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TOPIC HIGHLIGHT

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Is the present cut-point to define type 2 diabetes appropriate in Latin-Americans?

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Abstract

The diagnosis of diabetes mellitus type 2 (DM2) is based either on increased plasma glucose or Glycated hemoglobin levels. Since these measures are the only means for diagnosis of DM2, they must be well adapted to each population according to their metabolic characteristics, given that these may vary in each population. The World Health Organization (WHO) determined the cut-points of plasma glucose levels for the diagnosis of DM2 by associating hyperglycemia with the risk of a specific microvascular complication-retinopathy. Cardiovascular diseases are however the principal causes of mortality in patients with DM2 and we reported that in the Colombo-Ecuadorian population impaired fasting glucose and impaired glucose tolerance are both risk markers for myocardial infarction. We propose that the current cut-points accepted by the WHO need to be revaluated in populations such as Latin America and that there should be lower cut points for glycaemia in this population, to reduce the prevalence of cardiovascular complications associated with DM2.

Key words: Type 2 diabetes; Cut-off points; Cardiovascular diseases; Plasma glucose; Coronary disease

Core tip: We propose that the current cut-points to define type 2 diabetes accepted by the World Health Organization need to be revaluated in populations such as the Latin America and that there should be lower cut points for glycaemia in this population, to reduce the prevalence of cardiovascular complications associated with diabetes mellitus type 2.

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INTRODUCTION

The World Health Organization (WHO) issued technical reports relating to diabetes in the years 1965[1], 1980[2], 1985[3], and 1999[4]. Over this period, there have been significant changes in the diagnostic criteria and for the classification of diabetes mellitus (DM) and intermediate hyperglycemia[5], also known as dysglycemia or prediabetes. In the first report in 1965, the WHO set a DM cut-off of $\geqslant$ 130 mg/dL according to the patient's response to a two hour oral glucose tolerance test (OGTT) and

their clinical manifestations[1]. Then in 1980, specific criteria were introduced, such as retinopathy or the presence of glucose in urine, or a random plasma glucose tests of ⩾ 200 mg/dL, and values for Fasting Plasma Glucose (FPG) of ⩾ 145 mg/dL or glucose in venous plasma 2-h after glucose load (75 g) ⩾ 200 mg/dL for the diagnosis of DM[2]. In 1985, the cut-off points for FPG were decreased to ⩾ 140 mg/dL while the OGTT of ⩾ 200 mg/dL was maintained[3].

In 1997, The Expert Committee of the American Diabetes Association (ADA) released their new recommendations for the classification and diagnosis of diabetes. The stage impaired glucose tolerance (IGT) was retained but there were several major changes including: (1) the preferred use of the terms "type 1" and "type 2" instead of "insulin-dependent" and "non-insulin-dependent" to designate the two major types of DM; (2) The analogous intermediate stage of fasting glucose was named "impaired fasting glucose (IFG)"; and (3) a lower cutoff for FPG from ⩾ 140 mg/dL to ⩾ 126 mg/dL to diagnose diabetes was established (this level of FPG having been found equivalent to the 200 mg/dL value in the oral glucose tolerance diagnostic test)[5].

In 1999, the WHO then amended the cut-off points to ⩾ 126 mg/dL in fasting glucose and maintained the ⩾ 200 mg/dL for OGTT, which was established in 1980. The new fasting criterion was chosen to represent a value at the upper end of the range, which in many patients corresponds to the diagnostic significance of the 2-h post-load concentration, which was not modified[4].

The criteria currently used for the diagnosis of diabetes and intermediate hyperglycemia have been in place globally for almost a decade, and are widely accepted by the ADA[6] and the WHO[7,8] using the four following criteria: Symptoms of hyperglycemia such as polyuria, polydipsia, and unexplained weight loss, and a casual plasma glucose ⩾ 200 mg/dL; casual-defined as a result obtained at any time of the day; (2) A 2-h plasma glucose ⩾ 200 mg/dL during an OGTT. This test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water; (3) Fasting glycemia levels ⩾ 126 mg/dL; and (4) Glycated Hemoglobin (HbA1c) ⩾ 6.5%. Both the ADA and the WHO believe that sufficiently stringent quality assurance tests are in place and that assays are standardized to criteria aligned to the international reference values, so that there are no conditions present which preclude an accurate measurement of HbA1c.

HOW WERE THE CUT-OFF POINTS FOR DM DETERMINED?

While plasma glucose and HbA1c represent the basic criterion measures to define DM, the universally utility of these determinations has been questioned[9]. The diagnostic cut-off points for diabetes were based on two sets of evidence: (1) Plasma glucose levels associated with an increased risk of specific microvascular complications, particularly retinopathy; and (2) The distribution of plasma glucose in the general population[9-11].

However, there are a number of methodological weaknesses of the studies that have reported the cut-points for increased risk of retinopathy including inadequate statistical power for this type of analysis[10]. Moreover, these studies used different methods to diagnose retinopathy and some used patients already identified as diabetic, while others used non-diabetic patients[10,11]. In addition, some reports included people with diagnosed DM who were receiving blood glucose lowering treatment introducing a bias associated with treatment-induced effects on plasma glucose. Excluding people with treated diabetes from analyses eliminates the bias related to the treatment effect, but changes the characteristics of the diabetic population[12].

One of the most important studies to support the cut-points was conducted by Ito *et al*[11], which included 12.208 people and began in 1965 and lasted until 1997. The authors reported a significantly increased prevalence of retinopathy at a baseline FPG cut-point of 125 mg/dL and 198 mg/dL in 2-h post-glucose load.

Other microvascular complications are more weakly associated with plasma glucose levels than retinopathy[13]. Studies which have examined the relationship between plasma glucose and proteinuria, reported a significant association but weaker than with retinopathy[13]. For instance, among patients with DM, only 20%-40% of patients with microalbuminuria will progress to overt nephropathy, and only 20% will go on to end-stage renal disease within the next 20 years[14]. Moreover, the data showing a relationship between plasma glucose and biopsy confirmed diabetic renal disease is not totally convincing, since the prevalence of non-diabetic nephropathy in the patients with DM who underwent renal biopsy varies from 10% to 85% in different reports[15]. Furthermore, FPG and HbA1c values associated with the presence of diabetic nephropathy were exceptionally high: 183 ± 61.9 mg/dL and 8.6% ± 2.4%, respectively[16].

The distribution of plasma glucose in the general population was another source of data used to define cut-points. In 2006, the WHO reported that the distribution of plasma glucose among the population was either unimodal, in which the entire population is represented by a single curve, or bimodal, represented by two overlapping curves[7]. However, an analysis of DETECT-2, representing plasma glucose data measured during an OGTT in 26 different countries, found a wide variation in cut-points[9]. Cut-points for FPG in different countries ranged from 103 to 153 mg/dL (median 128.5 mg/dL), and for 2-h plasma glucose from 164.7 to 323.9 mg/dL (median 224.4 mg/dL). Moreover, when known diabetes was removed from the analysis, the distributions of plasma glucose do not generally give rise to a bimodal structure that is useful for deriving a cut point for diabetes. Thus, bimodality seems not to be a suitable method for defining diagnostic cut points for diabetes in population studies which include people of different origin[9].

Bimodal distribution has also been reported in a

number of populations with a high prevalence of diabetes, including the American Pima Indian, Micronesian of Nauru, Egyptian, Mexican, Papua New Guinea, and South African populations[9,17]; while few studies on bimodality have been conducted in populations with a low prevalence of diabetes[18].

Recently, and in support of the use of HbA1c as a diagnostic criterion, several studies have noted that HbA1c reflects average plasma glucose and does not require any special preparation such as fasting. These features led to it becoming the gold standard for assessing glycemic control in people with diabetes, and it has also become a means to assess glucose tolerance in those with undiagnosed diabetes[12]. The relationship between HbA1c and the presence of retinopathy is similar to that of plasma glucose, making it at least as accurate in defining the level of hyperglycemia at which retinopathy prevalence increases[19].

Moreover, HbA1c has appreciable superior technical attributes, including less pre analytic instability and biological variability, and is a more clinically convenient measure. HbA1c has been demonstrated to be more reliable than FPG, with a day to day coefficient of variation of less than 2% compared to 16% for FPG[20].

Studies have now established an HbA1c level associated with an increase in the prevalence of moderate retinopathy, providing strong justification for assigning an HbA1c cut-off point of $\geqslant$ 6.5% for the diagnosis of diabetes[8]. Although this cut-off point must not be used as an absolute dividing line between normal glycemia and diabetes, this value is sufficiently sensitive and specific to identify individuals who are at risk of developing retinopathy and who therefore, should be diagnosed as diabetic[20].

HbA1c however does have some limitations which should be considered when using it as criteria for the diagnoses of DM. First, the cost of the test precludes its routine use. Second, there are some specific conditions that can influence and therefore preclude HbA1c testing, including the following hemoglobin traits: HbS, HbC, HbF, and HbE, as well as various types of anemias, pregnancy, uremia and blood transfusions[21]. Some of these factors may represent an additional problem in under-resourced countries, due to their higher prevalence of anemia and hemoglobinopathies[21]. Moreover, it should be noted that there are normal age-related increases in HbA1c[22].

PROPOSED MECHANISMS TO EXPLAIN THE NEGATIVE EFFECTS OF HYPERGLYCEMIA ON THE VASCULAR WALL

Blood glucose level can also be a risk marker for cardiovascular diseases (CVD) among apparently healthy non-diabetic individuals[23-26]. The effects of elevated glycemia levels include non-enzymatic glycosylation of proteins, increased metabolism of glucose through the polyol and glucosamine pathways and the generation of free radicals[27-32]. Glycosylation of low-density lipoprotein makes it more susceptible to oxidization and therefore more atherogenic[27]. Advanced glycosylation end products (AGEs) can cross-link proteins, particularly in the extracellular matrix of the vascular wall[31,32]. Metabolism of excess glucose by secondary pathways can also alter cell function by modifying signal transduction and changing the oxidative potential of cells[30]. This may contribute to general cell damage and dysfunction[28]. These pathways can also activate tissue-specific protein kinase C[29] and increase in the activity of which decreases fibrinolysis and nitric oxide (NO) levels and increases cell proliferation and coagulation, contributing to the progression of CVD[28-30].

The association between intermediate hyperglycemia and coronary heart disease has been explained by the predisposition of these subjects to subsequently present DM2, a condition that as noted above, is directly related to the development of CVD[27]. However, hyperglycemia *per se* may also be directly involved in the development of atherosclerosis by promoting metabolic and structural changes in the endothelium that eventually produce irreversible damage. Therefore, the association between hyperglycemia and cardiovascular risk should be considered as a continuum, rather than one that depends only on reaching a specific cut point.

Experimental studies suggest that hyperglycemia reduces the activity of NO at the vascular endothelial level[28]. Hyperglycemia induces a series of cellular events that increase the production of reactive oxygen species that inactivate NO and lead to the formation of peroxynitrite[29,30]. In addition, mitochondrial production of reactive oxygen species increases the intracellular formation of AGEs[30], which affect endothelial function and activate the receptors for AGEs causing apoptosis and altered vascular structure[31-33]. In non-diabetic subjects, altered levels of post-load glucose have been associated with the presence of structural alterations at the level of the carotid arteries, manifested by increased carotid intima-media thickness[34-36]. Moreover, chronic hyperglycemia can also cause cellular structural changes, which would explain the known point of no return for the micro and macrovascular complications observed in diabetic patients[37-39]. Recent experimental studies with rats in which diabetes was induced using streptozotocin, demonstrated a loss of nitric oxide synthase function (NOS) in nitrergic neurons. This effect was mediated by an increased production of AGEs, oxidative stress and neuronal apoptosis, which was reversible only when treatment with insulin was introduced in early stages. After 12 wk of streptozotocin-induced diabetes, insulin therapy was not able to recover the function of the nitrergic neurons, which had suffered an increased apoptosis[37,38]. These experiments suggest that chronic hyperglycemia over time leads not only to an alteration of NOS function, but also in later stages to irreversible structural changes in different tissues. Since streptozotocin-induced DM is more similar to type 1 DM, it is therefore possible that the

underlying mechanism of vascular damage in type 2 DM is different to that described above. Nonetheless, this mechanism could be responsible for the development of atherosclerosis in the vascular wall of hyperglycemic patients. Thus, it is attractive to postulate that in the early stages of hyperglycemia, the use of hypoglycemic treatments could decrease the formation of AGEs, reversing endothelial dysfunction and preventing both structural disorder and the progression to CVD[39].

WHY SHOULD CUT POINTS OF PLASMA GLUCOSE TO DIAGNOSE DIABETES MELLITUS BE RE-EVALUATED?

We propose that CVD prevention depends on an early and aggressive intervention to control glycemia levels, probably at the prediabetes stage, to avoid reaching a "point of no return" with respect to structural alterations of the arterial walls. This proposal is supported by important clinical trials[40-44] such as the United Kingdom Prospective Diabetes Study which demonstrated that if an intensive treatment of hyperglycemia is started when DM2 is first diagnosed, there is a significant decrease in the number of cardiovascular events[41], maintained until 10 years after end of the study[40]. However, as recently demonstrated in clinical trials, if the intensive treatment is started after 8[42], 10[43], or 12[44] years of diagnosed DM2 the impact of the intensive treatment does not produce a decrease in the number of cardiovascular events (Table 1). These results highlight the importance of starting the hypoglycemic intervention earlier than is common practice currently.

The magnitude of the glycemia association with CVD risk has been reported in many studies[25,45], and although post-load blood glucose level has a linear relationship with CVD risk in the non-diabetic range, a possible threshold effect for FPG level appears to exist around 100 mg/dL[27]. There is an important body of information indicating that the cardiovascular risk starts at levels well below the cutoff point currently used for the diagnosis of DM2 and increases continuously[25,46]. Many studies show that non-diabetic patients with hyperglycemia have an increased risk of cardiovascular morbidity and mortality[46-51]. The meta-analysis of prospective studies conducted by Levitan *et al*[23] shows that the group with the highest post-load blood glucose level (midpoint range, 150-194 mg/dL) had a 27% greater relative risk (RR) for CVD compared with the group with the lowest level (midpoint range, 69-107 mg/dL) (RR = 1.27, 95%CI: 1.09-1.48).

Moreover, in a meta-analysis of studies that included a total of 95.783 people, Coutinho *et al*[25] found a linear relationship between glucose levels and subsequent cardiovascular events over a period of 12 years, reporting a RR = 1.33 (95%CI: 1.06-1.67) for those with FPG levels of 110 mg/dL and an RR of 1.58 (95%CI: 1.19-2.10) for patients with post-load blood glucose levels > 140 mg/dL.

The Whitehall Study[51] lasted 33 years and followed 17.869 male civil servants aged 40-64 years, of which 3.561 died of coronary diseases. In this study, the hazard of coronary mortality rose when 2-h blood glucose level reached 83 mg/dL (95%CI: 76-96). Between this level and 200 mg/dL, the age-adjusted hazard ratio was 3.62 (95%CI: 2.3-5.6). Although the data was applied at baseline in these male civil servants, this report has a limitation in that the findings are based on a 50 g OGTT, and a slightly differing dose-response relationship might be obtained with a 75 g glucose load.

The DECODE study[45] was a prospective European analysis of 22 cohorts with baseline glucose measurements for 29.714 subjects aged 30-89 who were followed-up for 11 years. After adjusting for other cardiovascular risk factors, the study reported an association between risk of death and both high glucose concentrations and very low glucose levels. Compared with a fasting plasma glucose of 81-110 mg/dL, the multivariate adjusted HR (95%CI:) for FPG < 81 mg/dL was 1.2 (1.0-1.4) for all causes, 1.3 (1.0-1.8) for CVD, and 1.1 (0.9-1.4) for non-cardiovascular mortality. For 2-h plasma glucose of 54.4-81 mg/dL, as compared with 2-h plasma glucose of 81.6-100 mg/dL the HRs were 1.1 (1.0-1.2) for all causes mortality, 1.1 (0.9-1.3) for cardiovascular mortality, and 1.1 (1.0-1.3) for non-cardiovascular mortality, respectively.

In the Asian Pacific Region, blood glucose data from 237.468 participants of 17 cohort studies are available[52]. Continuous positive associations were demonstrated between usual fasting glucose and the risks of cardiovascular diseases down to at least 88.6 mg/dL. Overall, each 18 mg/dL lower than usual fasting glucose was associated with a 21% (95%CI: 18%-24%) lower risk of total stroke, and 23% (95%CI: 19%-27%) lower risk of total ischemic heart disease. The associations were similar in men and women, across age-groups, and in Asian compared with Australasian (Australia and New Zealand) populations.

The China Heart Survey[53], a multicenter study, recruited 3.513 patients hospitalized for Coronary Artery Diseases (CAD), of whom 35.1% were admitted for acute CAD and 64.9% were elective admissions for CAD. At entry, 1.153 patients (32.8%) had known DM and 97 (2.7%) had newly diagnosed DM. Furthermore, 32.6% had IGT, and 4.7% had IFG. The proportion of patients with diagnosed DM increased from 32.8% at baseline to 52.9% post-OGTT analysis.

The GAMI study[54] of 181 patients admitted to two Swedish hospitals with acute myocardial infarction (AMI) and no history of DM, found a prevalence of 34% for prediabetes and 33% for de novo DM, leaving only 33% with no alteration in glucose metabolism. This distribution was similar when measurements were repeated at 3 and 12 mo. These findings were later confirmed by another study that included 4.961 patients with coronary disease enrolled in 110 centers throughout Europe[55]. In this study the prevalence of pre diabetes was 32% in those patients admitted with acute coronary syndrome and only 29% of enrolled patients had a normal carbohydrate metabolism.

Table 1 Differences in cardiovascular outcomes according to the time of disease (diabetes mellitus type 2) before the start of an intensive hypoglycemic intervention

Study	Time since diagnosis	Treatment	Mean outcomes
UKPDS 34 and 80[40,41]	Newly diagnosed	Metformin added to an experimental group, median glycated hemoglobin was 7.4% in the metformin group compared with 8.0% in the conventional group	↓ 32% for any diabetes-related endpoint ↓ 42% for diabetes-related death ↓ 36% for all-cause mortality A continued reduction in microvascular risk and risk reductions for myocardial infarction and death from any cause were observed during 10 yr of post-trial follow-up
The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial[42]	7.9 yr	Gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less and Perindopril + Indapamide	No significant effects on major macrovascular events, death from cardiovascular causes, or death from any cause
The Action to Control Cardiovascular Risk in Diabetes trial[43]	10 yr	Individualized intensive therapy of a combination of any hypoglycemic drug targeting a glycated hemoglobin level below 6.0% or standard therapy targeting a level of 7% to 7.9%	The intensive-therapy group did not differ significantly from the standard-therapy group in the rate of the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) but had more deaths from any cause (primarily cardiovascular)
The Veterans Affairs Diabetes Trial[44]	11.5 yr	Intensive-therapy group goal was an absolute reduction of 1.5% in the glycated hemoglobin level, as compared with the standard-therapy group, metformin plus Glimepiride or Rosiglitazone	No significant effect on the rates of major cardiovascular events, death, or microvascular complications

UKPDS: United Kingdom Prospective Diabetes Study.

In Latin America, the ongoing multicenter Colombian-Ecuadorian study which includes until now 439 subjects distributed in 8 hospitals of Colombia and Ecuador to determine the prevalence of pre diabetes in patients with a first AMI shows that the combined prevalence of DM2 and prediabetes is 69.47%. Ninety subjects (20.50%) presented with antecedents of DM2; another 85 (19.36%) were diagnosed with DM2 while hospitalized; and 130 (29.61%) presented with prediabetes. Only 134 subjects (30.53%) were normoglycemic[56].

The existence of a strong association between cardiovascular risk factors and IFG has also been reported in Colombia, with an even greater association with the presence of abnormal plasma glucose levels after an oral glucose load[57]. Additionally, in our population there is evidence indicating that hyperglycemia is common in patients with already established coronary disease[58].

Furthermore, a Colombian population study found that an IFG > 100 mg/dL was the risk factor with the highest degree of association with the presence of CAD in patients with stable angina pectoris, independent of the presence of other traditional cardiovascular risk factors[58]. Moreover, in this population fasting hyperinsulinemia and the socio-economic status of individuals with a first myocardial infarction were the only factors that remained significant predictors of a new cardiovascular event after a multivariate analysis[59]. We have previously shown that Colombian people present a higher vulnerability to present with insulin resistance at lower levels of abdominal obesity in youth adults[60,61], in pregnancy[62], and in children[63].

Many years ago Hales and Barker demonstrated that low birth weight is associated with an increased risk of developing obesity, metabolic syndrome and DM2[64-66]. Based on the results of their pioneering work and subsequent confirmatory studies, we have proposed[67-69] that the fetal programming during pregnancy of women that have deficient nutrition and/or an increased frequency of subclinical infection and preeclampsia, have an increased risk of giving birth to a low birth weight child with a higher risk of subsequently developing insulin resistance (IR) and low degree inflammation. It is well established that children with low birth weight have a decreased mass of beta cells, nephrons, hepatocytes, and fewer muscle fibres. We recently demonstrated, in children and adolescents that low muscle strength is associated with increased adiposity, C-reactive protein, HOMA index and metabolic risk factors, and that this association was stronger in with low birth weight[70]. Moreover, in a sub analysis of the ORIGIN study[71] we demonstrated that low handgrip strength is an important factor associated to an increased risk of cardiovascular mortality in prediabetic and diabetic patients[71]. To explain these results we have proposed that the dramatic increase of overweight and obesity, especially abdominal adiposity, in low and medium income countries[72], is promoting epigenetic adaptations which may alter the leptin/adiponectin (L/A) ratio. This L/A disturbance is in turn the determinant, in populations of low and medium income countries, of their increased vulnerability to the development of IR and an increased risk of cardiovascular events at levels of glycemia that are lower than those used to define DM2[73-76]. Moreover, there are possible regional differences in the risk of developing IR, DM2 and CVD as-

sociated with prediabetes and DM2, as we have recently demonstrated in relation to lung function[77].

PERSPECTIVES TO MODIFY THE CUT-OFF POINTS OF DM RELATED WITH THE RISK OF MACROVASCULAR COMPLICATIONS

The term diagnosis has typically been reserved to characterize or identify individuals with a specific disease. Because the term implies a condition that causes symptoms, tests are often required to confirm the diagnosis. In this order of ideas, when selecting the threshold glucose values, the National Diabetes Data Group[78] acknowledged that "there is no clear division between diabetics and non-diabetics in the FPG concentration or in their response to an oral glucose load" and consequently values were established for each method to identify diabetic patients based on retinopathy and the distribution of plasma glucose population.

Epidemiological studies[10-12] that included an Egyptian population, Pima Indians and the US National Health and Nutrition Examination Survey, all identified retinopathy using fundus photography or direct ophthalmoscopy and by measuring glycemia using FPG, 2-h post-glucose load, and HbA1c, demonstrated that glucose level is a continuous risk factor for retinopathy: the higher levels the higher risk.

Deriving cut points for normal glycemia level from distributions of FPG and 2-h post-glucose load might not be suitable to define cut points for DM because metabolic regulation could varies from population to population. It might be more relevant to base the diagnostic criteria on thresholds for diabetes-specific macrovascular complications, which are probably lower than those for microvascular complications such as retinopathy. Data from the DECODE study[45] which was carried out on behalf of the European Diabetes Epidemiology Group showed that the number of patients diagnosed with DM was one third higher for men and 44% higher for women when using 2-h post-glucose load measurement than when using the FPG, confirming that the 2-h post-glucose load criterion is more accurate than FPG criteria to identify DM. HbA1c is recommended and used in many countries to diagnose DM[12,20]. However the high prevalence of anemia and hemoglobinopathies in under-resourced countries such as ours, together with its high cost, limits its use and from our point of view should not be for now, recommended as a diagnostic test.

The data of the previously mentioned Latin American studies indicate the presence of macrovascular diseases at glycemia levels lower than the internationally established cut points for DM2. These data suggest that the present cut-off points accepted for our population might not be accurate and might have to be reconsidered. Recent studies have shown that the association between dysglycemia and CVD has a considerable increase at levels as low as 100 mg/dL[25,27,45], and therefore, we consider the re-defined cut-points to diagnose DM2 should be around this value. Nevertheless, it is noteworthy that these studies have not been designed for this specific purpose and have not been conducted in Latin America. Thus, as with the risk of microvascular complications, several limitations will be found if we try to re-define the cut-points for DM2 on this basis.

Moreover, as lowering the cut-off points will substantially increase the prevalence of DM2, several public health consequences should be considered before this adjustment. Certainly, diabetic patients require more health care, leading to greater use of resources. In this context, an increased prevalence of DM2 could cause an initial financial challenge of the health systems and household economies in Latin American countries[79]. Nevertheless, indirect economic costs and social consequences attributable to premature mortality and temporary and permanent disability generated as complications of DM should be also considered. Indeed, the direct annual cost associated with diabetes for the year 2000 in Latin America and the Caribbean was estimated as 10721 million US dollars; whereas, the total indirect cost was estimated at almost 54496 million US dollars (mortality, permanent disability and temporary disability accounted for 6%, 92% and 2% of this amount, respectively)[80]. These results suggest a long-term positive cost-effective ratio of an early intervention.

Furthermore, health systems in Latin American countries are based on a model of care with a biomedical curative approach[81], and this has not been favorable in controlling the epidemic of DM2. Thus, health systems should move from an approach of treating DM2 to one of preventing DM2 and its complications. In this way, various socio-medical models are currently being evaluated in Latin-America, such as the ongoing HOPE-4 study in Colombia, in which we are inviting community leaders and non-professional health care workers to form part of the health team to implement new strategies for the detection, prevention and control of non-communicable chronic diseases.

In conclusion, the present challenge for Latin American countries is to conduct population studies in accord with our specific socio-economic conditions, which will permit to establish the cut-point after which lifestyle and/or pharmaceutical interventions must be initiated with the objective of preventing macrovascular complications, associated with hyperglycemia. Further research to assess the economic, public health, and social perspectives is also warranted.

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