most popular insulin regimen (78%).[64] In the IDMPS main report, including 11,799 patients in 4 continents, the type of treatment was not related with an A1C <7.0%.[65] However, self-monitoring of blood glucose, short disease duration, and training by diabetes educators were predictors of glycemic

Table 3. Type of Diabetes Treatment in Venezuela (%)

	T1D	T2D
Insulin	100	34.8
Insulin alone	84.5	14.1
Insulin + any oral agent(s)	15.5	20.7
Basal insulin	6.1	48.1
Basal insulin + prandial insulin	78.0	42.6
Prandial insulin alone	2.4	1.9
Premixed insulin	13.4	7.4
Any oral agent	15.5	85.9
Metformin alone	60.0	25.3
Sulfonylurea alone	0.0	11.8
Metformin + sulfonylurea	13.3	44.7
Other oral agent(s)	26.7	18.2

T1D, type 1 diabetes; T2D, type 2 diabetes.[65]

control in Latin America.[60] Also in the fourth wave of the IDMPS, 86% of patients with T2D were treated with OGLD, with most receiving 1 or 2 drugs (81.3%), primarily metformin with or without sulfonylureas (44.7%).[64] One-third of patients with T2D received insulin treatment (n = 69; 34.8%), two-thirds of these patients (n = 41; 59.4%) in combination with OGLD.[64] In the IDMPS main report, in patients treated with OGLDs only, use of fewer OGLDs was a predictor for reaching targets in all regions.[65] Other factors related to A1C <7.0% in Latin America were short disease duration, lack of microvascular complications, old age, management by specialists, and existence of health insurance coverage.[65]

Diabetes clinical practice guidelines. The 2012 Guideline of Clinical Practice in Diabetes Mellitus for Venezuela[38] includes new criteria diagnostic and integral strategies on treatment and control, with evidence levels adherent with international guidelines of the IDF[38,66] and the American Diabetes Association.[67] The National Federation of Diabetes in Venezuela (FENADIABETES) has proposed the application of the 2013 Latin American Diabetes Association (ALAD) guideline in Venezuela.[68] Similar to the American Association of Clinical Endocrinologists clinical practice guideline in diabetes,[69] the ALAD guideline focuses on A1C levels, which is easy to apply in the primary care setting.[70] Unfortunately, these guidelines do not take into account regional problems with A1C availability and reliability or culturally sensitive recommendations for lifestyle changes.

The Transcultural Diabetes Nutrition Algorithm. In 2012, a transcultural Diabetes Nutrition Algorithm (tDNA) was proposed by an international group of expert health care professionals with recommendations to be adapted to different countries.[71] In 2014, the Venezuelan application of the tDNA was presented.[21] The tDNA is a tool to guide decisions and implement lifestyle changes in prediabetes and diabetes according current clinical practice guidelines. This algorithmic approach includes recommendations based on regional data in various lifestyle variables, including typical dietary patterns and physical activity; anthropometric recommendations, with optimal BMI cutoff points to categorize obesity ($\geq$27.5 kg/m^2)[27] and waist circumference to diagnose abdominal obesity ($\geq$94 cm in men and $\geq$90 cm in women)[33]; and the evaluation of prediabetes and occult diabetes applying the Latin America-modified FINDRISC.[54] Chief among the recommendations for Venezuela are complete and progressive programs of physical activity, as well as the practical implementation of the Mediterranean pyramid with specific menus adapted for the Venezuelan culture.[21,72,73]

Particularities in the Management of Diabetes in Venezuela

Misuse of insulin as diagnostic tool. In Venezuela, there is a problem with inappropriate use of insulin sampling as a diagnostic tool, particularly after substandard OGTT testing using high-carbohydrate breakfasts.[21] This behavior is facilitated by some private laboratories that provide the service without a medical order, although this practice lacks any evidence-based support or defense in clinical practice guidelines.

Improper diagnoses, such as hyperinsulinism, may prompt incorrect or, worse, harmful treatment. In Venezuela, there are frequent off-label uses of metformin to reverse insulin-resistant states, to decrease levels of plasma insulin, or to treat obese individuals with normal glucose homeostasis. Retrospective data from 924 patients attended in 3 health centers showed heterogeneity in the indications of metformin in Venezuela.[74] In a university hospital, metformin was correctly used and only used in patients with T2D.[74] However, in a nonuniversity health center, metformin was used in patients with T2D (24%), insulin resistance (34%), obesity (11%), impaired glucose tolerance (3%), and/or polycystic ovary syndrome (PCOS; 2%).[74] Finally, in a research university setting (pharmacology unit), metformin was indicated in T2D (9%), insulin resistance (68%), impaired glucose tolerance (21%), and PCOS (2%).[74] This widespread use of metformin is fueled by ease in acquisition (not requiring a medical prescription), relatively low price

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Table 4. Summary of Conclusions on Diabetes Care in Venezuela

Epidemiology	- Diabetes affects 7.7% of the population and prediabetes 11.2%. - Diabetes is the fifth leading cause of death and the 11th leading cause of DALY. - EVESCAM (Cardio-metabolic Health Venezuelan Study) is the first and currently ongoing national population survey to examine the prevalence of diabetes and cardiometabolic risk factors.
Causes/Drivers	- Genetic susceptibility to develop diabetes, epigenetic factors, nutritional status, unbalanced and unvaried diet, and sedentary habits.
Pathophysiologic peculiarities	- Lower waist circumference cutoff points with metabolic abnormalities. - Lower BMI cutoff (27.5 kg/m^2) to increase the detection of excesses in adiposity. - Obesity, insulin resistance, and metabolic syndrome are present at lower cutoffs for BMI, homeostatic model assessment, and epicardic fat respectively.
Prevention	- LA-FINDRISC (cutoff score >10 points) is efficient screening tool to detect those individuals requiring OGTT. - Structured lifestyle intervention in accordance with the DPP improves CV health. - Diabetes prevention programs are not structured.
Health system and national programs	- Most patients with diabetes (~ 87%) are cared for in public facilities in a fragmented health system. - Underfunded and uncoordinated health services. - Treatment programs support only a small proportion of the population affected by and at risk for diabetes.
Management	- Low success rate: only 8% of T1D and 4.3% of T2D patients attaining recommended targets; and only 24% having A1C values <7.0%. - An elevated proportion of T2D insulin-naive patients were reluctant to start insulin therapy. - Basal plus bolus insulin in T1D and 1 or 2 OGLDs in T2D were the most popular interventions. - Local clinical practice guidelines are available, but implementation is suboptimal and supporting information is limited. - Misuse of metformin is frequent with many targeted conditions not related with hyperglycemia.
Challenges and recommendations	- Increase resources and reduce costs - Reduce health system fragmentation - Improve education of health care team members and patients - Promote diabetes care units - Avoid misuse of serum insulin testing, misuse of OGTT, and misuse of metformin - Implement the use of the Venezuelan tDNA version that provides a complete and progressive program of physical activity, as well as the practical implementation of the Mediterranean pyramid with menus adapted to Venezuelan habits. - Implement the ALAD guidelines for pharmacologic interventions to guide primary care physicians in the decision-making process for diabetes management. - Implement DPP protocol to prevent diabetes

ALAD, Latin American Diabetes Association; BMI, body mass index; CV, cardiovascular; DALY, disability-adjusted life years; DPP, Diabetes Prevention Program; LA-FINDRISC, Latyin American Finnish Diabetes Rick Score; OGLD, with oral glucose–lowering drugs; OGTT, oral glucose tolerance test; T1D, type 1 diabetes; T2D, type 2 diabetes; tDNA, transcultural Diabetes Nutrition Algorithm.

(compared with international prices), and belief that weight loss and better health can result for anyone.

One of the first reports of the beneficial effect of metformin on menstrual irregularity in PCOS was obtained in Venezuela.[75] However, the only

approved indication of metformin in Venezuela is the treatment of T2D, although there have been calls to expand this to other clinical states, such as prediabetes.[76] The DPP Outcomes Study showed that, in individuals with prediabetes, normalization of blood glucose levels during the intervention was associated with a 56% reduction in the incidence of diabetes, regardless of treatment and whether the decline was temporary.[77] In those failing to normalize blood glucose despite lifestyle change, metformin was still beneficial.[77] The American Diabetes Association recommends consideration of metformin therapy for prevention of T2D.[78] Considering the data of the DPP Outcomes Study, cost-effectiveness data, and the greater Latin American population's sensitivity to develop insulin resistance and T2D with lower levels of visceral adiposity, a group of Latin American experts recommended identifying patients with early abdominal obesity and prediabetes to implement lifestyle changes and consider metformin if blood glucose levels fail to respond (López-Jaramillo P, Nieto-Martínez RE, Aure-Fariñez G, et al. Identificación y manejo de la Prediabetes: perspectiva Latinoaméricana. Unpublished data).

Psychological Resistance to Insulin. Although clinician and health system factors play an important role in diabetes care, patient reluctance to begin insulin is a critical issue.[79] Patients may refuse insulin outright, bargain with their health care providers to postpone treatment, or even drop out of treatment altogether. An unwillingness to start insulin, termed *psychological insulin resistance*, is relatively common. In Venezuela, about 33% of insulin-naive patients with T2D reported that they were unwilling to begin insulin if prescribed. Regarding those willing to start insulin, patients with psychological insulin resistance reported more negative and less positive beliefs about insulin and a more negative perspective in regard to their current oral medications. Beliefs most commonly attributed to insulin therapy were fear of injection and personal failure.[80]

National Programs for Prevention and Treatment of Diabetes

Health system and care levels. Venezuela began a major process of social and political transformation, affecting the health system. Despite the robust and substantive social provisions contained in a new Constitution, drafted in mid-1999 by a constitutional assembly that had been created by popular referendum, including a constitutional right to health and its correlative state obligations, an effective realization of the right to health has not been achieved. Conspicuous deficiencies exist in areas such as quality of public health care facilities, goods, and services, as well as access to information and the state obligations to produce reliable statistics in basic health indicators.[81] This is in part a result of a deficient, underfunded, nonregulated, and less-coordinated public health system.[82]

Total health care expenditure in Venezuela as a percent of gross domestic product in 2013 was 3.6% (down from 6% in 2007) with a total per-capita health expenditure of US $656.[83] Several public entities finance, regulate, and provide health services in Venezuela, including the Ministry of Popular Power for Health (MPPS), the Venezuelan Institute of Social Security (IVSS), the Institute of Social Security of Ministry of Education, the Institute of Social Security of the Armed Forces, and each of the state governments. Additionally, the Venezuelan government is directly involved in the delivery of primary health care through social missions. The main objective of the social missions is to reach the poorest sector of the population. The most relevant social mission is called Misión Barrio Adentro, which delivers mostly primary health care services.[81,82]

According to the Institute of National Statistics in 2011, 56.6% of the Venezuelan population used health care services as follows: public hospital (24.9%), Misión Barrio Adentro network (20.3%), public outpatient (16.1%), clinic or private hospital (12.7%), IVSS (5.6%), and other social security institutions (1.3%).[4] Therefore, it can be assumed that the majority of patients with diabetes are diagnosed and treated in public-sector facilities (~87%) and have some degree of social protection.[4] The private-care system in Venezuela comprises institutions and health care professionals who receive funding from private sources, such as prepaid medicine plans, surgery and maternity insurance, and, most frequently, out-of-pocket payments by patients. In Venezuela, according to 2013 World Health Observatory data, out-of-pocket expenditures represented 90.2% and private prepaid plans represented 3.7% of the total private financing of health care.[84]

As in other countries, there are social inequities in the distribution of access to health care in Venezuela that produce disparities in health outcomes. Moreover, the Venezuelan health system focuses on curative services at great cost and, in essence, neglects the preventive care approach, which could address about 70% of the disease burden.[3] Also, excessive fragmentation of health services is frequent in Latin American countries—this

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is certainly true in Venezuela—and leads to difficulties in access to services, services of poor technical quality, irrational and inefficient use of available resources, unnecessary increases in production costs, and lower user satisfaction.[3]

Diabetes Care Programs in the Health System of Venezuela. Since 2008, the MPPS implemented the Cardiovascular, Renal, Endocrine-Metabolic, and Anti-tobacco programs. This includes educational campaigns to prevent diabetes, training of health promoters from the communities, and provision of equipment to the health care network. The program was implemented by agreement between Cuban and Venezuelan governments. Patients benefit from cost-free medications, such as metformin and sulfonylureas, and in the IVSS, combination drugs (metformin/sulfonylurea) and insulin glargine. In 2011, the National Epidemiological Surveillance System reported 123,413 new cases of diabetes and 143,009 visits for patients with diabetes. Despite these government efforts, only a small proportion (about 24%) of known patients with diabetes in Venezuela[2,37] actually benefit. Moreover, it should be noted that these programs have operated during a period of neutral and/or negative trends of noncommunicable disease deaths.[85]

Diabetes Care Units in Venezuela: History, Structure, and Functions. In Venezuela, there are >40 diabetes care units distributed in 15 states that focus on comprehensive diabetes care and improved preventive care strategies. Fundadiabetes was created in 1971 by the Rotary Club (Caracas) and has >20,000 records. In 1976, the Vargas Hospital Diabetes Unit was created in Caracas. In 1985, the Cardiometabolic Unit of Zulia State, now with 14,000 records, was created. In 2002, the Cardiometabolic Unit 7 (12,500 records) in Barquisimeto and in 2011, the Andes Clinic of Cardiometabolic Studies (2500 records) were founded. By 2013, 13 units had incorporated diabetic foot care.

Most of the diabetes units in Venezuela collect data in a standardized manner and function as research centers. Some provide education to the community. Diabetes care in these units is provided by a multidisciplinary team that includes medical specialists, nutritionists, nurses, epidemiologists, psychologists, and physical trainers. The clinical evaluation includes cardiovascular and diabetes risk assessment via standardized questionnaires and anthropometrics. Most of these units have a specialized laboratory to measure fasting glucose, 75 g OGTT results, A_{1c}, lipid profile, and other hormonal tests. These diabetes units also provide nutritional care, physical activity counseling, and pharmacotherapy guided by current guidelines and with a highly qualified senior staff.

Costs Related to Diabetes and Its Complications. T2D represents a heavy financial burden, both in direct costs to the health system and indirect costs attributable to premature mortality and temporary and permanent disability attributable to complications.[86] Indeed, people with diabetes have more outpatient visits, use more medications, have a higher probability of being hospitalized, and are more likely to require emergency and long-term care than people without diabetes. The costs associated with diabetes treatment are already quite high, reflecting their increasing prevalence. In 2000, the total annual cost of diabetes in Latin America and the Caribbean was US $65 billion. This included US $15 billion in Mexico, US $2.6 billion in Central America, and US $44.4 billion in South America.[87]

No official figures regarding diabetes care costs exist in Venezuela. It is estimated, however, that in 2010, diabetes accounted for US $412 million, with an average expense of US $399 per person.[86] If the current epidemiologic trend continues, it is envisioned that diabetes care in Venezuela will amount to US $742 million by 2030.[86,88] Therefore, if no significant changes are made in the current health care model, costs will become prohibitive for quality care.

Challenges and Recommendations for Successful Management of Diabetes in Venezuela

Education. General practitioners in Venezuela often are responsible for making treatment decisions during the early stages of the disease. Therefore, the ALAD consensus statement should be promoted to help guide primary care physicians through a simple decision-making process for diabetes management. Additionally, the implementation of the tDNA algorithm adapted to Venezuela for prescribing changes in diet and physical activity is recommended. This tool also provides information on the proper selection of patients for bariatric surgery.[21] Furthermore, nonmedical members of the health care team, such as nurses, community health workers, and motivated patients, should be trained in the skills and knowledge necessary for diabetes care, including patient self-management.[87]

It is well established in Venezuela that population-based education of people with T2D is critical to achieve their active and effective participation in the control and treatment of their disease.[89,90] Previously, the IDPMS found that

diabetes education was associated with significantly improved glycemic control, greater use of insulin, lower rates of several chronic complications, and higher rates of employment.[91] In Venezuela, patients with T2D treated with insulin receive more frequently diabetes education interventions (63.7%) than those with only OGLD (56.6%).[64]

Availability of resources. To achieve glycemic target values and prevent the development of chronic complications, people with diabetes must have access to skilled health care providers, antidiabetes therapies, and supplies for self-monitoring of blood glucose (SMBG). Antidiabetes drugs should be accessible to every patient with diabetes, and strategic alliances should be created among all organizations involved in diabetes care. These organizations should call for public health policies that support appropriate coverage of diabetes treatment (eg, education, drugs, and SMBG).[87]

In Venezuela, the prevalence of uncontrolled T2D (A1C $\geq$7.0%) is 76%, one of the highest in Latin America.[92] Poor glycemic control demonstrates treatment inadequacy—but this is multifactorial and involves all stakeholders diffusely (patients, health care professionals, government, and industry). For example, the fear of inducing side effects (mainly hypoglycemia) and drug shortages may, in part, explain the poor diabetes management in Venezuela. In a recent study involving 40 developing countries, there was a low availability of medicines for chronic diseases, including diabetes, hypertension, and CVD (median of 36% in the public sector versus 54.7% in the private sector) and a wide range in purchase prices, with private-sector prices being much higher.[93]

Several studies in Venezuela demonstrated that combining dipeptidyl peptidase (DPP)-4 inhibitors and metformin offers many benefits beyond glycemic control.[94-96] Furthermore, it has been demonstrated that this combination has a minimal effect on the budget of the health system of Venezuela.[97] As a result, metformin and DPP-4 inhibitors are the main oral treatments for diabetes in the primary care setting. On the other hand, the only glucagon-like peptide-1 analog available in Venezuela is exenatide, which despite its benefits, is not sufficiently used because of its high cost.

Strategies to reduce diabetes costs. In a comprehensive care model for T2D, supplies for SMBG and continuing medical education for health care professionals are expensive relative to the total current health care budget. Therefore, optimization of resource usage and equity of resource distribution are important.[87] Evidence from a structured group education program for people with T2D simultaneously implemented in ten Latin American countries, showed improved quality of health care indicators and a decrease by 64% of the cost of drug treatment.[98] These results seem to suggest that a large-scale implementation of diabetes education programs at all levels of care could decrease the current disease burden and economic cost due to diabetes in Venezuela. These initiatives would be associated with reevaluation of the primary health care infrastructure and resource policy to ensure efficient use of every diabetes treatment resource, with the aim of effectively preventing the development and progression of chronic complications.

CONCLUSIONS

In Venezuela, diabetes affects 7.7% of the population and is the fifth leading cause of death and the 11th leading cause of DALYs, with a cost of US $412 million in 2010. These figures depend on genetic susceptibility to develop diabetes, nutritional status, and sedentary habits. The association of lower waist circumference cutoff points with metabolic abnormalities reflects an association to develop insulin resistance with visceral fat. Thus, a lower BMI cutoff (27.5 kg/m^2) has been used to increase the power to detect clinically relevant excesses in adiposity— tantamount to a diagnosis of obesity. The Latin America Finnish Diabetes Risk is probably the most efficient and frequently used screening tool to detect new cases of T2D and those individuals requiring OGTT, with a cutoff score >10 points proposed for Venezuela. In local populations, structured lifestyle intervention in accordance with the DPP improves cardiovascular health. Notwithstanding this, Venezuela faces a fragmented health system caught up in a torrent of social and political transformation. This leads to the prevailing underfunded and uncoordinated health services. Consequently, the Venezuelan diabetes prevention programs are not structured and the treatment programs support only a small proportion of the population affected by and at risk for diabetes.

Not unexpectedly, management of diabetes in Venezuela has shown a low success rate, with only 8% of T1D and 4.3% of T2D patients attaining recommended targets; and overall only 24% having A1C values <7.0%. Basal plus bolus insulin in T1D and 1 or 2 OGLDs in T2D were the most popular interventions. An elevated proportion of patients with insulin-naive T2D were reluctant to

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start insulin therapy. Misuse of metformin is frequent with many targeted conditions not related with hyperglycemia.

Strategies to improve diabetes care in Venezuela are summarized in Table 4 and should include increasing resources, reducing costs, improving education of health care team members and patients, promoting diabetes care units, avoiding misuse of serum insulin testing, OGTT, and metformin, and reducing health system fragmentation. It is recommended to implement the use of the Venezuelan tDNA version that provides a complete and progressive program of physical activity, as well as the practical implementation of the Mediterranean pyramid with menus adapted to Venezuelan habits. In addition to the tDNA, it is recommended that the ALAD guidelines be implemented for pharmacologic interventions to guide primary care physicians in the decision-making process for diabetes management.

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