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Research Article

Evaluation of a DNA-Based Screening Method for People at High Risk of Developing Diabetes in the Dominican Republic

Borbon Glenda[1] , Orozco Bernardo[2], Migliaccio Dominic[2], Arreguin Andrea[1,3*]

[1]International Iberoamerican University, Campeche, Mexico;[2]SD Wellness Center, Santo Domingo, Republic;[3]School of Nursing and Nutrition, Autonomous University of San Luis Potosi, San Luis Potosi, Mexico

ABSTRACT

Aim: The purpose of this research was to evaluate the effectiveness of DNA testing as a diabetes screening instrument for high-risk patients of developing diabetes.

Methods: Patients at of High-Risk (HR) and Low-Risk (LR) for developing Diabetes Mellitus (DM) according to risk factors established by the American Diabetes Association were divided into two groups, HR and LR. Both groups underwent nutrigenetic (*PPARG*, *SLC2A2*, Transcription Factor 7-Like-2 (*TCF7L2*), *FTO* genes), HOMA-IR score, and medical history screening. 26 patients were in the HR group and 38 were in the LR group.

Results: The mean age of participants in HR group was 47 (± 8.37) and 43 years (± 10.57) in the LR group, 69% of participants were male and 53% were female, respectively. In both groups, the mean of Body Mass Index (BMI) was 27.3 (± 3.86) kg/m^2. The *PPARG*, *SLC2A2*, *TCF7L2*, *FTO* genes showed some variation between HR and LR groups, but none reached statistical significance.

Conclusion: High risk individuals had an increased DM risk up to 3.7 times based on genetic variants of *TCF7L2*. Participants with genetic changes had up to 2.7 times higher than average risk for developing insulin resistance, but no statistical significance was obtained.

Keywords: Insulin resistance; Diabetes mellitus 2; Biotechnology; DNA tests; Diabetes prevention

INTRODUCTION

In Over time, different advances have been made regarding the detection of diseases in various fields of medicine. Diabetes mellitus is no exception, improving over the years through different technologies available to patients; from continuous insulin monitoring to novel developments for insulin administration in these patients [1]. Diabetes affected 9.3 percent of the global population in 2019; in the Dominican Republic, 13.4 percent of the population had diabetes and 9.3 percent had pre-diabetes in 2018 [2-3]. This disease is not only highly correlated with the appearance of different pathologies such as coronary and cardiovascular diseases, lipid disorders, and kidney diseases, among others; it is a multifactorial pathology for which culture, diet, inflammatory processes, and even genetic factors (either due to polymorphisms or environmental factors such as nutrition) play a crucial role at the time of its development [4–7].

Patients For the reasons stated above, a preventive approach to the management, education, and early diagnosis of these patients is critical to avoid and control the spread of this disease in the population. Thus, the focus of resources on different biotechnologies for the early diagnosis of insulin resistance could become the cornerstone for future advancement and its reduction worldwide. Currently, the early diagnosis and management of insulin resistance is very low, thus triggering obesity, inflammatory processes and finally diabetes. One of the main problems for this diagnosis is the presentation of glucose and insulin levels within normal values in patients, thus leading to underdiagnoses of this pathology. Through the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), insulin resistance can be detected early, providing essential information for the impact of patients [8,9]. However, the use of biotechnologies for its diagnosis, such as DNA tests for primary screening in high-risk patients, could lead to the early detection of different genes to address them through

Correspondence to: Arreguin Andrea, International Iberoamerican University, Campeche, Mexico; E-mail: andrea.arreguin@unini.edu.mx

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nutrigenomics, creating changes in the different patient factors such as nutrition, environment in general, lifestyle, among others [10,11].

The purpose of this study was to determine the impact of DNA testing as screening tool for patients at high-risk of developing diabetes. To achieve this, genetic information based on DNA Health tests from different patients with a high risk of developing diabetes was analyzed to determine possible insulin resistance, thus comparing it with serum insulin levels and HOMA-IR values. DNA Health provides the level of impact of genetic variants associated with metabolism and biological processes that could create a positive large-scale effect on the Dominican Republic population. Among the genes and their present variants evaluated by the DNA tests is *PPARG*, which is involved in the regulation of glucose and lipid metabolism. *TCF7L2*, which influences blood glucose homeostasis; and *SLC2A2*, which facilitates glucose-induced insulin secretion and is involved in food intake and regulation. And finally, FTO, which influences the susceptibility to obesity and the risk of type 2 diabetes [12-14]. The risk present in different populations according to their descent shows that in populations with European descent, the risk based on the factors correlated to the nutrigenomics could be up to twice as high for the development of diabetes mellitus as in other populations [15,16]. Therefore, this study intended to develop an early risk prediction and diagnosis system centered on frequent genetic variables in the Dominican population, facilitating more effective treatment.

METHODOLOGY

This study relied on a quantitative, retrospective, cross-sectional approach. There was a non-probabilistic sampling (for convenience) secondary to the number of DNA tests carried out by a Health Clinic in the Dominican Republic. The participants were recruited through healthcare professional between March 2021 and October 2021. Patients expressing interest in the research were then invited to participate in the study if they met the following inclusion criteria:

1) Participants aged 18 years of age;

2) Any body mass index; and

3) With or without comorbidities.

The following minimal sets of exclusion criteria were applied:

1) Pregnant or lactating;

2) Metabolic conditions were not controlled; and

3) Allergies or food intolerances.

The ethics committees at Iberoamerican University Foundation, Barcelona, Spain, granted approval for the study (N°CR-126). Before participation, potential volunteers completed an informed consent from the health Center. To measure the different variables taken into consideration in this study, a questionnaire was used to collect information regarding the risks present for the development of insulin resistance [17]. The questionnaire was created and validated by the Health Clinic, based on the risks described according to the ADA. In addition to this, the records of serum analytics pertinent to glycemia and insulin were used to calculate the HOMA-IR, these laboratory tests had been performed by Referencia Laboratorio Clínico S.A, reference values were basal glycaemia levels (≤ 100 mg/dL) and basal insulin values (3.0 U/mL-25.0 U/mL). HOMA-IR was calculated according to the formula: fasting insulin (micro health tests applied were performed by the Health Clinic. The saliva samples were shipped to Nordic Laboratories for the analyses [18]. The following single nucleotide polymorphisms of interest to the current dietary change and adherence study were analysed: *PPARG* (Pro12Ala), *TCF7L2*, (rs7903146), *SLC2A2*, (Thr110Ile) and FTO (rs99396099. Nordic Laboratories classified the results as without genetic variations, and with genetic variants such as mild, moderate, and beneficial, each according to the polymorphism present in a participant's results [22].

For statistical analysis, Student's t-test was used for continuous variables Fisher's tests were used for dichotomous variables. During analysis, $p<0.05$ was considered statistically significant with a 95% confidence interval. For the analysis of the descriptive demographic variables of the groups used in the sample (age and sex), the T-student test was used for independent samples for the analysis of the groups and the determination of a possible readjustment to avoid a confusion bias. For the analysis of the genetic variables in the participants, Fisher's exact probability test was used, thus determining the association between the risk of insulin resistance and genetic variations. In the same way, the comparison of the genetic variables was carried out by means of Fisher's exact probability test to determine the association of the possible presence of the genetic variables together with the diagnosis of insulin resistance through the HOMA-IR values in participant groups. SPSS V.26.0 (IBM Corporation) was used for all statistical analyses.

RESULTS

Study participants

Data from a total of 64 adults who underwent DNA testing at the Health Center was collected for the analysis between March 2021 and October 2021. Participants were divided into two groups based on their risk of developing insulin resistance (26 HR *vs.* 38 LR). Baseline characteristics of the participants are shown in Table 1.

At the time of the analysis, the results pertinent to the values necessary for the evaluation of insulin resistance that were considered were the glycemic values of the participants, basal insulin, and the calculation of the Homeostatic Model to Evaluate Insulin Resistance (HOMA-IR). As can be seen in Tables 2, it was found that in the HR group the participants had a mean glycemia of 93.9 mg/dL (± 12.73), a mean insulin of 11.3 mIU/L (± 6.93), and a mean HOMA-IR of 2.6 (± 1.89). On the other hand, in the LR group, the participants presented a mean glycemia of 89 mg/dL (± 6.76), mean insulin of 8.2 mIU/L (± 4.27) and a mean HOMA-IR of 1.7 (± 0.92). Upon analysis for the difference between both groups, it was observed that in comparison they presented a mean difference in glycemia of 4.9 (p value 0.04 (0.02-9.8)), a mean difference in insulin of 3 (p value 0.03 (0.22- 5.82)) and a mean difference in HOMA-IR of 0.91 (p-value 0.01 (0.19-1.6)) (Table 2).

Within the results, the values of insulin resistance in the participants were differentiated and as seen in Table 3, it was found that in the HR group, 38.5% (10) presented normal insulin levels, 15.4% (4) presented early insulin resistance and 46.2% (12) presented significant insulin resistance. On the other hand, in the participants of the LR group, 68.4% (26) had normal insulin levels, 15.8% (6) had early insulin resistance, and 15.8 (6) had significant insulin resistance; for a total of 56.3% (36) participants with normal insulin, 15.6% (10) with early insulin resistance, and 28.1% (18) with significant insulin resistance (Table 3).

DNA analyses

For the classification of the results obtained by the participants in relation to the present genetic data, four groups were defined for the different genes, without genetic variation, with mild genetic variations, with moderate genetic variations and with beneficial genetic variations. For this, the type of per polymorphism found in each gene and the variation in the presence of alleles present in the general population were considered:

1) *PPARG*, change of *Pro12Ala* or C>G,

2) *TCF7L2*, change of *rs7903146* C>T,

3) *SLC2A2*, change of *Thr110Ile* and

4) *FTO*, change from *rs9939609* T>A.

Nordic Laboratories classified the results as without genetic variations, and with genetic variants such as mild, moderate, and beneficial, each according to the polymorphism present in a participant's results [22].

Regarding the genetic results of the participants, the distribution of the different genes according to the group can be seen in Table 4. In the HR group for the PPARG gene, 92.3% (24) presented moderate genetic variations and 7.7% (2) presented beneficial genetic variations. For the *TCF7L2* gene, 50% (13) did not present any genetic variation, 42.3% (11) presented slight genetic variations and 7.7% (2) presented moderate genetic variations. Regarding the *SLC2A2* gene, 53.8% (14) did not present genetic variations and 46.2% (12) presented slight genetic variations. Finally, for the *FTO* gene, 26.9% (7) did not present genetic variations, 57.7% (15) presented slight genetic variations, and 15.4% (4) presented moderate genetic variations. The LR group, on the other hand, for the *PPARG* gene, 5.3% (2) had no genetic variations, 86.8% (33) had moderate genetic variations, and 7.9% (3) had beneficial genetic variations. For the *TCF7L2* gene, 26.3% (10) did not present any genetic variation, 57.9% (22) presented slight genetic variations and 15.8% (6) presented moderate genetic variations. Regarding the *SLC2A2* gene, 73.7% (28) did not present genetic variations, 23.7% (9) presented slight genetic variations and 2.6% (1) presented moderate genetic variations. Finally, for the *FTO* gene, 44.7% (17) did not present genetic variations, 34.2% (13) presented slight genetic variations and 21.1% (8) presented moderate genetic variations.

Table 1: Baseline characteristics of the participants.

Variables	High risk	Low risk
Total, n (%)	26 (100%)	38 (100%)
Sex, female, n (%)	8 (31%)	20 (53%)
Sex, male n (%)	18 (69%)	18 (47%)
Age years (SD)	47 (± 8.37)	43 (± 10.57)
Anthropometrics	-	-
BMI ($kg.m^{-2}$)	28.2 (± 4.59)	26.6 (± 3.17)
Risk Variables [a]	-	-
First degree family member with DM [b]	17 (65.4%)	20 (52.6%)
History of cardiovascular pathologies	18 (69.2%)	3 (7.9%)
Arterial hypertension	17 (65.4%)	1 (2.6%)
High levels of cholesterol or triglycerides	23 (88.5%)	15 (39.5%)
Absence of physical activity	10 (38.5%)	6 (15.8%)
Woman with PCOS [c]	3 (11.5%)	3 (7.9%)

Note: Data are presented as means (SD; standard deviation) or as % for categorical variables.
ADA [a]: American Diabetes Association,
DM[b]: Diabetes Mellitus,
PCOS[c]: Polycystic ovarian syndrome

Table 2: Description of insulin resistance variables in the participants.

Variables	High risk	Low risk	p-value*
Glycemia mg/dL	93.9 (± 12.73)	89 (± 6.76)	0.04
Insulin U/mL	11.3 (± 6.93)	8.2 (± 4.27)	0.03
HOMA-IR	2.6 (± 1.89)	1.7 (± 0.929	0.01

Note: Data are presented as means (standard deviation). HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.
* Fisher exact test was done for the comparison between groups.

Table 3: Classification of insulin resistance in participants.

Variables	High risk	Low risk
Normal	10 (38.5%)	26 (68.4%)
Early insulin resistance	4 (15.4%)	6 (15.8%)
Significant insulin resistance	12 (46.2%)	6 (15.8%)

Note: Data are presented as % for categorical variables. Normal insulin values (insulin-sensitivity) were defined for patients who presented scores below 2 on the HOMA-IR index, early insulin resistance values for participants with HOMA-IR values of 2.1 to 2.9, and significant insulin resistance values to participants with HOMA-IR values of 3 or more.

Table 4: Description of genetic results in the participants.

Variables	High risk				p-value*	Low risk				p-value*
	PPARG	TCF7L2	SLC2A2	FTO		PPARG	TCF7L2	SLC2A2	FTO	
Without genetic variation, n (%)	0(0%)	13(50%)	14(53.8%)	7(26.9%)	0.69	2(5.3%)	10 (26.3%)	28(73.7%)	17(44.7%)	0.125
With mild genetic variations n (%)	0(0%)	11(42.3%)	12(46.2%)	15(57.7%)	0.06	0(0%)	22 (57.9%)	9(23.7%)	13(34.2%)	0.18
With moderate genetic variations n (%)	24(92.3%)	2(7.7%)	0(0%)	4(15.4%)	0.11	33(86.8%)	6 (15.8%)	1(2.6%)	8(21.1%)	1
With beneficial genetic variations n (%)	2(7.7%)	0(0%)	0(0%)	0(0%)	0.19	3(7.9%)	0 (0%)	0(0%)	0 (0%)	0.45

Note: Data are presented as % for categorical variables. * Fisher exact test was done for the comparison between groups.

Once the genetic results of the participants in the different groups were obtained, the analysis was carried out looking for the relationship that these could have both with the risk of insulin resistance and with the appearance of it. In Table 4 these analyses can be observed, finding that in terms of the risk of developing insulin, the participants presented a difference of 0.49 for the PPARG gene (p value 0.69), for the *TCF7L2*gene a difference of 3.7 (value p 0.06), for the *SLC2A2* gene a difference of 2.6 (p value 0.11) and for the *FTO* gene a difference of 2 (p value 0.19). In the same way, when evaluating the relationship of the results obtained by the genetic tests with the presence of insulin resistance, it was found that for the PPARG gene there was a difference of 2.77 (p value of 0.125), for the *TCF7L2* gene there was a difference of 2.3 (p value 0.18), for the SLC2A2 gene a difference of 0.04 (p value 1) and for the FTO gene a difference of 0.61 (p value 0.45) (Table 4).

DISCUSSION

Over the years, Non-Communicable Diseases (NCDs) have become one of the most important focuses for the health sector because, for decades, they have been the main responsible for the leading causes of death and disability in the geographic region and in the Dominican Republic [23]. Due to its prevalence and the multifactorial impact that this pathology presents such as the cultural and the environmental factors of the population, diet, and many more, it has become arduous to achieve proper prevention. According to ENPREFAR-HAS 2017, more than 60.3% of the Dominican population has a Body Mass Index above 25kg/m2, increasing even more annually [23].

Due to the weight that this pathology carries at the national level in the health sector, the necessary measures to ensure its effective prevention have become the main component of its approach. Based on the above, the present study was designed to evaluate the usefulness of DNA tests for primary screening in the Dominican population at high risk of developing diabetes. For these purposes, patients seen at a Health Center between the period of March-October 2021 were evaluated. Different demographic characteristics of both high and low risk groups were evaluated during the analysis and no significant differences were observed between the groups with respect to their distribution by sex and age, following the characteristics of a normal distribution. Likewise, the participants were evaluated according to the current criteria for determining high risk for the development of diabetes, thus finding that 59.4% of the participants had high cholesterol or triglyceride values in the last 5 months. Similarly, 57.8% had a history of type 2 diabetes mellitus in a first-degree relative. This demarcates the impact of not only the environmental factors in the diet, which consequently lead to dyslipidemia (in some even at early ages), but also the genetic load that this pathology presents in the Dominican population. Other factors related to the risk of diabetes were present among the participants in an important way, since 32.8% of these had a history of heart disease and within these, 28.1% had high blood pressure, which confirms concerns by the Ministry of Health regarding non-communicable diseases. This reality is consistent with risks previously proposed by authorities such as the American Diabetes Association and the Oxford School in the European Journal of Cardiology, who have stated that diabetes increases the risk of developing cardiovascular pathologies from 2 to 4 times more normal in different populations and the fact of presenting the same increases the risk of diagnosis and morbidity even more in these [24]. Additionally, it was found that the mean body mass index in the participants was 27.3 (± 3.86), which, according to the World Health Organization, shows that according to the present mean, the majority of the participants presented pre-obesity (defined as a body mass index of 25-29) or obesity itself (defined as a body mass index>30) [25]. Further increasing the risk not only of diabetes but also of other pathologies such as cardiovascular diseases.

Within the evaluation for insulin resistance taken from the participants, it was found that 43.7% (28) of the participants had insulin resistance. Among these, 61.5% (16) of the participants who presented insulin resistance were at high risk of developing diabetes and 31.6% (12) were at low risk. The mean of the Homeostatic Model to Evaluate Insulin Resistance (HOMA-IR) presented by the group at high risk of developing diabetes was 2.6 (± 1.89) and the mean of the participants with low risk was 1.7 (± 0.92). Thus, demonstrating that the participants who met the criteria for high risk of developing diabetes presented a mean that already positioned them in patients with early insulin resistance, further increasing the risk of diabetes. These results agree with the data presented in different studies showing that body mass index, and cholesterol and triglyceride levels are significant predictors for the development of insulin resistance [26]. Likewise, insulin resistance has a high relation to arterial hypertension for the development of diabetes, which is another of the parameters taken to determine the high risk of developing diabetes [27].

Within the difference in means present at the time of the analysis of the results of both groups, it was found that the participants with a high risk of developing diabetes had a 0.91 greater probability of presenting high levels of HOMA-IR, putting them in insulin resistance. However, although there was a difference in both groups, they did not present statistically significant results (p value=0.01 (0.19-1.6)).

Although the results observed in the participants did not present statistically significant differences, previous studies have shown the impact and relationship of genetic factors for the development of diabetes mellitus 2 [28-30]. Additionally, it has been seen that some of these factors not only play a role in its development but also in the possible complications that these people may develop, as is the case of the *FTO* gene, which, in addition to increasing the risk of diabetes, also impacts the risk of developing diabetic nephropathy in already diagnosed patients [29]. Therefore, these results could possibly respond to the small size of the samples recruited in the present study due to the availability of patients with DNA results.

LIMITATIONS

On the other hand, when evaluating the results present in the participants in relation to genetic factors and the presence of insulin resistance in the different groups, it was observed that the difference for the *PPARG* gene was 2.77 (p value 0.125), for the *TCF7L2*gene was 2.3 (p-value 0.18), for the *SLC2A2* gene it was 0.04 (p-value 1.0) and for the *FTO* gene it was 0.61 (p-value 0.45). Although at first glance, these last values seem to indicate that there is a relationship between genetic factors and the development of insulin resistance, putting individuals at risk up to 2.7 times more than the average, these results did not present significant values, possibly due to the availability of patients with DNA results. However, although these results in the participants did not present statistical significance, they do indicate a possible relationship between these genes and the development of said pathology. These results are consistent with previous studies conducted in the health area that demonstrate the increased risk caused by different polymorphisms in individuals for the development of insulin resistance and type 2 diabetes mellitus [30-32].

There are several specific limitations to the present work that should be noted. This research uses a small sample size and a retrospective design. In contrast, a variety of risk factors for type 2 diabetes genotype risk scores have been published in prospective studies of middle-aged adults, with comparable results [33,34].

Consistent with most of the risk for type 2 diabetes genotype research, there were limitations related to the predicted risk categories. In this regard, the Net Reclassification Improvement (NRI) index was developed by Pencina et al., to assess the relative accuracy of two different risk prediction models [34]. Additionally, there are possible confounding factors, such as the age of the participants. However, these categories of risk do not inform widely accepted clinical prevention targets, as contrasted with the results of our research, which uses the ADA categorization. Nevertheless, additional research is required.

CONCLUSION

Finally, insulin resistance and diabetes mellitus are multifactorial pathologies that are affected by environmental aspects such as risk factors for its development and genetic factors in the different polymorphisms evaluated in the population. This is a multidisciplinary approach to the population with risk factors for early screening and a preventive approach are important, thus ensuring the reduction of morbidity at the national and international level.

The mean of the Homeostatic Model for Evaluating Insulin Resistance (HOMA-IR) in participants at high risk of developing insulin resistance was 2.6 (± 1.89), classifying them already as insulin resistant and had a difference in DNA test results increasing the risk up to 3.7 times (in the case of the *TCF7L2* gene) but did not obtain statistical significance. In general, participants with genetic changes had up to 2.7 times the average risk for insulin resistance development based on the present analysis but statistical significance was not obtained for which further research with a wider sample size is recommended.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Iberoamerican University Foundation, Barcelona, Spain (protocol code N°CR-126, September 17th, 2021). Informed consent was obtained from all subjects involved in the study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets analyzed during the current study are not publicly available because the report contains additional polymorphisms that were evaluated by the Nordic laboratories, but they are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTIONS

GB: Conceptualization, investigation, resources.

AA: General advisor and manuscript review.

BO: Software and data processing.

DM: Onsite clinic assistance, and English context editing.

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