Proceedings Of
Scientific
Research
Universidad Anáhuac
Multidisciplinary Journal of Healthcare

ISSN: in process

January-June 2022, Vol. 2, No. 3

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Proceedings of Scientific Research Universidad Anáhuac volume 2, number 3, January-June 2022, it is a biannual publication by Investigaciones y Estudios Superiores S.C. (known as Universidad Anáhuac Mexico), through of the Faculty of Health Sciences. Av. Universidad Anáhuac núm. 46, Col. Lomas Anáhuac, C.P. 52786, Huixquilucan, State of Mexico. Phone: 55 5627 0210. https://revistas.anahuac.mx/psrua. Responsible editor: María Teresa Ponce López. Reservation of Rights to Exclusive Use: 04-2021-051813525300-203, awarded by the Instituto Nacional del Derecho de Autor. ISSN: in process. Responsible for the latest update of this issue, Faculty of Health Sciences, María Teresa Ponce López, Av. Universidad Anáhuac núm. 46, col. Lomas Anáhuac, C.P. 52786, Huixquilucan, State of Mexico, date of last modification, March 18, 2022.

Proceedings Of
Scientific
Research
Universidad Anáhuac

January-June 2022, Vol. 2, No. 3

Contents

Proceedings of Scientific Research Universidad Anáhuac, 2022, 2(3): 5-10.
ISSN: in process.

Research Article

Prediabetic patients evaluated with Quantose™ IR and their relationship with anthropometric measurements through bioelectrical impedance analysis

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https://doi.org/10.36105/psrua.2022v2n3.01

ABSTRACT

Introduction: New metabolomic biomarkers as Quantose™ IR and anthropometric measurements using bioelectrical impedance analysis (BIA) provide relevant information on patients with insulin resistance and prediabetes. Quantose™ IR is a novel metabolomic test to assess insulin resistance for screening and monitoring. Establishing a correlation between these variables is useful in clinical practice and, to our knowledge, there are no published studies that explore the relationship between Quantose™ IR and anthropometric measurements using BIA in patients with prediabetes. **Objective**: To evaluate the correlation between Quantose™ IR and BIA anthropometric variables (fat mass, FM; fat mass index, FMI; and body mass index, BMI) in Mexican patients with prediabetes, overweight, and obesity. **Materials and Methods**: This is an observational, transversal analytic study in 135 patients of both genders between 20 and 65 years of age, BMI 25.0–34.9, with diagnosis of prediabetes. The Quantose™ IR test was performed as well as anthropometric measurements (FM, FMI, and BMI) using BIA taken with Inbody 230™. Pearson's correlations and independent sample t-tests were estimated with a significance level of $p < 0.05$. **Results**: 135 patients were studied; 77% were female, aged 46 years in average. The prevalence of insulin resistance by Quantose™ IR was 71.1%. A positive correlation was confirmed between Quantose™ IR and FM, FMI, and BMI ($p < 0.05$). Patients with altered Quantose™ IR had higher FM, FMI, and BMI ($p < 0.05$). **Conclusion**: The data here presented confirm the existence of a positive and statistically significant correlation between Quantose™ IR and anthropometric measurements using BIA. This information may be useful for diagnosis and treatment in prediabetic, overweight, and obese patients.

Key words: prediabetes; Quantose™ IR; bioelectrical impedance analysis; fat mass; fat mass index; BMI.

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Received: 17 November 2021.
Accepted: 4 February 2022.

RESUMEN

Introducción: Los nuevos biomarcadores metabolómicos, como el Quantose^{MR} RI y las medidas antropométricas por bioimpedancia eléctrica (BE), aportan información importante sobre los pacientes con resistencia a la insulina y prediabetes. La nueva prueba de metabolómica, Quantose^{MR} RI mide resistencia a la insulina para escrutinio y monitoreo. No se identifican estudios sobre la relación entre Quantose^{MR} RI y variables antropométricas de BE en pacientes con prediabetes y consideramos que establecer una correlación entre ellos es de utilidad en la práctica clínica. **Objetivo**: Evaluar la correlación entre Quantose^{MR} RI y variables antropométricas de BE (masa grasa (MG), índice de masa grasa (IMG) e índice de masa corporal (IMC) en pacientes mexicanos con prediabetes, sobrepeso y obesidad. **Materiales y Métodos**: Estudio observacional, transversal-analítico en 135 pacientes entre 20 y 65 años de edad, ambos géneros, IMC 25.0–34.9 y diagnóstico de prediabetes. Se realizaron prueba Quantose^{MR} RI y mediciones antropométricas de MG, IMG e IMC por BE, Inbody 230^{MR}. Se estimaron correlaciones de Pearson y prueba t-Student para muestras independientes. El nivel de significancia fue $p < 0.05$. **Resultados**: Se estudiaron 135 pacientes; 77% de ellos, mujeres con edad promedio de 46 años. La prevalencia de resistencia a la insulina por Quantose^{MR} RI fue 71.1%. Se confirma correlación positiva de Quantose^{MR} RI con MG, IMG e IMC ($p < 0.05$). Los pacientes con Quantose^{MR} RI alterada tienen MG, IMG e IMC superiores ($p < 0.05$). **Conclusión**: Los datos aquí presentados confirman una correlación positiva y estadísticamente significativa entre Quantose^{MR} RI e indicadores antropométricos por BE. Esto es de utilidad para el diagnóstico y tratamiento en pacientes con prediabetes, sobrepeso y obesidad.

Palabras clave: prediabetes; Quantose^{MR} RI; bioimpedancia eléctrica; masa grasa; índice de masa grasa; IMC.

INTRODUCTION

Currently, an epidemiological emergency has been declared for type 2 diabetes, overweight, and obesity in several countries, including Mexico.[1] In 2013, the global prevalence of prediabetes was between 15 and 25%.[2] In Mexican adults the rate is even higher, at 43.2%.[3] Some of the main causes of the rise in prediabetes are the growing rate of overweight and obesity and the delay in identifying risk factors that can be prevented.[1] Consequently, the early diagnosis of prediabetes becomes essential to slow the progression of and prevent type 2 diabetes and its complications.

The most frequently used biomarkers for diagnosing prediabetes are glucose and fasting serum insulin, homeostatic model assessment of insulin resistance (HOMA-IR), HbA1c, postprandial glucose, and oral glucose tolerance test. Recently, new biomarkers associated to insulin resistance (IR) and prediabetes have been developed.[4] Among these biomarkers, the Quantose™ IR test was developed through metabolomic studies and validated with the clamp technique. It is now used in different clinical settings in the Mexican population. The main advantage of Quantose^{TM} IR is the ease with which it measures insulin resistance before glycemic changes in one blood sample. Within this context, Quantose^{TM} IR allows clinicians to obtain a picture of intracellular analytes using an algorithmic analysis to identify insulin resistance.[5]

The implementation of the Quantose™ IR test can facilitate an early diagnosis and the possibility of establishing timely treatment strategies to promote long-term benefits. This is supported by the observation of altered insulin functionality (insulin resistance) up to 5 years before presenting symptomatology suggestive of prediabetes or type 2 diabetes. The Quantose™ IR test consists of the analysis of three metabolites: hydroxybutyric acid (α-HB), Linoleoylglycerophosphocholine (L-GPC), and oleic acid. All three play an important role in metabolic routes related to the action and secretion of insulin or beta cell function. In their Relationship between Insulin Sensitivity and Cardiovascular Disease (RISC) Study, Cobb et al. validated the Quantose™ IR test to measure insulin resistance. Then they predicted the risk of progression to impaired fasting glucose within three years. Fasting plasma levels of α-HB, L-GCP, oleic acid, and insulin significantly correlated with glucose stimulated by insulin.[5-6]

Additionally, the analysis of anthropometric measurements using bioelectrical impedance analysis (BIA) provides useful data for clinical practice, which can be correlated with metabolomic biomarkers.

Compared to the body mass index (BMI), fat mass (FM) correlates more precisely with health risk factors. BMI does not measure body composition. Conversely, FM and fat mass index (FMI) provide information about excess fat. FMI is more specific than BMI because it takes fat mass into account instead of body weight, which is composed of fat mass and fat-free mass constituents. It is useful to detect abnormalities in body composition and to establish reference criteria to estimate prevalence rates of obesity or sarcopenia in clinical studies.[7]

It is known that increased body mass and FM, as determined by BIA, are risk factors of insulin resistance and prediabetes.[8,9] The early identification of insulin resistance among these patients is crucial. Until now, no studies have explored the relationship between the Quantose™ IR test and anthropometric

https://doi.org/10.36105/psrua.2022v2n3.01

measurements, using BIA in prediabetic patients. Thus, it is of interest to conduct an analysis of these parameters to define prediabetic patients' characteristics.

The aim of the current study is to evaluate the correlation between metabolomic biomarkers (Quantose™ IR) and anthropometric measurements (FM, FMI, and BMI) in Mexican patients with prediabetes, overweight, and obesity.

MATERIALS AND METHODS

The study design was observational and transversal-analytical. The study was conducted in a primary care clinic between 2019 and 2020 and included 135 patients between 20 and 65 years of age with BMI of 25.0–34.9 and prediabetes diagnosis (American Diabetes Association criteria).[10] The patients showed glycated hemoglobin (HbA1c) levels of 5.7–6.4%, impaired fasting glucose of 100–125 mg/dL, or glucose intolerance of 140–199 mg/dL, with or without hypertension and/or dyslipidemia with medical management and no pharmacological treatment for prediabetes. Patients with medically uncontrolled comorbidities (i.e., cardiovascular diseases, chronic kidney disease, thyroid disease, adrenal disease, or liver disease), pregnant or breastfeeding females, and those with dehydration were excluded. Follow-up visits were scheduled with their physicians.

In accordance with the World Medical Association Declaration of Helsinki, the study was approved by the Research and Ethics Committees of the ABC Medical Center, (approval number ID ABC-17-13). Patients accepted participating in the study after they were explained the procedure and read and signed their informed consent.

For this study, the sample size required to estimate a proportion with an accuracy of 5% determined for $\alpha = 0.05$. The expected proportion of insulin resistance was 86.9%. The study by Vatcheva et al. (2020) was used as reference.[8]

Serum sample measurements. Quantose™ IR is a metabolomic test using bioanalytical strategies. The techniques used are mass spectroscopy and ultra-high performance liquid chromatography. Both identify and determine a set of metabolites and biomarkers highly discriminatory in biological diseases.[11] This test was conducted with a fasting blood sample. Blood samples were taken in a supine position after 10 h of fasting, confirmed verbally by patients. Medical laboratory technicians drew the samples at the laboratory of the ABC Medical Center. The laboratory is accredited by the College of American Pathologists (CAP). Quantose™ IR is given within a 1–120 range, where higher scores indicate more insulin resistance. When the value of Quantose™ IR was equal or higher than 63, the presence of insulin resistance was defined.[5-6]

Height and weight were measured with 0.5 cm and 0.1 kg precision using a BIA Inbody 230™ scale and a SECA 206™ wall-mounted stadiometer. FM was obtained from the BIA analyzer in absolute (kg) and relative (%) value. FMI and BMI were obtained from estimations with FM (kg), weight (kg), and height (m). After having been previously standardized, measurements were taken by the nutritionists.[12] Measurements were conducted on patients wearing disposable gowns after 4 h of fasting.

BIA is based on determining body volume, resistance to current, the distance covered by an electrical impulse, and body surface dimensions. BIA measures extracellular liquid and total body water when exposed to low and high electric frequency. FM does not conduct electric charge and is equal to the difference between body weight and fat-free mass. Fat-free mass is considered the conducting volume that helps an electric current impulse to travel thanks to the conductivity of electrolytes dissolved in body water. BIA measurements are obtained from the entire body and body segments using four electrodes, one on each limb.[13]

To conduct the BIA, subjects were placed in the center of the scale freely (without holding onto anything) and with equal weight distribution on both feet. The stretch stature method required that the subject stand with feet together and heels, buttocks, and upper back against the stadiometer. The head was supported on the Frankfort Plane without touching the stadiometer. The measurement was taken at the end of a long exhalation.[12]

FM was classified as obesity when the relative value was ≥ 25 and ≥ 32 for men and women.[14] The FMI was calculated dividing FM (kg) by the squared height (m). An excess fat or obesity due to FMI was defined by values > 9 and > 13 for all patients.[7] BMI was calculated dividing the weight (kg) by the squared height (m). BMI criteria were defined by the WHO. The value of ≥ 25 defined overweight and ≥ 30, obesity.[15] FM (kg), FMI (m/ kg^2), and BMI (m/ kg^2) were analyzed as continuous quantitative variables.

Statistical analysis

The qualitative and quantitative variables of the patients were calculated through frequencies and proportions and mean and standard deviation (SD). The prevalence of insulin resistance was estimated with Quantose™ IR. FM, FMI, and BMI were presented with means and SD. Pearson's correlations were obtained to measure the relationship between Quantose™ IR and FM, FMI, and BMI. T-tests for independent samples were conducted to compare the means of FM, FMI and BMI between groups, with and without alteration in the Quantose™ IR test. The significance level was determined with a value of $p < 0.05$. A statistical analysis was conducted with SPSS v 27.

RESULTS

The study sample consisted of 135 patients. Table 1 shows descriptive information with demographic and clinical variables. Of the total sample, 77% were female and the mean age was 46 (± 8.3) years. Average FM was 31.1 (± 8.3), indicating FM obesity. Average FMI was 12.7 (± 3.7) kg/m^2, indicating excess fat or obesity. BMI was 30.7 (± 4.0) kg/m^2, indicating obesity as well.

TABLE 1. Description of demographic and clinical variables of study sample (n = 135).

	Frequency	%
Female	104	77
Age, mean, and SD	46.0	8.3
FM (%), mean, and SD	31.1	8.3
FMI (m/kg^2), mean, and SD	12.7	3.7
BMI (m/kg^2), mean, and SD	30.7	4.0

FM: Fat mass. FMI: Fat mass index. BMI: Body mass index.

Figure 1 shows the prevalence of insulin resistance (71.1%) measured by Quantose™ IR. Figure 2–4 show the correlations between Quantose™ IR and FM (%), FMI (m/kg^2), and BMI (m/kg^2). Positive and statistically significant correlations were found between insulin resistance measured by Quantose™ IR and body mass and FM composition measured by BIA.

Table 2 shows the mean comparison of FM, FMI and BMI and the presence of insulin resistance measured by Quantose™ IR. Patients with altered Quantose™ IR had higher FM (%), FMI (m/kg^2), and BMI (m/kg^2) means than those with unaltered Quantose™ IR. Mean differences were statistically significant.

Based on our observations, it is suggested that the biomarker Quantose™ IR is positively correlated and statistically significant with anthropometric BIA parameters that indicate body fat composition.

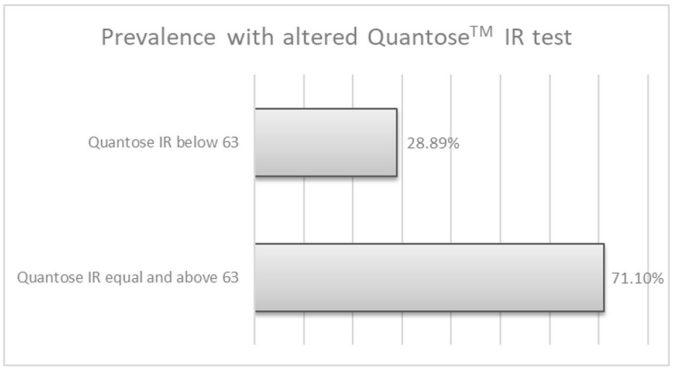

FIGURE 1. Prevalence of insulin resistance with Quantose ™ IR.

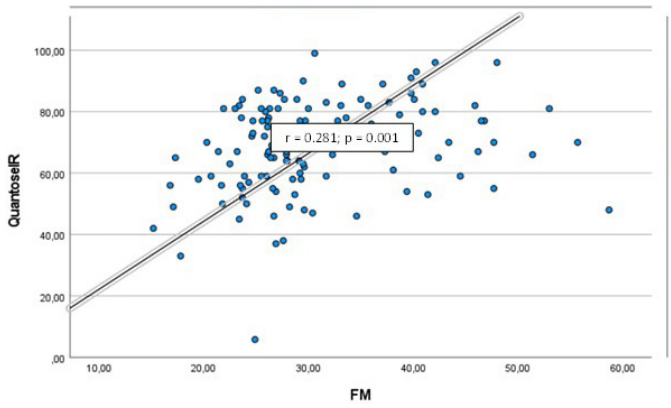

FIGURE 2. Correlation between Quantose™ IR and FM (%).

Pearson's correlation. FM: Fat mass.

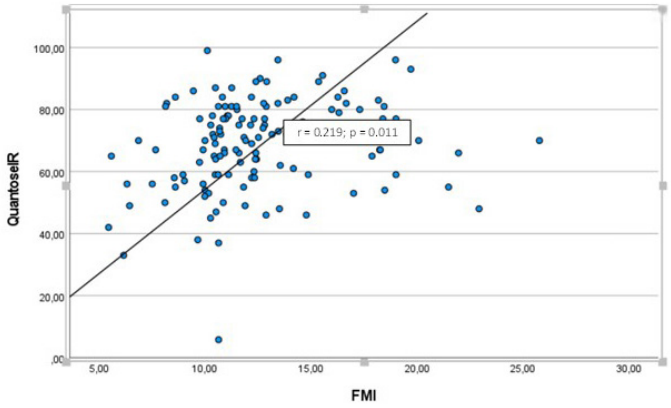

FIGURE 3. Correlation between Quantose™ IR and FMI.

Pearson's correlation. FMI: Fat mass index.

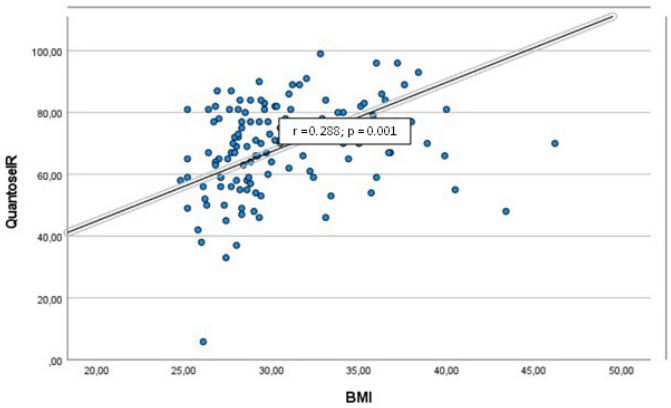

FIGURE 4. Correlation between Quantose™ IR and BMI.

Pearson's correlation. BMI: Body mass index.

https://doi.org/10.36105/psrua.2022v2n3.01

Table 2. Mean comparison between FM, FMI, and BMI and insulin resistance measured by Quantose™ IR.

	Altered Quantose™ IR				
	Present ≥ 63 (n = 94)		Absent < 63 (n = 41)		
	Mean	SD	Mean	*SD*	*p*
FM (%)	32.4	7.9	28.0	8.6	0.004
FMI (m/kg^2)	13.2	3.5	11.5	3.8	0.024
BMI (m/kg^2)	31.4	3.9	29.2	3.9	0.004

T-test for independent samples. FM: Fat mass. FMI: Fat mass index. BMI: Body mass index.

DISCUSSION

This study highlights the importance of the integral evaluation of patients with metabolomic and anthropometric measurements. Results show that Quantose™ IR positively correlates with FM, FMI, and BMI at a statistically significant level, indicating a physiopathological correlation. This evidence points at the importance of using tests as Quantose™ IR in patients with higher weight and body mass to identify their health status.

In our study, the prevalence of insulin resistance among patients with prediabetes was 71%, according to the Quantose™ IR test. In the pilot study by San Mauro et al. (2019) in a Spanish pediatric sample with risk factors for diabetes, the prevalence rate of insulin resistance measured with the Quantose™ IR test was 90.9%.[16] This is one of scarce studies worldwide that report the use of the Quantose™ IR test.

The prevalence of prediabetes in Mexico is 43%, while adult obesity rates are the second highest in the world.[3] It is necessary to implement medical nutritional strategies focused on modifying at-risk patients' lifestyle, following up with biomarkers as Quantose™ IR and BIA. Both of them can help establish strategies with pharmacological treatment. The results of this study identify a group of high-risk patients that can benefit from an early treatment strategy.

In our study, it was more common to see Quantose™ IR alterations among patients with a higher accumulation of FM and weight. Similarly, Cobb et al. (2013) showed that most patients with prediabetes are of a higher age group, overweight, and obese.[5] Cobb et al. suggest that traditional diagnostic tests do not measure insulin resistance directly, limiting the precision of an early diagnosis.[5] Tripathy et al. conclude that the Quantose™ IR test is a tool that may benefit patients due to its sensitivity in the early stages of the disease.[17]

It is important to contribute to the evidence through studies with larger sample sizes in populations with clinical characteristics similar to ours. This will enable the comparison of results to provide recommendations in clinical practice guides that prioritize tests such as Quantose™ IR and BIA anthropometric measurement indicators.

In addition, patients with prediabetes diagnosis and an altered Quantose™ IR test, who receive intensive pharmacological and non-pharmacological intervention, may have the possibility of remission.[18]

CONCLUSIONS

We can conclude that there is a positive and statistically significant correlation between the metabolomic biomarker Quantose™ IR and anthropometric measurements, such as fat mass, fat mass index evaluated through electrical bioimpedance, and body mass index in prediabetic patients. This is useful for everyday practice in the diagnosis and management of patients with prediabetes, overweight, and obesity.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest. This study was funded by the *Clínicas de Salud Incluyente y Educación* [Education and Inclusive Health Clinics] at *Centro Médico ABC* [ABC Medical Center].

ACKNOWLEDGMENTS

The authors would like to thank Casilda Suarez Hesketh, for her assistance with the translation of the paper.

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Appendix A. Measurement units.

FM %

FMI kg/m^2

BMI kg/m^2

Appendix B. Abbreviations.

Electrical bioimpedance analysis: BIA

Fat mass: FM

Fat mass index: FMI

Homeostatic model assessment of insulin resistance: HOMA

Hydroxybutyric Acid: α-HB

Linoleoylglycerophosphocholine: L-GPC

College of American Pathologists: CAP

https://doi.org/10.36105/psrua.2022v2n3.01

Proceedings of Scientific Research Universidad Anáhuac, 2022, 2(3): 11-19.
ISSN: in process.

Research Article

Social networks and COVID-19 vaccination hesitancy in Mexican older adults

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https://doi.org/10.36105/psrua.2022v2n3.02

ABSTRACT

Introduction: The importance of social networks is growing, impacting everyday life. At this stage of global COVID-19 vaccination roll-out, hesitancy to get immunized is slowing this process; it is thought that this decision could be impacted by information shared on social networks. **Objective:** Determine whether the use of social networks is associated with the willingness to get the COVID-19 vaccine. **Methods:** This is a secondary analysis of the ENSANUT COVID-19 study, that measures the impact of the pandemic on the Mexican population. Only older adults, aged 65 years or older, were included in this work. Face to face interviews were performed to determine social network utilization, willingness to get vaccinated, and socio-demographic information on health and COVID-19. Bivariate analysis and logistic regression were performed. **Results:** From a total of 1,490 older adults, 59.3 % were women whose mean age was 73.5 (SD 6.8), and 53.3% (n = 795) were willing to get a COVID-19 vaccine when available. In an adjusted multivariate logistic regression model, WhatsApp was found to be a significant variable related to lower risk of vaccine hesitancy (OR 0.43, 95% CI, 0.2–0.85; p = 0.016). Other variables related to vaccine hesitancy were being a woman (OR 1.58, 95% CI, 2–1.23; p < 0.001) and COVID-19 literacy (OR 1.32, 95% CI, 1.01–1.74; p = 0.047). **Conclusion:** The use of social networks such as WhatsApp is a factor that can influence older adult vaccination against COVID-19. Social networks, among other variables, should be taken into account when analyzing factors that lead to vaccination hesitancy in older adults.

Key words: ageing; social networks; COVID-19 vaccination; SARS-CoV-2; older adults.

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Received: 20 November 2021.
Accepted: 28 February 2022.

RESUMEN

Introducción: Las redes sociales ganaron importancia con la pandemia de COVID-19. Con la disponibilidad de vacuna COVID-19, la indecisión para vacunarse frena este proceso; uno de los factores que se estudian es la información compartida en las redes sociales. **Objetivo:** Determinar si el uso de las redes sociales está asociado con la disposición a recibir la vacuna COVID-19. **Métodos:** Este es un análisis secundario de ENSANUT-COVID-19, que midió el impacto de la pandemia en la población mexicana. Se realizaron modelos bivariados y regresiones logísticas. **Resultados:** De un total de 1490 adultos mayores, el 59,3% eran mujeres, cuya edad media fue de 73,5 (DE 6,8), y el 53,3% (n = 795) estaban dispuestos a vacunarse para COVID-19. En un modelo de regresión logística multivariada ajustado por variables sociodemográficas, se encontró que el uso de WhatsApp era una variable significativa relacionada con menor riesgo de indecisión para vacunarse (OR 0,43; IC de 95%; 0,2–0,85; p = 0,016). Otras variables relacionadas con la indecisión para vacunarse fueron ser mujer (OR 1,58; IC 95%; 2–1,23, p < 0,001) y conocimiento sobre COVID-19 (OR 1,32; IC 95%; 1,01–1,74, p = 0,047). **Conclusión:** El uso de redes sociales como WhatsApp es un factor que puede influir en la elección de vacunarse contra COVID-19 en adultos mayores. El uso de redes sociales, entre otras variables, debe tenerse en cuenta al analizar los factores que conducen a la indecisión de los adultos mayores para vacunarse.

Palabras clave: envejecimiento; redes sociales; vacunación COVID-19; SARS-CoV-2; adultos mayores.

INTRODUCTION

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the COVID-19 pandemic has changed the lifestyle of millions worldwide due to the implementation and adoption of preventive measures to ensure lower morbidity and mortality (lockdowns, social isolation).[1] The beginning of a massive worldwide COVID-19 immunization campaign has led to a continuous reduction in infections and hospitalization rates, along with other positive consequences, especially for populations at risk.[2,3] However, there are still groups of individuals—including older adults—reluctant to getting vaccinated, posing a risk not only for themselves but also for those around them, which fuels new waves of infections around the globe.[4] Vaccine hesitancy has different rates and varies according to availability and sociocultural and economic factors in countries across the world[5]; for example, in an international survey among low- and middle-income countries, vaccine acceptance was only 78.4% (Oct 2020–Dec 2020).[6]

Reports explore characteristics associated with the acceptance of the COVID-19 vaccine, evidencing that multiple factors play a role when it comes to making these complex health decisions.[7] For example, a study in the United States showed that 1 in 11 older adults were not willing to get vaccinated for COVID-19. Factors associated with acceptance were believing in the safety and efficacy of the COVID-19 vaccine (i.e., the belief that it would help protect oneself and others), willingness to accept possible side effects, opinion about the importance of vaccines, and safety concerns.[8] Furthermore, a study in Brazilian older adults showed a prevalence of vaccine hesitancy (17.5%) in which associated factors for not wanting the vaccine were the absence of COVID-19 symptoms, evangelical religion, and female sex.[9]

In addition to knowledge from past vaccination campaigns, the hesitancy to get immunized, and the recommendation for social isolation, the role of social networks (SN) has earned importance. It is linked to increased health misinformation[10] and affects health literacy, a well-known factor related to vaccination choices.[11] A worldwide study in the last year evidenced that Mexico is among the countries that share the most 'fake news' related to the current global health crisis.[12]

This phenomenon is evolving since older adults have to adopt SN to keep important interpersonal relationships during the pandemic.[13] There are a few reports on how SN could impact vaccine hesitancy; therefore, our aim was to analyze how, in the context of other factors, SN could affect Mexican older adults when deciding to get the COVID-19 vaccine.

MATERIALS AND METHODS

This is a secondary analysis of the ENSANUT COVID-19 (National survey of health and nutrition), a cross-sectional study aiming to determine the impact of the SARS-CoV-2 pandemic on a probabilistic sample of Mexican population. The methods and further information can be found in the ENSANUT COVID-19 executive report.[14] Our study focuses on the available data on the use of SN. only asked to older adults, which were defined as a person 65-years or older (n = 1,490). This survey was done from August 17, 2020 to November 14, 2020, including face-to-face questions on the individuals' health and social and lifestyle behaviors. The survey was carried out following the study protocols and recommendations to safely perform interviews. Importantly, the interviews were performed at the end of the first COVID wave in Mexico and just before the

https://doi.org/10.36105/psrua.2022v2n3.02

beginning of the second wave and a full lockdown (spring–summer of 2020).[15]

To evaluate the willingness to get a COVID-19 vaccine when available, a single question was asked "Will you accept to get the vaccine against COVID-19 when it becomes available?" The possible answers were "yes", "no", or "I don't know". We further collapsed the answer into "yes" and "no/I don't know." The SN variables included a first question in which the subject was asked "Do you use any SN?" It was followed by the specifications "WhatsApp (WA)", "Facebook (FB)", "Twitter", "YouTube", "chats (not specified)", and "other". The sum of the specific SN led to an ordinal variable for the total of social networks used. Other variables included: sociodemographic factors (age, sex, marital status, schooling level, indigenous language as first language/second language, household income, employment status, living situation), multimorbidity (two or more chronic diseases from a list of 14)[16], lifestyle behaviors (physical activity, alcohol binge drinking [≥ 5 alcoholic beverages for males and ≥ 4 alcoholic beverages for females], smoking status, vaccination against influenza and/or pneumococcus), and COVID-related factors (knowledge of COVID-19, preventive actions, and have/had COVID-19).

In the first step of the statistical analysis, the variables by willingness to get the vaccine were described, including means and standard deviations for continuous variables and frequencies (relative and absolute) for binary/ordinal variables, with t- and chi-squared tests accordingly. A logistic regression adjusted for all the variables was performed, followed by a regression for each specific network. The strength of the association was reported as odds ratios (OR) with 95% confidence intervals (CI). A term of interaction between the use of SN and financial status was used to prevent the moderating effect between finances or socioeconomic status and SN use (higher income-increased cellphone use). Finally, sampling weights provided in the data sets were used for all the analyses. The statistical software STATA/SE 17.0 (Copyright 1985–2021 StataCorp LLC; 4905 Lakeway Drive College Station, Texas, 77845, USA) was used. All the participants in the study signed an informed consent. ENSANUT COVID-19 follows the Helsinki declaration, and it was approved by the institutional ethics review board.

RESULTS

A total of 1,490 individuals (mean age 73.6 years, ± SD 6.8) were included, representing 4,162,301 older adults (> 65 years of age), of which 59.3% (n = 884) were women. The hesitancy to get the vaccine had a prevalence of 46.6% (n = 695). A total of 1,197 individuals (80.3%) reported no use of SN, while 9.5% (n = 142) used one and 10.1%, two or more (n = 151). According to the bivariate analysis, the individuals not implementing preventive measures showed the highest rate of hesitancy (59.2%), followed by those with low COVID-19 literacy (55.4%) and women (50.3%). On the other hand, individuals that had COVID-19 in the previous months presented the lowest rate of hesitancy (29.1%), followed by those with a higher income and using two or more SN (Table 1).

Regarding the use of specific SN, WA was the most frequently used (17.12%, n = 256), followed by FB (9.9%, n = 147) and YouTube (6.1%, n = 91). The "other" SN (Instagram, TikTok, among others) were reported to be used scarcely. As shown in Table 1, a lower hesitancy rate was found among those using chats (30.8%) and WA (36.7%), while those not using any SN in general showed ≥ 46.6%. The difference between WA users and non-users was the only one statistically significant ($p < 0.001$).

According to the fully adjusted logistic regression, the main factors associated with COVID-19 vaccine hesitancy were being a woman (OR 1.58; 95% CI, 1.23–2; $p < 0.001$), low COVID-19 literacy (OR 1.32; 95% CI, 1.01–1.74; $p = 0.047$), and income of 300–499 USD (OR 0.45; 95% CI, 0.29–67; $p < 0.001$). A positive effect on vaccine hesitancy was associated with previous vaccination (OR 0.62; 95% CI, 0.49–0.7; $p < 0.001$), multimorbidity (OR 0.74; 95% CI, 0.57–0.97; $p = 0.031$), and the use of two or more SN (OR 0.51; 95% CI, 0.27–0.97; $p = 0.041$).

In addition, the interaction term between income and SN use was also significant. This was included to prevent bias regarding income and SN access (Table 2). When including each specific SN, one at a time, into the regression, only WA remained significant (OR 0.43; 95% CI, 0.2–0.85; $p = 0.016$) (Table 3).

DISCUSSION

According to the results, the use of SN could play a role in the process leading to hesitancy to get COVID-19 vaccination. Those older adults who use two or more SN or WA presented the strongest association with the willingness to get vaccinated, even after adjusting by other variables and evaluating the possible interaction term between SN use and socioeconomical status. On the other hand, factors such as income, low COVID-19 literacy, previous COVID-19 infection, multimorbidity, and being female were independently associated with hesitancy.

The COVID-19 vaccine has been developed collaboratively between the CEPI (Coalition for Epidemic Preparedness Innovations), the WHO (World Health Organization), and the NIH (U.S National institute of health) to accelerate the process.

Table 1. Description and association between sociodemographic variables and vaccine acceptance.

	Total (n = 1,490)	Willing to get vaccinated?		
		Yes (n = 795 [53.3%])	No (n = 695 [46.6%])	p-value
Age, mean (SD)	73.6 (6.8)	73.3 (6.7)	73.8 (7)	0.1
Women, n (%)	884 (59.3)	440 (49.7)	444 (50.3)	$Chi^2 = 14$ p = 0.001
Men n (%)	606 (40.67)	355 (58.8)	191 (31.5)	
Indigenous language, n (%)	89 (5.9)	50 (56.2)	39 (43.8)	0.582
Employment status, n (%)	237 (15.9)	125 (52.7)	112 (47.3)	0.76
Marital status, n (%)	649 (43.6)	361 (55.6)	288 (44.4)	0.123
Schooling level, median (IQR)	3 (2)	3 (5)	3 (2)	< 0.001
Living situation, n (%)	324 (21.7)	160 (49.4)	164 (50.6)	0.105
Income*, n (%) None 0.1–299 USD 300–499 USD 500–699 USD 700–1,099 USD 1,100 USD or higher	 235 (15.8) 766 (51.4) 273 (18.3) 97 (6.5) 71 (4.7) 48 (3.2)	 104 (44.2) 384 (50.1) 171 (62.6) 64 (65.9) 40 (56.3) 32 (66.6)	 131 (55.8) 382 (49.9) 102 (37.4) 33 (34.1) 31 (43.7) 16 (33.4)	0.001
Physical activity, n (%)	313 (21.1)	183 (58.5)	130 (41.5)	0.045
Smoking, n (%)	125 (8.4)	73 (58.4)	52 (41.6)	0.238
Binge drinking, n (%)	234 (15.7)	130 (55.5)	104 (44.5)	0.463
Low COVID-19 literacy, n (%)	392 (26.3)	175 (44.6)	217 (55.4)	< 0.001
No preventive measures, n (%)	125 (8.4)	51 (40.8)	74 (59.2)	0.003
Previous COVID-19, n (%)	31 (2.1)	22 (70.9)	9 (29.1)	0.047
Previous vaccines, n (%)	963 (64.6)	549 (57)	414 (43)	< 0.001
Multimorbidity, n (%)	310 (20.8)	186 (60)	124 (40)	0.008
Social networks used, n (%) 0 1 2	 1,197 (80.3) 142 (9.5) 151 (10.1)	 620 (51.8) 82 (57.7) 93 (61.6)	 577 (48.2) 60 (42.3) 58 (38.4)	0.041

* Income converted to USD with an exchange rate of 20.01 according to the Mexican National Bank exchange (26/07/2021).

The solidarity trial was made to evaluate risks of each COVID-19 candidate vaccine within 3–6 months.[17] Now that the vaccine is available, there is a continuous rollout around the world.[2] In Mexico, the first vaccination wave (February–April 2021) started with those at higher risk, such as sanitary workers and older adults aged +60 years.

Even as the vaccination against COVID-19 seems to gain relevance and different countries establish strategies to reach most of the population, only 26.5% of the world seems to have received at least one dose of the vaccine.[18] In Mexico, by the end of July, 2021, only 20% of the population had received the full immunization and 30% had at least one shot of the vaccine against COVID-19.[18]

According to data from the Mexican Health Ministry, 74% of the adults aged 60 years or older are currently fully vaccinated. The percentage exceeds the expectations from the hesitancy prevalence in late 2020. Following the Mexican national plan for vaccination, efforts are made so adults and young adults can access the vaccine. This is performed assuming that the older population has now been vaccinated and ensuring that every unvaccinated older adult has open access to the vaccine at any given time.

However, approximately 4 millions of older adults remain hesitant to get vaccinated[19], which is important due to the higher risk they face and the prevalence of frailty and higher mortality rates against COVID-19.[20] Similar trends are shown

https://doi.org/10.36105/psrua.2022v2n3.02

Table 2. Factors associated with hesitancy to get COVID-19 vaccination using fully adjusted logistic regression.

	Odds ratio	95% confidence interval	p-value
Age	1.01	0.9–1.02	0.238
Women	1.58	2–1.23	< 0.001
Indigenous language	0.8	0.51–1.25	0.34
Employment situation	1.12	0.82–1.7	0.169
Marital status	1.01	0.78–1.29	0.949
Schooling level	0.97	0.93–1.02	0.393
Living situation	1.01	0.75–1.34	0.946
Income*			
None	Reference		
0.1–299 USD	0.71	0.51–0.9	0.04
300–499 USD	0.45	0.29–67	< 0.001
500–699 USD	0.5	0.27–0.91	0.024
700–1,099 USD	0.59	0.26–1.34	0.212
1,100 USD or higher	0.24	0.08–0.73	0.01
Physical activity	0.95	0.72–1.25	0.747
Current smoking	0.87	0.58–1.29	0.491
Binge drinking	1.1	0.81–1.52	0.485
Low COVID-19 literacy	1.32	1.01–1.74	0.047
No preventive measures	1.2	0.76–1.84	0.38
Previous COVID-19	0.51	0.23–1.14	0.104
Previous vaccines	0.62	0.49–0.7	< 0.001
Multimorbidity	0.74	0.57–0.97	0.031
Number of social networks used			
0	Reference		
1	0.82	0.4–1.54	0.553
2	0.51	0.27–0.97	0.041
Interaction term income* network use	1.16	1.03–1.3	0.012

* Income converted to USD at an exchange rate of 20.01 according to the Mexican National Bank exchange (26/07/2021).

Table 3. Specific social networks association with hesitancy to get COVID-19 vaccination adjusted logistic regression*.

	Odds ratio	95% confidence interval	p-value
WhatsApp	0.43	0.2–0.85	0.016
Facebook	1.07	0.5–2.09	0.83
YouTube	1.31	0.7–2.31	0.348
Twitter	1.5	0.6–3.74	0.37
Chats	0.7	0.2–2.43	0.584
Other	2.04	0.46–9.02	0.343

* Entered one social network at a time in the regression and adjusted for the same variables in Table 2.

in different regions according to data available on the website Our World in Data.[21]

It is impossible to deny that vaccination efforts face challenges, such as those related to vaccine supply, vaccination logistics, access, and specially those related to the willingness of the population.[22]

Factors linked to a lower willingness to vaccinate were mostly tied to beliefs about safety and efficacy of the vaccine.[8] The findings in this study show that misconceptions about COVID-19 could lead to a higher hesitancy. In contrast, being previously vaccinated against influenza and pneumococcal pneumonia had a better disposition towards getting the vaccine (i.e., those individuals are aware of the positive effect of vaccines and the lower adverse effects).[23,24]

Moreover, this hesitancy has been partly attributed to the spread of misinformation and false beliefs that transform into fake news and anti-vaccine data.[24] The reach of misinformation depends on how believable and extended it is. Then, SN can be a channel for sharing these harmful views as they ensure that conceptions against vaccination reach a considerable number of people. [25,26] Still, in this study WA had the opposite effect, which could indicate that the value of communication, social interaction, and better SN takes a heavier toll on hesitancy than the risk of receiving harmful information.[27] Older adults prefer WA over other SN because of its special features: It is a direct channel between two or more individuals, provides sources of information usually identifiable (e.g., person, group), and has a user-friendly interface, among others.[28]

The COVID-19 pandemic has presented challenges for socialization; for example, one study found that adults who live alone were more reactive to social contact during the COVID-19 outbreak.[13] However, our results show that older adults could get positive impact from SN usage. Further studies on the effects of increased SN use and adaptation are needed to understand this relationship and could be considered for public health policies.[27]

In addition to vaccine hesitancy, other factors can affect the vaccination rates, such as the Peltzman Effect (i.e., people typically adjust their behavior in response to perceived levels of risk) in which the vaccination programs and the previous low rates of COVID-19 gave a "false sense of security" and increasing exposure to potential infection risks.[4] Therefore, France, the United States, and Mexico, among others, have recently made serious calls to their population to stop hesitating and get vaccinated.[29-31]

Vaccination is a choice, but it must be an informed one; misconceptions and information without scientific evidence can be seen as a risk against the freedom of choice in older adults. This population is vulnerable to misinformation but also to verified information, given the current need for SN to keep relationships during lockdowns. Then, efforts could be made to improve this situation.

Some studies have shown that information and communication through technology can impact health, mediated by the effect of loneliness and social isolation.[32] This seems to be true, since other studies evidenced that the use of technology by older adults is primarily a way to make and keep social connections.[33] A recent report argues in favor of a better use of technology in the older adults and the creation of infrastructure that allows implementation of benefits, such as information in a controlled fashion and for those already vulnerable, such as Low- and Middle-income Countries.[34]

Indeed, SN can be seen as a useful with several benefits when used correctly, as they would help with sharing and communicating updated and relevant information. So, older adults play an active role in the decision to get vaccinated against COVID-19. The way these channels can influence older adults is elegantly approached in a recent manuscript[35] in which loneliness, lower life satisfaction, and more depressive symptoms were improved with the use of internet. Then, SN could be a mediator for vaccine hesitancy.

To the best of our knowledge this is the first report to explore the impact of SN in older adults when making decisions related to getting the COVID-19 vaccination. This is a large representative sample, while the latest national sample of COVID-19 information shows important relationships and information that could be of interest for public health policies. Furthermore, it helps to reduce the gaps in knowledge and increases opportunities for future studies.

The limitations of our study are related to the misconceptions among the population on what COVID-19 is and the lack of qualitative data to improve the knowledge of social network use in older adults. This, in turn, can be seen as a gap that could be bridged with further studies on this phenomenon. The information on COVID-19 vaccination was obtained before the efficacy of the vaccine had been proven. Still, these data are important due to the sample size and being one of the few larger studies made in Latin American populations.

CONCLUSIONS

Keeping in mind the new infection outbreak and the potential risk for older adults, stronger campaigns to reach out and convince them seem to be a matter of life and death. Considering the results and understanding the multifactorial nature of the decision process, social networks, particularly WhatsApp, could be useful in lowering the numbers of hesitant older adults.

https://doi.org/10.36105/psrua.2022v2n3.02

Similar strategies could be also implemented in regions where hesitancy is even higher and authorities struggle to advance in the vaccination campaigns.

ACKNOWLEDGEMENTS

The authors thank the ENSANUT team.

STATEMENT OF ETHICS

This research was conducted ethically in accordance with the Declaration of Helsinki of the World Medical Association. Informed consent was obtained from the original ENSANUT.

CONFLICT OF INTEREST

The authors have no economical, personal, or potential conflict of interest.

FUNDING SOURCES

There were no funding sources for this study. The funding of ENSANUT are described elsewhere.

AUTHOR CONTRIBUTIONS

All authors revised and approved the submission of this manuscript. MUPZ contributed to the concept and design of this study, MUPZ, JFV, VGC & JSSM contributed to the procurement, analysis, and interpretation of the information and data. All the authors worked on the draft for this manuscript and contributed to revisions of the manuscript. MUPZ, JFV were responsible for the statistical analysis.

DATA AVAILABILITY STATEMENT

Publicly available datasets were used in this study. These can be found in ENSANUT at https://ensanut.insp.mx/encuestas/ensanutcontinua2020/index.php[36]

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Proceedings of Scientific Research Universidad Anáhuac, 2022, 2(3): 20-26.
ISSN: in process.

Research Article

Effect of early or late nutritional intervention with psychological support on symptoms associated with Anorexia Nervosa: a comparative study

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https://doi.org/10.36105/psrua.2022v2n3.03

ABSTRACT

Introduction: Anorexia nervosa (AN) is a disease with increasing incidence and prevalence, favored by biological, psychological, familial, and social factors. Management must be interdisciplinary, involving the intervention of nutritionists and psychologists. Additionally, it is important to evaluate the effect of an early or a late onset of the intervention. **Objective:** To determine if early nutrition-based intervention along with psychological support leads to a decrease in the symptoms associated with Anorexia Nervosa, when compared with late intervention. **Methods:** To evaluate the above parameters, an exploratory study was proposed with a design of non-randomized clinical trial and a non-probability purposive sampling of n = 17 women with AN between 12 and 25 years of age ($\bar{x}$ = 16.8 ± 3.6). According to the moment of the nutritional intervention with psychological support, the 17 women were divided into two groups: Group 1 (n = 10) start the intervention in the first six months after the onset of the disease while Group 2 (n = 7) started 3 years after the disease. The nutritional and psychological carried out consisted of three phases: individualized nutritional assessment, design of the meal plan according to the metabolic needs of each patient and nutritional indications, and an individualized psychological intervention. Both interventions were carried out once a week for six months, for a total of 24 psychological and nutritional sessions. The physical variables of body mass index (BMI) and arm muscle area (AMA) were measured. To assess emotional changes, the body image dissatisfaction subscale of the Eating Disorder Inventory (EDI) was used. **Results:** Six months after follow-up, the results showed statistically significant changes in the BMI ($p <,0.01$), AMA ($p <,0.01$) and body image dissatisfaction ($p <,0.01$) after the intervention. It was found that the early-intervention group presented lower values in BMI and AMA as compared to the late-intervention patients while both groups showed a marked reduction in body image dissatisfaction values. The late-intervention group presented the sharpest reduction. There was no significant difference in the variables BMI and AMA in the intragroup comparisons. **Conclusion:** The early-onset nutritional intervention with psychological support decreased the physical and emotional symptoms associated with AN.

Key words: anorexia nervosa; nutrition disorder; psychology; early intervention; late intervention.

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Received: 13 December 2022.
Accepted: 18 March 2022.

RESUMEN

Introducción: La anorexia nerviosa (AN) es un padecimiento cuya incidencia y prevalencia va en aumento, favorecido por factores biológicos, psicológicos, familiares y sociales. Por lo anterior, el manejo debe ser interdisciplinario e involucrar la intervención no solo de nutriólogos sino también de psicólogos que apoyen el estado emocional del paciente. Además se debe analizar cuál es el efecto de estas intervenciones cuando se inician de forma temprana o tardía. **Objetivo:** Determinar si una intervención nutricional con apoyo psicológico de inicio temprano produce una disminución de la sintomatología asociada a la Anorexia Nerviosa en comparación con una intervención tardía. **Métodos:** Con la finalidad de evaluar los parámetros anteriores, se planteó un estudio exploratorio con diseño de ensayo clínico no aleatorizado y una muestra no probabilística intencional de n = 17 mujeres con AN entre las edades de 12 y 25 años ($\bar{x}$ = 16.8 ± 3.6). De acuerdo con el momento de la intervención nutricional con apoyo psicológico, se dividió las 17 mujeres en dos grupos: el Grupo 1 (n = 10) inició la intervención en los primeros seis meses posteriores al inicio del padecimiento y el Grupo 2 (n = 7) inició 3 años después del padecimiento. Se realizó una intervención nutricional de tres fases: valoración nutricional individualizada, diseño del plan de alimentación según las necesidades metabólicas de cada paciente e indicaciones nutricionales y una intervención psicológica individualizada. Ambas intervenciones se llevaron a cabo una vez por semana durante seis meses (un total de 24 sesiones de psicología y nutrición). Para conocer el efecto de la intervención se midieron las variables físicas de índice de masa corporal (IMC), y área muscular de brazo (AMB). Para medir los cambios emocionales se utilizó la subescala de insatisfacción corporal del Inventario de desórdenes de alimentación (EDI). **Resultados:** A los seis meses de seguimiento, los resultados mostraron que el grupo de inicio temprano presentó valores significativamente menores en IMC ($p < 0.01$) y AMB ($p < 0.01$) en comparación con el grupo de intervención con inicio tardío. Ambos grupos presentaron una disminución significativa en la variable de insatisfacción corporal con respecto a sus valores basales ($p < 0.01$), pero el grupo de inicio tardío presentó una mayor disminución. No hubo diferencia significativa en las variables IMC y AMB en las comparaciones intragrupales. **Conclusión:** La intervención temprana nutricional con apoyo psicológico disminuyó la sintomatología física y emocional asociada a la AN.

Palabras clave: anorexia nerviosa; desorden nutricional; psicología; intervención temprana; intervención tardía.

INTRODUCTION

Anorexia nervosa (AN) is the most common psychiatric disease among young women. The studies report a prevalence of 1.7% in women against 0.1% in men.[1] As the eating disorder most often seen in adolescent females, AN is characterized by a refusal to maintain a minimally normal body weight. This behavior is due to self-imposed severe dietary restrictions or other weight-loss actions, such as purging or excessive physical activity, motivated by an intense fear of weight gain and distorted body image.[2,3] This disease shows a large variability in its presentation and severity, which conditions different therapeutic approaches and the need to individualize the treatment. Therefore, a multidisciplinary approach is necessary.[4] AN is considered the third most common chronic disease in girls between the ages of 15 and 19 and affects 0.5% of adolescent girls in western countries.[5] Mortality is increased in AN patients, usually due to starvation-related medical problems, particularly heart-related complications and severe infections.[2] Although AN occurs mainly in adolescence, a trend has now been observed to occur in both preadolescents and later ages (after 20 years); individuals aged 10–29 years reported to account for almost 100% of cases.[6] Biological, psychological, familial, social, and cultural factors determine the origin of AN and act as predisposing, triggering, or maintaining aspects of the disease, considered a multifactorial disorder.

It is necessary to implement a therapeutic intervention against AN at an early stage of the disease due to its clinical characteristics, etiology, increasing incidence, costly treatment, and morbidity and mortality rates of adolescent girls in western countries.[2] The treatment of AN requires a multidisciplinary approach that includes pediatricians, nutritionists, and psychologists. The therapeutic approaches vary depending on the patient's condition but have the common purpose of refeeding the patient and improving their psychological functions.[7] Psychological therapy plays a central role in identifying the basis for concerns about weight gain and alterations in food intake.[8] This is the reason why the initial focus is behavioral change supported by changes in family dynamics that allow risk behaviors to be identified.[9] Early therapy in individuals with AN may have significant benefits and lead to sustained weight gain.[10] Consequently, the gain above 1.8 Kg in the first 4 weeks of treatment increases the recovery rate at 12 months.[11]

It is important to highlight the role that the environment plays in individuals suffering from AN and the need for a family support network, particularly in young populations.[10–12]

This study aimed to find out whether nutritional intervention (calorie supply according to metabolic needs) with

psychological support effectively reduces the symptoms associated with AN. Additionally, the investigation intended to determine if there are differences between the early or late start of this intervention.

MATERIALS AND METHODS

Informed consent was obtained from the patients prior to their participation in the study. The parents of patients under the age of 18 signed the consent and the minors had to agree to participate in the study. The study was conducted in accordance with the ethical principles specified in the Declaration of Helsinki and Good Clinical Practice guidelines. It was approved by the institutional review board and the research committee (number of registration: 201315) before its start.

Study design: As this is an exploratory study, no sample size was calculated. In this first stage, a non-probability purposive sample of 17 patients. Ten patients had an early nutritional intervention with psychological support during the first six months after the onset of the disease. The other seven received a late nutritional intervention with psychological support three years after the onset of the condition. This sample size allowed the detection of an effect size of 0.1 or larger.

Study population: Patients were eligible for participation if they were between ages 12 and 25 and required no hospitalization. The inclusion criteria included: diagnosis of restrictive or purgative AN, female gender, BMI in 3–25 percentiles according to the NIH growth charts[13], and minimum schooling of 5th grade to read the instructions and understand the reagents of the tests and questionnaires applied. The exclusion criteria were patients who presented risky eating behaviors, received nutritional treatment in the last six months prior to the start of the study, were outside the proposed age range, had a borderline or psychopathic personality disorder, suffered euthyroid sick syndrome, and received previous pharmacological treatment.

Procedure: A complete assessment (individual interview) was carried out to select the subjects. Once the diagnosis was obtained, patients who met the inclusion criteria were invited to participate in the study. All the patients provided their informed consent and, if they were underaged, their parents' approval was requested. The nutritional treatment began was provided for six months, once a week in 30-minute sessions with each patient as follows:

1. The Nutrition intervention included an meal plan that met the energy requirements of each patient to recover body composition by weight. Likewise, the nutritional goals for the patient and the family at home were established.
2. The anthropometric evaluation of BMI[14] and AMA[15] followed the Manual of Procedures of the Ministry of Health, Mexico (2002).

The study subjects were weighed and measured; then, the BMI was calculated as follows:

$$\frac{Weight\ (Kg)}{Height\ (mts)^2} = Body\ Mass\ Index\ (BMI) \qquad (14)$$

For the measurement of the AMA, the triceps fold was taken by the thumb and index finger on the posterior midline of the upper arm at the mid-acromiale-radiale site; it was taken vertically and parallel to the longitudinal axis of the arm. The arm circumference was taken at the midpoint between the acromion and the olecranon; the tape was placed perpendicular to the longitudinal axis of the humerus, the elbow was extended, and the muscles relaxed. Subsequently, the AMA was calculated with the following formula:

$$MAC-(\pi \times TSF)]\ 2/4\pi = Arm\ Muscle\ Area\ (cm^2) \qquad (15)$$

MAC = Arm circumference.

TSF = Tricipital skinfold.

3. Attendance to a therapeutic dining room reestablished the eating pattern and aimed to reintroduce different foods and preparations as well as eliminate inappropriate behaviors at mealtimes, such as breaking food into very small pieces, hiding food, cleaning fat from food, and spreading food.
4. During the psychological support (45-minute sessions), the patient worked with the internal conflicts manifested through the eating behavior and concern for their body, managing to communicate what happened to them through words.
5 At the end of the six-month treatment, a psychological and nutritional evaluation was carried out to observe possible changes.

Evaluation Measure: For the evaluation of emotional symptoms, the Eating Disorders Inventory (EDI) test was used. The EDI-1 consists of 64 items with six response options (never, almost never, sometimes, quite a bit, almost always, and always). The first three options are scored 0 and the last three, on a continuum from 1 to 3, respectively. The items are grouped into eight subscales; however, for the purposes of this research, only body image dissatisfaction was analyzed. For the evaluation of the physical symptoms, BMI and AMA were used.[16]

https://doi.org/10.36105/psrua.2022v2n3.03

Statistical analysis

For the statistical analysis, Prisma GraphPad was used. A Mann–Whitney U test evaluated the difference between the groups, assessing weight and BMI, AMA, and body image dissatisfaction. Additionally, a Wilcoxon test was used to perform intragrupal analysis. To calculate the size of the effect, we used Rosenthal's r effect size for data with non-normal distribution. This test can be used alongside Mann–Whitney U-test results.

RESULTS

Patient Demographics: seventeen female patients were included in this study, all of them diagnosed with AN, single, and aged between 12 and 25 years (12 minors and 5 adults) (16.8235 ± 3.66120; $\bar{x}$ ± SD) (Table 1). Nearly half of the participants (47%) reported secondary schooling; 29.4%, high school; and 23.5%, undergraduate degree. Most of them were students (88.2%) and 11.8% were professionals. Regarding the initial nutritional status, the participants presented a minimum weight of 25.9 kg and a maximum weight of 52.7 kg (41.62 ± 7.115; $\bar{x}$ ± SD) (Table 1).

Improvement assessments: To observe if there was a significant difference between the early- and late-intervention groups (intergroup comparison), a Mann–Whitney U test was performed. Figure 1 shows that, at the baseline, both groups presented similar BMI values ($p > 0.05$). Six months later, early-intervention patients showed a lower BMI as compared to the late-intervention group ($p < 0.01$). In order to strengthen these results, we calculated Rosenthal's r effect size (clinical efficacy of the intervention). The results showed a large size effect in the early-intervention group ($r = 0.68$). There was no significant difference when comparing baseline versus six-month values in each studied group ($p > 0.05$).

In the case of AMA, the groups also started with similar basal values ($p > 0.05$; Figure 2); however, six months later, the early-intervention group presented the lowest values ($p < 0.01$). In this case, we also calculated Rosenthal's r effect size and found a large effect in the early-intervention group ($r = 0.62$). The comparison between baseline and six-month values did not

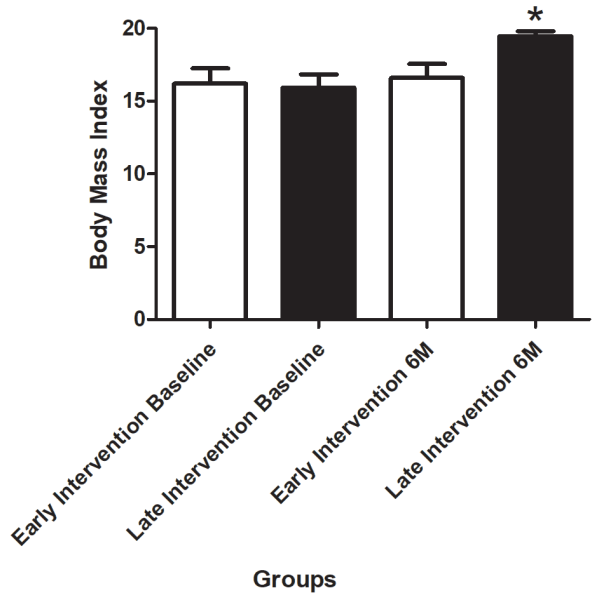

Figure 1. Body mass index (BMI) of the evaluated groups. BMI improved in early-intervention group vs late-intervention patients; *p < 0.01. The p value was calculated by Mann–Whitney U test. Each bar represents the mean ± SD of 10 (early onset group) and 7 (late onset group) individuals.

Table 1. Characteristics of the participants at baseline.

Variables	Description	Percentage %	Mean ± SD	Median-range
Age (years)	12-25		16.82	
Marital Status				
Single	17	100		
Occupation				
Student	15	88.2		
Employee	2	11.8		
Schooling				
Secondary	8	47.1		
High school	5	29.4		
Degree	4	23.5		
Weight (Kg)	25.9–52.7		41.629 ± 7.115	
BMI*	14.90–17.29			16.0–2.39

*Body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

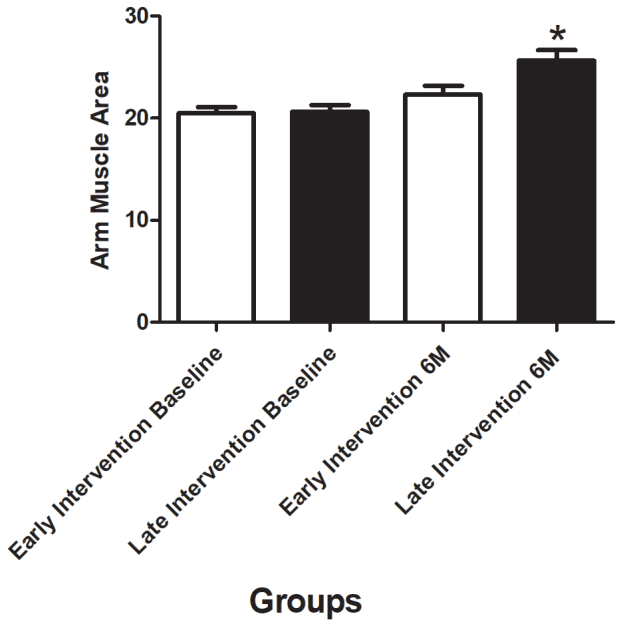

FIGURE 2. Arm muscle area (AMA) in evaluated groups. AMA was lower in early-intervention patients vs late-intervention group. *p < 0.01; Mann–Whitney U test. Each bar represents the mean ± SD of 10 (early-intervention group) and 7 (late-intervention group) individuals.

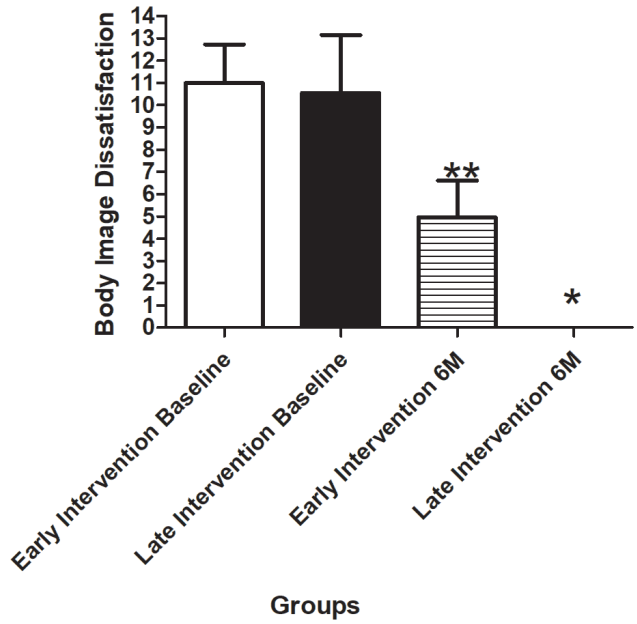

FIGURE 3. Body image dissatisfaction of the assessed groups. Late-intervention group showed a higher improvement. *p < 0.01 vs baseline values; Wilcoxon test. ** p < 0.05 vs baseline values; Wilcoxon test. Each bar represents the mean ± SD of 10 (early-intervention group) and 7 (late-intervention group) individuals.

show a significant difference in any group (p > 0.05). With respect to the psychological variable (body image dissatisfaction), the groups presented similar values of dissatisfaction from the beginning (p > 0.05). Six months later, there was a significant improvement in both groups. In this case, the late-intervention group improved more as compared to the early-intervention group (p < 0.01; Figure 3).

DISCUSSION/CONCLUSION

According to the results, the early-intervention participants showed improvement in physical (BMI, AMA) and emotional (body image dissatisfaction) variables, while there was only emotional improvement in the late-intervention group. These observations allow understanding the importance of an early intervention. Additionally, the results suggest that psychological intervention could be an important therapeutic element to improve the patients' physical features and their emotional perception of themselves, a key aspect in AN therapy. This could be supported by the results observed in the late-intervention group, where the emotional perception of their image improved despite the absence of important changes in physical variables. This topic should be deeply studied in future research since this improvement likely favors a change in physical parameters in the long term as compared with the early intervention. To date, there are no works comparing anthropometric indicators (BMI, AMA) and emotional changes in AN patients and the time treatment starts with respect to the onset of the disease. Further research is suggested in this regard.

The Academy of Nutrition establishes that, within nutritional management, the first thing to do when faced with AN is to determine whether it can be managed from an outpatient setting or meets hospitalization criteria.[17] For the purposes of this study, all cases met the criteria for outpatient treatment.[17] In line with this, Roob et al. suggest that treatment for patients with early AN must be through outpatient programs, in the company of a multidisciplinary team.[18] This observation supports our finding that AN patients are treated by a multidisciplinary team.

It has been observed that AN patients tend to choose the same types of foods at each meal for fear of eating foods they consider caloric or inappropriate. These eating behaviors persist during short-term recovery. Therefore, the participants in our study were able to modify their eating habits, reducing the restriction by normalizing their eating pattern. They consumed portions according to their eating plan, including a greater variety of foods, complying with the meal schedules and liquid consumption.[19] In addition, it has been seen that those responsible for providing food at home should be included to achieve a better compliance with the meal plan and the nutritional indications. Therefore, nutrieducational sessions for the families were carried out; in them, portion sizes and food groups were taught, as well as the reason for the nutritional indications. Similarly, it has been suggested that

https://doi.org/10.36105/psrua.2022v2n3.03

nutritional indications should be followed at the treatment location and at home.[7]

In the present study, the participants became aware of some situations that triggered unpleasant emotions; for example: weighing themselves, exam periods at school, getting grades, discussions/arguing with relatives at home, discussions/arguing with their partner. Then, they learned to recognize and express their emotional states without having to control their diet and their body by being able to differentiate and separate them from eating. Consequently, body dissatisfaction decreased and the participants showed improvement because they managed to positively relate to their body while they restructured distorted thoughts.

In conclusion, the nutritional intervention with psychological support decreased the physical and emotional symptoms associated with AN. The present study was carried out in a Mexican population and included nutritional and psychological variables. It acquires a particular relevance since the studies that are typically carried out are only psychological. In summary, it is advisable that the restoration of both the nutritional status and body weight be gradual, according to each patient's tolerance. In addition, there should be a focus on nutrient intake and not calorie intake, along with psychotherapy, to encourage increased quantity and diversity in food selection. The aim is to restore the nutritional status, restructure thoughts, and modify behaviors characteristic of an eating disorder.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors thank the Angeles Clinic for Eating Behavior Disorders for allowing us to use its data in this research and the Anahuac Health Sciences Research Center for its mentoring.

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https://doi.org/10.36105/psrua.2022v2n3.03

Proceedings of Scientific Research Universidad Anáhuac, 2022, 2(3): 27-35.
ISSN: in process.

Review Article

Bioinformatics approaches for Biomedical Research

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https://doi.org/10.36105/psrua.2022v2n3.04

ABSTRACT

An enormous amount of data is generated and compiled in several databases every year. Along with this, comes a demand for the analysis and interpretation of the entirety of this biological information. Taking care of this task, bioinformatics promises breakthroughs in research and development in complex biomedical areas. In just a few years since its beginning, bioinformatics has led to great progress and demonstrated its potential. It has created an opportunity to solve arising medical and molecular issues faster and more efficiently, as compared to the traditional approach. The present review aims to present some of the main applications of bioinformatics in the field of biomedicine, such as comparative genomics, biomarker identification, computer-aided drug design, vaccine design, and personalized medicine. In addition, we also cover some of its steadily reduced limitations.

Key words: bioinformatics; biomedicine; comparative genomics; biomarkers; computer-aided drug design; vaccine design; personalized medicine.

RESUMEN

Cada año se genera una enorme cantidad de datos recopilados en bases de datos. Junto con esto surge una demanda de análisis e interpretación de la totalidad de la información biológica; esta importante tarea es atendida por la bioinformática, la cual promete grandes avances en la investigación y desarrollo de áreas biomédicas complejas. En tan sólo unos años desde su inicio ha llevado a un gran progreso y ha demostrado su potencial, creando una oportunidad para resolver los problemas médicos y moleculares de manera más rápida y eficiente en comparación con el enfoque tradicional. El presente artículo pretende discutir algunas de las principales aplicaciones de la bioinformática en el campo de la biomedicina, tales como, genómica comparativa, identificación de biomarcadores, diseño de fármacos, diseño de vacunas y medicina personalizada. De manera adicional, se enlistan algunas de sus principales limitaciones, las cuales están en constante disminución.

Palabras clave: bioinformática; biomedicina; genómica comparativa; biomarcadores; diseño computarizado de fármacos; diseño de vacunas; medicina personalizada.

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Received: 19 November 2021.
Accepted: 14 February 2022.

INTRODUCTION

With the increasing development of next-generation sequencing (NGS), large-scale high-throughput molecular profiling studies and omics sciences, we now have a better understanding of the complex nature of numerous illnesses.[1] Each year, large amounts of data are generated and compiled in freely accessible databases[2], bringing along a high demand for their analysis and interpretation. This is managed by evolving bioinformatics.

Bioinformatics is defined as an interdisciplinary science that applies computational tools and analysis to the capture and interpretation of biological data, which brings together computer science, mathematics, physics, and biology.[3] It requires research, development, and application of informatics tools and approaches to acquire, store, visualize, and interpret biological and medical data.[4] It allows to test hypotheses through *in silico* methods to have a better knowledge before proceeding with expensive studies. In addition, bioinformatics provides results that are more accurate when assembling reliable interpretations. Therefore, it promises breakthroughs in research and development in complex biomedical systems as well as public health, drug design, comparative genomics, and personalized medicine, among others.[5]

From the first use of molecular sequences for evolutionary studies by Zuckerkandl and Pauling (1965)[4] to the massive up-to-date sequencing programs, bioinformatics has evolved just as much as its matter of study.[6] It has branched out into bioinformatics tools applicable in genomics, proteomics, drug design, and simulations of molecular dynamics. Combined, they provide a more complete understanding of how diseases work.[7] As an emerging field, it is essential for managing data in modern biology and medicine; for instance, it is a major protagonist in the development of all vaccines against COVID-19.[8] (Fig. 1).

In the present review, the main points on topics of novel interest in the area of applied bioinformatics in biomedicine are discussed.

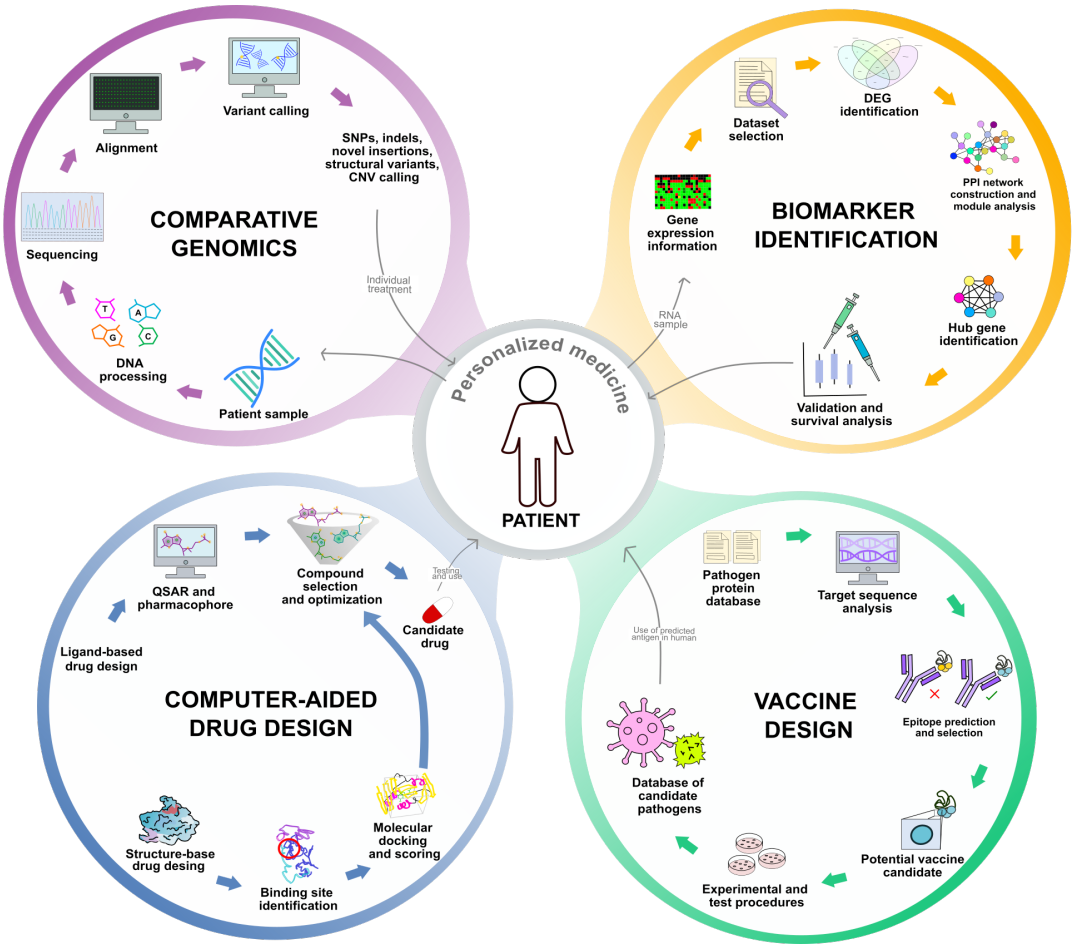

FIGURE 1. Applications of bioinformatics in biomedicine. The general workflow starting from the patient is summarized for each bioinformatics application: Comparative genomics, biomarker identification, Computer-aided drug design, and vaccine design. SNPs: single nucleotide polymorphisms; CNV: copy number variation; DEGs: differentially expressed genes; PPI: protein-protein interaction; QSAR: quantitative structure–activity relationship.

https://doi.org/10.36105/psrua.2022v2n3.04

Comparative genomics

Since the sequencing of the human genome, scientists have developed a special interest in the field of biological research called comparative genomics (CG).[9] CG can be defined as the comparison of biological information derived from whole genome sequences.[10] It aims to determine similarities and differences between genomes to provide information about the biology of the respective organisms, describing the structure and identifying coding and non-coding regions of the genome.[11] The comparison of DNA sequences can be applied in several areas. This information reveals the molecular basis of individuality, uncovers novel regulatory mechanisms, predicts the metabolic capabilities of an organism, and enables the prediction of gene function, among others.[10] Assuming that you have a complete genome, the steps in CG start with genome annotation; that is, gene finding and function assignment.[12] The process of gene search predicts the section of the genome that contains genes while the function assignment seeks to predict the function of the coded proteins. This process is performed by automated software algorithms, called pipelines, using resources from databases and biological data. Annotation allows for clustering genes in homolog or ortholog families.[12] Diverse applications can be inferred with comparative genomics; in definition, unique signatures can be detected by forensic microbiology.[13] For instance, virulence and antibiotic resistance genes can be identified as targets for genetic manipulation in public health. Sequence comparison can be used to identify specific types of parasites for treatment or diagnosis.[14] Nowadays, the comparison of SARS-COV-2 distribution, spread, and evolution uses CG for multiple purposes.[15] It can also be used in the advanced molecular characterization of infectious agents in clinical environments. This could improve both the identification and genetic characterization including resistance profiles, promoting outbreak investigations and molecular surveillance.[16] For instance, the comparison of metagenomes could help to understand the dynamics of a given microbiota, disease versus healthy states (e.g., cancer tumor versus normal tissue)[17], different diets[18], and different geographical locations.[19]

Biomarker identification

Biomarkers can be defined as "an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention"[20], which may have a monitoring, diagnostic, or predictive value[21]. They can be single nucleotide polymorphisms (SNPs), structural variants, circulating DNAs, methylated DNAs, mRNAs, microRNAs (miRNAs), proteins, and metabolites.[22]

In genomics, there are two approaches, the search for unique genetic variants that can act as predictors of disease and the composite predictor in the form of a genetic risk score.[23] On their behalf, the RNA and protein profiling strategies have an important biological impact. Despite current practical limitations, transcriptomic assays together with proteomics can provide essential biological information.[24] This kind of analysis is performed thanks to high-throughput technologies, including RNA sequencing and microarrays.[24] Bioinformatics analysis is a valuable tool with great potential, especially when there is a discrepancy between genomic alterations and gene expression. Statistical tools are used to differentiate signal and noise in the output of gene expression.[25] Gene expression meta-analysis is increasingly used in many fields to improve the reproducibility of a study and discover new robust biomarkers.[26] The necessary data are frequently obtained from the gene expression omnibus (GEO) database. Additionally, metabolomics, the profiling of metabolites in biofluids, cells and tissues, is routinely applied as a tool for biomarker discovery.[27] A metabolome-based strategy for identifying candidates with biological activity would consist of statistically analyze a list of metabolites generated from databases. Metabolic pathways and bioinformatics analysis of interaction networks can be used to reduce data complexity.[28] The most important step in determining the activity is to use an appropriate screening strategy. This includes gene expression, protein expression, and protein activity, the modulation of desired cellular phenotypes.[28]

The protein/gene-protein/gene interaction networking, hub gene identification, gene enrichment, and functional gene annotation analyses are powerful tools for the identify potential diagnosis and treatment biomarkers in diseases such as cancer[1,2,29-31], bipolar disorder[2], depression[32], diabetes[33], arteriosclerosis[34], and others. For instance, Wan et al. in 2020 applied bioinformatics analysis to identify eight candidate genes that could be a potential prognostic marker of thyroid carcinoma based on expression analysis profiles from the GEO database.[31] Liu et al. in 2019 identified several hub genes and key pathways associated with bipolar disorder (BD) based on a gene co-expression network analysis, which might have important clinical implications for BD treatment and diagnosis.[35]

Computer-aided drug design

The traditional methodology for novel drug discovery is a costly, extremely risky, and time-consuming process. Indeed, 75% of the total cost of drug development corresponds to lead molecules in clinical trials that never enter the consumer clinical market.[36] The steps of traditional drug discovery can be summarized as follows: target identification, target validation, lead identification, lead optimization, preclinical stage, and clinical trial stage.[37]

To address the challenges of traditional drug discovery, new strategies such as computer-aided drug design (CADD) have been developed. CADD comprises approaches such as *ab*

initio design, toxicity profile, quantitative structure–activity relationship (QSAR), docking, molecular dynamics (MD), quantitative free-energy calculations, and homology modeling.[38]

These approaches can be classified in two categories: structure-based drug design (SBDD) and ligand-based drug design (LBDD). The first depends on the availability of the 3D target structure to screen promising ligand molecules by calculating the interaction energies between the target and compound. The knowledge of the binding site in the target protein structure is used to identify and evaluate ligands based on their interactions with the residues present in the active site.[39] LBDD is used when the drug target structure is unavailable. The knowledge of the molecules interacting with the drug target is applied to develop pharmacophore and 3D-QSAR models to understand the characteristics a molecule must possess to bind to the target.[40]

CADD has emerged as a crucial ally in the design of therapeutic agents against COVID-19 since the beginning of the outbreak. For instance, Elfiky (2020) used homology modeling, MD, and molecular docking to report the relevance of sofosbuvir, ribavirin, galidesivir, remdesivir, and others as candidate drugs for clinical trials.[41]

Vaccine design

Vaccine design is supported by bioinformatics, which identifies and predicts the essential components of a vaccine (target antigen, B and T epitopes, linker, and adjuvant). These could be coupled with molecular modeling, MD simulations, and protein–protein docking, among others, to help scientists predict the adequate properties of vaccine construction in a shorter time by making conscientious decisions. Vaccine design allows the analysis of pathogenic organisms that cannot be cultivated *in vitro* and improves the allergen filter process for a better selection.[3,42]

Reverse vaccinology (RV) and Structural vaccinology (SV), two bioinformatics procedures, result in fundamental steps to achieve an optimum vaccine. RV defines the process of antigen discovery for further vaccine development, starting from genome information.[43] It involves the identification of novel antigens and the design of B- and T-cell epitopes through the study of the genome of an organism.[44] It is also useful to find genes encoding proteins that could reveal adequate epitopes.[45-47] RV employs software to determine antigenic and physicochemical characteristics associated with antigenic epitopes.[48] On the other hand, SV uses 3D structural information to design novel and/or improved peptide-based vaccine antigens.[49] It assesses the 3D molecular structure of the epitope in the antigen–antibody complex, creates MD simulations to predict and model the epitope and its interactions, tests reengineered antigen into immunoinformatics platforms (i.e., epitome), and finally assesses vaccine candidates (VC) for efficacy and safety *in vivo*.[50]

Diverse platforms exist with the purpose of exploring epitopes and simulating antigen-protein docking, present antibody structures, and antigen-antibody reactions, among others. Many of these pipelines have been created or refocused before the advent of the pandemic.[44,51]

Recently, the procedures mentioned above have been used extensively in the face of the emergence of the COVID-19 pandemic. Due to the current context, whole genome sequences have been available since December 2019 and, therefore, were perfect candidates for vaccine design. In this sense, Grifoni et al. (2020) made predictions for effective epitopes that can facilitate a vaccine design against the SARS-COV-2 virus, especially supported by the platform IEDB and its incorporated tools as ViPR[52] designed a multi-epitope peptide vaccine against COVID-19 using immunoinformatics. They used IEDB for T-cell epitope prediction and RaptorX[5] for 3D structural modeling.[53]

Personalized medicine

Personalized precision medicine is a new strategy where different methods, diagnoses, and therapies are applied to the peculiarities each patient presents. It also serves as prevention of emerging diseases, considering the patient's genome, lifestyle, and environment. This may improve side effects related to medications and generate successful therapies. Thanks to the advances in bioinformatics in recent years, changes have been generated in medicine and treatments for patients. An earlier detection of diseases has been achieved, along with a better targeted therapy. In addition, genome sequencing and data analysis have played a key role in the development of efficient personalized medicine.[22]

The main tools of precision medicine are multi-omics techniques and the data obtained from these, such as DNA sequences, transcriptomes, proteomes, metabolomes, epigenomes, and microbiomes. There are different bioinformatic tools for the data processing and analysis of genomic sequences, while the software to be used depends on the origin of the genetic information.[54]

The new sequencing technologies and their rapid development gave rise to the so-called new P4 medicine (predictive, preventive, personalized, and participatory), with novel approaches, opportunities, and challenges.[55] Firstly, because of prediction and a deeper knowledge of biology and diseases using genomic technologies, individuals prone to certain diseases can be identified even before they show symptoms. Secondly, prevention depends on early detection. People can be

https://doi.org/10.36105/psrua.2022v2n3.04

guided to improve their lifestyle, due to the risk of contracting certain diseases, avoid health problems, and choose the best treatment for their disease. Thirdly, personalization is related to the knowledge of the patient's genome and lifestyle. By understanding the biology of the disease in a better way, an adequate therapy can be prescribed, resulting in fewer unwanted side effects.

Finally, the participatory approach uses the patient's information. Platforms and tools are created for the discussion of diseases and allow for general knowledge.[55,56]

Advances in bioinformatics in precision medicine improve efficiency in the way people are characterized and the way personalized medicines are made and tested to demonstrate their usefulness. With the big data obtained, there is a better understanding of the diseases of certain groups of patients, a better diagnosis, as well as a better development of specific drugs. It is possible to reduce the adverse effects of aggressive treatments and generate more information on rare and complex diseases. The holistic approach of personalized precision medicine will help to gain more information to improve people's quality of life.[56]

Limitations of bioinformatics

Bioinformatics has proven to be a useful tool in scientific research fields. It provides an exceptional and outstanding platform and opportunity for scientists to integrate omics science[57], bioinformatics tools and data, clinical research, disease-specific biomarkers[58], dynamic networks, and precision medicine.[59] It creates an opportunity to solve arising issues faster and more efficiently.

Nevertheless, technological biases and limitations may not have been sufficiently considered in the development of bioinformatics tools. Herein, we mention and further explain what we consider to be the main limitations bioinformatics face and how technology must move forward in order to bridge these gaps.

1. Amounts of data

Contemporary sequencing technologies are capable of generating as much as 600–1000 GB per run. Further analysis of raw sequences will increase the amount of data by a factor of ten to twenty in each analysis. This general development of sequencing techniques has led to an increase in the depth of sequencing, generating a critical problem of data storage.[60] The rapid development of sequencing techniques has brought sequencing-based research to bear in all areas of life sciences. However, as the technology grew faster than its computational counterpart did, unforeseen amounts of sequencing data were generated, posing a real challenge for data analysis and bioinformatics in general.

2. Dependence on reference databases

Most bioinformatics analysis pipelines depend on sequence comparison against reference databases.[61,62] This can be problematic considering the potential incompleteness of databases. The increased error rate of the current emerging long-read technologies can have a negative impact on biological interpretations. For example, errors in protein-coding regions can affect the accuracy of protein predictions.[63] Recent studies apply correction methods (hybrid error correction) to show that the original error rate of 19% is the limit for perfect correction; beyond that, long reads are too error-prone to be corrected by these methods. Therefore, updated databases with better quality data and innovative bioinformatics tools are necessary to support a stable and effective analysis.[64]

3. Genetic information privacy

Genetic testing companies that offer direct-to-consumer (DTC) services are in constant growth, raising new privacy and ethical concerns. These companies collect data from increasing numbers of people, some of whom may have shared their data without knowing the consequences for themselves and their blood relatives.Privacy breaches can have serious social implications and adversely affect genomic-driven research by decreasing data collection and data sharing.[65,66] Then, it is essential to ensure privacy as both a fundamental right for individuals and a strategy to support responsible data sharing.

4. Experimental proof and lab work are still required

Bioinformatics findings and research may provide evidence for the progress of potential biomarkers and help understand the role of certain genes and/or proteins in any given ailment. Still, these theoretical breakthroughs are still to be proven experimentally if they are used as therapeutic treatments.[67-69] So, public and private investment for the generation and transfer of knowledge could support the development of high-quality translational and collaborative research. This, in turn, will prevent and help to face menacing situations, as the current COVID-19 pandemic, or older issues such as obesity and cancer.[70]

5. Bioinformatics: not for everyone

Every novel or inexperienced user of bioinformatics, from ecologists to population geneticists or cell biologists, deal with bioinformatics matters. As stated above, bioinformatics plays an increasingly central role in biological research, medicine, and other areas of human life. Then, we need sophisticated and user-friendly bioinformatics resources to accompany it. The

ability to access and study molecular sequence data should not be reserved for those with exceptional computer skills but be made available to all scientists, medical professionals, and the general population.[71]

CONCLUSION

Bioinformatics is a relatively young field compared to other areas. It is rapidly growing and has a great impact in biomedicine. Despite its limitations, it has led to great progress over the years and has demonstrated its potential use for a better understanding of molecular mechanisms of diseases. This allows us to identify biomarkers, create 3D molecular models, screen drugs, predict vaccines, and achieve personalized medicine. In brief, the rapid development of bioinformatics tools, software, genomics, transcriptomics, proteomics, and metabolomics data has greatly facilitated biomedical research. It has also enhanced the understanding of the biological meaning of DNA/RNA/protein modifications, interactions within complex organism networks, and the discovery of new ways to accurately apply this knowledge, enabling new therapeutic measures. This helps us to better face diseases from an increasingly broader perspective, safer, more effective, and more specific.

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Proceedings of Scientific Research Universidad Anáhuac, 2022, 2(3): 36-40.
ISSN: in process.

Case report

Philadelphia-positive atypical chronic myeloid leukemia, BCR/ABL negative: a case report

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https://doi.org/10.36105/psrua.2022v2n3.05

ABSTRACT

Atypical myeloid leukemia is a myeloproliferative neoplasm in which patients have a dysplastic increase in blood cells of the myeloid lineage as a result of hypercellular bone marrow. Our patient presented a positive Ph karyotype and a negative ABL/BCR transcript. Moreover, her age does not correspond to the mean of diagnosis. Her first treatment was hydroxyurea 1 g/kg for 60 days, which was not positive for the evolution of the disease and thus the elective treatment was changed to imatinib 400 mg/day. After two months, the treatment has produced a favorable response, which leads to think that the therapy with imatinib offers better clinical results than other conventional ones. This text presents the study carried out at the Manuel Ávila Camacho National Medical Center and compares it with the existing literature regarding diagnosis and treatment to assess similarities and highlight specific points that may help in future case management.

Key words: atypical CML; Ph positive; ABL/BCR negative; hydroxyurea; imatinib.

RESUMEN

La leucemia mieloide atípica es una neoplasia mieloproliferativa en la que los pacientes presentan un incremento displásico de células sanguíneas del linaje mieloide como resultado de una médula ósea hipercelular. Nuestra paciente presentó un cariotipo Ph positivo y un transcrito ABL/BCR negativo y se encuentra en una edad no correspondiente a la media de diagnóstico. Su primer tratamiento fue hidroxiurea 1 g/kg durante 60 días, el cual no resultó positivo para la evolución de la enfermedad. Por ello, el tratamiento electivo se cambió a imatinib 400 mg/día y, tras dos meses de tratamiento, tiene una respuesta favorable, lo cual inclina a pensar que el tratamiento ofrece mejores resultados clínicos que otras terapias convencionales. En este texto se busca presentar el estudio realizado en el Centro Médico Nacional Manuel Ávila Camacho y compararlo con la literatura existente respecto a diagnóstico y tratamiento para evaluar similitudes y destacar puntos específicos que puedan ayudar al manejo de casos futuros.

Palabras clave: LMC atípica; Ph positivo; ABL/BCR negativo; hidroxiurea; imatinib.

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Received: 2 December 2021.
Accepted: 15 February 2022.

INTRODUCTION

Chronic myeloid leukemia (CML) is a hematologic disease characterized as a myeloproliferative disorder that gives rise to an overproduction of cells of the myeloid lineage[1]. It was first described in 1845, and ever since, multiple studies have led to a better understanding of its pathophysiology, genetics, treatment, and prognosis.[2] Genetically, it is characterized by presenting the Philadelphia chromosome, a consequence of a reciprocal translocation between the long arms of chromosomes 9 and 22. This produces the BCR/ABL transcript, a constitutively active abnormal tyrosine kinase that causes an abnormal proliferation of the entire hematopoietic line, preserving its differentiation. Atypical chronic myeloid leukemia (aCML) is a rare clonal hematopoietic stem cell disorder with the absence of a detectable BCR-ABL1 fusion or the Philadelphia (Ph) chromosome.[1,3]

CML incidence varies depending on geographical areas, and it is estimated to affect about one in 100 000 people per year.[3] Due to the low incidence of aCML compared to other hematologic disorders, it is hard to estimate a global report of aCML epidemics. Nevertheless, a study by Smith et al. (2015) using the SEER database 18, spanning from 1973 to 2011, reported a total of 114 cases with negative BCR/ABL CML and a final analysis of 82 cases of negative BCR/ABL CML.[4] The mean age of the patients was 69 years, 57% were male, and 81%, Caucasian.[4]

Signs and symptoms of CML can be classified in three phases and, depending on the stage, patients may present fatigue, night sweats, malaise, weight loss, left upper quadrant pain, discomfort, satiety, and splenomegaly. Less commonly, they may refer priapism, retinal hemorrhages, thrombosis, bleeding, or hepatomegaly.[1] The clinical features of BCR/ABL-negative CML resemble those of BCR/ABL-positive and thus specific genetics studies must be done to identify BCR/ABL and other genetic abnormalities. The 2019 American Cancer Society guidelines suggest blood count with blood film differential, cytogenetics, and bone marrow aspirate with differential to include percentages of blasts, promyelocytes, myelocytes, eosinophils, and basophils. In addition, karyotyping by G-banding is recommended to identify chromosomal abnormalities other than t(9;22) while translocation and reverse transcriptase PCR for BCR-ABL1 mRNA transcripts help in CML diagnosis. However, health care systems and technology variations between countries might hinder the fulfillment of those recommendations.[5]

In the past, the treatment for CML consisted of chemotherapeutic agents such as busulfan and hydroxyurea, but they are not very effective in eliminating the malignant clones. Novel therapies targeting specific genetic characteristics of the disease, as tyrosine kinase inhibitors (TKIs) like imatinib, have revolutionized CML therapy by improving clinical outcomes and patient prognosis.[5] However, the use of TKIs in aCML has not been vastly studied and new outcomes are evaluated every year to adequate this therapy for aCML patients.[5,6] In this work, we present the case of a 19-year-old female diagnosed with aCML and the early outcomes of her treatment with imatinib. We also show the challenges for the diagnosis and the expectations for her prognosis based on the current literature.

Case report

On June 23, 2021, a 19-year-old female patient attended our health center; she had no personal or family medical history relevant to the current pathology. Respecting the current ailment, the patient referred asthenia, adynamia, headache, and nausea for a month. Moreover, the patient informed she had suffered considerable weight loss (around 12 kg). The physical examination revealed pallor and splenomegaly of 4 cm (ULCB).

Hematic biometry was requested and the results are summarized in Table 1, showing compatibility with a myeloproliferative disorder. Due to the tests and abnormal laboratory results, a cytogenetic analysis was performed and revealed a 46, XX,t(9;22)(q34.1;q11.2) Philadelphia positive. A molecular biology analysis of negative p210 BCR/ABL fusion gene by RT-PCR was performed twice. The patient was diagnosed with aCML.

Table 1. Initial hematic biometry results (06/21/2021).

	Initial hematic biometry	Reference values
Total leukocytes	243 x 10 L	4-11 x 10 L
Hemoglobin	9 g/dL	13.0-16.0 g/dL
Hematocrit	25%	35.5-44.9%
Lymphocytes	13%	24-38%
Platelets	1.295 x 10 L	120-400 x 10 L

An initial treatment with hydroxyurea (1 g/kg/day) as single dose was established, with a monthly progress schedule checked by hematic biometry. The first month analysis reported total leukocytes of 243,000/mcL, hemoglobin of 9,3, blasts at 4%, and platelets at 1,295,000. There was no improvement on anemia since the normal range of hemoglobin normal is 9.7–9.3 g/dL (Table 1), that of thrombocytosis is 1.128,000–1,295,000 mcL, and leukocytes range from 204 to 243/mcL. In addition, no reduction in the spleen size was observed. Then, the treatment was changed to imatinib (400mg/day), with a monthly schedule for progress check-up by hematic biometry.

After two months of therapy with imatinib (monthly check-ups), the patient's laboratory tests showed remarkable clinical changes in hematologic parameters. As shown in Figure 1, there was an improvement in hemoglobin, blasts, and platelets. After the first month (30 days), the results showed an increase in total leukocytes versus the last hydroxyurea report. However, the second measurement (60 days after beginning the treatment) showed a slight reduction in the total leukocyte count with respect to the previous report.

This report was written before the check-up in the third month.

DISCUSSION

An initial CML diagnosis can represent a severe challenge due to several factors, such as epidemiological differences between countries and regions, lack of laboratory and genetics diagnosis equipment, the inexperience of clinicians, and even the ignorance of the pathology itself.[7] CML is a myeloproliferative neoplasm commonly, characterized by a triphasic natural history: an indolent chronic phase, followed by an accelerated phase, and finally, an aggressive blast phase. Depending on the phase, signs and symptoms might be confused with other diseases by the time patients see a clinician.[7,8] Likewise, it must be noted that our patient's age is outside the diagnostic mean (between the sixth and seventh decade of life) in addition to the incompatibility with the epidemiological male predominance.

The initial blood studies suggested a hematological disorder with abnormal cell proliferation. Nevertheless, the literature reports several differential diagnoses (chronic myelomonocytic leukemia, chronic neutrophilic leukemia, and essential thrombocythemia, among others) that must be excluded before a final diagnosis is established. Simple differences in hematological biometry can lead clinicians to suspect a specific blood disorder.[7] The characteristic blood count features of CML are absolute leukocytosis (median of 100,000/µL), a normal or elevated platelet count, and thrombocytopenia suggesting an alternative diagnosis or an advanced stage of the disease.[1,8]

Once the suspected CML has been established, additional tests are necessary to identify specific genetic and morphologic characteristics. If it is intended to differentiate CML from aCML, the initial tests should focus on excluding the BCR-ABL1 fusion. Cytogenetics, FISH, and PCR can help to distinguish other aCML common genetic alterations, like PDGFRA, PDGFRB, and FGFR1, among others.[7,9] In our diagnostic approach, we performed a cytogenetic analysis that revealed a 46, XX,t(9;22)(q34.1;q11.2) karyotype, and the result confirmed the existence of Philadelphia. A molecular biology analysis of BCR/ABL by RT-PCR was performed twice with a negative result for the p210 gene fusion. Despite the current American Cancer Society guidelines recommending karyotyping by G band as well as other blood parameters, the lack of technology resources and professionally trained physicians made it impossible to follow those recommendations. The sum of the results of all the studies performed led us to the diagnosis of aCML. We consider it important to highlight that if the diagnosis of aCML or other myeloproliferative disorders is unclear, recent guideline updates suggest implementing mutation sequencing, targeting JAK2, CALR, MPL, TET2, and SRSF2 among others, to reach the correct diagnosis.[5]

As stated before, the treatment for CML used to consist of hydroxyurea in combination with low doses of cytarabine or interferon. Still, the literature has reported that this therapy has poor results in increasing life expectancy and reducing

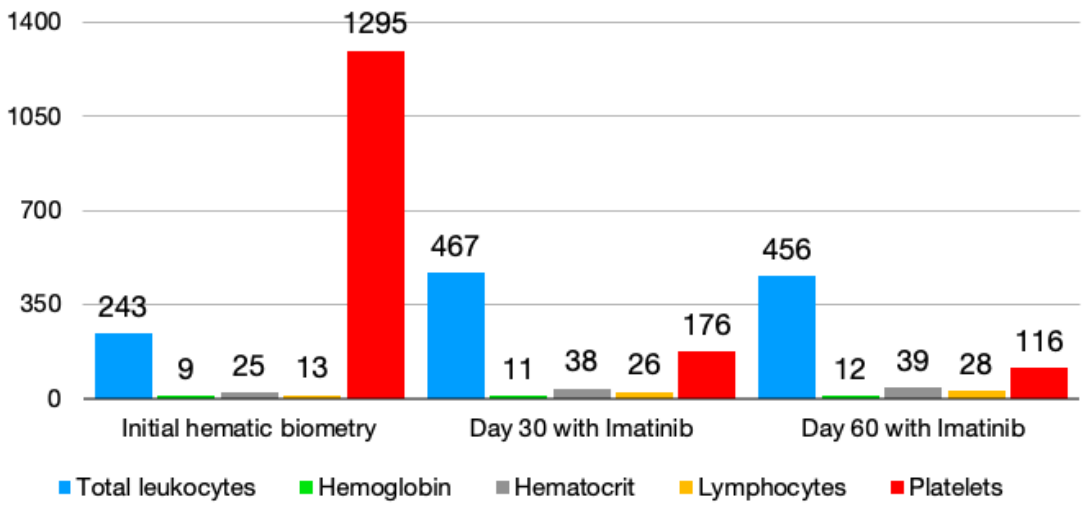

FIGURE 1. Hematic biometry (total leukocytes, hemoglobin, blasts, and platelets). Results after treatment with Hydroxyurea and first and second month after treatment with Imatinib.

https://doi.org/10.36105/psrua.2022v2n3.05

laboratory parameters worsening after 8–10 months of treatment.[7] Over the last 20 years, novel therapies, specifically TKIs, have shown promising results in treating this disease as well as other neoplastic pathologies. Focusing on aCML, several studies (most of them case reports) have shown that treatment with imatinib has succeeded in improving laboratory parameters like total leukocytes, blasts, hemoglobin, myeloid-lymphocytic rate, and symptomatology.[10] Although life expectancy has not been specified in the literature, we suggest some causes might the be absence of follow-up and reports of results after several years and death of patients due to other causes, just to mention a few examples.

Despite the reported success of imatinib usage in aCML patients, some reports suggest that specific BCR-ABL and other genetic mutations may produce resistant clones against imatinib.[11] For example, studies correlate the expression of the Ikaros variant Ik6 with high BCR-ABL1 mRNA levels and imatinib resistance in Ph+ cases.[12] Furthermore, a report from 2011 strongly suggested the existence of another oncogene present in CML and aCML that might be responsible for imatinib resistance by activating the PI3K/AKT1/mTOR pathway.[13] Nevertheless, further research must be done before establishing a direct relation between genetic aberrations and imatinib resistance.

Due to the availability of medications and the costs policy for initial therapies in oncology at our health center, our patient started treatment with hydroxyurea (1 g/kg/day) for two months. After two check-ups, the treatment showed no favorable results, so it was changed to imatinib 400 mg/day (being this the standardized initial dose recommended), providing a favorable clinical response so far.[5] Further molecular tests must be performed to identify a possible molecular improvement. The total leukocytes increased in the first measurement of this treatment, which can be explained by the null response of the patient to the two-month treatment with Hydroxyurea. Furthermore, the second measurement after imatinib treatment showed a decrease in this parameter. We expect this decrease to continue and our patient to present better hematic parameters and clinical response.

The reported side effects related to imatinib treatment include developing nonspecific clinical symptoms, such as the appearance of diarrhea, muscle aches, and fatigue. According to laboratory findings, persistent leukopenia and thrombocytopenia might also be present. In these cases, it is recommended to readjust the dosage of imatinib and evaluate a possible treatment resistance. Moreover, cases of genetic alterations as trisomies and tetrasomies have been reported after the abandonment of treatment due to non-compliance with cycles adapted to the needs of the patients.[14,15]

Some of the adverse prognostic factors have been reported in patients with a leukocyte count greater than 50 x 10^9/L, hemoglobin lower than 10mg/dL, the presence of blasts examined by peripheral blood smear, and some genetic mutations like trisomy 8 clones. Nevertheless, no reports confirm that these abnormalities directly affect patient prognosis.[12] According to the Sokal index, our patient has an intermediate risk of 0.85. Using this therapy for three months, we expect a positive hematological response, along with a normalization of the abnormalities in the hematic cytometry and the disappearance of the splenomegaly.

It would be premature to discuss the prognosis of our patient; sometimes genotypic diagnosis is usually omitted since the karyotype of patients with CML is obviated. Obtaining the karyotype of each patient is essential to proceed to an accurate diagnosis and personalized treatment. In the literature reviews consulted, leukocytosis, blasts in peripheral blood, anemia, splenomegaly, and the atypical age of the patient remain negative factors in the prognosis of this disease, while the mean survival reported does not usually exceed 25 months.[1] For these reasons, the most pertinent route is to wait for the response to the treatment with constant clinical and molecular monitoring to evaluate the response to the treatment and its follow-up over the months. It is planned to perform a third RT-PCR after the third month of treatment to find possible genetic alterations in our patient.

CONCLUSION

Due to the complexity of its diagnosis and high mortality rate, aCML is an important hematological disease. As seen in the ongoing treatment of our patient and confirmed data of the existing literature, hydroxyurea is not an efficient treatment for this pathology. Still, the treatment with imatinib has shown promising results, improving the patient's symptomatology and laboratory measurements, which correlates with previous reports of TKI usage in aCML patients. Our case faced technological and clinical limitations for the initial diagnosis. Regarding the follow-up of the patient's condition, molecular tests were performed to identify molecular improvement, molecular aberrations, or side effects likely related to the treatment. More research of common treatments for CML applied to aCML patients must be done to identify possible side effects and prognosis. We aim to contribute to this purpose by reporting significant outcomes of this patient as the treatment with imatinib goes on.

DECLARATION OF COMPETING INTEREST

The authors declare no competing financial interests.

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