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Evaluation of risk factors in the development of type 2 diabetes in a Mexican population

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ABSTRACT

Type 2 diabetes (T2D), which causes many adverse effects such as endothelial dysfunction and cardiovascular disease, affects approximately 425 million people worldwide. However, about half have not yet been diagnosed. For what is recommended the use of screening tools to identify individuals at risk for T2D or in the early stages of the disease in order to impement preventive strategies or early treatment. According to a widely used survey, the FINDRISC scale, a hereditary family history of T2D (FH-T2D) is as important a risk factor as having had high glucose levels. The aim of the present study was to carry out non-probabilistic sampling in a Mexican population to evaluate key factors in the development of diabetes. The participants were divided into three groups: with and without FH-T2D and diagnosed with T2D. A comparison of the groups with and without FH-T2D revealed higher values in the former for body mass index (BMI: 24.5 vs 21.9 kg/m^2), glycosylated hemoglobin [Hb1Ac: 5.775% (39 mmol/mol) vs 4.825% (29 mmol/mol)] and triglycerides (164.18 vs 68.12 mg/dL), and a lower value for the BH_4/BH_2 index (0.7846 vs 1.6117). These results indicate significant metabolic alterations and endothelial dysfunction for the FH-T2D group. This strongly suggests the need to screen individuals with a family history of inherited T2D based on their level of HbA1c, triglycerides and BH_4.

1. Introduction

Type 2 diabetes (T2D) is one of the four priority noncommunicable diseases identified by the World Health Organization, the other three being cardiovascular disease (including myocardial infarction and stroke), cancer and chronic respiratory disease [1,2]. The global prevalence of T2D is growing rapidly due to the aging of the population, urbanization and

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changes associated with lifestyle [3,4]. In Mexico, the prevalence of diagnosed diabetes went from 9.2% in 2012 to 9.4% in 2016, consistent with the trend of a continual increase that has paralleled the rise in obesity since the 1980s. By 2045, the number of people suffering from diabetes is estimated to reach 629 million worldwide, which represents 9.9% of the total adult population (20–79 years old) [4,5]. By 2030, based on the current data, the number of cases will rise by 37.8% and the incidence by 23.9% [6].

T2D is characterized by serious tissue damage and microvascular complications, such as retinopathy, heart disease, nephropathy and neuropathy. The macrovascular complications of T2D include acute myocardial infarction, a cerebral vascular accident (stroke), and peripheral vascular disease [7]. Overall, this metabolic disease increases the risk of several life-threatening conditions: cardiovascular disease [8,9], stroke, kidney failure, and certain types of cancer [10]. It may also lead to mood disorder and dementia [11]. All these comorbidities bring about a poor quality of life, poor health and premature death [9,12,13].

1.1. *The importance of risk factors in the detection of diabetes*

Apart from significantly lowering the quality of life of affected individuals, the growing prevalence, incidence and mortality of T2D is affecting more and more population, and is overburdening health services (implying a high social cost) [14,15]. To reduce the impact of T2D, it is essential to go beyond the predominant focus on the efficacy of treatment and give greater priority to prevention in individuals at risk for the disease. An outstanding screening tool for identifying those at risk for diabetes is the Finnish Diabetes Risk Score (FINDRISC), which takes into account age, body mass index (BMI), waist circumference, and the level of glucose in the blood, among other parameters. This test predicts the risk of developing T2D in the subsequent 10 years and has been validated by epidemiological analysis, being effective for the detection of diabetes and undiagnosed diabetes [16,17,18].

1.2. *Glucose and metabolic risk factors*

Hyperglycemia (high blood glucose levels) is a factor clearly associated with the development of vascular disease. Some researchers consider that it is not directly involved in the pathogenesis of vascular complications, but instead produces metabolic and biochemical alterations in the vascular wall that lead to abnormalities in the function and structure of the vascular tissue. For the complications of T2D, a pivotal role has been proposed for the non-enzymatic glycation of proteins because the greatest damage occurs in tissues rich in collagen where the entrance of glucose is not regulated by insulin. In such tissues, including the kidney, retina and vascular endothelium, glucose is able to form reversible bonds with the amino group of proteins, giving rise to Schiff bases. Later these bases undergo restructuring to afford an Amadori product. The final product, glycated hemoglobin (HbA1c), is used clinically to evaluate the evolution of patients with diabetes [5,9,19]. HbA1c is characterized by the presence of a monosaccharide moiety attached to the amino terminus of a beta chain, the point at which hemoglobin is glycated more easily. In 1976, a relationship was established between hyperglycemia and HbA1c values in individuals diagnosed with diabetes [17,19].

The association between hyperglycemia and the development of vascular disease is increased blood pressure (whether acute or chronic). This causes the deterioration of the endothelium and morphological changes in the arterial intima, including the growth of the endothelium into the lumen and the thickening of the subendothelial space. As a consequence, vascular smooth muscle has a reduced access to nitric oxide (NO) derived from the endothelium, which generates greater hypertrophy and hypertension. The chronic inhibition of NO production triggers severe arterial hypertension, characterized by atherosclerosis and loss of vascularity in the central nervous system and kidneys [20,21].

Hypertension is also correlated with other risk factors that are difficult to detect at the early stages because of the lack of prominent symptoms, such as dyslipidemia, insulin resistance and salt sensitivity. One of the main mechanisms linked to endothelial dysfunction is the decoupling of the nitric oxide synthase enzyme caused by a low level of the cofactor tetrahydrobiopterin (BH_4), leading to a decrease in NO synthesis [22,23,24,25].

1.3. *Biopterins*

Biopterins constitute a group of compounds that act as cofactors for various enzymes (hydroxylases or oxygenases). The most important biopterin is BH_4, which by donating electrons allows enzymatic systems to maintain their activity. For example, it is an indispensable cofactor for the proper functioning of endothelial nitric oxide synthase (eNOS). Since this enzyme is a dimer and each monomer has a binding site for the cofactor in its oxygenase domain, two molecules of BH_4 are required for adequate eNOS activity. The cofactor donates electrons to the Heme-Fe-O-O complex of the enzyme, enabling the oxidation of L-arginine and the release of NO. The radical trihydrobiopterin-H + (BH_3-H+) is reduced by the action of flavins bound to eNOS by electron transfer, thus transforming it into BH_4 [20,23].

With a low concentration of BH_4 in endothelial cells (due to a decrease in its synthesis or an increase in oxidation), there is a decoupling between oxygen and the oxidation process of L-arginine. This decoupling generates superoxide anions and reduced NO production, eventually leading to the development of endothelial dysfunction. High oxidative stress in endothelial cells favors the oxidation of BH_4 to BH_2 (dihydrobiopterin), the latter of which has no activity as a cofactor and competes with BH_4 for the oxygenase domain of eNOS. The consequence is interference with the activity of the enzyme resulting in reduced NO production and endothelial dysfunction. It was recently reported that the BH_4/BH_2 index is more relevant than the absolute value of BH_4 for assessing the adequate functioning of eNOS [22,24,25].

1.4. *The risk of cardiovascular disease with diabetes*

The mechanisms responsible for the accelerated evolution of atherosclerosis in patients with T2D are not yet completely

clear. Epidemiological data of the UK Prospective Diabetes Study (UKPDS) shows that at the time of diagnosis, people with T2D have potentially modifiable risk factors, including a high concentration of low density lipoprotein (LDL), a reduced level of high density lipoprotein (HDL), hyperglycemia and hypertension. Sometimes these are accompanied by tobacco use [26]. One of the most frequent characteristics in patients with T2D is an atherogenic lipid profile, characterized by hypertriglyceridemia, decreased HDL, and a high concentration of LDL and Apolipoprotein B (Apo B). Approximately 80% of individuals suffering from T2D and having excess abdominal fat present insulin resistance, which may be the mechanism of dyslipidemia [27]. Hence, people with T2D tend to develop cardiovascular disorders [18,28,29].

2. Material and methods

2.1. Study population

In the Laboratory of Research in Chronic Degenerative Diseases in the Escuela Superior of Medicina of the Instituto Politécnico Nacional (Mexico City), an observational and analytical study was conducted from May 2015 to May 2016, implementing non-probabilistic sampling according to convenience. After explaining the objectives of the investigation to selected individuals, they were asked to sign informed consent. For those who decided to participate, a clinical history was elaborated and complemented with the FINDRISC. Based on this information, the subjects were categorized in three groups: those with a family history of T2D (FH-T2D), without such a family history (W/O-FH-T2D) and with a diagnosis of T2D (D-T2D). The protocol was approved by the Ethics Committee and carried out in accordance with the Declaration of Helsinki regarding ethical standards for research involving human subjects.

2.2. Clinical and biochemical studies

Fasting blood samples were obtained to quantify the serum concentration of total cholesterol (SPINREACT CHOLESTEROL-LQ; 1001091) and triglycerides (SPINREACT TRIGLYCERIDES-LQ; 1001311), as well as the percentage of glycated hemoglobin (SPINREACT HbA1c; 1001230). The atherogenic index was calculated with the following formula:

Atherogenic Index = Total Cholesterol/HDL Cholesterol

The determination of BH_4 was based on area capillary electrophoresis with fluorescence detection by laser excitation by using a P/ACETM MDQ (BeckmanCoulter).

2.3. Statistical analysis

Data are reported as the mean ± SEM unless otherwise specified. Associations between static measurements of triglycerides, HbA1c and BH_4/BH_2 were examined with one way ANOVA. Statistical significance was considered at $p < 0.05$. The odds ratio (OR) for low BH_4 was evaluated for each group.

3. Results

3.1. Demographic characteristics

The average height of participants was 1.63 ± 0.03 m for the W/O-FH-T2D group, 1.60 ± 0.02 m for the FH-T2D group and 1.61 ± 0.04 m for the D-T2D group. No statistically significant differences existed between groups in relation to this parameter. The average weight was 58.7 ± 3 kg for the W/O-FH-T2D group, 63.6 ± 3 kg for the FH-T2D group, and 74.4 ± 4.7 kg for the D-T2D group. Although the FH-T2D and W/O-FH-T2D groups did not display overweight or obesity, the former had a significantly higher weight than the latter. Regarding the BMI (kg/m^2), the highest value was 28.2 ± 0.3, found for the D-T2D group, compared to 24.5 ± 0.06 for the FH-T2D group and 21.9 ± 0.8 for the W/O-FH-T2D group (Table 1).

3.2. The finnish diabetes risk score

The score from the FINDRISC evaluation was 5 for the W/O-FH-T2D group and 11 for the FH-T2D group (Fig. 1).

3.3. Blood pressure

The systolic/diastolic blood pressure was within the normotensive range for all groups. However, the value for the D-T2D group (120 ± 3.1/75 ± 3.0 mmHg) was significantly higher than the values of 103 ± 2.6/67 ± 1.9 and 105 ± 4.2/70 ± 1.8 mmHg for the FH-T2D and W/O-FH-T2D groups, respectively (Table 2).

3.4. Lipidic profile

The concentration of triglycerides was 176.8 ± 8.12 mg/dL for the D-T2D group and 148.61 ± 17.95 mg/dL for the FH-T2D

Table 1 – Demographic characteristics of the participants in the three groups: without a family history of type 2 diabetes (W/O-FH-T2D), with a family history of type 2 diabetes (FH-T2D), and diagnosed with type 2 diabetes (D-T2D).

	W/O-FH-T2D	FH-T2D	D-T2D
Height (m)	1.63 ± 0.03	1.60 ± 0.02	1.61 ± 0.04
Weight (kg)	58.7 ± 3.0	63.6 ± 3.0	74.4 ± 4.7
BMI (kg/m^2)	21.9 ± 0.8	24.5 ± 0.6	28.2 ± 0.3

BMI = body mass index. Statistically significant differences ($p < 0.05$) were determined by one-way ANOVA followed by the Tukey post-hoc test.

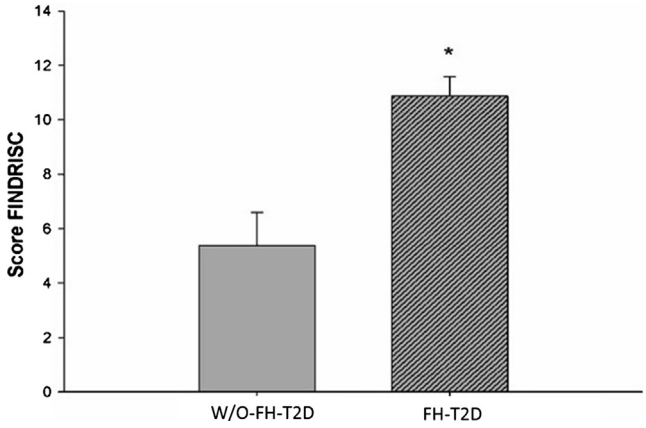

Fig. 1 – Distribution of the Finnish Diabetes Risk Score (FINDRISC) in individuals without a family history of type 2 diabetes (W/O-FH-T2D) and with a family history of type 2 diabetes (FH-T2D). The analysis was performed by using one-way ANOVA followed by the Tukey post-hoc test. $^{*}p < 0.05$.

Table 2 – The blood pressure and atherogenic index of the participants in the three groups: without a family history of type 2 diabetes (W/O-FH-T2D), with a family history of type 2 diabetes (FH-T2D) and diagnosed with type 2 diabetes (D-T2D).

	W/O-FH-T2D	FH-T2D	D-T2D
SBP, mm Hg	104.61 ± 3.12	105 ± 3.75	108.33 ± 7.92
DBP, mm Hg	69.2 ± 2.1	67 ± 2.13	68.33 ± 5.43
AI	2.47 ± 0.13	2.53 ± 0.1	2.38 ± 0.11

SBP = systolic blood pressure; DBP = diastolic blood pressure; AI = atherogenic index; Statistically significant difference ($p < 0.05$) based on one-way ANOVA followed by the Tukey post-hoc test.

group, showing no significant difference. Between these two values and the 87.94 ± 9.54 mg/dL found for the W/O-FH-T2D group there was indeed a significant difference (Fig. 2).

The level of total cholesterol was 194.6 ± 12.53 mg/dL for the D-T2D group, 182.5 ± 5.83 mg/dL for the FH-T2D group and 167.75 ± 11.55 mg/dL for the W/O-FH-T2D group, with no significant difference between groups. The values of HDL and LDL were also similar between the three groups, without significant differences (data not shown).

The atherogenic index values were 2.2854 ± 0.1422, 2.4078 ± 0.0998 and 2.6533 ± 0.1920 for the W/O-FH-T2D, FH-T2D and D-T2D groups, respectively, which did not reflect significant differences. There was a tendency to a higher value in the latter group (Table 2).

3.5. *Glycated hemoglobin*

The level of HbA1c was 5.1 ± 0.14% (32 mmol/mol) for the W/O-FH-T2D group, 5.77 ± 0.13% (38 mmol/mol) for the FH-T2D group and 6.17 ± 0.27% (43 mmol/mol) for the D-T2D group, corresponding to significant differences between all groups (Fig. 3).

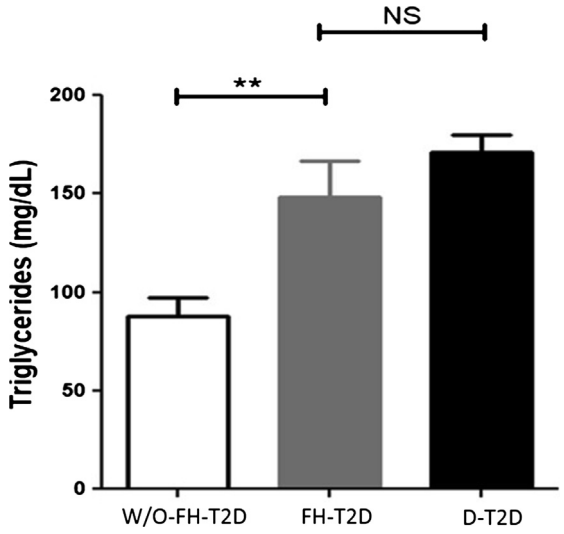

Fig. 2 – Comparison of triglycerides in individuals without a family history of type 2 diabetes (W/O-FH-T2D) (87.94 ± 9.54), with a family history of type 2 diabetes (FH-T2D) (148.61 ± 17.95) and with a diagnosis of type 2 diabetes (D-T2D) (176.8 ± 8.12). The statistical analysis was performed by using one-way ANOVA followed by the Tukey post-hoc test. $^{**}p < 0.001$; NS, not significant.

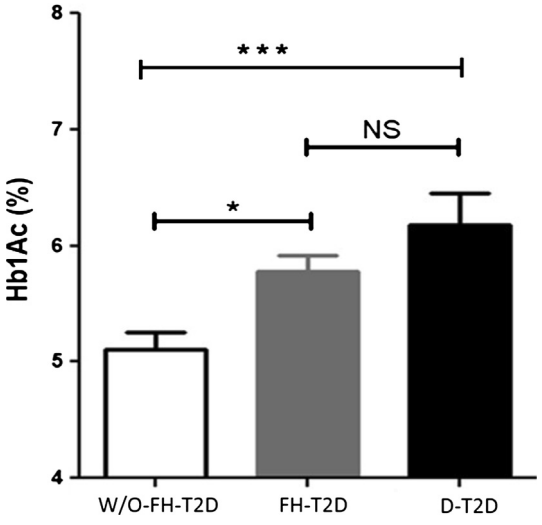

Fig. 3 – Comparison of the percentage of glycated hemoglobin in participants without a family history of type 2 diabetes (W/O-FH-T2D) [5.1 ± 0.14 (32 mmol/mol)], with a family history of type 2 diabetes (FH-T2D) [5.77 ± 0.13 (38 mmol/mol)] and with a diagnosis of type 2 diabetes (D-T2D) [6.17 ± 0.27 (43 mmol/mol)]. The statistical analysis was performed by using one-way ANOVA followed by the Tukey post-hoc test. $^{*}p < 0.05$, $^{***}p < 0.001$; NS, not significant.

3.6. *Biopterins*

The concentration of BH_4 was 12.1375 ± 3.52 pmol/mL for the W/O-FH-T2D group, representing a significantly higher value

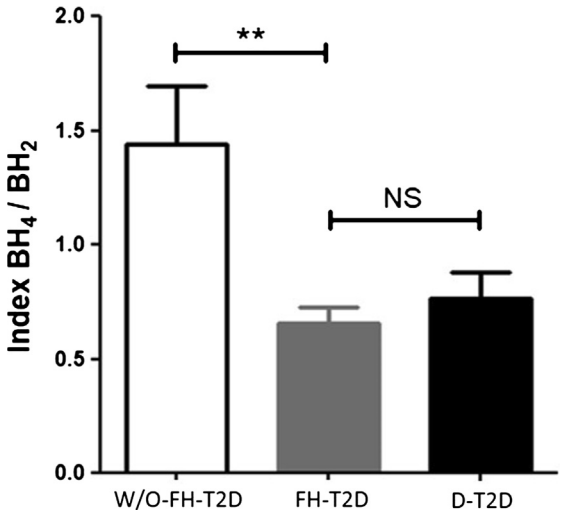

Fig. 4 – Comparison of the BH_4/BH_2 index in participants without a family history of diabetes (W/O-FH-T2D) (1.44 ± 0.25), with a family history of type 2 diabetes (FH-T2D) (0.66 ± 0.07) and with a diagnosis of type 2 diabetes (D-T2D) (0.76 ± 0.11). The analysis was performed by using one-way ANOVA followed by the Tukey post-hoc test. $^{**}p < 0.001$; NS, not significant.

Table 3 – Odds ratio (OR) for determining the probability of low BH_4 in the distinct groups.

Markers	Risk of low BH_4
FH-T2D	OR: 12.75
HbA1c (elevated)	OR: 10
Triglycerides (elevated)	OR: 0.545

than the 5.9863 ± 0.6936 and 4.9980 ± 1.0477 pmol/mL for the FH-T2D and D-T2D groups, respectively (data not shown). Concerning the BH_4/BH_2 index, the calculated value of 1.44 ± 0.25 for the W/O-FH-T2D group was significantly higher than the values of 0.66 ± 0.07 and 0.76 ± 0.11 for the FH-T2D and D-T2D groups, respectively (Fig. 4).

The determination of BH_4 revealed a value 12.75 times greater in the individuals without versus with FH-T2D. The value was 10-fold lower when there was a high level of HbA1c. Finally, an elevated level of triglycerides generated a 0.545-fold greater risk of a low level of BH_4 (Table 3).

4. Discussion

The International Diabetes Federation (IDF) has emphasized the importance of identifying people at risk for T2D as a first step in prevention and/or early diagnosis. Among the strategies suggested for this task is the application of surveys like the FINDRISC screening tool, which was developed in 2001 in Philadelphia and validated by the National Institute of Public Health of Helsinki, and is now widely used to identify patients at risk for developing T2D [1,18].

This study was observational, cross-sectional and analytical, whose objective was to look for the possible participation of risk factors in a population with common characteristics (family inherited history of T2D). The selection of the sample was determined as non-probabilistic at convenience because it is useful for this study, and it is not possible to extract a probability sample due to time/cost considerations. The study was considered as an open population, through an invitation to participate and assessing who met criteria for inclusion and acceptance. However, to know the progression of the disease, it is necessary to follow up the patients through another observational cohort study within a period of time and to know how many patients with a positive family history developed diabetes since within the results obtained there is a big difference between being at risk of developing diabetes and developing it, as detailed below.

In the current contribution, a higher score (11) was found for the participants with a family history of T2D compared to those without such a history, representing a slightly elevated risk for the former group. Hence, a prevenative strategy and/or early primary intervention is recommended for these individuals. The application of a screening tool in a 2010 study carried out in Cali, Colombia, revealed that 88.3% of the population was at low risk and 11.7% at moderately high risk [34]. In 2013 in Mexico, high risk was reported for 80.5% of the surveyed population, low risk for 14.6% and no risk for 2.6% [30]. Overweight and obesity, common in Mexico, are conditions favorable for the development of insulin resistance and therefore increase the risk of acquiring T2D. Insulin resistance is an alteration of the tissue response to the action of insulin that causes an inadequate insulin-dependent glucose uptake, especially in liver, muscle and adipose tissues. This disorder is manifested as hyperglycemia accompanied by hyperinsulinemia due to the overproduction of insulin by the pancreas. Additional consequences are dyslipidemia, arterial hypertension, endothelial dysfunction and inflammation [28,29,31].

In the present study, participants in the FH-T2D and W/O-FH-T2D groups had normal weight, which rules out any influence of overweight or obesity on the markers evaluated. The risk of diabetes is known to go up as the BMI increases, being double at 30–33 BMI, five-fold higher at 34–36, and 10-fold higher at 40. On the other hand, functional alterations in adipose tissue accompanying obesity, lipoatrophy and lipodystrophy are related to insulin resistance [28,32].

The patients in the D-T2D group were overweight, likely resulting from insulin resistance. Normal lipid metabolism includes the release of free fatty acids from adipocytes into the bloodstream. In the liver, some of these free fatty acids are oxidized and most are re-esterified to triglycerides. Thus, the hyperflux of fatty acids to the liver caused by insulin resistance increases the synthesis of triglycerides and very low density lipoprotein (VLDL), rich in Apo B. Under normal conditions, insulin inhibits the secretion of VLDL to the bloodstream and reduces lipoprotein lipase activity in adipose tissue and muscle [29].

Although the precise mechanisms by which T2D accelerates the evolution of atherosclerosis are not clear, cardiovascular risk factors are involved. The positive impact of reducing such risk factors in patients with T2D is equal to or greater than that manifested in participants without diabetes. One of the most frequently observed negative effects

in individuals with T2D is an atherogenic lipid profile, characterized by hypertriglyceridemia, decreased HDL, small and dense LDL (diameter < 25.5 nm), and an increase in the concentration of Apo B (120 mg/dL) [32]. In contrast, the concentration of total cholesterol and LDL is usually not higher in the diabetic versus non-diabetic population [28].

The reason for establishing the lipid profile and atherogenic index in the present groups was to determine the correlation between the hereditary family history of T2D and the early risk of dyslipidemia that may favor hyperglycemia. The level of triglycerides turned out to be extremely high in the FH-T2D group (even though the respective participants were not overweight or obese), thus contributing to the risk of cardiovascular and metabolic disorders. These results are consistent with those found in other studies of Latin populations. In Cuba, for instance, relatives of people with T2D had a higher risk of metabolic syndrome compared to persons without a family history of diabetes [33,34]. In Mexico, a randomly selected population of first-degree relatives of individuals with T2D of the Mexican Social Security Institute (a large nation-wide health care system) showed that 73% had a history of arterial hypertension, 27% myocardial infarction, and 45.3% a high-risk abdominal perimeter. Such characteristics put these relatives at high risk for metabolic and cardiovascular alterations [35,36].

HbA1c, on the other hand, reflects the blood glucose values present in a person over the last 3 months. Accordingly, the American Diabetes Association (ADA) has recommended the inclusion of HbA1c values >6.5% in diagnostic criterion for T2D, as well as values from 5.7 to 6.4% as markers of prediabetes and an increased risk of cardiovascular disease [37,38]. This coincides with the suggestions of several researchers [1,43]. In the current study, the value of HbA1c for the FH-T2D group was 5.775 ± 0.1377% (39 mmol/mol), classifying it as being at risk for diabetes and cardiovascular disease [8,19,31]. For people at risk for diabetes and having HbA1c levels between 5.7 and 6.4% (38–46 mmol/mol), consideration should be given to changes in lifestyle or even pharmacotherapy to prevent or delay the development of the disease [39,40].

The concentration of HbA1c in the blood is generally regarded as the average level of glycemia during the previous three months [41]. However, a recent study found that 50% of the HbA1c in the blood is formed in the month before the blood sample was taken, and that 25% is attributed to each of the previous two months [42]. A study published in The New England Journal of Medicine compared fasting blood glucose and HbA1c as parameters for the detection of individuals at risk for diabetes and cardiovascular events. A significant association was established between high HbA1c values and such risks. Specifically, HbA1c values of <5.0% (31 mmol/mol), 5.0 to <5.5%, 5.5 (36 mmol/mol) to <6.0% (42 mmol/mol), 6.0 to <6.5% (47 mmol/mol) and ≥6.5% represent a progressive increase in the risk for new diabetes and for death from coronary heart disease [30,44].

A higher level of HbA1c corresponds to a lower level of BH_4, which in turn indicates a 10-fold greater probability of endothelial dysfunction and cardiovascular risk, calculated by OR [32,45]. The function of the vascular endothelium is to preserve the integrity of the vascular system, which requires the production and constant availability of NO. Endothelial dysfunction develops when the bioavailability of NO decreases (due to reduced synthesis or accelerated degradation), leading to a proinflammatory state that facilitates atherosclerosis [4]. In the current contribution, participants with a family history of T2D and those previously diagnosed with T2D presented low values for BH_4 and the BH_4/BH_2 index, evidencing the existence of endothelial dysfunction. Given the important relationship of this marker to T2D, and a family history of inherited T2D, and cardiovascular disease, the OR of having a low level of BH_4 was determined for the distinct groups. Such a low level was 12.75 times more likely in people whose progenitors suffered from T2D, and 10 times more likely with a high level of HbA1c (which leads to endothelial dysfunction). Additionally, with an elevated level of triglycerides (implying cardiovascular risk), a 0.545-fold greater probability of a low level of BH_4 existed. In humans, glucose taken orally is known to induce endothelial dysfunction in patients with diabetes and in healthy subjects. Contrarily, the oral administration of BH_4 restores endothelial function via eNOS-dependent pathways [30,40,42]. There is evidence that the BH_4/BH_2 index is more indicative of the proper functioning of eNOS than BH_4 values [42,46]. Since this index coincides with flow-mediated vasodilation as well as coronary vasodilation induced by acetylcholine, it has been proposed as a better marker of endothelial dysfunction than the level of BH_4 [30,32].

5. Conclusions

Monitoring the levels of HbA1c, triglycerides and BH_4 as well as the BH_4/BH_2 index in individuals with a family history of inherited type 2 diabetes would facilitate early detection of diabetes and implemenation of strategies aimed at preventing the disease. The family hereditary background of type 2 diabetes implies a greater susceptibility not only to diabetes but also to cardiovascular disease.

Declaration of Competing Interest

The authors have no conflicts of interest in relation to the products or techniques reported in this article. Only the authors are responsible for its content and writing.

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Author Contributions

Arellano-Mendoza MG, Tamay-Cach F, participated in research design.

Martínez-Venegas M, Rodríguez-Bazán JL, conducted experiments.

Rubio-Guerra AF, Del Valle-Mondragon L, contributed to new reagents or analytical tools.

Valdez-Guerrero AS, Quintana Pérez JC, performed data analysis.

Arellano-Mendoza MG, Tamay-Cach F, wrote or contributed to writing of the manuscript.

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