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EDITORIAL

WHAT DO WE EXPECT FROM 2022?

2022 is the year of ***HOPE!***

We all believe that 2022 is the year we will become victorious in the battle against *Coronavirus*! Are we being too optimist?

It doesn´t matter the amount of bad news coming all days from media, we are still confident that our lives are going back to normality despite *Coronavirus* mutations. We now have vaccines and no matter what people that do not believe in Science say or people that turn the subject a politic discussion, the fact is that vaccines are pure Science and as scientists, here we are in behalf of active immunization with vaccines, in behalf of life!!

As human beings, faith and hope are what move us and make us “thirsty” for living, “hungry” for survival; Faith in God ... hope in vacines, Science and humanity!

Having said that, **what do we wish for 2022?**

Health and quality of life...

Vaccine for poor and rich people...

Peace... Are we able to really live in peace?

Tolerance and respect to diferences...

Liberty for living...

Equality among nations...

Fraternity...

To enjoy our Family and Home ... our greatest treasures...

To be able to hug and kiss who we love!

Work, jobs and money (the last one is really important as it give us comfort, dignity and security)...

Compromised politics...

Patriotism (love your contry!)...

Care for environment...

A healthy planet four our children and grandchildren...

These are the wishes of our editors for all of you!

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ORIGINAL ARTICLE
MOBILE HEALTH MONITORING: DEVELOPMENT, IMPLEMENTATION AND EVALUATION OF AN APP FOR CHRONIC DESEASES IN COVID-19 CONTEXT

MONITORAMENTO DE SAÚDE MÓVEL: DESENVOLVIMENTO, IMPLEMENTAÇÃO E AVALIAÇÃO DE UM APLICATIVO PARA DOENÇAS CRÔNICAS NO CONTEXTO DE COVID-19

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Key words: MHealth, Georeferencing, COVID-19

Abstract

One of the most vulnerable sectors of the population to the COVID-19 pandemic are people with chronic diseases. Most of these patients require specialists in referral hospitals. Identifying and geo-referencing these patients is fundamental for Public Health. This work aims to develop, implement, and evaluate an application for mobile devices to detect and perform georeferenced follow-up by governmental health agencies to patients carrying chronic diseases at risk of COVID-19. The use of the application has the potential to benefit chronic patients in terms of the possibility of accessing medication and obtaining primary care from specialists without the need to travel to health centers. The tests carried out show the ability of the georeferencing system to monitor patients and to continue the corresponding patient-physician interaction. **Endocrinol diabtesclin exp 2021 / 2234 - 2240.**

INTRODUCTION

Driven by a technological and health sector, the use of apps in public health has come to be known as “mHealth”. mHealth is, as defined by the World Health Organization (WHO), “the practice of medicine and public health supported by mobile devices such as phones, patient mon-itoring devices, digital assistants and other wireless devices” (1).

Health apps open doors to new opportunities for the optimization of public health resources: in the commitment to prevention, in aiding the sustainability of health systems, and even in tele-medicine (2)

In Latin America, the use of mobile applications for patients and healthcare professionals is emerging as the most promising market (3). Applications for chronic patient management could be the fastest growing in the coming years.

Studies show good results regarding the use of mHealth for the management and control of patients with different chronic diseases (4,5), including older adult patients (6). Most of these studies are focused on the monitoring and control of different chronic diseases such as blood pressure or diabetes (6, 10). They combine the benefits of mHealth with the use of sensors and wearable technology. Other studies complement it with georeferenced systems for emergency cases (11). One of the benefits of the use of mobile applications that should be mentioned is their effectiveness in improving diagnosis and medication adherence (12). The challenge of Infor-mation Communications Technology (ICT) is to ensure the interoperability of applications with Electronic Health Record data, as well as to ensure the privacy and security of patients’ sensitive health information (13).

Coronaviruses (CoV) are a large family of viruses that can cause a variety of conditions, from the common cold to more serious diseases, such as the SARS-CoV virus that appeared in China in 2002 and the coronavirus causing Middle East respiratory syndrome (MERS-CoV) that appeared in 2012. Both were originally transmitted by bats and palm civets (14). Coronaviruses generally do not cause severe clinical disease in children, but are characterized by causing severe pneumonia in elderly patients and in patients with comorbidities (15). The new SARS-CoV2 virus, which causes COVID-19 disease, is believed to have originated from a live market in Wu-han City, China (16).

COVID-19 viral infection, like other infections, triggers an inflammatory response that is usually confined to the respiratory system. However, there is evidence that in a full-blown case, almost all systems of the body may be involved. In addition, there is the syndrome of cytokine storm, characterized by severe systemic inflammation and a massive release of proinflammatory cytokines (17). It is well established that obesity and diabetes are major risk factors for COVID-19 infections and that the morbidity and mortality in association with these conditions is marked-ly increased. Since both obesity and diabetes are associate-ed with chronic inflammation, it is likely that the inflammatory response to COVID-19 in such patients is affected by the back-ground of chronic inflammation.

In relation to hypertension and cardiovascular disease according to (18), the key points to keep in mind are: hypertension and cardiovascular disease are more frequent in those who have a worse evolution by COVID-19 Patients over 60 years of age, as well as those with cardio-vascular disease, should especially avoid exposure to SARS-CoV-2, not self-medicate and con-sult promptly at the appearance of symptoms.

In the face of a pandemic, there is an urgent need for appropriate technology to, among other things, facilitate the identification of chronic patients. According to statistics from Paraguay, in 2017, 44.3% of the 14,870 deaths corresponded of people under

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70 years of age with chronic non-communicable diseases (19)]. The treatment of chronic patients infected withCOVID-19 is a challenge for physicians and the health care system. It should be said that COVID-19 cases in patients with comorbidities represent a majority in fatal cases (20).

This paper presents the development, implementation and evaluation of a mobile application that allows the georeferencing of chronic patients and their communication with professionals of public health agencies.

The paper is structured as follows: the Methods Section presents the description of the mobile and web software and database development process. The Results section shows the results obtained in the analysis, design, implementation, and evaluation process. The Discussion section presents the limitations of the application. The Conclusions section presents the conclusions of the evaluations reported by the health professionals.

MATERIAL AND METHODS

The georeferencing system for patients with chronic diseases, within the framework of Covid-19, was carried out through the implementation of a web and mobile system that allows communication to a database with exclusive access to Public Health professionals. The mobile application is oriented to patients and the web application to physicians. The development was carried out in four stages: **Analysis, Design, Implementation and Evaluation.**

Analysis

At this stage, with the help of health care professionals, the data survey was carried out to obtain the system requirements.

Two physicians with specialization in public health participated in the study. The first profes-sional carried out a review of existing regional applications for comorbidity monitoring. Based on this, a list was drawn up of the main functionalities that the application could have, adjusting them to the health reality of Paraguay. Subsequently, the second professional proceeded to adapt the functionalities of the application based on the specific requirements of a Chronic Diseases Health Care agency.

The survey of regional practices, the drafting of the requirements and their adaptations for Public Health lasted one week each.

Design

Based on the results of the analysis, the design of the application for mobile devices and the design of the web application and database for information storage were carried out.

Implementation

At this stage, the tools to be used for the implementation of the application were decided. **Fig.1** details the technological stack of the web and mobile application and database.

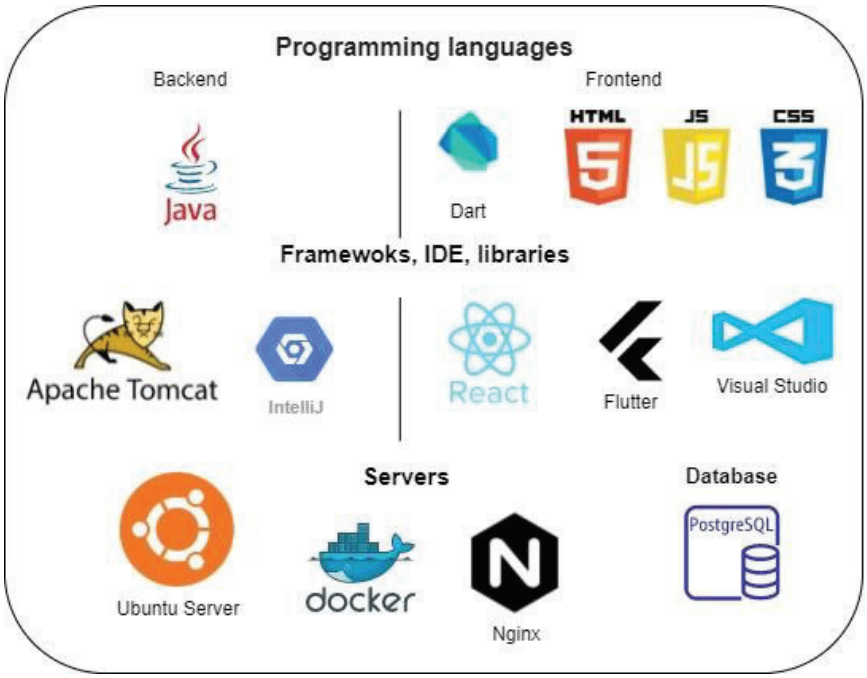
The Kanban software development methodology was used, where user stories were created to be fulfilled in the following phases:

1st phase: Minimum Viable Product (MVP) backend development.

2nd phase: Development of the hybrid mobile application.

3rd phase: Development of tests with the app.

4th phase: Development of the web interface for physicians.



Evaluation

To test the performance between the components, integration tests were performed between the frontend and backend and integration tests between the mobile application and the backend. To evaluate the execution of different user scenarios, tests of use cases and their flows were per-formed. These tests were performed by the Development team through a test server. They were performed on a pilot version of the product that included two physicians and thirty-eight volun-teered persons in Paraguay.

In addition, to measure the usability of the application, a survey to 16 people who previously used the app was carried out. The methodology adopted was the System Usability Scale (SUS) (21).

RESULTS

Analysis

The following requirements were specified for the mobile application and the web applica-tion:

The mobile application is patient-oriented. Through it, patients can register, enter and update their clinical and demographic data, identify care centers near them, and request assistance from a public health agency. In addition, patients can complete the baseline disease form, symptom form and logistic data form.

The data collected by the mobile application are ID card, name, date of birth, gender, ad-dress, geographic location (lati-

tude, longitude), email and phone number. These are necessary for patient identification. Through the demographic location, patients are assigned to the health center closest to their location and, in turn, to the specialist physician.

The web application is oriented to public health care physicians and professionals. Through it, physicians can contact patients and access answers to forms completed by patients. Coordinating physicians can assign patients to physicians in their region. In addition, a list of patients, physicians, coordinating physicians, coordinators, patient assignments and hospital centers can be accessed through the application.

The database server records data related to patients, health--care professionals and healthcare centers.

Medical professionals can create the forms as needed through the web application and can assign them to patients through the web application. Patients through the mobile applica-tion can complete the forms and save the answers, which will be updated in the database.

Design

An initial design was created for the web and mobile application view. The web application has a component-oriented design. The web server has a Model View Controller (MVC) design, where the models are the representation of the database tables.

The database was represented through an entity-relationship diagram. The main data en-tities were: hospital, district, province, person, form, message. The user interface of the mobile application includes the following functionalities: login, personal data, forms, hospital form, base disease form, symptom form, hospitals, asynchronous doctor-patient messaging.

The user of the mobile application can enter the application with his/her e-mail address and password and register his/her data if it is the first time, he/she accesses the application. The per-sonal data option allows the user's data to be registered or updated. The forms option presents the list of forms that the user must fill out as a patient. The hospital, base disease, and symptoms form option allows the patient to answer about logistic data, diseases he/she suffers from, and if he/she has COVID-19 symptoms respectively. The hospital option presents the geo-graphic dis-play of the hospitals closest to the patient's location. The messaging option allows the patient to communicate with the assigned physician.

The web application interface comprises the following functionalities: home, forms, patients, patient assignment, care centers, physicians, coordinators, messages, support. The home button redirects the user to the main page of the application. The forms button presents the list of forms created their descriptions together with the questions contained. The patients button displays the list of patients. The patient assignment button presents the list of patients and the physicians assigned to them. The hospitals button presents the list of health centers and their data such as code, name, district and region. It is also possible to import hospital data from an official health agency website. The doctors and coordinators button lists the data of the doctors and coordina-tors respectively. The messages button shows the messages received from treated patients.

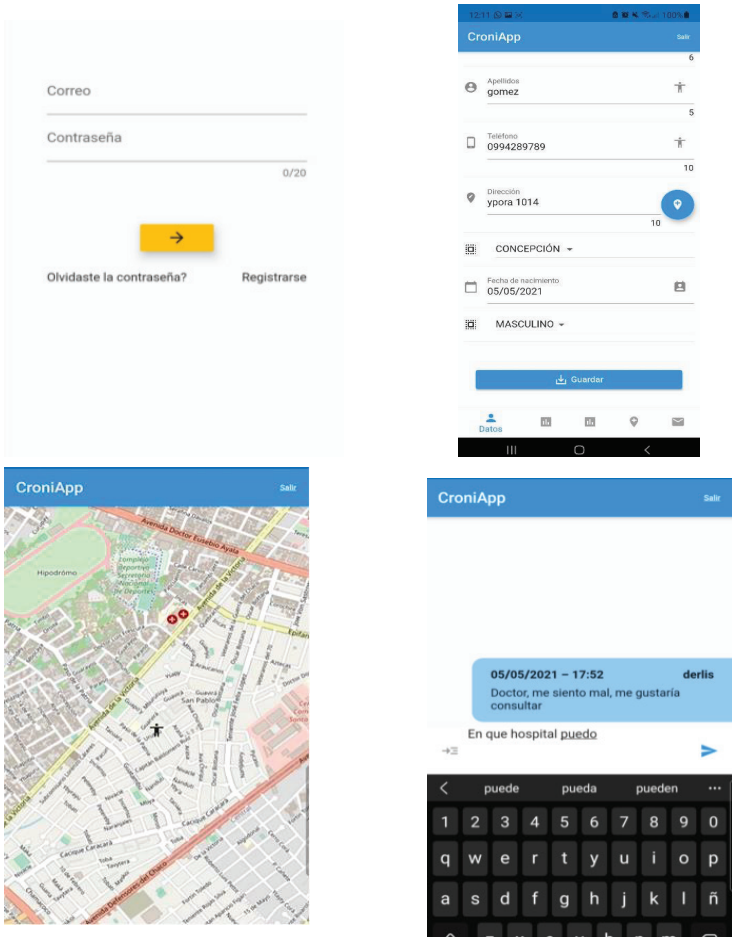
Implementation

The mobile application was developed for the Android operating system, which is the majori-ty system in the population. The security and privacy of the data was guaranteed with strict secu-rity controls for access to the database and the web system. Communication is done via HTTPS and passwords are not shared.

Fig. 2 shows some of the screens of the mobile application such as the login screen, personal data, hospitals, and the doctor-patient messaging.

The login screen allows access to the mobile application and registration in case of first time access.

Fig. 2. Technology stack of web, mobile and database applications.



In the data screen patients update their personal data; the phone number field is required to allow instant messaging with medical professionals.

The hospitals screen displays the location of the healthcare centers closest to the patient's ge-olocation. The geographic location is obtained by requesting permissions from the user and stor-ing latitude and longitude data. To implement geo--referencing, open source data from Open-StreetMap (220] were used, upon user request. To visualize the nearest hospitals, a radius-based algorithm (23) was implemented to obtain the Nearest hospitals in an increasing R radius.

Fig. 3 shows the baseline disease, symptom, and logistic data forms screen. In the baseline disease and symptom forms screens patients select the underlying disease they have and if they are suffering from symptoms. In the logistic data form screen, patients can detail the hospitals they frequent and the medication they withdraw from those hospitals.

Fig. 3. Login screen, personal data, hospitals and asynchronous doctor-patient messaging of the mobile application.

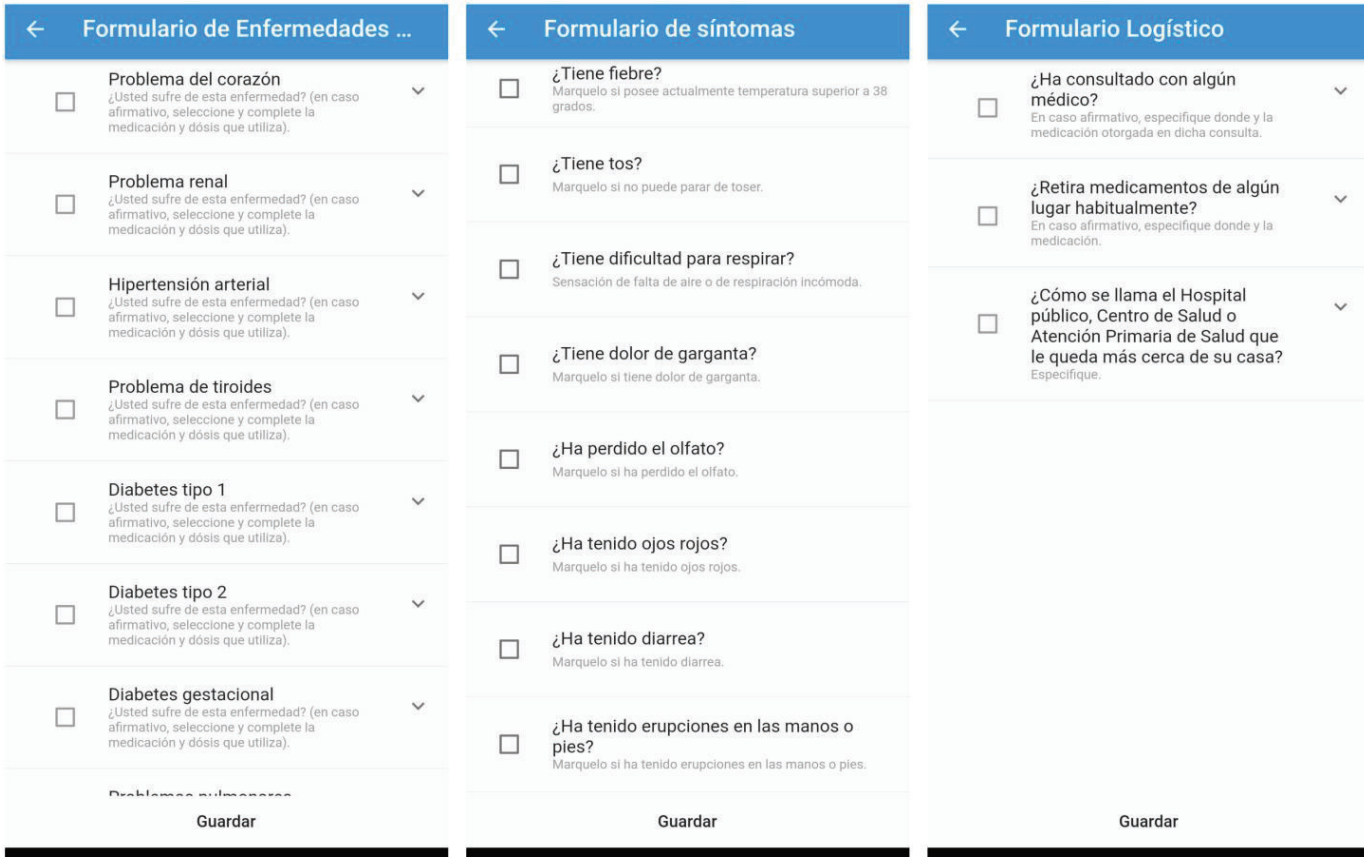


Fig. 4 shows some screens of the web application. The patient assignment screen shows the list of patients and whether they are already assigned to a physician. The care centers screen displays the existing care centers with the option to edit their data or delete them from the list. The physician screen displays the names of the physicians with the option to edit their data, delete them from the list or assign them to specific care centers. The messages screen shows the messages received from patients with the option to enter the corresponding chat and send or re-ply to the messages.

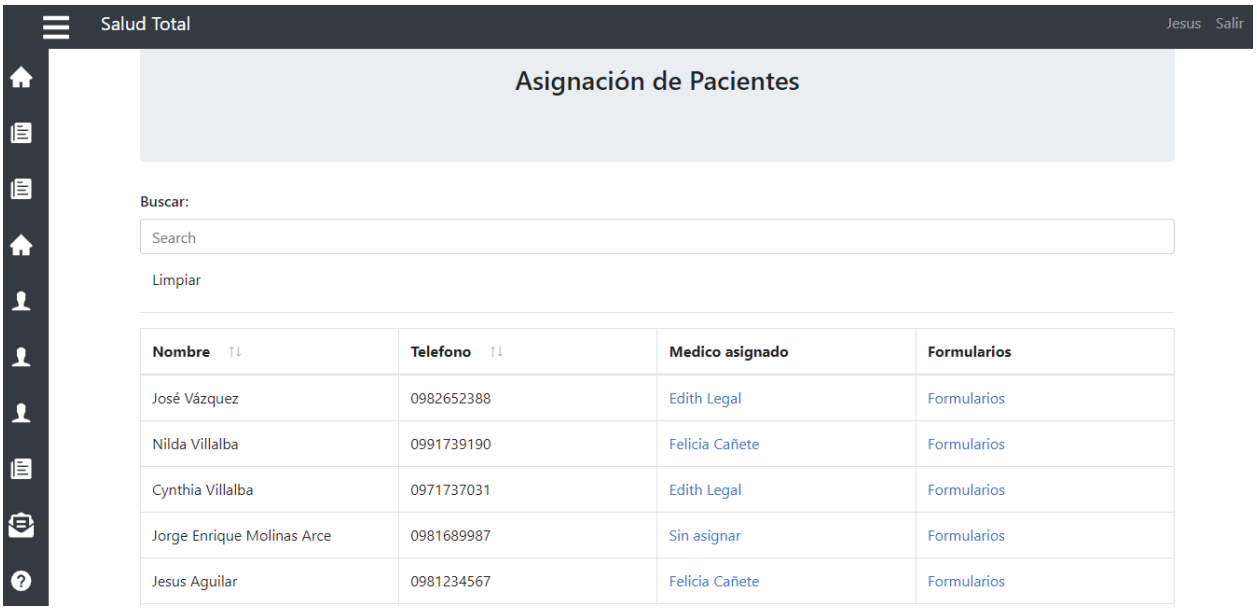
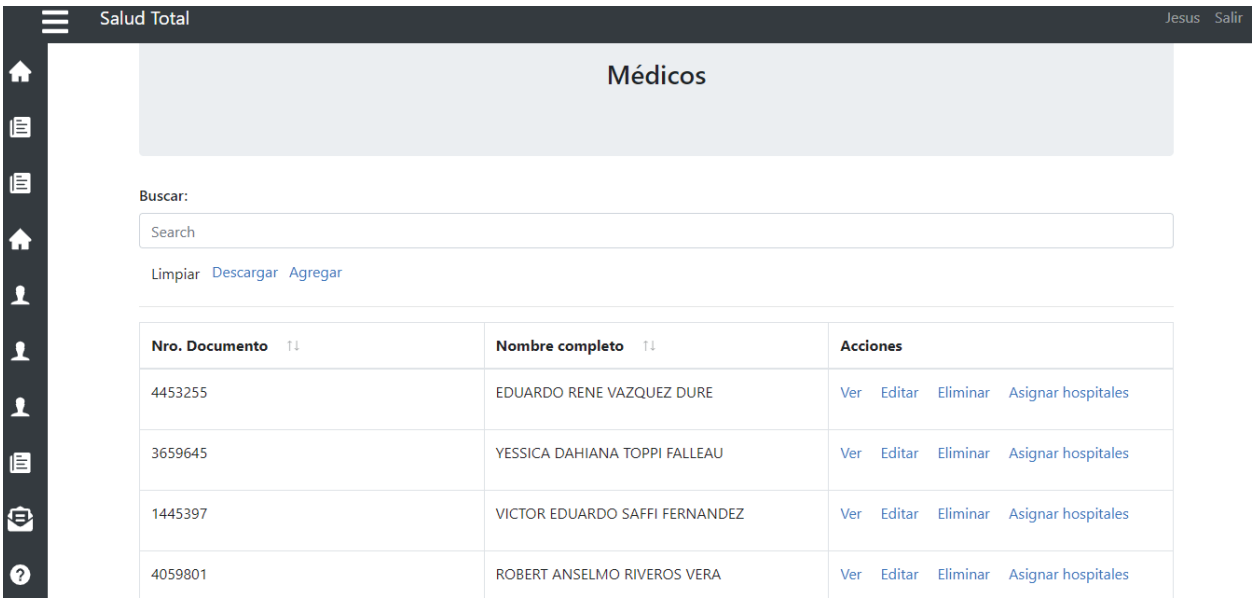
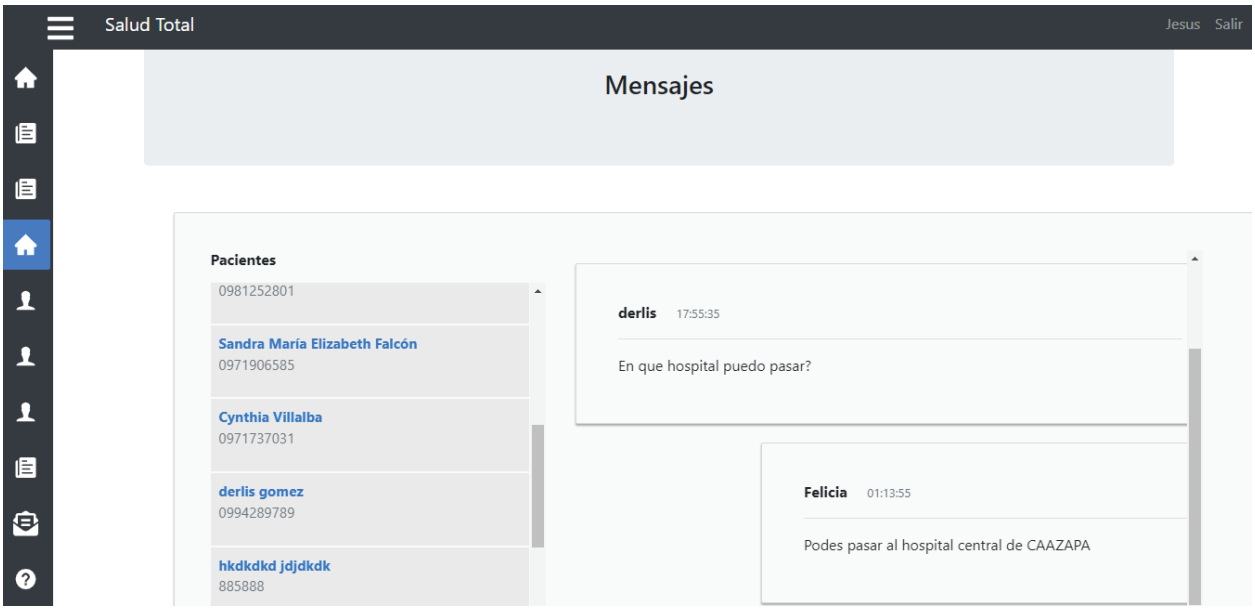


Fig. 4. Web application screenshots: assignment of patients, care centers, physicians, and messages





Evaluation

In the tests conducted, it was verified by the healthcare professionals that the flow between the mobile application and the physician web application is sufficient as a means of com-munication and obtaining clinical data of patients, as well as for monitoring the gravity status of the patients they contact.

In the usability evaluation, according to the SUS scale, the system obtained a score of 68, which denotes a C grade of usability, i.e., it is a usable system on an acceptable level.

DISCUSSION

The application achieves restricted access to patient data by the corresponding professionals. However, in the absence of a policy of correct use of information, there is a risk of publication of sensitive health and patient location data, as well as data leakage by the official health agency.

CONCLUSION

Pilot user acceptance tests indicate that the implementation of a mobile application that feeds a geo-referenced database were able to identify the location of patients and continue with their primary care. In this way, it will be possible to anticipate the care needs of the community, the number of people in the vicinity of a family health unit in order to better allocate the human re-sources necessary for care and visualize the needs of a certain community through the forms and/or messages that patients complete.

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Ministry of Public Health and Social Welfare of Paraguay and the Polytechnic Faculty- UNA. All participants in the use of the software accepted the informed consent document.

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ORIGINAL ARTICLE
FUZZY LOGIC USE IN CLASSIFICATION OF THE SEVERITY OF DIABETIC RETINOPATHY

USO DA LÓGICA FUZZY NA CLASSIFICAÇÃO DA SEVERIDADE DA RETINOPATIA DIABÉTICA

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Key words: Fuzzy logic; Ultrasound imaging; Fundus retinal image; Diabetic retinopathy; Diabetes mellitus.
Descritores: Lógica Fuzzy; Imagem ultrassonográfica; Oftalmoscopia; Retinopatia diabética; Diabetes mellitus.

Abstract

Objective: Employ fuzzy logic to auxiliary in identification and diagnosis the gravity of diabetic retinopathy (DR). **Methods:** A cross-sectional study was performed, being assessed 100 diabetes mellitus patients with DR. The following ultrasound findings were measured employing a semi-quantitative punctuation method: vitreous hemorrhage, posterior vitreous detachment, epiretinal fibrosis, retinal detachment. The fundus photography (FP) aspects evaluated for diagnosis of DR were at least four or more micro aneurysms with or without hard or soft exudates, and neovascularization, graded using the Early Treatment of Diabetic Retinopathy Scale. With the combination between ultrasound punctuation and FP aspects through fuzzy logic, a classification for DR has been built. **Results:** Micro aneurysms were the findings which presented the better interaction with the DR severity on ultrasound, while the hard exudates showed the minors estimation errors when compared to soft exudates. A classification for DR was suggested based on the 95% confidence interval of number of micro aneurysms: mild group (< 24.6); moderately mild (24.6 - 48.0); moderate (48.1 - 64.5); moderately severe (64.6 - 77.0); severe (77.1 - 92.7); and very severe (> 92.7). Conclusion: By the fuzzy logic, a DR classification was constructed supported on number of micro aneurysms measurement with a simple practical application. **Endocrinol diabetes clin exp 2021 / 2241 - 2246.**

Resumo

Objetivo: Empregar lógica Fuzzy para auxiliar na identificação e diagnóstico da gravidade da retinopatia diabética (RD). Métodos: Foi realizado um estudo transversal, sendo avaliados 100 pacientes diabéticos com RD. Os seguintes resultados de ultrassonografia foram medidos empregando um método de pontuação semi-quantitativa: hemorragia vítrea, descolamento de vítreo posterior, fibrose epirretiniana, descolamento de retina. Os aspectos do fundo de olho (FO) avaliados para diagnóstico de RD foram pelo menos quatro ou mais microaneurismas com ou sem exsudados duros ou moles, e neovascularização, graduados pelo uso da Escala de Tratamento Precoce de Retinopatia Diabética. Com a combinação entre a pontuação por ultrassonografia e os aspectos do FO através da lógica Fuzzy, foi construída uma classificação para RD. **Resultados:** Microaneurismas foram os achados que apresentaram a melhor interação com a gravidade do RD com a ultrassonografia, enquanto os exsudados duros mostraram erros de estimativa menores quando comparados aos exsudados moles. Uma classificação para RD foi sugerida com base no intervalo de confiança de 95% do número de microaneurismas: grupo leve (< 24,6); moderadamente leve (24,6 - 48,0); moderado (48,1 - 64,5); moderadamente severo (64,6 - 77,0); severo (77,1 - 92,7); e muito severo (> 92,7). **Conclusão:** Através da lógica Fuzzy, foi construída uma classificação para a RD com base na mensuração do número de microaneurismas com uma aplicação prática simples. **Endocrinol diabetes clin exp 2021 / 2241 - 2246.**

INTRODUCTION

Diabetes mellitus (DM) is a public health problem, and diabetic retinopathy (DR) is a complication of DM and its detection is fundamental for prevention of blindness. The DR is neurovascular disease of retina which generates visual impairment and blindness in working-age diabetic patients. Study has evaluated that circa 93 million individuals must have DR, and approximately 28 million individuals may have DR in advanced stages (1). The pathophysiology of DR is heterogeneous and includes inflammation and oxidative stress, having as a final result micro vascular and neuronal disorder (2). The micro vascular complications of DR include micro aneurysms, vascular occlusion, retinal neovascularization, retinal edema, vitreous hemorrhage, fibro vascular proliferation leading to retinal detachment, which is clinically represented by two stages, the early stage that called non-proliferative DR, and a more advanced stage denominated of proliferative DR (3).

Although recent advances of ophthalmologic examination techniques, analyze of retinal changes DR secondary frequently features a diagnostic defiance. Usually, the diagnostic of DR mainly relies on fundus photography (FP) obtained by mydriatic or nonmydriatic fundus cameras that will be diagnosed by ophthalmy specialist. Ocular sonography is useful in detecting of DR, because the eye can be rated dynamically during ocular movements, principally in eyes with opaque media, besides being superior to computed tomography and magnetic resonance imaging in diagnosis of DR (4).

Fuzzy logic performs a significant function in medicine, be-

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cause the difficulties of medicine exercise become usual quantitative approaches of analysis inadequate. Fuzzy logic goes back to 1965, and it deals with common sense reasoning, in other words, with estimated logic. Fuzzy logic ('almost certain'/'very unlikely'), in contrast to classical propositional logic (true/false), is a multi-valued logic acquired starting fuzzy group theory agreement with the human argument (5). Fuzzy logic is mathematical tool to deal with the inaccuracy and doubt human being, and has been applied in countless accost to model diagnosis. Thus, to analyze and diagnose early the diabetic retinopathy is one of the examples of advantage of using fuzzy logic.

The DR diagnosis is one of the essential steps of clinical conduct execution that in general is followed by a phase of insecurity and doubts. Hence, the aim of this study was outline fuzzy logic to auxiliary in identify and diagnosis gravity of DR.

MATERIAL AND METHODS

In this study we propose Fuzzy logic use for severity classification of DR through a cross-sectional study, being assessed 100 FP and ultrasonography of DM patients with DR.

The ocular ultrasonography was used to show secondary complications signals and define the Proliferative Diabetic Retinopathy stage, and correlate with FP.

The manuscript was ethical approval of Ethics Committee of the Hospital de Base Luis Eduardo Magalhães - Itabuna - Bahia - Brazil.

Ultrasound evaluation

Ultrasonography evaluation was fulfilled by a single physician with gray-scale sonographic equipment (Toshiba Aplio XG - Tokio, Japan) using a 10-12MHz linear multifrequency probe. The exams were interpreted by B-mode by transverse and longitudinal section of the four major eye quadrants, and following ultrasound findings were measured employing a semi-quantitative punctuation method: vitreous hemorrhage, posterior vitreous detachment, epiretinal fibrosis, and retinal detachment. The following values were given to the score of ultrasound ocular abnormality: 0= no retinal abnormality; 1= vitreous hemorrhage; 2= posterior vitreous detachment; 3= epiretinal fibrosis; 4= retinal detachment.

Fundus photography evaluation

The gold standard photography method for diagnosis of DR is stereoscopic color FP in 7 standard fields (30°) as established by Early Treatment Diabetic Retinopathy Study (ETDRS) group(6). The ETDRS severity level in the worse eye: minimal nonproliferative retinopathy, mild nonproliferative retinopathy, moderate nonproliferative retinopathy, severe nonproliferative retinopathy, and proliferative retinopathy. The FP evaluation was fulfilled by a single ophthalmy specialist with Canon CX-1 Digital Retinal Camera equipment. The FP aspects evaluated for diagnosis of DR were at least four or more micro aneurysms with or without hard or soft exudates, and neovascularization. The following values were given to the score of FP abnormality: 0= no retinal abnormality; 1= four or more micro aneurysms; 2= four or more micro aneurysms without hard or soft exudates; 3= four or more micro aneurysms with hard or soft exudates; 4= neovascularization.

Study design and data analysis

With the combination between ultrasound punctuation and FP aspects through fuzzy logic, a classification for DR has been built.

The level of statistical significance was set at $p < 0.05$. Prism version 6.0 software free was used for data analysis (GraphPad Software Inc., La Jolla, CA, USA).

A DR classification was performed by the sharing among ultrasonography scores and FP scores through fuzzy logic. The fuzzy edge detection technique was grounded in a fuzzy inference system **(Figure 1)**. The secondary alterations to DR were identified using the fuzzy k means, and a pre-processing was performed by histogram equalization.

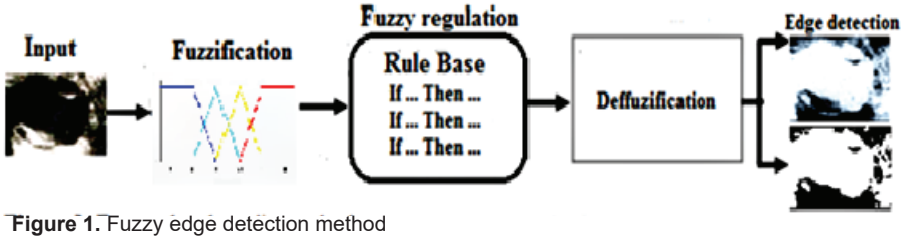

Figure 1. Fuzzy edge detection method

The steps utilized in pre-processing phases consisted of RGB to Gray Scale, noise elimination, contrast upgrading, and image processing. The ultrasonography and FP input images are transformed in gray scale image, using the equation IC = 0.333MR + 0.5MG + 0.1666MB, where IY indicates magnitude of tantamount gray quality image of RGB. The noise elimination was utilized the Hard Thresholding (HT) and Soft

$$\text{Thresholding (ST): } HT(x) = \theta\_\_\_\_ \begin{cases} 0 \text{ if } |Y| < \lambda t \text{ and ST= } \theta(y,\lambda t) = \text{sign}=(Y)(y,\lambda t) \\ Y \text{ otherwise} \end{cases}$$
$$H(t)$$

The λ_t represents universal Threshold that was evaluated using the equation:

$\lambda_t = \sigma \sqrt{2 \log N}$ wherein σ indicates noise difference and N the dimension of image.

The contrast enhancement was calculated with the equations:

$$P_N = 255 \left[\frac{[\phi_W(p) - \phi_W(Min)]}{[\phi_W(Max) - \phi_W(Min)]} \right] \text{ and } \phi_W = 1 \left[\exp \left(\frac{\mu_w - p}{\phi_W} \right) \right.$$

Wherein min and max matches to minimum and maximum value of full image, μw is equivalent to local window mean, and ϕ W is equals local window standard deviation.

The image morphological processing implied equations for dilatation and erosion: Dilation: $I_i \oplus A_1 = \{(p+q)/p \in I_i,\ q \in A_1\}$ and Erosion: $I_i \Theta A_1 = \{p \in \approx^2/(p+q) \in I_i\}$. In dilation and erosion image Ii is symbolized by the structural element Ai.

The Fuzzy-Calc (http://fuzzy-calc.appspot.com), an app to calculate fuzzy indicators was used with the objective to obtain a synthetic performance value for the study variables. The **figure 2** demonstrates the simulation model of evaluation indexes using Fuzzy-Calc:

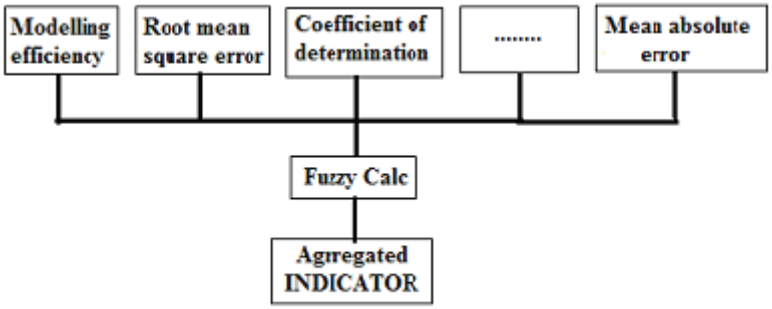

Figure 2. Fuzzy-Calc simulationa model

The segmentation of according input variables in fuzzy logic system has been divided in two pattern: 1) the ultrasonography for determine to score of ultrasound ocular abnormalities (no retinal abnormality, vitreous hemorrhage, posterior vitreous detachment, epiretinal fibrosis, and retinal detachment), and, 2) the FP for determine to score of FP abnormalities (no retinal abnormality, four or more micro aneurysms, four or more micro aneurysms without hard or soft exudates, four or more micro aneurysms with hard or soft exudates, and neovascularization).

The classification was suggested upon the estimated mean having a 95% confidence interval, based on the standard error of the mean from the Student's t test. Three decisions were considered to define the classification: the presence of at least three classes (mild, moderate and severe), necessity of 95% confidence intervals superposition, and minimization of estimation errors (7).

The value T is assigned for each retinal structure was calculated with follow equations: $\mu = 1/9\sum_{i-1}^{n} xi$ and $\sigma = \sqrt{1/n\sum_{i-1}^{n}(xi-\mu)^2}$, on what, N correspond total number of pixels, xi indicate pixel values of full image.

RESULTS

We calculated the ratio of detected micro aneurysms in FP to the total ultrasound image alterations. We categorize these images into mild group RD, moderately mild RD, moderate RD, moderately severe RD, severe RD, and very severe RD according to the percentage of the area damaged.

The ultrasonography images show the input no retinal abnormality, vitreous hemorrhage, posterior vitreous detachment, epiretinal fibrosis, and retinal detachment (**Figure 3**).

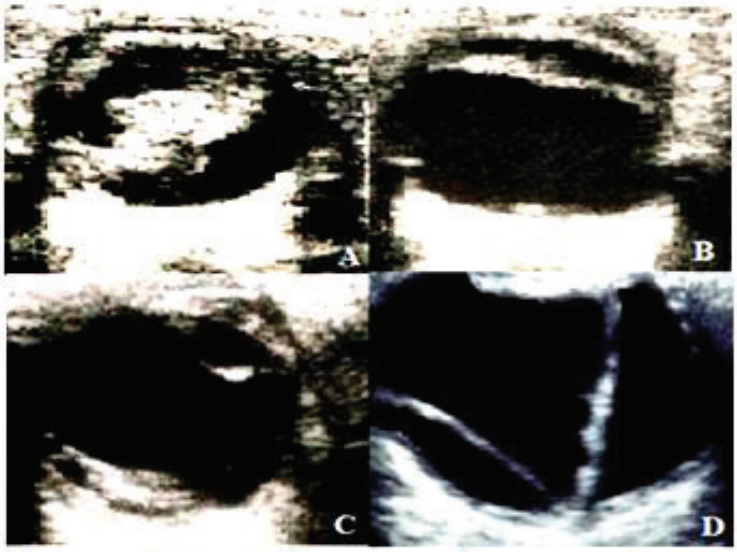

Figure 3. A: vitreous hemorrhage; **B:** posterior vitreous detachment; **D:** epiretinal fibrosis; **D:** retinal detachment
Source: author's collection

The FP images show the input no retinal abnormality, four or more micro aneurysms, four or more micro aneurysms without hard or soft exudates, four or more micro aneurysms with hard or soft exudates, and neovascularization (**Figure 4**).

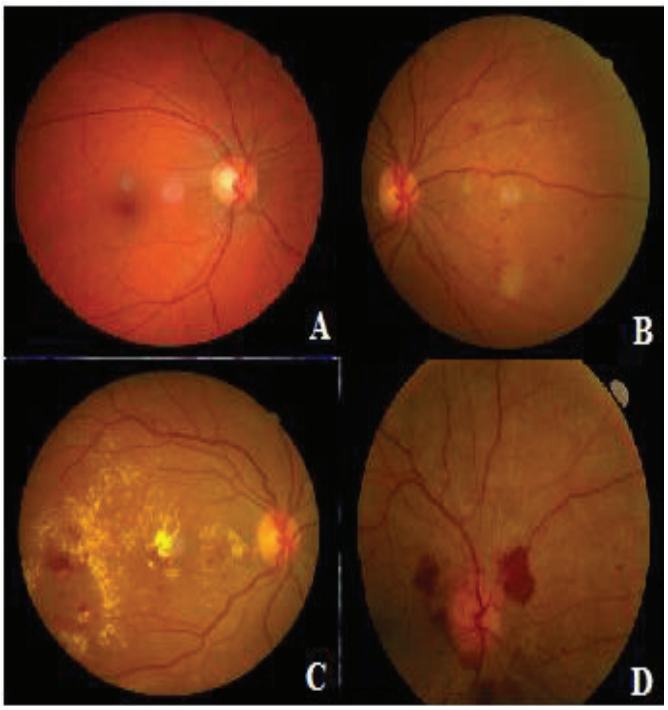

Figure 4. A: microsaneurysms; **B:** soft exudates; **C:** hard exudates; **D:** neovascularization
Source: author's collection.

Using MATLAB software (https://la.mathworks.com/products/matlab.html), automatic detection of secondary changes to DR is quickly performed. The images were pre-processed after a contrast improvement step that consisted of resizes the images to a uniform size of 500 × 500 pixels, morphological operators and then binarization. A total of 100 fuzzy rules extracted as a rule-base based on ophthalmologist and physician expert's opinion. The FP images after pre-processing show the output no retinal abnormality, four or more micro aneurysms without hard or soft exudates, four or more micro aneurysms with hard or soft exudates, and neovascularization (**Figure 5**).

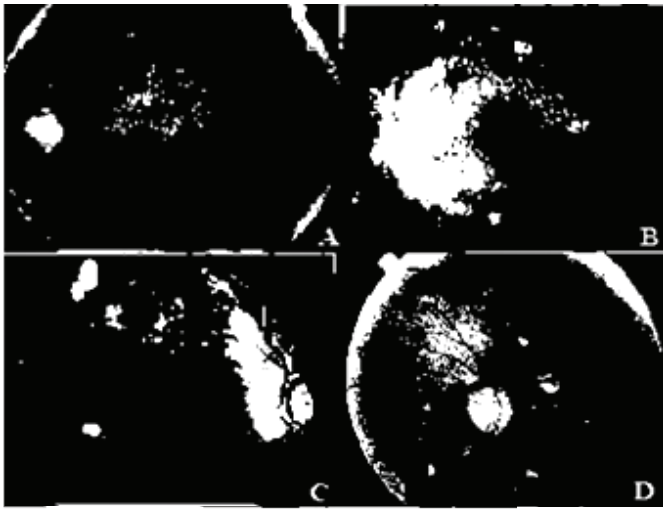

Figure 5. A: microaneurysms; **B:** soft exudates; **C:** hard exudates; **D:** neovascularization.
Source: Research result

The **table 1** shows the classification for DR suggested based on the 95% confidence interval of number of micro aneurysms.

Classification DR suggested	95% confidence interval
Mild group	< 24.6
Moderately mild	24.6 - 48.0
Moderate	48.1 - 64.5
Moderately severe	64.6 - 77.0
Severe	77.1 - 92.7
Very severe	> 92.7

Table 1. Classification DR suggested based number of microaneurysms.

We present in **table 2** the results for the detection DR using fuzzy logic for six different ultrasound images. Therefore, the proposed DR severity classification considers the various 95% CI for the previously described classes, grounded on relationship with the found on ultrasound, as demonstrated in **table 2**. The results showed that is possible to develop fuzzy systems that can DR severity classification. Moreover, the results demonstrate that the fuzzy logic too can diagnose the various stages of DR.

Original image						
	mild	moderately mild	moderate	moderately severe	severe	very severe
Classification DR using fuzzy logic	< 24.6%	24.6 -48.0%	48.1 -64.5%	64.6 – 77.0%	77.1 – 92.7%	> 92.7%

Table 2. Shows the results for the detection of DR using fuzzy logic for six different ultrasound images

DISCUSSION

In this paper, we used the fuzzy logic with the severity classification proposal of DR, and results found demonstrated that the technique used can classify DR with elevated precision. Several scientists have introduced different fuzzy logic approaches for DR classification to raise confidence and decrease wrong classification secondary to human error, and language strategies has been implemented in decision-making with fuzzy interface (8).

Ophthalmic ultrasonography has been used associated to associate with eye examination to complete the correct diagnosis in diabetic's patients. Current evidence demonstrates the excellent performance of ocular ultrasound in evaluation of DR. Use of ophthalmic ultrasonography in patients with DR can provide essential information in detection and evaluation of DR complications (9).

FP is one of the most practiced imaging procedures, owning a sensitivity and specificity quite superior to direct and indirect ophthalmoscopy. The FP is gold standard method for diagnosis of DR established by ETDRS group (10). In 2016 Google company elaborated an algorithm to diagnose DR in retinal FP, and a study to evaluate this algorithm demonstrated a high specificity and sensitivity, with an area under the ROC curve of 0.99 (11).

The automation in evaluation of DR has been simplified by use of combining FP images and ocular ultrasonography using high resolution equipment, associated the processing digital and analysis of images through modern computational techniques. Thus, the diagnosis by computerized systems of the DR has been related by several authors (12). In the present work we use morphological evaluations with FP and ultrasonography for fractionation and fuzzy logic for the identification process of features of DR. The FP aspects evaluated for diagnosis of DR were at least four or more micro aneurysms with or without hard or soft exudates, and neovascularization, while following ultrasound findings were evaluated employing a semi-quantitative punctuation method, measuring the degree of vitreous hemorrhage, posterior vitreous detachment, epiretinal fibrosis, and retinal detachment.

Fuzzy logic was first described in 1965, it is a tool that produces a mechanism for reply to imprecise information based in qualitative language and transcribed to a numerical language (Boolean logic). Thus, fuzzy logic has been used indeed in medicine to diagnose the diseases based clinical and imaging data (13,14). The fuzzy logic has been used in clinical research, especially in diabetes and your complications as DR, diabetic neuropathy, and diabetic nephropathy (15,16). As already described above, we used the fuzzy logic with the severity classify objective of DR.

The fuzzy logic suggested in this study was based in four FP variables and four ultrasonography variables that went easy to do in routine eye exams. The analysis exposed here demonstrated that fuzzy logic is appropriate to classify the severity of DR likewise that retinal medical specialists.

The DR is a progressive microvascular complication of diabetes producing irreversible retinal deterioration. Thus, precocious diagnosis and preventive intervention are the best tools that may prevent or retard blindness, and consequently improve the quality of life of these individuals (17). Taking into consideration the DR characteristics, we apply fuzzy logic to rank characteristics sonographic and FP related to DR. Posteriorly, a transformed fuzzy neural network was produced to improve the classification precision, and lastly we extract association rules between the chosen characteristics of DR to characterize their severity degree.

In the last years, several fuzzy system free and open source software were produced, through which simulations fuzzy logic can be performed quickly. In this work the evaluations were performed with Fuzzy-Calc, and the MATLAB package, the first an app was used calculate fuzzy indicators with the objective to obtain a synthetic performance value for the study variables, and MATLAB fuzzy logic toolbox was used for comparative study between FP and ultrasonography. The MATLAB software offer several tools and module used in this work was the Image Processing Toolbox (18).

The medical diagnostic depend upon practice and expertise of medical practitioner. Fuzzy logic is a technique to establish whit accuracy what is imprecise in medicine, and has been playing a considerable role in the diagnosis and treatment of diseases (19). Several researches employing models identification and image manipulation techniques to diagnose DR have been developed (20). Our study as compared to the other studies was more embracing, because as it involved the use of FP and ultrasonography in different stages of the DR using fuzzy logic, and classifying the DR with high precision.

CONCLUSION

Thus, by the fuzzy logic, a DR classification was constructed supported on number of micro aneurysms measurement with a simple practical application. Thus, the fuzzy logic technique use has been applied in many knowledge areas, and in medicine it has been used for diagnosis, diseases classification, and optimization of medical treatments.

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ORIGINAL ARTICLE
GESTATIONAL DIABETES: AN EARLY WINDOW OF FUTURE CARDIO-METABOLIC RISK

DIABETES GESTACIONAL: UNA VENTANA TEMPRANA DEL RIESGO CARDIO-METABÓLICO FUTURO

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JULIO C. GONZÁLEZ[1]

Key words: Diabetes Gestacional, Riesgo cardio-metabólico, Seguimiento post-parto
Descritores: Gestational Diabetes, Cardio-Metabolic Risk, Post-partum follow-up

Abstract

Objective: To determine cardio-metabolic risk factors in women with gestational diabetes (GD) during pregnancy and recent post-partum **Methods:** 73 women with GD, between two and ten months postpartum, underwent oral tolerance test with a load of 75 grams of glucose (PTOG-75 g), determination of basal insulin and 2 hours post-loading, triglycerides, cholesterol, LDL cholesterol (LDL-c) and HDL cholesterol (HDL-c). The insulin resistance index was calculated using the HOMA-IR model **Results:** At the diagnosis of GD, the mean age was 31.32 years ± 6.25, baseline glycemia 102.61 mg/dL ± 24.35 and 2 h post-load glycemia was 166.0 mg/dL ± 26.03. 46.57% received insulin and 27.39% had arterial hypertension (AHT). In the post-partum period, the mean Body Mass Index (BMI) was 30.42 ± 6.51; waist circumference, 92.84 cm ± 13.74; retained weight, 5.40 kg ± 6.41; systolic blood pressure, 112.29 mm Hg ± 15.45; diastolic blood pressure, 75.30 mm Hg ± 12.30; basal glycemia 82.79 mg/dL ± 16.33; 2 h post-loading glycemia, 109.75 mg/dL ± 42.01; basal insulin, 15.04 U ± 13.49; 2 hours post-loading insulin, 46.74 U ± 59.57; HOMA-IR, 3.57 ± 4.01; triglycerides, 123.03 mg/dL ± 78.91; cholesterol, 177.62 mg/dL ± 35.67; LDL-c, 112.32 mg/dL ± 29.05; HDL-c, 44.85 mg/dL ± 10.07. 6.94% had diabetes; 15.27%, prediabetes; 49.31%, obesity; 53.42%, abdominal obesity; 28.78%, AHT; 79.44%, dyslipidemias and 42.46%, high insulin resistance index. **Conclusion:** Women with GD had multiple cardio-metabolic risk factors during pregnancy and recent postpartum. **Endocrinol diabetes clin exp 2021 / 2247 - 2254.**

Resumo

Objetivo: Determinar factores de riesgo cardio-metabólico en mujeres con Diabetes Gestacional (DG) durante el embarazo y el post-parto reciente **Métodos:** A 73 mujeres con DG se les practicó entre dos y diez meses post-parto, prueba de tolerancia oral con carga de 75 gramos de glucosa (PTOG-75 g), determinación de insulina basal y 2 horas post-carga, triglicéridos, colesterol, LDL colesterol (LDL-c) y HDL colesterol (HDL-c). Se calculó el índice de resistencia insulínica mediante el modelo **Resultados:** Al diagnóstico de DG, la media de edad fue 31,32 años ± 6,25, glucemia basal 102,61 mg/dL ± 24,35, glucemia 2 h post-carga, 166,0 mg/dL ± 26,03. 46,57% recibieron insulina y 27,39% presentaron hipertensión arterial (HTA). En el post-parto, la media del Índice de masa corporal (IMC) fue 30,42 ± 6.51, perímetro de cintura, 92,84 cm ± 13,74, peso retenido 5,40 kg ± 6,41, presión arterial sistólica, 112,29 mm Hg ± 15,45, presión arterial diastólica, 75,30 mm Hg ± 12,30, glucemia basal 82,79 mg/dL ± 16,33, glucemia 2 h post-carga, 109,75 mg/dL ± 42,01, insulina basal 15,04 U ± 13,49, insulina 2 horas post- carga 46,74 U ± 59,57, HOMA-IR, 3,57 ± 4,01, triglicéridos 123,03 mg/dL ± 78,91, colesterol, 177,62 mg/dL ± 35,67, LDL-c, 112,32 mg/dL ± 29,05, HDL-c, 44,85 mg/dL ± 10,07. 6,94% presentaban diabetes, 15,27%, prediabetes, 49,31%, obesidad, 53,42%, obesidad abdominal, 28,78%, HTA, 79,44 %, dislipidemias y 42,46%, índice de resistencia insulínica elevado. **Conclusión:** Las mujeres con DG presentaban múltiples factores de riesgo cardio-metabólico durante el embarazo y el post-parto reciente. **Endocrinol diabetes clin exp 2021 / 2247 - 2254.**

INTRODUCTION

Diabetes Gestacional (DG) es una de las complicaciones del embarazo identificada como predictora de riesgo cardio--metabólico en mujeres en edad reproductiva. La detección oportuna y el manejo adecuado de ese riesgo tienen el potencial de prevenir la aparición de enfermedades cardiovasculares (ECV), con la consiguiente disminución de sus repercusiones y de los costos de atención de salud (1), ya que la diabetes tipo 2, la enfermedad isquémica coronaria y los accidentes vasculares cerebrales aparecen desde hace varios años, dentro de las primeras causas de morbilidad y mortalidad femenina en el mundo, representando una alta carga para los servicios de atención de salud, particularmente en los países de bajos y medianos ingresos (2).

Desde la etapa pre-concepcional ya se describen factores asociados al desarrollo futuro de diabetes tipo 2 y ECV, como la pertenencia a etnias diferentes a la blanca, la edad avanzada, los antecedentes familiares de diabetes, el sobrepeso la obesidad y la multiparidad (3)(4) . Durante la gestación, se ha encontrado que los niveles elevados de glucosa plasmática en ayunas, la terapia con insulina y los síndromes hipertensivos aumentan el riesgo a largo plazo de diabetes (3) (5) (6) y con menor frecuencia, los valores de glucosa 2 horas post-carga en la prueba de tolerancia oral al momento del diagnóstico de DG (6) (7). De tal manera, que cualquier grado de anormalidad de la homeostasis de la glucosa en el embarazo predice de manera independiente, un aumento del riesgo de disglucemia en el post-parto (8).

Las mujeres con DG previa, además del alto riesgo de desarrollar diabetes e independiente del mismo, tienen doble riesgo cardiovascular comparadas con las mujeres sin este antecedente (9). Presentan un incremento de factores de riesgo convencionales, como son: cifras elevadas del IMC, el perímetro de cintura, la presión arterial sistólica y diastólica, los valores de glucemia, triglicéridos, colesterol, LDL-c, insulina, Índice HOMA-IR y el descenso significativo de HDL-c, algunos de los cuales pueden estar presentes antes del primer año post-parto (10) (11). Se han propuesto otros indicadores de riesgo resultantes de pruebas usadas en la práctica clínica, como el aumento de ácido úrico, fibrinógeno y alteraciones bioquímicas del funcionamiento hepático (12) (13) y se continúa investigando en mujeres con historia de DG, marcadores de

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disfunción vascular endotelial y de inflamación sub-clínica, que puedan identificar tempranamente el riesgo cardio-metabólico y por tanto, a quienes se debe priorizar en las estrategias de prevención (11) (14). Por otra parte, se ha observado que la lactancia materna (15) y los estilos de vida con patrones nutricionales saludables (16) y actividad física regular (17) disminuyen ese riesgo, mientras que factores psico-sociales como el estrés (18), la depresión (19) (20) y las alteraciones del sueño (21) se han vinculado a la DG.

Al ser considerada actualmente la prevención de la diabetes y las ECV una prioridad de salud pública universal y conociendo que la identificación de factores de riesgo constituye la base fundamental para conducir dicha prevención, se realizó la primera etapa de esta investigación, con el fin de determinar los factores de riesgo cardio-metabólico presentes en el embarazo y el postparto reciente en mujeres con DG.

MATERIAL Y MÉTODOS

La investigación es descriptiva de corte longitudinal.

Población y muestra

Se inició el seguimiento de 123 embarazadas con diagnóstico de DG referidas a la Unidad de Diabetes y Salud Reproductiva de un hospital público de III Nivel durante los años 2013, 2014 y 2015. 98 asistieron posteriormente a la pesquisa inicial post-parto de diabetes y otros factores de riesgo cardio-metabólico. Se excluyeron 25 pacientes que no tenían registrados de forma completa, los datos en el formulario diseñado para el seguimiento, quedando 73 pacientes, que constituyen la muestra del estudio, en este primer punto de corte del seguimiento.

Procedimientos

El diagnóstico de DG se realizó a partir de la semana 24, mediante dos glucemias en ayunas o una prueba de tolerancia oral a la glucosa (PTOG) con una carga de 75 gramos de glucosa, siguiendo los criterios de la Asociación Latinoamericana de Diabetes (ALAD) 2008 (22), registrándose datos demográficos, clínicos y antropométricos: edad, etnia, paridad, antecedentes familiares de diabetes en primero y segundo grado, antecedentes de ovarios poliquísticos, peso pre-embarazo y talla, las cifras de presión arterial, la administración de insulina como medida terapéutica y las cifras de HbA1c al final del embarazo. Se definió hipertensión arterial en el embarazo como las cifras de presión arterial > 140/90 mmHg en dos mediciones, de acuerdo al criterio del Grupo de Trabajo del Programa Nacional de Educación sobre la Presión Arterial Alta (23).

Entre los dos y los doce meses post-parto, se realizó la pesquisa de diabetes mediante dos glucemias en ayunas o una PTOG con una carga de 75 gramos de glucosa, de acuerdo a los criterios de la Asociación Americana de Diabetes (ADA, por sus siglas en inglés) (24). Además, se evaluaron parámetros clínicos y antropométricos: peso, talla, perímetro de cintura, presión arterial y presencia de acantosis nigricans. Se realizaron las siguientes determinaciones de laboratorio: insulina basal y 2 horas post-carga de glucosa, triglicéridos, colesterol, LDL colesterol (LDL-c), HDL colesterol (HDL-c), ácido úrico, fibrinógeno, alanino-aminotransferasa (ALT) y aspartato-aminotransferasa (AST). Se tomaron datos de la historia clínica sobre los hábitos nutricionales, tabáquico y alcohólico, la actividad física, las características y duración del sueño y la percepción de estrés psico-social.

Se definió multiparidad como más de dos nacimientos previos. Se calculó el Índice de masa corporal (IMC) pre-embarazo y en el post-parto, dividiendo el peso (kg)/talla (m2). Se definió sobrepeso como IMC entre 25 y 29,99, y obesidad ≥ 30. Se definió obesidad abdominal tomando como punto de corte 90 cm, establecido para la población femenina latinoamericana (25). Se calculó el peso retenido, restando el peso (kg) postparto - el peso (Kg) pre-embarazo. Se definió hipertensión arterial de acuerdo al reporte del Séptimo Comité Nacional de Prevención, Detección, Evaluación y Tratamiento de Hipertensión Arterial (26). Se consideró hiperinsulinemia cuando los niveles eran > 12 mU/l en ayunas (27) (28). Se determinó el índice de resistencia insulínica (RI) mediante el modelo de evaluación de la homeostasis (HOMA-IR), considerándose el punto de corte cuando el resultado fuese > 2,5 (29). Se definió dislipidemia como un valor de colesterol ≥ 200 mg/dl, de LDL-c ≥ 130 mg/dl, de triglicéridos ≥ 150 mg/dl y de HDL-c < 50 mg/dl (30). Se calculó el Índice Triglicéridos/HDL-c dividiendo los valores de ambas variables expresados en mg/dL y se estableció como punto de corte ≥ 3,5 (31). Se establecieron valores elevados de ácido úrico > 5 mg/dl, de fibrinógeno, > 400 mg/dl, de ALT, > 31 U/l y de AST, > 32 U/l. Se definió sedentarismo como < 150 minutos de actividad física moderada/semana.

El proyecto de investigación fue aprobada por el Comité de Ética del Hospital

Métodos de los análisis

Las determinaciones séricas de glucemia, colesterol total y triglicéridos se efectuaron por métodos enzimáticos (Linear Chemicals, España). La del colesterol asociado a las lipoproteínas de alta densidad (c-HDL) y a las lipoproteínas de baja densidad (c-LDL) se realizó por precipitación y posterior determinación enzimática (Linear Chemicals, España). La determinación de insulina se efectuó usando el método Elisa inmunoensayo de fase sólida de 2 puntos (Mercodia, Suecia). La determinación de ácido úrico se realizó utilizando el método enzimático colorimétrico (Wiener Lab.Argentina), la de fibrinógeno, el método inmunoturbidométrico (Wiener Lab. Argentina) y las de (ALT) y (AST), métodos cinéticos UV (Wiener Lab. Argentina).

Análisis estadístico

Los resultados obtenidos se expresaron como porcentajes y medias ± desviación estándar. Se utilizó el programa estadístico Statisix versión 8.

RESULTADOS

Al momento del diagnóstico de DG, el rango de edad de las mujeres objeto del estudio, oscilaba entre 16 y 44 años, con 58,90% ≥ 30 años. Todas habían completado la educación básica y15,06% tenía una carrera universitaria. 16,46% eran nulíparas, 58,89% tenían uno o dos nacimientos previos y 24,65% tenían más de dos nacimientos previos. En la **Tabla 1** se muestran características seleccionadas de las embarazadas. La pesquisa cardio-metabólica post-parto se realizó a los 4,65 meses ± 3,20. 64,38% ya tenían edad ≥ 30 años y la multiparidad subió a 56,16%. Los resultados de parámetros clínicos y metabólicos obtenidos en la misma aparecen en la **Tabla 2**. La **Tabla 3** expresa resultados referidos por las pacientes sobre lactancia materna, hábitos, estrés y características del sueño. La frecuencia de factores convencionales y menos convencionales de riesgo cardio-metabólico en el post-parto reciente se observa en la **Tabla 4**. Y el **grafico 1** muestra la distribución de diez factores de riesgo cardio-metabólico seleccionados en las mujeres con DG en el post-parto reciente.

Tabla 1: Características seleccionadas de embarazadas con diagnóstico de DG

Edad (años)	31,32 ± 6,25
Etnia mestiza	100,00
Nivel educativo ≥ secundaria completa	65,76
Paridad (n)	1,84 ± 1,42
IMC pre-embarazo (Kg/m^2)	28,21 ± 5,13
Antecedentes familiares de diabetes	65,76
Antecedentes de ovario poliquístico	18,05
Glucemia basal PTOG (mg/dL)	102,61 ± 24,35
Glucemia 2 h post-carga PTOG (mg/dL)	166,0 ± 26,03
Tratamiento con insulina	46,57
Dosis total diaria de insulina (UI)	30,52 ± 18,88
HbA_{1c} final (%)	5,87 ± 0,84
Síndromes hipertensivos	27,39

Datos expresados como media ± desviación estándar o n (%)

Tabla 2: Parámetros clínicos y metabólicos de mujeres con DG en el post-parto reciente

Índice de Masa Corporal (Kg/m^2)	30,42 ± 6,51
Perímetro de cintura (cm)	92,84 ± 13,74
Peso retenido (Kg)	5,40 ± 6,41
Presión arterial sistólica (mm Hg)	112,29 ± 15,45
Presión arterial diastólica (mm Hg)	75,30 ± 12,30
Acantosis nigricans (n)	13,69
Glucemia basal PTOG (mg/dL)	82,79 ± 16,33
Insulina basal (µU/mL)	15,04 ± 13,49
Glucemia 2 horas post- carga (mg/dL)	109,75 ± 42,01
Insulina 2 horas post- carga (µU/mL)	46,74 ± 59,57
Índice HOMA-IR	3,57 ± 4,01
Triglicéridos (mg/dL)	123,03 ± 78,91
Colesterol total (mg/dL)	177,62 ± 35,67
LDL-c (mg/dL)	112,32 ± 29,05
HDL-c (mg/dL)	44,85 ± 10,07
Índice triglicéridos/HDL-c	2,96 ± 2,03
Ácido úrico (mg/dL)	4,96 ± 3,96
Fibrinógeno (mg/dL)	315,94 ± 116,51
ALT (UI/L)	21,47 ± 10,31
AST (UI/L)	25,18 ±14,26

Datos expresados como media ± desviación estándar o n (%)

Tabla 3: Lactancia materna y hábitos de mujeres con DG en el post-parto reciente

Lactancia materna	92,53
Exclusiva	58,21
Mixta	34,32
Hábitos nutricionales	
Consumo diario de:	
Vegetales y frutas	19,17
Azúcar y CHO pobres en fibra	82,19
Grasas saturadas	43,98
Carnes rojas/procesadas	27,39
Grasas insaturadas	20,54
Agregado de sal en la mesa	83,56
Actividad física	
≥ 50 minutos tres veces/semana	47,76
Hábito tabáquico	
Actual	11,94
Pasado	4,47
Hábito alcohólico	
≥ 2 tragos juntos/semana	52,94
Sueño	
Duración (horas)	6,59 ± 1,27
Ronquidos y otras alteraciones	44,64
Estrés auto-percibido	65,51

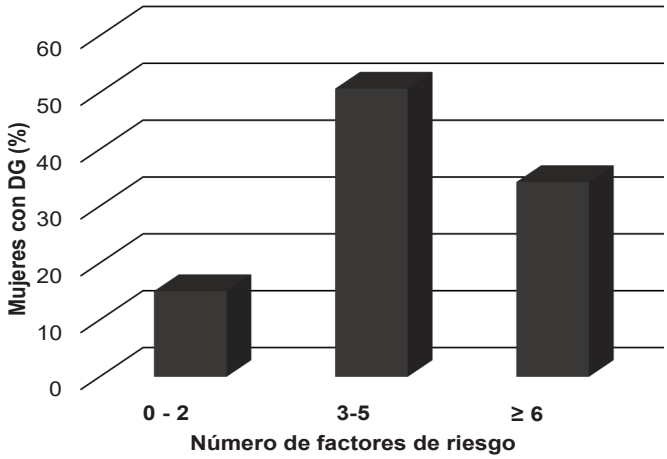
Datos expresados como media ± desviación estándar o n (%)

Tabla 4: Factores de riesgo cardio-metabólico en mujeres con DG en el post-parto reciente

Multiparidad	56,16
Obesidad general	49,31
Sobrepeso	30,13
Obesidad abdominal	53,42
Hipertensión arterial	28,78
Diabetes tipo 2	6,85
Intolerancia a la glucosa	9,72
Glucemia alterada en ayunas	5,55
Insulina basal elevada	38,35
Índice HOMA-IR elevado	42,46
Dislipidemias	79, 44
Triglicéridos elevados	24,65
LDL-c elevado	19,17
HDL-c bajo	65,75
Radio Triglicéridos/HDL-c elevado	24,65
Fibrinógeno elevado	27,39
Ácido úrico elevado	19,17
ALT y AST elevados	23,28
Hábito tabáquico	11,94
Inadecuado consumo de frutas/ vegetales	80,83
Inadecuado consumo de CHO simples	82,19
Inadecuado consumo de grasas saturadas	43,98
Inadecuado consumo de sal	83,56
Sedentarismo	52,24
Alteraciones del sueño	44,64
Manifestaciones auto-percibidas de estrés	65,51

Datos expresados como n (%)

Grafico 1: Frecuencia de factores de riesgo cardio-metabólico en mujeres con DG en el post-parto reciente



*Factores de riesgo cardio- metabólico seleccionados: Obesidad/ sobrepeso, obesidad abdominal, hipertensión arterial, diabetes / prediabetes, dislipidemias, HOMA-IR elevado, hábito tabáquico actual, sedentarismo, bajo consumo de frutas y vegetales, multiparidad.

DISCUSSION

El presente estudio muestra que las mujeres con DG presentaban desde antes de la gestación varios factores de riesgo cardio-metabólico. Dos tercios tenían antecedentes familiares de diabetes y presentaban obesidad o sobre-peso, coincidiendo con los resultados de diferentes publicaciones (3) (4) (32). Durante el embarazo, en la PTOG-75 diagnóstica de DG, los valores de la glucemia en ayunas estaban elevados en cerca de la mitad de las pacientes y la de 2 horas post-carga en más de los dos tercios, siendo consideradas estas alteraciones, unos de los principales predictores de diabetes (3) (5) (6) (7) (33) (34), junto al tratamiento requerido con insulina (35) y a los síndromes hipertensivos, variable que aun cuando se asoció en menor proporción, incrementa el riesgo cardio-metabólico futuro por si misma (36).

En el momento de la pesquisa post-parto inicial, la mayoría de las mujeres eran multíparas, factor asociado con diabetes a largo plazo (3). La incidencia de diabetes de 6,85% y de prediabetes de 14,97% fue similar a la de otros estudios (5) e inferior a la encontrada previamente por nuestro grupo (ALAD), donde se usó un criterio diferente para el diagnóstico de DG (37). Los parámetros antropométricos indicaron sobrepeso, obesidad general y abdominal en una proporción bastante alta, lo cual aumenta el riesgo de diabetes tipo 2 (38) (39), Outro factor de riesgo fue el hecho de no haber regresado al peso pre-embarazo, parámetro aun temprano de evaluar por no haber llegado todas a los seis meses post-parto, etapa cuando esta meta debe ser alcanzada, pero de gran importancia por conocerse que el peso retenido se asocia al riesgo cardio-metabólico venidero (40). El marcador de insulino-resistencia HOMA-IR elevado puede jugar un rol relevante en la etiología de la diabetes tipo 2 posterior a la DG, particularmente si se asocia a obesidad, como en los casos donde estaban presentes ambas alteraciones (41). La dislipidemia, uno de los factores de riesgo cardio-metabólico obtenido con mayor frecuencia, se diferenció de los resultados de otros autores, en el predominio de la disminución de HDL-c, más que en la elevación de triglicéridos (42) y el radio triglicéridos/ HDL-c, propuesto como un marcador temprano de disfunción endotelial y riesgo cardiovascular en mujeres con DG previa (43), también se encontró aumentado en menor escala. La presencia de estos factores de riesgo es similar a la obtenida por nosotros en años anteriores, notándose que la edad de aparición de la DG ha descendido (44). Factores de riesgo cardio-metabólico menos convencionales como ácido úrico, fibrinógeno y ALT (45) (46) (47) se encontraron elevados en proporciones no desestimables.

Por otra parte, los hábitos nutricionales reportados por las mujeres estudiadas revelan muy bajo consumo de frutas y vegetales y alta ingesta de azúcares, grasas saturadas y sal, constituyendo lo opuesto a patrones saludables que se asocien con menor riesgo de diabetes (48) y la mayoría reconoció la práctica escasa de actividad física regular, conducta que se ha encontrado asociada a la progresión a diabetes en mujeres con historia de DG (17). En menor magnitud refirieron el hábito de fumar, el cual es un factor de riesgo cardiovascular pero con resultados contradictorios cuanto se ha buscado la asociación con DG (49) (50). Si bien ninguna expresó ingerir más de un trago diario de alcohol o de siete a la semana, patrón que aumenta el riesgo cardio-metabólico (51), es de notar que aun dando lactancia, la mayoría refirió el consumo de bebidas alcohólicas, siendo controversial si esto pudiera tener un efecto de disminución del riesgo. Cerca de la mitad referían alteraciones del sueño que han sido asociadas con riesgo de DG (21) y de síndrome metabólico en mujeres en edades medias (52) y en mayor proporción, manifestaciones de estrés, difíciles de manejar, tal como ha sido descrito desde la gestación (21) y de ansiedad, lo cual se ha encontrado asociado al riesgo cardiovascular y al menor cumplimiento de medidas de estilo saludable en mujeres (53).

Es de resaltar la asociación de diferentes factores de riesgo cardio-metabólico, ya que de diez factores de riesgo seleccionados, más de los tres cuartos de las mujeres presentaban tres o más y de estas, más de un tercio, seis o más factores de riesgo, incrementando la posibilidad futura de diabetes y ECV.

Como contraparte de la presencia de factores de riesgo cardio-metabólico, estaba presente mayoritariamente, la práctica de la lactancia materna, considerada un atenuante de dicho riesgo (54) y un nivel educativo alto, que pudiese favorecer la adherencia a las medidas preventivas a indicar.

La fortaleza principal de este estudio radica en haber explorado un aspecto poco investigado en nuestro medio. El hecho de no disponer de los datos de más de un tercio de las mujeres diagnosticadas de DG en el periodo de estudio, constituye una limitante, por el posible sesgo que pudiera generar en los resultados, hecho frecuente en estudios similares, debido principalmente a las dificultades para lograr la asistencia de todas las mujeres con DG a la pesquisa post-parto. De la misma manera, la información sobre hábitos nutricionales y aspectos psico-sociales por provenir de la historia clínica y no de la aplicación de instrumentos específicos validados, no permite conclusiones definitivas, sin embargo resulta bastante orientadora en la práctica del programa educativo a llevar a cabo como parte del seguimiento a continuar con las mujeres estudiadas.

CONCLUSIÓN

En conclusión, al mirar a través de la ventana que nos permite la DG, se vislumbra un panorama pleno de factores de riesgo cardio-metabólico, algunos clásicos como la obesidad, las dislipidemias, la hipertensión arterial, las disglucemias e indicadores de resistencia a la insulina y otros menos convencionales. En ambos casos, se manifiestan en alta proporción ya en los primeros meses del post-parto, indicando la urgencia de aplicar intervenciones individuales en las mujeres con DG previa y políticas poblacionales en su entorno, con el fin de prevenir las ECV y sus consecuencias.

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ORIGINAL ARTICLE
NEGATIVE ANA SCLERODERMA: A RETROSPECTIVE STUDY IN A BRAZILIAN SAMPLE.

ESCLERODERMA E ANA NEGATIVO: ESTUDO RETROSPECTIVO EM UMA AMOSTRA BRASILEIRA

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Key words: Systemic sclerosis, scleroderma, antinuclear antibody, calcinosis, renal crisis
Descritores: Esclerose sistêmica, Esclerodermia, Anticorpo antinuclear, Calcinose

Abstract

Background: Most scleroderma patients have positive ANA. However, those with absence of this autoantibody appears to have a distinct clinical profile. **Aim:** To compare ANA positive with ANA negative scleroderma in a sample of Brazilian patients. **Methods:** Retrospective study of 211 scleroderma patients seen in the last 15 years in a single tertiary sample. Epidemiological and clinical data were collected. **Result:** About 7.1% of patients were negative for ANA. Those without this antibody were males (p=0.04; OR=3.8;95%CI=1.09-13.3), had more calcinosis (p=0.02; OR=4.4; 95%IC=1.3-14.7), and more renal crisis (p=0.03; OR=11.4 95%IC=1.7-76.2.) than those with the antibody. **Conclusion:** ANA negative patients represent a distinct subset of patients who have male predominance, more calcinosis and more renal crisis than positive ANA systemic sclerosis. **Endocrinol diabetes clin exp 2021 / 2255 - 2257.**

Resumo

Justificativa: A maioria dos pacientes com esclerodermia tem FAN (anticorpo antinuclear) positivo. Entretanto, aqueles nos quais este anticorpo está ausente parecem possuir um perfil clínico distinto. **Objetivo:** Comparar pacientes de esclerodermia com e sem FAN em uma amostra de pacientes brasileiros com esclerodermia. **Métodos:** Estudo retrospectivo de 211 pacientes com esclerodermia acompanhados nos últimos 15 anos em um único hospital terciário. Dados epidemiológicos e clínicos foram coletados. **Resultados:** Cerca de 7,1% dos pacientes eram FAN negativos. Aqueles sem o anticorpo tinham maior proporção de homens (p=0.04; OR=3.8;95%CI=1.09-13.3), tinham mais calcinose (p=0.02; OR=4.4; 95%IC=1.3-14.7), e mais crise renal do que os sem anticorpos (p=0.03; OR=11.4 95%IC=1.7-76.2.). **Conclusão:** Pacientes de esclerodermia com FAN negativo representam um subtipo de pacientes com predominância de homens, com mais calcinose e com mais crise renal do que aqueles FAN positivos. **Endocrinol diabetes clin exp 2021 / 2255 - 2257.**

INTRODUCTION

Scleroderma or systemic sclerosis is a connective tissue disease of autoimmune origin. Autoantibodies are considered the hallmark of this disease. Antinuclear antibody (ANA) is the most common of them being present in the majority of the cases; large series shows a positivity of around 90–95% (1-3). Nevertheless, a small percentage of patients is negative for this autoantibody and seems to have a disease with peculiar phenotype (3).

Scleroderma is a disease that has a clinical and serological spectrum that changes according to patients' ambiental exposition and genetic background (4-6). In this context, studies of local population are needed to guide the clinician in the clinical and prognostic evaluation.

Herein we studied a sample of scleroderma patients comparing those who were ANA negatives with those ANA positives aiming to know the differences in these two groups in a population from South Brazil.

MATERIAL AND METHODS

This is a retrospective study of all scleroderma patients seem in the last 15 years (2005 to 2020) from a single University Hospital. To be included the patients should fill at least 9 points of the 2013 Classification Criteria of ACR (American College of Rheumatology) /EULAR (European League against Rheumatism) for Scleroderma (7,8). This study was approved by local Committee of Ethics in Research from Faculdade Evangélica Mackenzie de Medicina, PR, Brazil.

Epidemiological (age, age at disease onset, tobacco exposure, and ethnic background) and clinical data (scleroderma subset; cardiovascular, respiratory, renal and digestive system; skin and subcutaneous tissue), were obtained through charts review. The presence of organ involvement was considered in a cumulative way and classified according to ACR definition (9). The skin involvement was measured by the modified Rodnan (Rodnan m) (10) index and disease severity was evaluated by the Medsger scale (11).

Patients ANA positive were compared with those ANA negative using Fisher and chi-squared tests for nominal data and Mann Whitney or unpaired t test for numeric data. The adopted significance was 5%.

RESULTS

The sample had 211 patients: 196/211 (92.8%) were positive for ANA and 15/211 (7.1%) were negative. In those with positive ANA titer went from 1/80 to 1/5120 (median of 1/640). In this sample 31/178 (17.4%) were positive for Scl-70, 30/154 (19.4%) were positive for anti RNP, 38/179 (21.2%) were anti Ro positive and 53/196 (27.0%) were anticentromere positive.

The comparison of the sample ANA positive with the negative is on **table1.**

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Table 1- Comparison of ANA positive with ANA negative scleroderma patients.

	Total sample n=211	Positive ANA n=196	Negative ANA n= 15	P
Gender	Females= 190 Males= 21	Females-179 Males-17	Females=11 Males=4 OR=3.8;95%CI=1.09-13.3	**0.04**
Classification of scleroderma				
limited	119/211	110/196	9/15	0,32
diffuse	58/211	52/196	6/15	
overlap	25/211	25/196	0	
Without esclero	8/211	8	0	
Age at diagnosis	16 a74 Median= 44 (34-53)	16 a 74 Median =44 (33-52.2)	17 a 67 Median= 44 (36.2-56.2)	0,65
Ethnic background				
Eurodescendants	119/177-	110/167	9/10	0.16
Afrodescendats	58/177	57/167	1/10	
Medsger Index	0-16 Median=5 (3-7)	0-16 Median=5 (3-7)	2-12 Median=4 (2-5)	0.40
Rodnam modified	0-48 Median=10 (3-19)	0-48 Median=10 (3-19)	0-36 Median=9 (6-20,5)	0.63
Esophageal involvment	123/194 (63.4%)	116/181 (64.0%)	7/13 (53.8%)	0.45
Pneumonitis	99/197 (50.2%)	91/183 (49.7%)	8/14 (57.1%)	0.59
Myositis	19/200 (9.5%)	18/186 (10.7%)	1/14 (7,1%)	1.0
Myocarditis	9/196 (4.5%)	7/181 (3.8%)	2/15 (13.3%)	0.14
Raynaud	194/204 (95.0%)	179/189 (94.7%)	15/15 (100%)	1.0
Fingertip scars	104/194 (53.6%)	98/180 (54.4%)	6/14 (42.8%)	0.40
Digital ulcers	22/178 (12.3%)	21/166 (12.6%)	1/12 (8.3%)	1.0
Telangiectasis	79/187 (42.2%)	72/17 (41.3%)	7/1 (53.8%)	0.38
Calcinosis	26/182 (14.2%)	21/169 (12.4%)	5/13 (38.4%) OR=4.4; 95%IC=1.3-14.7	**0.02**
Pericarditis	11/197 (5.5%)	11/182 (6.0%)	0/15	1.0
Pleuritis	13/192 (6.7%)	13/17 (7.3%)	0/15	0.60
Pulmonary hypertension	27/177 (15.2%)	27/167 (16.1%)	0/10	0.36
Articular involvment	69/185 (37.2%)	61/171 (35.6%)	8/14 (57.1%)	0.11
Renal crisis	5/186 (2.6%)	3/174 ((1.7%)	2/12 (16.6%) OR=11.4 95%IC=1.7-76.2.	0.03

DISCUSSION

The prevalence of negative ANA scleroderma found presently (7.1%) is similar to the other samples. Salazar et al, in a large cohort of 3249 American patients found that 208 (6.4%) were ANA negative (3). Another, found a prevalence of 7.7% of negative ANA (12). A third one, in Japanese population showed a prevalence of 5% (13). Some authors have found that seronegative systemic sclerosis is associated with malignancy such as multiple myeloma or breast cancer but such patients were also negative for Raynauds phenomenon (14,15). In this context, Watad et al. (16) found that ANA positivity is considered to be an independent predictor of cancer favorable prognosis, possibly suggesting that humoral autoimmunity may have some benefit. We did not study this variable presently.

It was also found currently that ANA negative had higher proportion of male patients than the ANA positive group as other did (3). Females also were the majority of the sample as it is found in most of connective tissue diseases.

In this work, ANA negative patients had more calcinosis and renal crisis than those with this antibody. Calcinosis is defined as subcutaneous calcium deposition and may be seen on imaging and/or physical examination. They may favor the appearance of skin breakdown that is difficult to heal and may extrude calcium if located superficially (17). They are commonly seen in the hands and associated with digital ischemia; not rarely they cause disability and hand dysfunction (17).

Renal crisis, one of the most feared complications in scleroderma, was also seen in more commonly in those negative for ANA. Renal crisis is a life treatment situation and occurs in 10% of patients with systemic sclerosis (18). Progression to renal failure occurs in half of patients which can lead to further complications necessitating dialysis. It can be divided in narrowly defined SRC (nd-SRC) and systemic sclerosis associated thrombocytic micro-angiopathy (SSc-TMA). The first is associated with glucocorticoid use and exhibits prominently elevated blood pressure and worsening of renal function initially, followed by mild thrombocytopenia (19). The second exhibits signs of microangiopathy and severe thrombocytopenia (19). Salazar et al. (3) could not prove association of ANA negative scleroderma with renal crisis. This may be due to peculiarities of the genetic background associated with this disease. Nevertheless, our number of patients with renal crisis was small and subject to statistical bias. So, studies in our population with higher number of patients than presently done are needed.

CONCLUSION

Concluding, it was observed that ANA negative patients represent a distinct subset of patients who have male predominance, more calcinosis and more renal crisis than positive ANA systemic sclerosis.

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