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CONTENTS
CONTENIDO

RESEARCH ARTICLE

VOL. 44 | NO. 3 | **SEPTEMBER - DECEMBER 2023** | PP 6- 23

Revista Mexicana de Ingeniería Biomédica

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Neuromarkers based on EEG Statistics in Time and Frequency Domains to Detect Tinnitus

Neuromarcadores basados en Estadística de EEG en el Dominio Temporal y Frecuencial para Detectar Acufeno

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ABSTRACT

Tinnitus detection and characterization requires a carefully elaborated diagnosis mainly owing to its heterogeneity nature. The present investigation aims to find features in Electroencephalographic (EEG) signals from time and frequency domain analysis that could distinguish between healthy and tinnitus sufferers with different levels of hearing loss. For this purpose, 24 volunteers were recruited and equally divided into four groups: 1) controls, 2) slow tinnitus, 3) middle tinnitus and 4) high tinnitus. EEG signals were registered in two states, with eyes closed and opened for 60 seconds. EEG analysis was focused on two bandwidths: delta and alpha band. For time domain, the EEG features estimated were mean, standard deviation, kurtosis, maximum peak, skewness and shape. For frequency domain, the EEG features obtained were mean, skewness, power spectral density. Normality of EEG data was evaluated by the Lilliefors test, and as a result, the nonparametric technique Kruskal-Wallis H statistic to test significance was applied. Results show that EEG features are more differentiable between tinnitus sufferers and controls in frequency domain than in time domain. EEG features from tinnitus patients with high HL are significantly different from the rest of the groups in alpha frequency band activity when shape and skewness are computed.

KEYWORDS: clinical diagnosis, frequency features, hearing loss, neuromarkers, tinnitus, time features

RESUMEN

La detección y caracterización del acúfeno requiere un diagnóstico cuidadosamente elaborado debido principalmente a su naturaleza heterogénea. La presente investigación tiene como objetivo encontrar características en las señales electroencefalográficas (EEG) a partir del análisis del dominio del tiempo y frecuencia que podrían distinguir entre pacientes sanos y con acúfeno con diferentes niveles de pérdida auditiva. Para ello, se reclutaron 24 voluntarios y se dividieron por igual en cuatro grupos: 1) controles, 2) acúfeno bajo, 3) acúfeno medio y 4) acufeno alto. La actividad EEG se registró en reposo en dos condiciones: ojos cerrados y abiertos durante un minuto. El análisis de EEG se centró en anchos de banda delta y alfa. Para el dominio del tiempo, las características del EEG estimadas fueron la media, la desviación estándar, la curtosis, el pico máximo, la asimetría y la forma. Para el dominio de la frecuencia, las características de EEG obtenidas fueron media, asimetría, densidad espectral de potencia. La normalidad de los datos del EEG se evaluó mediante la prueba de Lilliefors y, como resultado, se aplicó la técnica no paramétrica del estadístico H de Kruskal-Wallis para probar la significación. Los resultados muestran que las características del EEG son más diferenciables entre los pacientes con acúfeno y los controles en el dominio de la frecuencia que en el dominio del tiempo. Las características del EEG de los pacientes con acúfeno con alta pérdida de audición son significativamente diferentes del resto de los grupos en la actividad de la banda de alfa cuando se calculan la forma y la asimetría.

PALABRAS CLAVE: acúfeno, características en frecuencia, características en tiempo, diagnóstico clínico, neuromarcadores, pérdida auditiva

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INTRODUCTION

Tinnitus refers to listening to a sound but without an external source. Being a public health problem with a prevalence from 4 % to 37 % in the worldwide population and a frequent heterogeneous auditory condition with no standard and effective treatment [1]. It is well known that tinnitus tends to mostly affect elderly population, possibly due to the hearing loss (HL) as result of aging. Youthful population who suffers from tinnitus has been, however, significantly increased recently because of frequent exposure to recreational and occupational sounds without protective standards [2]. The diversity of tinnitus suffering is due to instability in how it is perceived, how it is generated, to psychological problems and to the efficacy of treatment [3]. Regarding the perception by humans, the buzz can be heard by all people, who have some kind of hearing loss as well as those who do not; can be heard in one ear in both ears; and pure tones, high-frequency whistles and cicada noises can be perceived [4]. As for the factors that cause tinnitus, the origin cannot be determined in most people. Recently it was considered a neurological problem [5]. The history of tinnitus is complex, as it is the result of a cortical reset at the tonotopic level due to neural desynchronization in the auditory cortex and limbic system [6]. The origin is due to many factors, including acoustic trauma, ototoxicity, multifactorial corticopathy, and vascular or tumor factors. Regarding the psychological effects, patients suffering from tinnitus frequently experience anxiety, depression, anguish, fear, anger and suicide. However, so far there are some treatments, including medication, surgery and hearing aids, psychological counseling and cognitive behavioral therapy (CBT), herbal treatments, acupuncture, acoustic therapies and serious auditory training games [7]. Still, the response to treatment is in most cases uncertain. The accurate identification and characterization of tinnitus is still a controversial issue. So far, three types of clinical methods are applied to diagnose tinnitus: 1) psychometric, 2) audiology, and 3) electrophysiological testing. For psychometric testing, there exists many questionnaires to monitor tinnitus status, evolution and side effects. Some of the most commonly applied questionnaires for monitoring tinnitus includes tinnitus handicap inventory [8], hospital anxiety and depression scale [9], tinnitus reaction questionnaire [10], insomnia severity index [11], quality of life inventory [12], clinical global impression-improvement [13], tinnitus acceptance questionnaire [14], Beck depression inventory [15], tinnitus functional index [16], health utilities index score [17], tinnitus sample case history questionnaire [18], tinnitus catastrophizing scale [19], perceived stress questionnaire [20], and hyperacusis questionnaire [21]. In addition, several authors prefer make their own questionnaires to evaluate the condition for example [22] who monitored patient reported outcomes and self-reporting of treatment, and [23] who applied several questionnaires to evaluate tinnitus severity. For audiology testing, a detailed assessment of the auditory system is recommended, or even mandatory, to detect and characterize tinnitus. Most of the applied audiology methods includes otoacoustic emissions, transient evoked otoacoustic emission, high frequency audiograms (125Hz - 16kHz), speech in noise test, and threshold equalizing noise [24]. For electrophysiological testing, electrocochleography (ECochG) and electroencephalography (EEG) techniques are usually undertaken as well. In addition, other neuroimaging techniques have been used such as functional magnetic resonance imaging, magnetoencephalography (MEG), and near infrared spectroscopy (NIRS) [2]. As can be seen, tinnitus detection and characterization require a carefully elaborated diagnosis mainly owing to its heterogeneity nature. An inappropriate diagnosis often leads to inefficient treatment. Therefore, the present investigation aims to find EEG features in time and frequency domain that could distinguish between healthy and tinnitus sufferers with HL. In addition, this investigation pursues to give an insight into the group of tinnitus sufferers to search tendencies of those EEG features related to the HL of the sufferers. The latter through statistical analysis that demonstrate which is a promising neuromarker and stabilizing the differences between them. As a result, neuromarkers to

identify tinnitus, along with the associated HL, can be proposed for diagnosis and monitoring of this auditive condition.

Diagnostic Approach to Tinnitus

It can be inferred that the diagnosis of tinnitus is complex, in terms of distinguishing between causal factors, types and location of the tinnitus perception. The patient perception of the noise that it is experienced due to tinnitus is classified as: tonal, pulsatile, filtered noise and musical [25]. Tonal tinnitus is perceived continuously by superimposed sounds with defined frequencies, the intensity is diverse, it is associated with subjective tinnitus. Instead, the pulsatile is a sound that can be in sync with the patient heartbeat, being an objective tinnitus. On the other hand, the filtered noise is a continuous broad band noise filtered at tinnitus frequency of the patient. Finally, musical tinnitus is characterized by the perception of simple or complex melodies that are referred to as musical instruments, sometimes accompanied by a singing voice, it is also often called musical ear syndrome [26]. Because the level of signal processing in patients with tinnitus implies a deficient procedure in the ascending auditory pathways and the cerebral cortex, there is currently no effective method for diagnosing tinnitus, much less an effective cure. There is a clinical follow-up of this complex symptom, being the task of audiologists and otolaryngologists to carry out an evaluation of the patient to achieve the most accurate diagnosis. Such as an otological test of the neck, a test of temporomandibular function, and a detailed evaluation of the patient history. For example, in audiometry, determining air conduction and bone conduction threshold levels helps differentiate between two types of HL: sensorineural hearing loss and conductive hearing loss. In addition, high-frequency audiometry (at least up to 16 kHz) is recommended [27]. The tinnitus pitch test (acufenometry) includes a set of audiological techniques to characterize the tinnitus frequency based on pure tones. Tinnitus is highly dependent on the ability of patients to identify the sound of their tinnitus. It also depends on the experience of the doctor. In the case of unilateral tinnitus, the test is easier as it is compared with the tones given on the opposite ear. In bilateral cases, these circumstances increase gradually, with different frequencies until match the tinnitus pitch [28]. Typically, tinnitus is in the 3.5-8.5 kHz frequency range. In a recent work, there is a study of influence of tinnitus in the audiometry test concerning of hearing threshold. They evaluated the hearing thresholds of 136 volunteers (tinnitus with HL, tinnitus without HL and healthy group). The outcomes showed that the tinnitus group without HL are more probable to have HL than the healthy group [29]. In several studies about the high frequency audiometry, there is an association between laterality and asymmetry of tinnitus and the high frequencies loss due to tinnitus etiopathogenesis, which establishes as decreased neural output from the cochlea [30][31]. The issue with these approaches that focus on the region of the perceived tinnitus frequency, is that the tone of the tinnitus is not directly observable, due to the complexity of its frequency components. Since this parameter is essential for its proper design and application of acoustic therapies, it is necessary to propose and explore new techniques that characterize and diagnose tinnitus objectively and accurately. As well as being proposed in this work, the development of innovative algorithms and diagnostic tools that can provide comprehensive and reliable assessments of tinnitus symptoms should be prioritized. These tools should aim to capture the subjective experience of tinnitus while also incorporating objective measurements and metrics.

Affectation of hearing loss in tinnitus

The HL is related in most cases with tinnitus [32] and it can almost always be seen that the tinnitus problem increases with the level of HL [33][34]. According to various authors, between 85 % and 96 % of tinnitus patients have some level of HL and only between 6 % and 8 % do not [35][36]. Studies in patients with tinnitus are restricted and may even be tonal audiometry that

is limited to the study of otoacoustic emissions [37], brainstem auditory evoked potentials, auditory processing, and high-frequency audiometry [38]. A recent study compared the tinnitus characteristics of a pilot group with normal hearing to another group with tinnitus and HL [39]. It was possible to observe that in the tinnitus group there is a deficit of afferent activity from the cochlea, and it is expected that a decrease in functionality will be generated in the rest of the auditory pathway. However, it is just the opposite, as it generates more activity at the level of the subcortical nuclei of the central auditory pathway, which releases neural plasticity throughout the auditory system, contributing to the progression of tinnitus [40]. This hyperactivity is expressed as an increase in the suprathreshold amplitude of wave V of the Auditory Evoked Potentials of the encephalic trunk, which would be representative of an increase in the response capacity to balance the poor activity of the auditory nerve in the auditory system, and consequently an increase in profit is generated. It has been suggested that the ventral and dorsal cochlear nuclei would be fundamental in the gain at the encephalographic trunk level [41]. The dorsal cochlear nuclei present a structure very similar to the cerebellum, so they could play a role in adjusting the auditory system, just as the cerebellum does at the level of the vestibular system. As it can be seen in [39], the patients with tinnitus and normal hearing developed HL, where tinnitus could be the first indicator of impairment in the auditory system.

Neurometrics for Tinnitus Detection

Using the EEG, it can be studied local processing, which has been related with activity in high frequency (gamma band), and connectivity between areas through the coordination of electrical activity in low frequency (delta and theta bands) [42]. In patients with tinnitus, an increase in gamma band EEG activity has been found in temporary electrodes located in the vicinity of the auditory cortex [43]. This type of measurement is interesting in the study of tinnitus, since there is evidence that during the conscious perception of a sound there is an increase in brain activity at the local level in multiple regions in gamma band [44], and for a stimulus to be consciously perceived, the activity between these areas must occur in a coordinated way [45]. To address this issue, techniques of inter-frequency coupling analysis have been developed, in which it is evaluated how the phase of the activity in low-frequency bands modulates local neuronal activity in each area through the modulation of the amplitude of the high-frequency activity [46], thus allowing the study of both the connectivity between regions of a network and the local activity at each point of the neural network. Using these tools, the pathophysiology of tinnitus has been studied, observing that under normal conditions during wakefulness there is a coordination of the activity between the thalamus and the cerebral cortex by means of alpha band activity [47]. When a stimulus enters the auditory system, it generates gamma band activity at the cortex. In patients with tinnitus, it has been observed that the activity increase in the theta range during wakefulness, altering the role of baseline alpha activity [48], which is consistent with a partial deafferentation of the system, the increase of the gain of the same, and an alteration in the predominant rhythms in the thalamic-cortical communication in the auditory system. This alteration in the communication between the thalamus and the cortex has been called thalamic-cortical dysrhythmia, which in addition it has been related to the presence of tinnitus, and it has been related to various neurological diseases, including Parkinson disease, pain and depression [49]. Other authors [50] used the measurement of the coupling value between frequencies, showed that in patients with tinnitus, the modulation of local gamma activity begins to be more preferentially modulated by frequencies in the theta range (associated with deafferentation), than by alpha frequencies, and these changes are present not only in the primary auditory cortex, but also are extended to other areas of the tinnitus brain network such as the cingulate cortex and the prefrontal cortex. In recent years, several studies have been carried out in order to

understand the underlying mechanisms of the tinnitus condition and to find different ways to describe this disorder objectively, one of these, is the identification of neurometrics. Recent works have extracted amplitude and latency characteristics of evoked potentials on the auditory cortex when auditory stimuli are used through EEG recordings, due to evaluate and find differences between a group with tinnitus and a control group [51]. Similarly, other authors [52] acquired EEG records from a group with tinnitus prior to and after the application of sound therapy. Features of the signals were extracted for each of the EEG frequency bands to identify differences between patients who presented improvement upon receiving therapy versus those who did not present improvement. Some authors have used machine learning techniques to discriminate groups of patients with and without tinnitus, and even classify subgroups of these. For example, in a study [53], they employed a Support Vector Machine algorithm to create patient groups based on a set of features extracted from EEG records applying theory of graphs. With the above, it is possible to identify groups that allow differentiating patients with tinnitus from control group. In another research [54] they performed a two-stage cluster analysis to identify possible subgroups that reflect different spectra of tinnitus. On the other hand, [55] they used a neural network model to predict the residual inhibition of tinnitus, although the accuracy of the neural network was 97 %, the EEG recorded data are limited to identify cortical regions that are generating the activity. Nevertheless, it isn't easy to obtain information from such machine learning algorithms about the cerebral regions and features considered in the classification decision.

MATERIALS AND METHODS

Sample

Twenty-four volunteers were recruited for this study, 13 females and 11 males. They were between 37 and 80 years old, median (Mdn) 54.9 years old and standard deviation (SD) of 11.7 years were divided in four groups: 1) controls (individuals with no tinnitus and no HL), Mdn=59.5 and SD=6.5, 2) low HL tinnitus sufferers, Mdn=52 and SD=9.3, 3) middle HL tinnitus sufferers, Mdn=59 and SD=1.4, and 4) high HL tinnitus sufferers, Mdn=59.7 and SD=13.8. Tinnitus patients were previously attended in the Rehabilitation National Institute in Mexico City. They had been taken homeopathic aids without any effect and were invited to participate in this investigation. Control patients had the same inclusion criteria such as tinnitus but without suffering it and without HL. All the patients were informed that their doctors will monitor them. Volunteers were notified about the experimental procedure and signed a consent form. After patients have given their consent and signed a written agreement, they are placed into groups, through a random selection process. They are then instructed to engage in their assigned therapy for one hour each day, at any time of their choosing. The protocol was validated by the ethical committee of ITESM, and the number is ISRCTN14553550. The database is contained in Mendeley Data at https://data.mendeley.com/ datasets/kj443jc4yc/1.

Experimental Procedure

Experimental procedure for this study is presented in Figure 1 and was conducted as follows. Participant information was collected from two sources: 1) audiology evaluation (audiometry and tinnitus characterization), and 2) EEG baseline activity. In audiometry tests, the hearing level from 0.125 to 16 kHz was analyzed at four scales: 1) 0 - 20 dB (normal hearing), 2) 20 - 40 dB (low HL), 3) 40 – 60 dB (middle HL), and 4) > 60 dB (high HL). In addition, buzz was characterized for tinnitus patients, measuring its laterality, frequency and intensity.

Table 1 shows the central tendencies of audiometry and tinnitus characterization. As can be seen from the table, most participants had unilateral tinnitus around 6 kHz with an approximate intensity of 16 dB. The

control group presented a normal audition. With respect to EEG activity, signals were recorded to estimate the tonotopic cortical reorganization owing to neural synchrony abnormalities that provokes tinnitus.

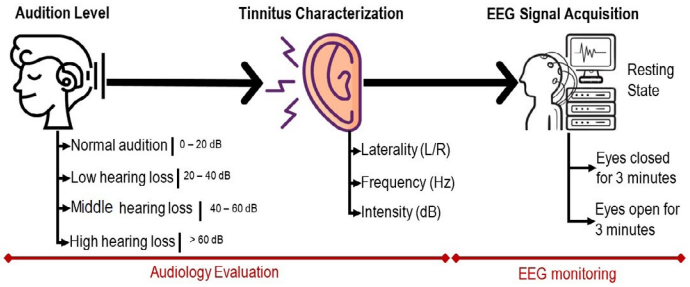

FIGURE 1. **Experimental procedure scheme.**

TABLE 1. **Shows the central tendencies of audiometry and tinnitus characterization. As can be seen from the table, most participants had unilateral tinnitus around 6 kHz with an approximate intensity of 16 dB. The control group presented a normal audition. With respect to EEG activity, signals were recorded to estimate the tonotopic cortical reorganization owing to neural synchrony abnormalities that provokes tinnitus.**

Men	Women	Tinnitus Laterality			Tinnitus Frequency	Intensity
		Left	Right	Both	{kHz}	dB
11	13	6	7	5	5.875 ±2698	15.93 ±10.68

Analyzing the neurophysiological signals can help to diagnose and to treatment neurological diseases like tinnitus [56]. EEG signals were registered in calm (in two stages: eyes closed (EC) and open (EO)) for 180 seconds (each stage). To register EEG signals, a g. USBamp was employed, with 16 EEG channels, this is a high-performance and high-accuracy biosignal amplifier for the acquisition and processing of physiological signals and it was set up to record signals with 256Hz of sampling frequency and a bandwidth of 0.1 to 100 Hz. The Cz channel was the reference with respect to the international 10-20 system, and ground was the left lobe ear.

Electrode and Frequency Band Selection

The EEG analysis was focused on frontal (Fz) and occipital (O1 and O2) lobes within two bandwidths: delta (0.1-4 Hz) and alpha (7-14 Hz) band, respectively. Frontal delta activity has been extensively discussed as a major EEG abnormal synchronicity for tinnitus and neuropathic pain, and occipital alpha activity is the dominant synchronicity at resting state condition in the human beings. Note that temporal lobe was not considered for the analysis, although it is associated with auditory processing and perception of language. It is well known that temporal lobe is around 18 % of the size of the complete cortex, 17 % in the right hemisphere and 18 % in the left hemisphere. However, a large surface of the temporal lobe is into the temporal gyrus, what nullified dipoles and minimizes EEG magnitude.

EEG Signal Preprocessing

To preprocess EEG signals, EEGLAB toolbox for Matlab was used. The principal objective of signal cleaning is to maximize the dynamic range by deleting internal and external unwanted sources such as line interference, involuntary movements, cardiac and muscular signals. The procedure was divided into 5 steps: 1) baseline suppression, 2) IIR Butterworth filter from 0.1 to 100 Hz. Note that this digital filter was applied, even when a previous similar filter had been applied in the signal acquisition process. Owing to some OpenViBE bugs during the acquisition that randomly filtered the signals, the filtering process was guaranteed in the preprocessing stage, 3) IIR Butterworth filter to reject 60 Hz component, 4) transient artefacts rejection (which refer to unexpected change of signal trajectory due to electrode pop-ups or cable movements) by artifact subspace reconstruction (ASR) algorithm (this approach learns a statistical model on clean calibration data and reduce unwanted signal by dividing small segments of EEG signals and comparing them in the component subspace), 5) auto-

matic elimination of stationary artefacts (which refer to periodic or quasiperiodic biological (such as ocular and cardiac activity) or nonbiological (line noise) signals) by the compound algorithm based on wavelet decomposition and independent component analysis (ICA).

EEG Signal Processing

Having cleaned EEG data, different processing steps were performed depending on the domain analysis (time or frequency).

For time-domain analysis, each signal:

1. Was filtered on Alpha (7 - 14 Hz) and Delta; (0.1 - 4 Hz) frequency bands

2. Was segmented into 2s time-windows without overlap, resulting in 30 windows per signal.

For frequency-domain analysis, each signal:

1. Was segmented into 2s time-windows without overlap, resulting in 30 windows per signal.

2. For each window, the magnitude frequency spectrum using the fast Fourier transform algorithm was computed.

3. Specific frequency bands from magnitude frequency spectrum were selected, this is, Alpha (7 - 14 Hz) and Delta (0.1 - 4 Hz) bands.

To this point, a dataset of 300 instances for every participant was produced; this is, 2 bands × 5-time courses (F_z, O1 and O2 channels plus bipolar O1–O2 and average (O1 + O2)/2) × 30 windows. Finally, all participant instances were characterized using time and frequency domain features.

EEG Feature Extraction

Feature extraction is the process that allows obtaining information about data. It can be performed in several manners (i.e., time-domain –data samples domain– or frequency-domain –analyzing time-frequency data representations– but also in spatial-domain –spatial location of the measure–). In this work, a feature extraction in time and frequency domains for three different locations on the brain resulted in 300 instances for each participant. Thus, the feature is a combination of time-domain or frequency domain metric with a specific brain location of the brain denoted by the electrode placement. Below, different metrics in different domains are presented. Basic Statistical Measures section presents basic statistical metrics used for both time and frequency domain. Time Domain and Frequency Domain sections describe how each statistical metric could be interpreted and additional non-statistical metrics.

Basic Statistical Measure

Mean. The mean is one of the measures of central tendency that gives us information about the average value of the set of amplitude values over the number of samples of a signal (see Equation 1).

$$\bar{x} = \frac{1}{N}\sum_{i=1}^{N} x_i \tag{1}$$

where xi correspond to the ith position of the signal, N is the sample size, and $\bar{x}$ the average value [57].

Standard Deviation (STD). The standard deviation is a measure that tells how dispersed the values of the signal samples are with respect to their mean, being a value close to zero an indicator that the values are very close to the mean value and much higher values are an indicator that these values are further from the mean value. In other words, STD is the square root of the average of the squared differences from the Mean (see Equation 2).

$$STD = \sqrt{\frac{\sum_{i=1}^{N}(x_i - \bar{x})^2}{N-1}} \tag{2}$$

where x_i correspond to the i_{th} position of the signal, N is the sample size, and x the average value [58].

Kurtosis (KRT). Kurtosis is a measure that reveals the peak or flatness of a distribution. To calculate the kurtosis value, it is necessary to use Equation (3), which considers the difference of the signal data with respect to the mean [59].

$$Kurtosis = \frac{\frac{1}{N}\sum_{i=1}^{N}(x_i - \bar{x})^4}{[\frac{1}{N}\sum_{i=1}^{N}(x_{i-}\bar{x})^2]^2} \quad (3)$$

Skewness (SKW). Its value is zero when it has a symmetric distribution and as some non-zero value when it has an asymmetric distribution compared to the baseline [60]. To calculate the value of the skewness, it is necessary to use Equation (4), which considers the dispersion of the signal data with respect to the mean.

$$Skewness = \frac{\sum_{i=1}^{N}\frac{(x_i - \bar{x})^3}{N}}{[\sum_{i=1}^{N}\frac{(x_{i-}\bar{x})^2}{N}]^{3/2}} \quad (4)$$

Time Domain

Time domain or data samples domain is a representation of how data is organized after acquisition step. Simple measurements on this data representation can be done to obtain some information. These basic measurements are the same that are used in statistics for data sequences. Thus, time domain features are very related to statistical features. In the next paragraphs a description of non-statistical measures is presented.

Time domain statistical measures such as mean, standard deviation, kurtosis and skewness (see Basic Statistical Measures section) describe tendencies in the time domain. For example, EEG data basic statistics, such as mean and standard deviation (see Equations 1 and 2), computed for each time window, describe how the average of EEG amplitudes change from one window to another (Mean) along with their dispersion (STD). On the other hand, there are more elaborated statistics such as kurtosis and skewness (see Equations 3 and 4). Kurtosis indicates if EEG amplitudes consist of isolated peak values (positive kurtosis) or consist of low frequency (negative kurtosis) while Skewness indicate the degree of symmetry deviation from a normal or Gaussian distribution (skew) of EEG amplitudes and if this change from one window to another. Non-statistical measures can be used as time domain descriptors. For example, the maximum amplitude of the signal (a.k.a maximum peak) and the shape which is a descriptor of the symmetry, number of peaks, obliquity, and uniformity of a measured signal. In the next lines, the equations for these features are presented.

Maximum Peak (MPK). The maximum peak corresponds to the instantaneous absolute value of the higher amplitude of the signal measured from the zero level. This metric is expressed by Equation (5).

$$x_{peak} = \max(|x_i|) \quad (5)$$

where x_i corresponds to the i^{th} position of the signal with $i \in \{1, 2, 3, ..., N\}$ and N being the sample size. Finally, x_{peak} corresponds to the maximum peak.

Shape (SHP). Shape is not precisely a statistical parameter but is a measure that describes the characteristics of symmetry, number of peaks, obliquity, and uniformity of a signal. To calculate it, the root mean squared amplitude value must be divided by the mean absolute value (see Equation (6)).

$$shape = \frac{\sqrt{\frac{1}{N}\sum_{i=1}^{N}{x_i}^2}}{\frac{1}{N}\sum_{i=1}^{N}|x_i|} \quad (6)$$

Other data representations, such as frequency-domain, can also benefit from these statistical measures to describe the frequency spectrum. In the next paragraphs, the statistical descriptors used in frequency domain are presented.

Frequency Domain

In the frequency domain, statistical measures such as the mean and skewness can be used as descriptors. For example, in the case of EEG signals, the Mean of a signal segment obtained for each one of several magnitude spectrum windows can tell us how the average of EEG spectrum (energy) changes from one window to another. On the other hand, more elaborated statistics such as the skewness can explain the degree of deviation from symmetry from a normal or Gaussian distribution (skew) of the EEG spectrum and, if exist a change from one window to another. Other measures can be used as frequency domain features and are described as follows.

Power Spectral Density (PSD). The PSD refers to distribution of spectral energy observed in each unit time. This total power can be calculated by performing the summation or integration of the spectral components which, as dictated by Parseval's theorem [60].

$$PSD = \sum_{k=1}^{K} s(k) \tag{7}$$

where s(k) is a spectrum for k = 1, 2, ..., K, K is the spectrum resolution [61][62][63].

P5 (MNF or Xfc). Another specific frequency spectrum metric, P5 may show how the position is changing of principal frequencies that are predominant in the frequency spectrum and is basically the sum of the product of the frequency value by its magnitude divided by the sum of the magnitudes of all the elements of the spectrum (see Equation (8)).

$$P5 = \frac{\sum_{k=1}^{K} f_k s(k)}{\sum_{k=1}^{K} s(k)} \tag{8}$$

where s(k) is a spectrum for k = 1, 2, ..., K, K is the number of elements in the spectrum and fk is a value of the k spectrum line [61][62][63]. To perform the feature extraction, for each instance of every participant, the metrics corresponding to time and frequency domain were computed. Thereafter, the participant data were organized in a matrix shape where the rows correspond to the participant instances and the columns to different audition levels. The instances corresponding to all participants with the same audition level are concatenated one after the other. The matrices were labeled according to their information. For example, the label O2_alpha_STD corresponds to a matrix with all participant instances corresponding to the occipital 2 channel (O2), on Alpha band, characterized by the standard deviation feature (SD). Table 2 depicts an example of the matrix O2_alpha_STD.

TABLE 2. Example of the matrixO2_alpha_STD

Participant	Control/ Normal	Tinnitus/ Low	Tinnitus/ Middle	Tinnitus/ High
1	6.299	4.615	8.474	4.641
1	6.068	7.491	6.775	9.594
:	:	:	:	:
1	4.334	8.194	4.507	5.113
:	:	:	:	:
6	6.626	3.757	4.067	8.462
6	10.058	6.298	8.395	10.705
:	:	:	:	:
6	5.262	4.18	3.571	10.977

To identify one or several neuromarkers that differentiate between participants with different audition levels based on their EEG signals, first, the dataset distribution and the appropriate non-parametric statistical test are determined.

Statistical Analysis

In statistical analysis it is important to know which distribution a sample is drawn from, to make correct inferences. According to the data of this study, the analysis is performed using the Lilliefors test based on the Kolmogorov-Smirnov test in R with the nortest package. The Lilliefors test for normality is an adaptation of the Kolmogorov-Smirnov test for the case when the parameters of the mean and variance of the normal distribution is unknown [64]. The Lilliefors test is defined by:

$$D = max_{x \in R} |F_n(x) - F^*(x)| \quad (9)$$

where $F_n(x)$ is the empirical cumulative distribution function and F*(x) is the function of cumulative distribution of the normal distribution with $\mu = \bar{x}$ and s^2. If D exceeds the corresponding critical value, then the null hypothesis is rejected.

All time and frequency metrics were analyzed using the Kolmogorov-Smirnov test with the Lilliefors correction, showing $p<0.05$. Consequently, the normality hypothesis is rejected. The nonparametric technique to test whether the populations differ in location, the Kruskal-Wallis H statistic analysis does not require actualized observation values, the ranks of the observations to complete the analysis is known. The test of Kruskal-Wallis is based on H for comparing k population distributions [65]:

H_0: The distribution of k population is the same.
H_a: The population distributions differ in two locations.

Test statistic: $H = \{12/[n(n+1)]\} \sum_{i=1}^{k} R_i^2/n_i - 3(n+1)$, where ni =number of measurements in the sample from populations i, R_i= rank sum for sample *i*, where the rank of each measurement is computed according to its relative size in the overall set of $n = n_1 + n_2 + \cdots + n_k$ observations formed by combining the data from all k samples. Reject H_0 if H x_α^2 with $(k-1)$ df.

RESULTS AND DISCUSSION

After statistical analysis, the bipolar O1 – O2 and the average (O1 + O2)/2 produced nonsignificant differences in alpha nor in delta; thus, they were not further analyzed. Only the results from 180 out of 300 sets (2 bands × 3 channels (Fz, O1 and O2) × 30 windows) are reported here. To evaluate the performance of every feature and its possibility to become a neuromarker, two different strategies were pursued. First, a depiction of the probability distribution of the data using violin plotting along with a statistical summary using box plots are presented (Figures 4 to 3). Secondly, an statistical significance analysis was performed with the Kruskal-Wallis test and reported on Tables 3 and 4. The data distribution for features Fz-delta-MPK and Fz-delta-STD respectively in the time domain for delta band and electrode Fz among the studied groups are observed in Figures 2 and 3. Apart from the skewed distribution of these two features it can be easily observed that Fz-delta-MPK and Fz-delta STD distributions in each group looks very similar as it was for electrode O2 in the alpha band for the same features. Looking into distributions of Fz-delta-MPK and Fz-delta-STD features, we can easily observe that median value.

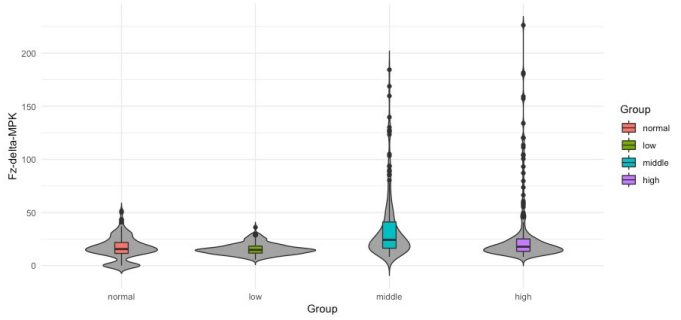

FIGURE 2. **Fz-delta-MPK time-domain.**

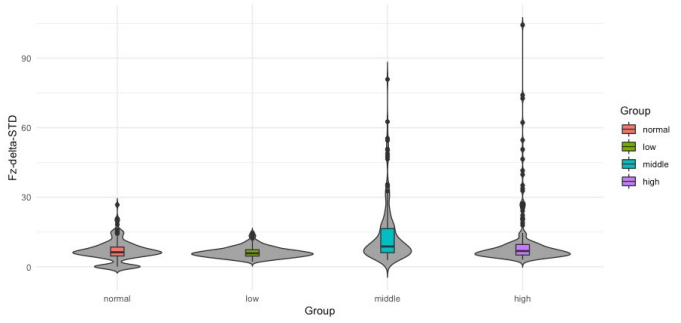

FIGURE 3. **Fz-delta-STD time-domain.**

from normal group differs significantly from the median value of group middle. It is hard to see but there are also significant differences between median values of groups low and middle and middle and high for both features. However, in the case of Fz-delta-STD there are not significant differences between the median values of groups normal and high as there are

present for the case of Fz-delta-MPK (see Table 3, fifth column). In Figure 4 to 6, the data distribution for features O2-alpha-PSD, O2- alpha-STD and O2-alpha-MPK in the frequency domain for alpha band and electrode O2 among the studied groups is shown. Apart from the skewed distribution of these three features and the longer tails for O2-alpha-PSD feature, it can be easily observed that O2-alpha-STD and O2-alpha-MPK distributions in each group looks very similar. Nevertheless, if it can be looked carefully out of its tails, distribution for O2-alpha-PSD is almost proportional to O2- alpha-STD and O2-alpha-MPK distributions with exception of normal group.

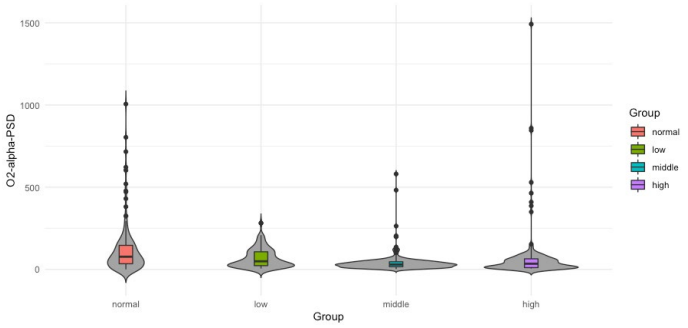

FIGURE 4. **O2-alpha-PSD frequency-domain**

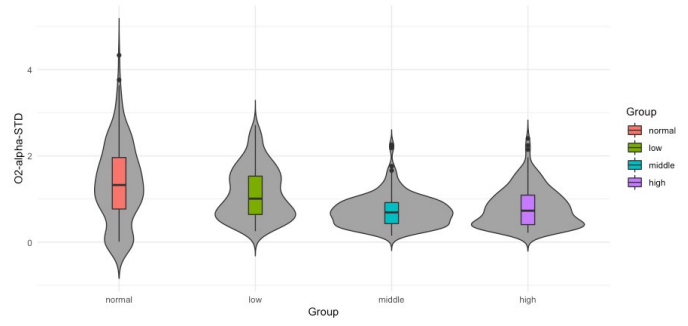

FIGURE 5. **O2-alpha-STD frequency-domain**

However, for the three groups it seems that median value from normal group differs significantly from the median values of groups middle and high. Also, is possible to observe that median values of middle and high groups differ significantly from the median of group low. It is hard to visually determine if the medians of groups normal and low possess significant differences. However, there exist significant differences as confirmed in the third column (Tinnitus/Low vs. Control/Normal) of Table 4 where p-values of 0.0251, 0.036 and 0.039 report significant differences for groups normal and low. It can be also observed that medians from groups middle and high are not significantly different, which is also confirmed in Table 4 in the last column (Tinnitus/High vs. Tinnitus/Middle) where there are no p-values reported since only p-values lower than 0.05 are presented. In Figures 7 and 8 the data distribution for features O1-alpha-SHP and O1- alpha-SKW respectively in the frequency domain for alpha band and electrode O1 among the studied groups is presented. Apart from the skewed distribution of these two features it can be easily observed that O1-alpha-SHP and O1-alpha-SKW distributions in each group look very different. Nevertheless, if it can be looked carefully for both O1-alpha-SHP and O1-alpha-SKW features, the median value from normal and low groups differs significantly from the median value of groups middle and high. Visually from these plots, it is easy to see that median values of groups normal and low do not possess significant differences (Table 4 third column, no p-values are reported); however, it can be easily observed that median values from groups middle and high are significantly different. In the other hand, significant differences between median values of normal and high groups are only difficult to be observed from plots for O1-alpha-SKW feature, but there exists as reported in Table 4 sixth column, p-value equal to 3.1 × 10-3.

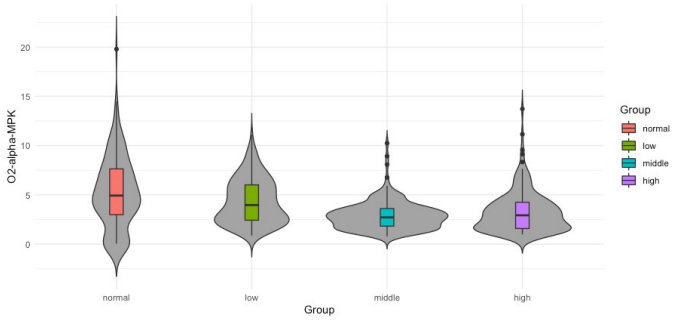

FIGURE 6. **O2-alpha-MPK frequency-domain**

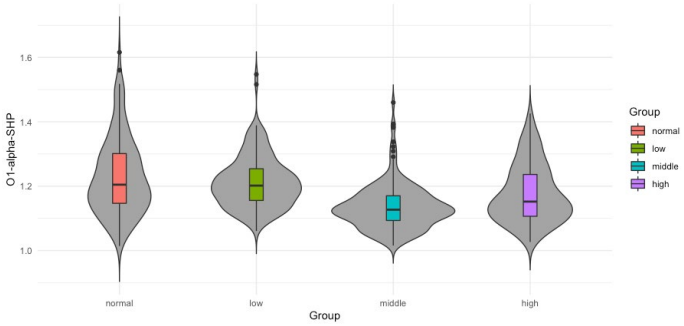

FIGURE 7. **O1-alpha-SHP frequency-domain.**

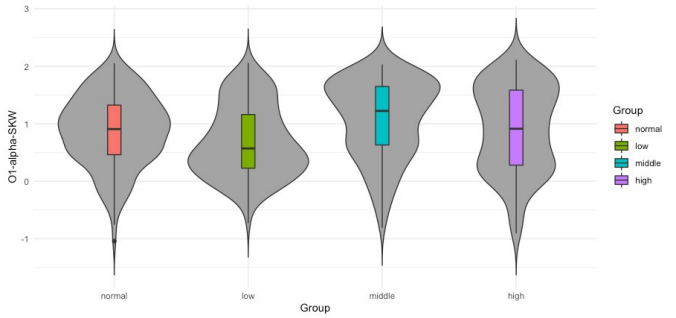

FIGURE 8. **O1-alpha-SKW frequency-domain.**

Tables 3 and 4 present time and frequency features (combination of the frequency band, channel, and metric) that first, maximizes the differences between groups of participants with different audition levels and second, fulfills the criteria of $p < 0.05$, for time and frequency domain, respectively. Based on the concept that the ideal neuromarker would be a metric in a data domain for a specific location capable to distinguish among all groups, each group was compared to another (i.e., all non-repeated pairs of groups), testing the features obtained for time and frequency domains for specific head locations to grade the easiness for such a feature to distinguish among groups.

TABLE 3. **P-values for Time-domain analysis on Delta band and Fz channel**

Feature		Audition Levels					
Channel	Metric	Tinnitus/Low vs Control/Normal	Tinnitus/Middle vs Control/Normal	Tinnitus/Middle vs Tinnitus/Low	Tinnitus/High vs Control/Normal	Tinnitus/High vs Tinnitus/Low	Tinnitus/High vs Tinnitus/Middle
Fz	MPK	-	3.5×10^{-13}	2×10^{-16}	0.0041	2×10^{-16}	0.0001
Fz	STD	-	1.3×10^{-9}	1.1×10^{-14}	-	0.0004	0.0005

TABLE 4. **P-values for Frequency-domain analysis on alpha band**

Feature		Audition Levels					
Channel	Metric	Tinnitus/Low vs Control/Normal	Tinnitus/Middle vs Control/Normal	Tinnitus/Middle vs Tinnitus/Low	Tinnitus/High vs Control/Normal	Tinnitus/High vs Tinnitus/Low	Tinnitus/High vs Tinnitus/Middle
O2	PSD	0.0251	2.1×10^{-11}	7.7×10^{-6}	6.4×10^{-7}	0.0002	-
O2	STD	0.036	8.9×10^{-14}	4.2×10^{-10}	3.7×10^{-10}	5.2×10^{-7}	-
O2	MPK	0.039	2.3×10^{-13}	3.9×10^{-9}	5.0×10^{-9}	4.4×10^{-6}	-
O1	SHP		2.2×10^{-16}	$< \times 10^{-16}$	9.1×10^{-5}	8.9×10^{-5}	8.0×10^{-5}
O1	SKW		1.9×10^{-10}	2.9×10^{-11}	3.1×10^{-3}	0.0037	0.0033

Many features are helpful to distinguish among several groups; however, the interest is only in features capable of distinguishing most of the groups. In our study, apparently it is observed that for time-domain and frequency-domain there is no such a metric capable of distinguishing the six groups presented here. Nevertheless, some metrics were found in the frequency domain that in combination with a channel location are capable to distinguish 5 out 6 groups and in the time domain only with the MPK metric is possible to distinguish 5 out 6 groups with a p value < 0.05. Tables 3 and 4 present only the features that meet this number of groups distinguished with this significance. From Table 3 it is observed possible neuromarkers in the time domain, all of them are located on the frontal lobe and described by two metrics on the delta band. These metrics are the standard deviation (STD) and maximum peak (MPK), being the latter the one that can help us to distinguish at least 5 out of 6 groups presented here. In addition, on Table 4 it is observed features identified as possible neuromarkers in the frequency domain, all of them are located on the occipital lobe and described by several metrics on the alpha band such as its power spectral density (PSD), standard deviation (STD), maximum peak (MPK), shape (SHP) and skewness (SKW). As seen in Table 4, the shape (SHP) and skewness (SKW) of the alpha frequency band does not present significant differences between Tinnitus/Low and Control/Normal groups of subjects; on the other hand, PSD, STD, and MPK did not present significant differences between Tinnitus/High and Tinnitus/Middle groups. However, if we consider the occipital lobe as one region for which we have two measurements, we can distinguish among the six groups presented here using a different metric for each side of the occipital lobe.

The non-significant differences among Tinnitus/Low and Control/Normal groups of subjects for SKW metric in the alpha band could be since SKW explains the degree of deviation from symmetry from a normal or Gaussian distribution (skew) of the EEG spectrum. In this case, as it was presented before (see Frequency Domain section) the data distribution of the tested metrics in all groups was non Gaussian which implies the existence of similarities between groups from the point of view of this metric. Metrics such as PSD, STD and MPK in the frequency domain gives information about power differences in a frequency band (i.e., there are certain frequencies that prevailed). Thus, it is possible that the group Tinnitus/High and Tinnitus/Middle share some frequencies maybe related to tinnitus, and in this context from the point of view of this metric is impossible to distinguish between both groups. Regarding these results, frequency domain metrics seem to be more robust than time domain metrics because they can help to distinguish more different groups than most of the time domain metrics tested here. However, it is important to remark that both frequency and time domain metrics can be used together to distinguish among groups. For example, by analyzing MPK metric in both domains over their respective EEG channels Fz and O2 at the same time, it is possible to distinguish both Tinnitus/Low vs Control/Normal and Tinnitus/High vs Tinnitus/Middle, which is not possible if we analyze the feature in one domain only. The non-Gaussian distribution of data for the metrics presented here makes that parametric statistical test such ANOVA cannot be used in this analysis and thus, equivalent non-parametric tests need to be used.

Other options are transforming data with a function forcing it to fit a normal model and then applying ANOVA or another parametric test. However, when data distribution is skewed and fitting another distribution type as in our case, it is recommendable to use non-parametric tests (i.e., these tests do not assume that data fits a specific type of distribution). Even though it has been presented several neuromarkers distinguishing control participants with no HL from tinnitus participants with some level of HL, and tinnitus participants with different levels of HL among them. These neuromarkers identify significant differences between instances by analyzing one feature.

Additionally, the effectiveness of using a particular neuromarker for tinnitus or HL level estimation cannot be assessed. Therefore, based on results of the present work, and as a future work, these features will be used along with several machine learning techniques to first, evaluate the performance of the combination of the neuromarkers proposed here for predicting tinnitus condition or HL level on participants; finally, the evaluation of the efficiency of such predictions will be performed.

CONCLUSION

A methodology to characterize and identify subjects from different audition levels (Normal, Low, Middle, and High) was presented. The results show that it is possible to perform a pairwise differentiation of patients with different HL conditions in both time and frequency-domain. It was shown that the resulting EEG characterization does not fit the normal probability distribution, so the Kruskal-Wallis test was required to measure the significant difference between pairwise combinations. There are more metrics in the frequency-domain that allow differentiating audition levels than those from the time-domain; with MPK and STD being shared by both domains. The results indicate that for every audition level pairwise comparison, there is at least one combination of an electrode, band, and metric (feature) in which such pairwise combination is differentiable. On frequency-domain on the Alpha band, PSD, STD, and MPK are neuromarkers that distinguish a Control/Normal subject from a Tinnitus participant with Low, Middle, and High audition level. And, to distinguish from different tinnitus audition level participants, SHP and SKW are the neuromarkers to be selected. Moreover, combination of both domains allows to distinguish among all the groups presented here as is the case of metric MPK (Fz-Delta-MPK, in time domain and O2-Alpha-MPK in frequency domain).

It's important to note that tinnitus is a subjective experience, and its perception can vary greatly among individuals, regardless of age. Some individuals may habituate to the sound and experience minimal distress, while others may find it highly bothersome and experience significant negative effects on their well-being. Additionally, individual characteristics, such as personality traits and psychological factors, can influence how tinnitus is perceived and coped with, irrespective of age.

A small sample size may limit the generalizability of the findings and reduce the statistical power of the analysis. Or maybe using machine learning techniques to distinguish between different groups. To draw more reliable conclusions, a larger and more diverse sample should be used in future studies. The outcomes of this study are specific to the parameters and methods used in this research. The same neuromarkers and metrics to different populations or other hearing disorders cannot be generalized. Replication of the study with different populations and in different settings would help assess the generalizability of the results.

AUTHOR CONTRIBUTIONS

R.A.S.R. designed and defined methodology and performed analyses, obtained resources, participated in the preparation of the original draft. S.T.R. performed formal analyses and data curation, participated in the preparation of the original draft. D.I.I.Z. oversaw the project, participated in all the writing stages of the manuscript (preparation of the original draft, review and edition of the different versions and the final document), and obtained funding and financial resources. A.E.V. Validation of the research, participated in the writing of the original draft. L.M.A.V. conceptualized the project, carried out investigation, participated in the preparation of the original draft, obtained funding and financial resources. I.R.G. use and programming of specialized software and participated in the writing of the original manuscript. All authors reviewed and approved the final version of the manuscript.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of the National School of Medicine of the Tecnológico de Monterrey, and the registration trial number is ISRCTN14553550.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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A Review on the Advances of Biocompatible Materials and Their Processing Via Additive Manufacturing for Tissue Engineering Applications

Una Revisión de los Avances en Materiales Biocompatibles y su Procesamiento Mediante Manufactura Aditiva Para Aplicaciones en Ingeniería de Tejidos

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ABSTRACT

About two decades ago, medicine experienced a revolutionary approach, driven by technological development in manufacturing techniques and scientific advances in the medical and life sciences, the field took on the challenge of regenerating tissue and organs damaged by disease, trauma, or hereditary issues, incorporating additive manufacturing as one of its strategies. Since its inception, regenerative medicine has developed techniques like tissue engineering, cellular therapy, medical devices, and artificial organs to provide wound healing and orthopedic applications. The incorporation of additive manufacturing allowed to recreate biologically appropriate environments for cell reproduction and growth that, eventually, lead to useful, regenerated tissue or organs. The objective of the present work is to review recent advances in the application of additive manufacturing techniques and *ad hoc* biomaterials in the field of regenerative medicine, to determine their impact in the development of new therapies for tissue engineering.

KEYWORDS: biomaterials, bioprinting, regenerative medicine, tissue engineering

RESUMEN

Hace aproximadamente dos décadas, la medicina experimentó un enfoque revolucionario, impulsado por el desarrollo tecnológico en técnicas de fabricación y los avances científicos en las ciencias médicas y de la vida. El campo asumió el desafío de regenerar tejidos y órganos dañados por enfermedades, traumatismos o problemas hereditarios, incorporando la fabricación aditiva como una de sus estrategias. Desde su inicio, la medicina regenerativa ha desarrollado técnicas como la ingeniería de tejidos, la terapia celular, los dispositivos médicos y los órganos artificiales para proporcionar cicatrización de heridas y aplicaciones ortopédicas. La incorporación de la fabricación aditiva ha permitido recrear entornos biológicamente apropiados para la reproducción y crecimiento celular, lo que eventualmente ha llevado a la obtención de tejidos u órganos regenerados útiles. El objetivo de este trabajo es revisar los avances recientes en la aplicación de técnicas de fabricación aditiva y biomateriales ad hoc en el campo de la medicina regenerativa, para determinar su impacto en el desarrollo de nuevas terapias para la ingeniería de tejidos.

PALABRAS CLAVE: bioimpresión, biomateriales, ingeniería de tejidos, medicina regenerativa

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INTRODUCTION

Rather than replacing tissue or organs damaged by disease, trauma, or hereditary reasons, the current clinical approach focuses on organ transplantation which, despite great improvements in their success rate, still poses a rejection risk from the recipients, and the life-long need for immunosuppressants [1][2][3][4][5].

For a long time, the regeneration or manufacture of fully functional, living tissues was conceived as a product of imagination. Nonetheless, regenerative medicine (RM) arose two decades ago as a branch of medicine focused on the treatment of pathologies for which the only treatment available was the use of prosthetics, organ transplantation, or the removal of damaged tissue [2][4][6].

Over time, this area has divided into two main medical strategies [4]: cell therapy, which seeks to restore the vital functions of the damaged tissue through drugs applied in vivo [7], and tissue engineering, which makes use of scaffolds fabricated via additive manufacturing (AM) to provide cells with support and favorable conditions for proliferation and differentiation [3][4][8][9][10][11][12][13][14][15], and the biological functions of the tissue or organ to be replaced. This represents a challenge, as the number of apropos available materials is greatly reduced.

The construction and optimization of scaffolds is not without challenges [16]. It requires multidisciplinary efforts spanning from materials science to medicine [2]. One of the most ambitious issues regarding tissue engineering is the construction of highly complex, porous structures that imitate the biological function of the extracellular matrix [13][17][18][19]. Developments in this area have been driven by the application of AM; particularly, 3D printing [8][20][21][22], a materials engineering technique to form intricate structures by depositing fine threads of material, layer by layer [11][21][22][23][24][25]. This has made it possible to manufacture parts with customized morphological characteristics [18][26], intended to fulfill specific biological functions. Other advantages of this approach are scalability, control of physical characteristics, cost-benefit relationship [27], and the possibility of manufacturing parts with greater complexity than those that could be achieved with classical manufacturing techniques [28].

The first AM systems, developed in the 1980s, were aimed at the production of small prototypes [25]; only until recently they been extensively applied in the field of tissue engineering, implants for cranial and spinal surgery, and prosthetics, among others [8][11][21]. Despite of it, the extensive application of additive manufacturing for medical purposes is hindered by several issues like the need to fabricate highly porous structures, the development of biocompatible materials suited for AM, the need to improve mechanical strength, and the need to improve printing resolution [2][16][17].

In conclusion, RM has made great strides in recent years, and the development of AM has played a key role in this progress. However, there is still much work to do to increase the availability of RM therapies based on this manufacturing technology. With continued research and development, it is likely that we will see more and more innovative applications of AM in the medical field.

This search aimed to gather relevant information on the limitations, significance, and applications of additive manufacturing in regenerative medicine.

MATERIALS AND METHODS

The method employed in the development of this review article involved a systematic literature search to identify recent advances in tissue engineering and the utilization of additive manufacturing techniques. The following steps were undertaken:

Literature Search

Comprehensive bibliographic research was conducted to identify relevant articles, research papers, reviews,

and conference proceedings related to tissue engineering, additive manufacturing, and regenerative medicine. Multiple academic databases were utilized to ensure a wide coverage of the literature. Keywords and phrases used in the search included "tissue engineering," "regenerative medicine," "additive manufacturing," "3D printing," "bioprinting," "scaffolds," and "recent advances." In the composition of this review article, an exhaustive examination of scholarly literature was undertaken, encompassing a comprehensive array of 104 distinct works. Within this assemblage, a discerning selection process led to the incorporation of 61 articles that not only facilitated the synthesis of pertinent information but also served as foundational references for the present work. The curation of these sources was meticulously governed by predefined inclusion criteria, the succinct explication of which shall be provided.

Inclusion and Exclusion Criteria

Articles were screened based on predetermined inclusion and exclusion criteria. Inclusion criteria included peer-reviewed articles published within the last five years to ensure the inclusion of recent advancements. The articles that focused on the application of additive manufacturing techniques in tissue engineering and regenerative medicine were considered for further analysis. Articles not written in English or lacking relevance to the topic were excluded.

Data Extraction and Analysis

The selected articles were carefully reviewed, and relevant information regarding additive manufacturing techniques, materials, and their applications in regenerative medicine were extracted. The information extracted included details about the types of materials used, fabrication methods, bioprinting techniques, and their impact on cell viability and tissue regeneration. Additionally, information related to challenges and future directions in the integration of additive manufacturing technologies with regenerative medicine was also extracted.

Data Synthesis and Manuscript Organization

The extracted information was synthesized and organized into coherent sections, following the logical flow of the review article. The sections were structured to provide a comprehensive understanding of recent advances in additive manufacturing techniques for regenerative medicine. Special attention was given to the categorization and presentation of the materials used, additive manufacturing techniques employed, and their integration with regenerative medicine.

RESULT AND DISCUSSION

Biomaterials

Biomaterials are characterized by their capability to be used within or in conjunction with biological organisms. It is necessary that these materials have characteristics such as biocompatibility, resistance to corrosion, apropos mechanical properties, and absence of carcinogenic factors [15][29][30]. Current literature clearly distinguishes between natural and synthetic materials [9][10][23]. These, in turn, can be classified as polymers, ceramics, glasses, and metals [31], which we proceed to discuss in the following sections.

Metals

Some metals and alloys are biocompatible and have been widely used in the medical field as support structures due to their high mechanical strength, good conformity, and resistance to corrosion. However, some of their main disadvantages are low biocompatibility and high corrosion in biological environments, shortening the useful lifetime of these materials.

Applications where metals are mostly used include, fracture repair screws, and replacement prosthetics for limbs and joints.

Stainless Steel

Stainless steel represents a set of alloys with a high chromium content and different concentrations of

nickel. Chromium is an element with a high affinity for oxygen, which is why it forms a rich oxygen layer on the surface of the piece, preventing it from advancing to the internal areas. The first compound used as an implant was stainless steel 316. Later, this alloy was substituted by a low-carbon version known as the 316L. However, this alloy also has a high nickel content, which can cause allergic reactions. Nitrogen has also been found to be a stabilizer of the austenitic phase of iron, so it could serve as a replacement for this element in the 316L SS, forming the ASTM 1686 variant, even though it does not have sufficient resistance to corrosion; thus, it is only used as a temporary implant. For this reason, new alloys are currently being sought that meet the demands of clinical medicine.

Cobalt-based alloys

These alloys are specially used in applications where resistance to wear is required. This alloy was first used in the aerospace sector, but due to its higher resistance to corrosion, compared with stainless steel, and excellent mechanical properties, it began to be used to manufacture medical implants.

Titanium-based alloys

Titanium is a low-density material that hardens considerably when alloyed, or by mechanical treatment. It is widely used in the manufacture of prosthetics and implants due to its high resistance to corrosion. Titanium alloys are part of the category of bioinert materials, which means they do not interact with surrounding tissue.

Polymers

Polymers are long chains of smaller carbon molecules, called monomers. These exist both naturally and synthetically [25][32][33]. Biopolymers are a special class of naturally derived polymers.

Natural Polymers

The main advantage of these materials is that cells can easily adhere and proliferate, and that they also have excellent biocompatibility [6]. One of the disadvantages, compared to synthetic polymers, is their reduced mechanical properties [13][30], difficulty in processing, and reduced availability [34]. Still, it is possible to use both types of polymers by combining the mechanical stability of synthetic polymers and the biocompatibility of natural ones [3].

Alginate

It is a polysaccharide derived mainly from marine algae. It has been widely used in bioprinting due to its low cost, good biocompatibility, and rapid gelation [35]. Alginate undergoes a sol-gel reaction in the presence of Ca2+ ions, which are found in compounds such as CaCl2 and CaSO4 [30], making it suitable for certain additive manufacturing techniques such as drop printing, which will be addressed later.

Synthetic Polymers

These materials usually allow for more efficient control of degradation rate and mechanical properties [9][13]. For this reason, they have been developed as rapidly as biomaterials in recent years [36]. Of the synthetic polymers that have been used, the following stand out:

Polycaprolactone (PCL)

Polycaprolactone is a biodegradable polymer [37] with a low melting point [17]. It is one of the most used polymers due to its physical and chemical properties, as well as its pliability [38] most importantly: PCL has been approved by the Food and Drug Administration (FDA) for use in humans [39]. The use of this material in combination with other elements such as hydrogel has been studied to form scaffolds with physical and chemical characteristics that are more suitable for certain applications, such is the case of Liang Dong, *et al.* who created one of these hybrid scaffolds for use in bone tissue [40].

Polylactic acid (PLA)

PLA is a biodegradable aliphatic polyester. It is a hydrophobic material with a relatively long degradation

period [41]. Due to its mechanical properties, various applications for this material have been explored, ranging from tendon regeneration [41][42] to the design of temporary implants that release drugs at a given place, while degrading [43].

Pluronic F-127

Pluronic F-127 is a synthetic copolymer based on three blocks: polyethylene glycol, polypropylene glycol, and polyethylene glycol (PEO-PPO-PEO) [35][44]. This substance has the characteristic of forming micelle structures that solidify at a certain temperature, called the micelle temperature. At lower temperatures, this substance is in a liquid state [35].

Bioinks

These materials consist of admixtures of hydrogels and cells [22]. Hydrogels are polymeric substances capable of absorbing large amounts of water [26][30][45] and play an important role in tissue engineering providing mechanical support for the cells. Although they have been tried extensively, they still lack certain mechanical properties such as rigidity and high Young's modulus, necessary for applications requiring support for high mechanical loads [46]. However, their physical and chemical characteristics are quite malleable to fit a wide range of tissue engineering needs [47]; additionally, it has been possible to create hybrid bioinks that promote proliferation and differentiation [48]. Conductive hydrogels are being developed to be used as biosensors [49].

Ceramics

Ceramics are high-hardness materials [2], suitable for applications requiring high resistance to corrosion and low friction; their main disadvantage is that they are brittle and do not support high mechanical loads.

Hydroxyapatite

Among the ceramics most used in tissue engineering is hydroxyapatite; this material is naturally found in bones and tooth enamel.

Glasses

These are materials composed primarily of silicon, tempered with sodium, calcium, and phosphorus oxides [50]. The advantage of bio-glasses has been determined for bone regeneration, due to their capability to maintain osteoblasts and bond with both soft and dense tissue [31]. However, they may have low degradation rates.

Composite Materials

Sometimes a material is not suitable on its own to support high mechanical loads; this is the idea behind composite materials, where the goal is to give the scaffold greater mechanical strength and retain characteristics of interest such as its propensity for cell fixation.

Scaffolds can also be provided with growth factors that interact with cells to attract, differentiate, or guide them in the desired direction [34].

Bioprinting

Manufacturing techniques have been designed with the hope of creating increasingly complex morphologies using biomaterials to create different prosthetics and implants impossible to achieve through subtractive manufacturing techniques - as they are known nowadays.

The integration of AM as part of the RM arsenal of solutions has led to the conception of a new medical subarea known as tissue engineering, based on the use of scaffolds, cells and growth factors [2][13][15][22][51]. The first three-dimensional printing techniques were not conceived as a tool for regenerative medicine, so materials were used that had a high melting point or crosslinking agents that caused damage to cells [52], for this reason new techniques and materials have been developed to forward the field of tissue engineering.

Each of these materials processing forms has its advantages and disadvantages [26]. The most used techniques are based on extrusion, laser and drop [11][33][53][54].

Drop Printing

It was the first bioimpression technique used [27] although there are variations in this technique, they all have a common ink reservoir. The ink is conducted to a small orifice or nozzle, where, due to the liquid's surface tension, it cannot come out.

To force the ink out through the nozzle, pressure is applied by means of thermal, acoustic, or piezoelectric methods [11][30][52]. In the first method, a thermal actuator is used to heat the solution. This increase in temperature causes the material to expand, which generates the necessary pressure to expel the drop [11]. It has been found that the increase in temperature can cause cell damage, reducing cellular viability [54].

In the second case, a piezoelectric actuator drives the drop out, through the nozzle. Although this method has the advantage of uniformity in drop size, it is possible to cause lysis to cells if used at high frequency [11].

Finally, there is the acoustic actuator, it is designed to converge sound waves at the tip of the nozzle, forcing the drop down.

The disadvantage in this system is that the material must be in liquid form to form the drops. However, this problem can be solved by using a prepolymer. Which, as its name implies, would be a more fluid molecular antecedent of the intended polymer.

Once the prepolymer is expelled, cross-linking between molecules is facilitated to induce material gelation. With this reaction, the newly gelled polymer molecules will remain fixed at the desired location. It is important to note that the deposited layer must be fully gelled before printing a new layer on top of it. Therefore, the gelation time must be shorter or like the drop deposition time [55].

Different configurations have been explored to facilitate cross-linking. These range from printing the prepolymer directly onto the cross-linking agent, to spraying the prepolymer with the cross-linking agent [53].

This technique has the advantage of high resolution, high speed, and low equipment cost. These advantages have allowed commercial inkjet printers to be modified to work with bio-inks, as is the case of Arai *et al.* (2011) [56], who modified a commercial printer to work with a prepolymer (sodium alginate), which was deposited in two-dimensional patterns, dictated by a bitmap image. In the end, the ability of the equipment to create complex structures in three dimensions was demonstrated, using simple cross-sections.

The viscosity of the bioink is one of the important parameters during the printing of alginate with the technique described in this section. However, this has been easily modified by adding a small percentage of the cross-linking agent [30][57].

Finally, one of the main problems that has been tried to solve is that this technique is based on the use of hydrogels, which lack the mechanical properties necessary to be used in in vivo applications. Therefore, to increase the effectiveness of this technique, new materials must be developed, which must have mechanical properties like the tissue they intend to replace [11].

Extrusion

Printers that use extrusion create pressure on the material by means of pneumatic valves or mechanical pressure [30][32][57][35]. They have the disadvantage of low resolution compared to other techniques [35]. However, due to the simplicity of operation and low fabrication cost, these have become widely disseminated.

Fused deposition modeling

This is the most widely spread and popular technique. It is based on the deposition of melted thermoplastic material through a small opening or nozzle [8][23]. The material deposition follows a calculated trajectory using CAD software [18][52]. Material rheology and ther-

mal transfer properties are critical to determine its suitability for this technique [8].

The scaffold is built layer by layer and it is important that the temperature of the material being worked is kept within a range where it can flow without dripping [6]. The temperature must also be suitable for melting and adhering to the deposited material, giving the scaffold rigidity and integrity [8]. To maintain the piece temperature at the appropriate level, it is common to use a heated construction bed. Figure 1 is a schematic representation of the operation of this technique.

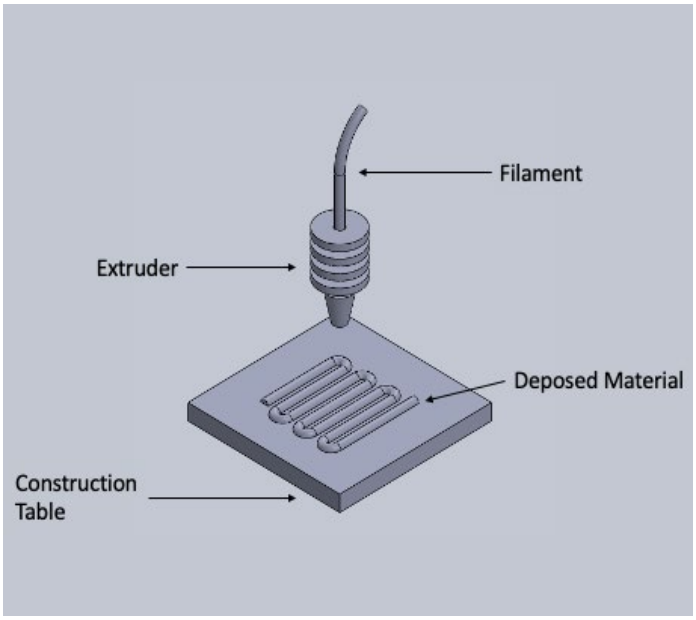

FIGURE 1. **Fused deposition modeling technique functional scheme.**

Although there have been many advances in this technique, there are still problems to be solved, one of which involves the difficulty of incorporating cell deposition during the printing process, since the working temperature is high enough to cause cell damage and the extrusion can cause shear stresses which also impact in the cell viability [6]. Fahmy, *et al.* (2016), addressed this problem by means of a low melting point polymer, such as PCL, used as a thermal shield, and a high melting point polymer, such as PLA, as a mechanical support material. In the end, they concluded that PCL can completely block heat flow and increase cell viability.

A different approach consists of printing the scaffold without cells, then colonizing it in a bioreactor. However, in these cases, there is a cell concentration gradient with a high concentration on the scaffold surface and a decline in central areas. To avoid this situation, Ozbolat, *et al.* (2014) [58] developed a double-nozzle bio-printer, in which one of the nozzles injects a biogel, and the other cell spheroids. This way, the cell distribution is uniform and can reach the central parts of the scaffold.

In principle, as many nozzles and materials can be incorporated as required, meaning there is no limitations to the composition gradients in any of the three axes [8]. Using this, Kang, *et al.* (2016) [59] designed and built a printer with 4 nozzles, capable of depositing polycaprolactone, a hydrogel as a support and two different types of cells. The work mentioned stands out in its importance when it is considered that one of the challenges faced by additive manufacturing is the generation of hollow structures that emulate body structures, for example, capillary vessels, which are highly desirable structures. With aims of building these structures systems have been designed that deposit a support material that acts as a support for the upper layers. Once the printing has finished, the support material can be removed. This material is known as sacrificial material or fugitive ink.

On the other hand, Adamkiewicz and Rubinsky (2015) modified a commercial printer to work with cryogenic materials. This work concludes that one of the advantages is the possibility of producing highly complex and detailed structures. These structures, in addition, are ready to be preserved for a long period of time.

Selective Laser Sintering

It is a technique in which the base material is in the form of powder, stored in a container with a moving bottom that rises to feed the system [12]. The building table has a second container, like the first, which moves vertically during the process. The powder is dispersed in a thin and uniform layer on the building table by means of a roller. Once in this form, a laser heats the material above the glass transition temperature in amorphous materials and just below the melting point in crystalline materials. This causes the powder particles to undergo a sintering process and maintain their shape.

Once a layer is completed, the building table drops by means of a piston and simultaneously a second piston rises loaded with new material to supply a new layer of powder. The process is repeated until the piece is completed. A diagram of this process is shown in Figure 2.

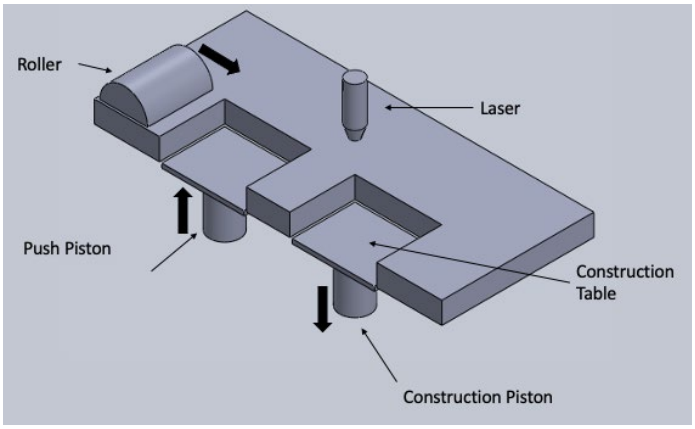

FIGURE 2. **Selective laser sintering diagram technique.**

Unlike the others, in this technique it is not necessary to use support structures for the hollow channels, as the unsintered material serves as a support structure, although the disadvantage is that this material can be difficult to extract from small structures [37]. Another advantage is that it can be used practically any powder material whose degradation temperature is higher than the sintering temperature. Naing and colleagues (2006) designed a digital system responsible for creating the porosity of a piece by means of geometric shapes. After this, the piece was printed using polyether ether ketone, which is a biocompatible polymer with a high degradation temperature. In the end, they conclude that the system is capable of satisfactorily printing the desired figure.

It has been found that due to excessive material inside the pores of the piece, the actual porosity is 60% to 70% lower than the porosity of the piece when it was conceived [37]. In the work carried out, polycaprolactone scaffolds were manufactured using the previously described technique. In the end, it is concluded that this technique is appropriate for printing scaffolds that require supporting mechanical loads up to 27.4 MPa. However, it is mentioned that there is still work to be done in increasing the printing resolution, which is directly related to the laser focus and the size of the powder particle used. It is important to control the porosity of the piece because with this parameter the load supported by the bone can be controlled, which if not adequate can lead to the loss of normal functions of the bone, caused by the Wolff law also known as stress shielding.

Stereolithography

It was the first three-dimensional printing technique, invented by Charles Hull and patented in 1986 [57]. Although at that time it was not conceived for use with biocompatible materials.

In this technique, photopolymerization is induced in the desired points, by means of a laser light source [6][11][28]. This causes a phase change in the material. Once a cross-section is finished, the bed lowers, and a new section is begun, and so on. A diagram with the principle of operation of the technique is shown in Figure 3.

It has the advantage of easy removal of unused material and the resolution that can be achieved, 1.2 μm, by focusing the laser beam [11][28] however, one of the disadvantages is the slow printing speed [28].

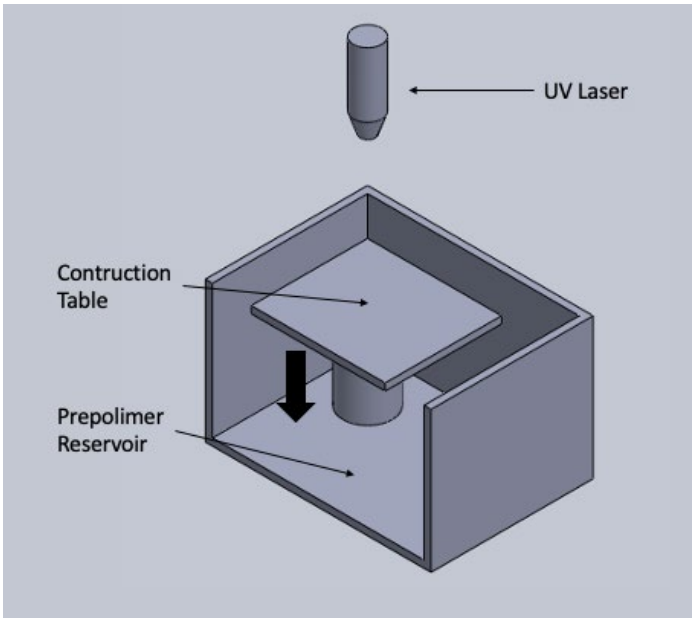

FIGURE 3. **Stereolithography functional diagram.**

One way to increase speed is to use ultraviolet light and a digital micro-mirror device (DDM); in this way, a cross section is worked on and speed increases. A deficiency of materials capable of being used with this technique has also been found [11], as well as the phototoxicity of the photoinitiator when polymerizing together with cells [55]. However, work has been done to develop photocurable, biocompatible compounds (Kweon, *et al.*, 2003) [61], where PCL was chemically modified to favor crosslinking in the presence of ultraviolet light. In the end, it is concluded that the scaffolds manufactured have a compression modulus of 6.9 MPa and a faster degradation rate, so they are suitable for use in certain tissue engineering applications.

CONCLUSIONS

Regenerative medicine has widely benefited by the integration of additive manufacturing techniques, converging into a new medical field: tissue engineering. This new area of medicine opens the possibility to solve problems until now intractable: avoiding the need for immunosuppressants due to organ transplantation and shortening the waiting time for the procedure. One of the biggest challenges that still needs to be solved is the printing of hollow structures, this has become the biggest challenge of tissue engineering and it is expected that when achieved, access to the printing of more complex and functional parts will be obtained, which will bring us closer to the manufacture of complete organs.

CONFLICTS OF INTEREST

The author does not report any conflicts of interest.

AUTHOR CONTRIBUTIONS

A.J.M. conceptualized the project, participated in the visualization, conducted research and investigation, contributed to the writing of the original draft of the manuscript. I.D.L. conceptualized the project, developed the methodology, performed project administration duties, and participated in the writing, reviewing, and editing of the manuscript. J.C.S.S. conceptualized the project, developed the methodology, performed project administration duties, and participated in the writing, reviewing, and editing of the manuscript. A.L.G.G. conceptualized the project, developed the methodology, oversaw the project, and participated in the writing, reviewing, and editing of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Hydrogels in the Treatment of Degenerative Tendinopathy

Hidrogeles en el Tratamiento de la Tendinopatía Degenerativa

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ABSTRACT

Degenerative tendinopathy is a significant health problem, and its incidence increases yearly. This condition causes functional deficits in young and adult patients and sedentary or active individuals, resulting in health, social, and economic consequences. Due to limited blood supply, drug administration is complex for tendon diseases, such as degenerative tendinopathy. Biomaterials, such as hydrogels, have gained significant attention in designing drug delivery systems to treat musculoskeletal pathologies due to their attractive characteristics and the challenges posed by conventional drug delivery routes. This paper provides an overview of tendon pathology and discusses the use of hydrogels as drug carriers and release agents in emerging treatments.

KEYWORDS: drug release, hydrogel, tendinopathy

RESUMEN

La tendinopatía degenerativa es un importante problema de salud, y su incidencia aumenta cada año en todo el mundo. Esta condición genera déficits funcionales en pacientes jóvenes o adultos, así como en personas sedentarias o activas, trayendo consigo repercusiones sanitarias, sociales y económicas. Debido al suministro de sangre limitado, la administración de medicamentos es compleja para las enfermedades de los tendones, como la tendinopatía degenerativa. El uso de biomateriales, como los hidrogeles, ha ganado una atención significativa en el diseño de sistemas de administración de fármacos para tratar patologías musculoesqueléticas debido a sus atractivas características y los desafíos que plantean las rutas convencionales de administración de fármacos. Este documento proporciona una descripción general de la patología del tendón y analiza el uso de hidrogeles como transportadores de fármacos y agentes de liberación en tratamientos emergentes.

PALABRAS CLAVE: hidrogel, liberación de fármaco, tendinopatía

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INTRODUCTION

Worldwide, 30 % of all medical consultations for musculoskeletal issues are related to tendon injuries, with 4 million new cases reported each year, indicating that it is a frequent health concern. The tendon is an essential dynamic stabilizing element in the human body, enabling the transmission of force generated by muscles to the bone segment, allowing movement to occur. Additionally, it absorbs external forces to reduce muscle overload and prevent injuries [1].

Tendinopathy is a common tendon injury with social and economic repercussions in the population. The tendon can undergo an acute pathological process named tendinitis (inflammatory tendinopathy) or tendinosis (degenerative tendinopathy), mainly caused by overuse, resulting in pain and functional limitations that negatively impact the patient's daily activities. Today, more information is available on the pathophysiological processes of tendons, which allows for more specific treatments that alleviate symptoms and address the underlying problem. Tendinopathy can be treated through various options such as relative rest, physiotherapy, nutritional changes, surgery, regenerative medicine, pharmacology, which is the most widely used, and new techniques that use polymeric materials to treat musculoskeletal pathologies [2][3].

Tendinopathy is a challenging condition to treat. An incorrect diagnosis and indiscriminate use of anti-inflammatories and analgesics can lead to degeneration of the tendon and loss of its mechanical properties, resulting in tendon damage and rupture in severe cases [2][3][4]. Systematic reviews of tendinopathy treatments encompass non-invasive and invasive options, depending on the stage of the condition's progression [4][5]. The approach to treatment includes various therapies, such as physiotherapy, platelet-rich plasma infiltrations, prolonged rest, drug use, and, ultimately, surgery [6]. These treatments, such as physiotherapy, primarily aim to reduce pain, stiffness, and tendon thickness and increase mobility range, elasticity, and muscular strength through exercises, manual therapy, thermotherapy, and electrotherapy [7]. However, these treatments only reduce the patient's pain, and the degenerative issues associated with tendon pathology are often overlooked.

Pharmacological treatment is one of the most utilized approaches for managing musculoskeletal system pathologies. While it may be effective in other pathologies, it presents a challenge in tendinopathy due to the low blood supply to the tendon. As a result, higher doses are required to achieve therapeutic effects, which can increase the progression of the disease. Moreover, there is a limited understanding of the pathophysiological mechanisms that cause tendinopathy, which adds to the complexity of managing the condition and impeding patient recuperation [8].

Hydrogels are promising materials in the pharmacological treatment of tendinopathy, derived from natural or synthetic polymers with a structure that resembles a three-dimensional porous network capable of retaining significant amounts of water [9]. This retention capacity makes them attractive as support and drug-releasing agents at the injured site. Hydrogels as drug carriers can prevent drug denaturation and aggregation after exposure to inorganic solvents, helping to avoid enzymatic and environmental degradation of the drug [10][11]. In addition, they provide a favorable environment for cell or drug infiltration, compensating tendon damage [5][12][13][14][15]. On the other hand, studies have shown that hydrogels also maintain tissue homeostasis, promoting faster tissue recovery in *in vitro* and *in vivo* models [16][17][18].

The use of polymer hydrogels is highlighted due to their numerous characteristics and advantages, in contrast to conventional methods, as supports for drug administration in the management of degenerative tendinopathy. Given the necessity for drug delivery strategies in tendinopathy, hydrogels present an attractive alternative with potential application in this bio-

medical field [18][19]. The relevance of hydrogels in tendon pathology lies in the fact that, thanks to their properties, they can simulate the tissue structure, replace damaged tissue without the body rejecting it, and also act as a support to store drugs that stimulate repair at the cellular level of the damaged area, controlling the speed and the desired dose [20][21][22][23]. This work offers a review of the literature on the pathophysiology of tendinopathy, the challenges involved in its treatment, the utilization of hydrogels, and the advantages they provide as drug carriers.

MATERIALS AND METHODS

A literature review of articles was carried out to collect information on tendon pathology, biopolymers, hydrogels, and drug carriers, using the keywords: tendinopathy, tendon regeneration, tissue engineering, composite, stimuli-responsive polymers, and polymer-drug complex. The databases consulted included: Medline, Web of Science, PubMed, ScienceDirect, and Google Scholar. This review covers articles published during the last 10 years; and reviews the title, abstract, results, and conclusion of each publication according to the following selection criteria: 1. The study must contain information on the current challenges of tendinopathy and their treatments, 2. The work must report on hydrogels as treatments for tendinopathies, 3. The research must include the applications of hydrogels for administering drugs to the tendon. In accordance with the above, 200 articles were reviewed, and 90 were selected, of which 20 met the selection criteria, and 70 served to support the related fundamental concepts.

RESULTS AND DISCUSSION

Tendinopathy

Tendons are part of the musculoskeletal system and transmit force from the muscle to the bone, facilitating joint movement [13]. Tendons are composed of collagen (30 %), extracellular matrix (68 %), and elastin (2 %), which give them their mechanical properties [24]. Tendinopathy is a degenerative pathology in the tendon, regularly associated with age but also occurring in young people. It is a tendon injury mainly caused by overuse, leading to microtrauma and degeneration [3][6].

The prevalence of tendinopathy has increased worldwide since the early 2000s [5], resulting in long-term permanent functional deficits in athletes and sedentary individuals of all ages. Furthermore, its incidence varies between different anatomical regions, with joints with greater mobility being more commonly affected. Several factors, such as age, sex, type of sport, and environment, can influence a patient's predisposition and recovery [4]. Chronic tendon damage is characterized by a disorder of collagen fibers, as well as the presence of type III collagen fibers [13] and increased expression of metalloproteases (MMP) MMP-1, MMP-3, MMP -9 (collagenases, gelatinases, and stromelysins) responsible for the degradation of the extracellular matrix and the limited expression of MMP inhibitors [25]. While tendons continuously undergo degradation and regeneration to maintain homeostasis and attempt self-repair in the event of damage, the degenerative process progresses if the underlying causes persist [26]. MMPs are zinc hydrolases involved in physiological functions such as organogenesis, healing, uterine involution, as well as pathological conditions like inflammatory processes, autoimmune diseases, and carcinogenesis. Various cell types, including polymorphonuclear leukocytes, keratinocytes, monocytes, fibroblasts, and mesenchymal cells, generate MMPs in the presence of growth factors. MMPs are secreted as inactive proenzymes into the extracellular milieu and require activation in the pericellular environment of tissues [27]. In degenerative tendinopathy, hyperactivity of MMP-1, MMP-8, and MMP-13 degrades extracellular matrix elements such as tendon collagen. The body has endogenous inhibitors of MMPs in tissue (TIMPs) to help repair degeneration and maintain tendon homeostasis, but often they are insufficient to control MMP activity [28].

Treatments for tendinopathy

Pharmacological treatments utilize different routes of

administration, including intravenous, intradermal, nasal, and oral. The latter is the most used route, but it may not always be the most appropriate for certain pathologies or patients due to the associated disadvantages, among which an incorrect biodistribution stands out. This can require higher doses to achieve the desired effect, especially in poorly irrigated such as tendons [10][29]. One major obstacle faced by drugs intended for tendinopathy is poor vascularization, which restricts the drug's access through the bloodstream and can cause toxicity when high doses are required to achieve the desired effect [30]. Pain and inflammation also contribute to movement restriction, making recovery more challenging.

The most used drugs for tendinopathy administered orally or intramuscularly are non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics. NSAIDs inhibit cyclooxygenase activity, decrease the synthesis of proinflammatory prostaglandins involved in the inflammatory response, and increase tissue permeability and blood flow. However, prolonged use can lead to side effects such as gastrointestinal, renal, and cardiovascular disturbances [31]. Corticosteroids are less frequently used for tendinopathy but have shown beneficial effects in the short and medium term, such as in infiltrations for chronic tendinopathy of the middle portion of the achilles tendon.

Tissue engineering represents an alternative approach used to investigate tissue injury repair. Biomaterial-based drug carriers have been proposed, with natural polymers being the preferred choice due to their biocompatibility, high availability, and low cost. Similarly, synthetic polymers like polylactic acid have been suggested for their adaptability, reproducibility, and low immunogenicity [32]. These biomaterials should possess adequate architecture, good biomechanical performance, and be bioresorbable, biomimetic, biodegradable, biocompatible, and exhibit low immunogenicity. Natural polymers, such as collagen, gelatin, and cellulose, have been evaluated for tendon regeneration due to their availability and affordability, and they have shown promising results in both *in vitro* and *in vivo* studies [33].

Hydrogels and their relationship with the tendon extracellular matrix

The mechanical characteristics of the extracellular matrix have been evaluated in terms of elasticity, which is the resistance of an object to undergo reversible deformation in response to an external force. Thanks to its high-water content, the extracellular matrix is viscoelastic, and viscoelasticity plays a fundamental role in matrix mechanics [34]. Due to matrix composition and organization changes, the response to mechanical stress and strain differs between human body organs [35]. Viscosity is a property that arises from a fluid's resistance to deformation. The combination of elasticity and viscosity results in time-dependent stress dissipation, known as viscoelasticity [36]. Unlike materials that possess only elasticity and store and retain energy, viscoelastic materials can dissipate energy in the face of time-related stresses, making the elastic modulus dependent on the strain rate. Thus, viscoelasticity is an intrinsic property of the extracellular matrix recognized in biological systems [37]. As previously mentioned, tendons tend to break due to the tissue composition and the constant load they experience, making it essential to pay attention to their mechanical properties. Deepthi, *et al.* [38] used a layered chitosan-collagen hydrogel to mimic native extracellular matrix glycosaminoglycans for tendon regeneration. These results showed that layered chitosan-collagen hydrogel is ideal for tendon regeneration and for preventing tendon adhesion.

Hydrogels are water-swollen polymeric networks (Figure 1) that are used as *in vitro* systems to simulate the extracellular matrix [9]. When producing hydrogels, it is necessary to consider the raw materials, which are mainly natural or synthetic polymers. Additionally, the appropriate crosslinking technique, whether physical or chemical, must be chosen. Physical crosslinking

does not require a crosslinking agent for the reaction to occur since the hydrogel is in a liquid state, and a change in the environment, ionic concentration, temperature, or pH trigger the gelation. On the other hand, chemical crosslinking occurs through a crosslinking agent, enzymatic reactions, radiation, click reactions, or polymerization, and these processes are irreversible [39][40].

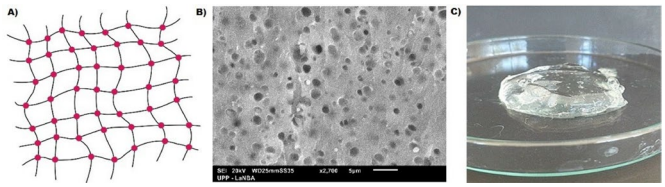

FIGURE 1. A) Representation of the macroscopic structure of the hydrogel. B) Surface morphology of a hydrogel observed by Scanning Electron Microscopy C) Carboxymethylcellulose hydrogel.

Regulating the mechanical characteristics of hydrogels is essential for assessing their suitability in tissue applications. Mechanical properties, such as viscoelasticity, depend heavily on the polymer structure, type, molecular weight, swelling index, and crosslink density.

The hydrogels must have adjustable viscoelastic properties since the similarity with the extracellular matrix of the tissue depends on this, allowing cellular regulation and diffusion of drugs, depending on the method used for the application. Therefore, the hydrogels must have adequate stress relaxation kinetics that matches what occurs in biological processes *in vivo* [41]. Sun, *et al.* [42] report tendon-mimetic hydrogels constructed from anisotropic assembly of aramid nanofiber composites and had a high modulus of ~1.1 GPa, strength of ~72 MPa, fracture toughness of 7333 J/m^2, characteristics matching those of natural tendons.

With the rise of biomaterials, viscoelastic hydrogels have been designed to construct a dynamic mechanical microenvironment that more closely mimics the mechanics of the native extracellular matrix. Native tissues behave as viscoelastic materials and play critical roles in maintaining physiological activity, such as energy dissipation by tendons during daily movement and exercise, protecting them from continuous or periodic high stresses or strains [41]. Tissue bioengineering has developed collagen I hydrogels, and it has been emphasized that the mechanical characteristics of hydrogels must match those of tissues to achieve adequate physiological behavior [43]. The mechanical characterization of viscoelasticity can be carried out through dynamic mechanical analysis in tension, compression, and torsion. However, such data for living tissues are sometimes unavailable. For instance, tendons and muscles undergo rapid stresses and relatively high strains and are anisotropic, whereas most tissues undergo relatively small stresses under physiological conditions and exhibit linear behavior.

Hydrogels continue to be studied because their mechanical properties can be improved for specific applications. Chou *et al.* [44] prepared thermosensitive hydrogels-based poly(N-isopropylacrylamide) *in situ* to prevent postoperative peritendinous adhesion. This provides mobility and flexibility during injection application, allowing for gap-filling after surgery. Nevertheless, synthetic hydrogels have low gel strength, poor tenacity, and slow water absorption.

It is important to mention the swelling capacity of hydrogels, especially in cases where the drug is released through swelling. In these instances, the drug is dispersed within a polymer, and when it comes into contact with a fluid, the polymer starts to swell [45]. The swelling rate is calculated by measuring the change in weight before and after water absorption, expressed as a percentage of weight gain. In swelling-controlled delivery systems, the higher the rate of hydrogel swelling, the higher rate of hydrogel swelling corresponds to a higher rate of drug release. For example, a novel injectable doxorubicin-loaded hydrogel achieved equilibrium swelling within 72 h with high swelling ratios

ranging from 3,500 % to 4,000 %, depending on the pH values of PBS solutions [46].

Porosity is another crucial characteristic as it simulates tissue permeability for cell growth or migration or as a support. This characteristic is defined by pores of different sizes, shapes, spatial distribution, and interconnections [47]. Hydrogels exhibit limited internal diffusion, wherein a hydrogel placed in a liquid medium swells or collapses until it reaches equilibrium due to the balance between the osmotic forces originating from water entering the macromolecular network and the cohesive-elastic forces exerted by the polymeric chains that oppose this expansion [48]. Likewise, the porosity of the hydrogel is an essential physiological factor as it promotes the transport of oxygen and nutrients to maintain cell survival. Additionally, it acts as a reservoir with a high loading capacity for therapeutic actives (drugs, proteins, among others), protecting them from environmental degradation and subsequently releasing them through various mechanisms [14].

In such a way that the pore is an important parameter that can affect drug diffusion. Optimal porosity is necessary for increased drug release, which is supposed to depend on the size relation of hydrogel pores. However, it has been observed that very high porosity does not necessarily result in increased drug release. Pore size distributions narrow as the concentration of the polymer chosen for the hydrogel design increases. Such is the case of a polyethylene glycol methacrylate hydrogel. Pore sizes were determined from bulk hydrogels by cryo-SEM. Smaller pore sizes (30-150 nm) were obtained by increasing polymer concentration due to an increase in network density. They concluded that small substances encapsulated in hydrogels prepared with low concentrations of polymer show an initial burst release. They observed a very slow initial and accelerated release starting on day 6. This indicates that a fraction of the substance resides in the large pores from which diffusion could rapidly release it [49]. The size of hydrogel pores can be modulated by controlling the crosslink density [50]. These interconnected pores vary in size from a few micrometers to hundreds. Analyzing hydrogel pores presents a challenge in accurately determining their size and distribution [47]. It is necessary to consider that the pore sizes are more significant for proper storage and subsequent release of any loaded substances, such as drugs or biomolecules [51]. Similarly, the morphology of the hydrogel affects the degree of degradation. In porous hydrogels where the pore size exceeds the molecular dimensions of the drug, the diffusion coefficient is related to the hydrogel´s porosity and tortuosity [52]. In hydrogels with pore sizes similar to the molecule size or non-porous hydrogels, the drug diffusion coefficient decreases due to steric hindrance caused by the polymer chains. In such cases, the volume available for mobility decreases, and the hydrodynamic resistance increases, resulting in an increased drug diffusion path length compared to hydrogels with larger pore sizes [53].

According to Stoppato *et al.* [21], injection of a 2-methacryloyloxyethyl phosphorylcholine hydrogel around the tendon in a murine model with achilles tendinopathy and a chicken model with deep flexor digitorum tendinopathy resulted in a hydrogel with nanometer-sized pores. When injected, it would allow the penetration of signaling molecules, inhibiting tendon filtration and cell adhesion without adverse effects.

Finally, regarding the hydrogel's physical and chemical degradation, physical degradation provides a space for cell migration and vascular infiltration for tissue regeneration [54]. The degree of hydrogel degradation must match the degree of new tissue formation to maintain tissue integrity and mechanical properties. The physical degradability of hydrogels depends on the properties of the materials that compose them and the microenvironment conditions [23]. To ensure tissue regeneration, the degradation process must be synchronized with cell proliferation and blood vessel infiltration [55]. After being placed, hydrogels begin to

degrade, directly impacting the controlled drug release and the final result of tissue repair. It is essential to control the degree of degradation of hydrogels, which is determined by the crosslinking density of the network that forms the hydrogel [56]. Silva *et al.* [57] report a photocrosslinkable magnetic-responsive hydrogel composed of methacrylated chondroitin sulfate and enriched with platelet lysate for application in the tendon-to-bone interface; hydrogel degradation was completed in 17 days. Sundaram *et al.* [58] developed a chitosan hydrogel reinforced with twisted poly (L lactic acid) aligned microfibrous bundle to mimic the tendon extracellular matrix. The degradation pattern was observed over time due to the degradation of the chitosan hydrogel layer from the final construct. Chitosan is a polymer that has been extensively studied, and its degradation rate can range from six months to a year. The degradation occurs via hydrolysis or enzyme attack.

Therefore, it is important to design hydrogels that mimic the properties of the extracellular matrix and the changes to which it will be subjected. Additionally, it is necessary to study these hydrogels according to their characteristics to replicate them in an *in vivo* model of tendon pathology.

Hydrogels as carriers for drug delivery

Routes of drug administration, such as nasal, intravenous, intradermal, and oral, are utilized, with the latter being the most common. However, due to various obstacles, oral administration may not always be the best option for all patients or diseases. These obstacles include low biodistribution, especially in poorly irrigated tissues such as tendons, where the drug will take a long time to reach the target site, low solubility, high toxicity at larger doses, and short circulation times in the blood (less than 12 hours) [10]. Conventional pharmaceutical formulations include tablets, capsules, injections, patches, sprays, and drops. Nevertheless, in tendinopathy, minimal irrigation makes it difficult to control plasma concentration and renders these treatments inefficient [59].

Hydrogel-based drug delivery systems overcome the barriers of conventional methods and contribute to effective patient treatment. These systems enable the control of drug availability in tissues for extended periods. They have been developed to modify administration routes to benefit patients, improve bioavailability, and alter release profiles [60]. Dong *et al.* [61] reported the development of an injectable cyclodextrin-adamantane hydrogel to encapsulate and modulate insulin release *in vivo* and *in vitro* for 30 days.

Furthermore, hydrogels are an alternative in drug delivery to injured areas due to their soft, elastic consistency, high water content, and important interaction with living tissues. Some hydrogels are inert materials, so cells and proteins do not adhere to the surface [59]. In this context, Prucker *et al.* [62] developed a poly-dimethyl-acrylamide hydrogel with a blood protein-repelling surface. However, some hydrogels can adsorb proteins and cells and may remain on the surface or migrate depending on the application [16]. Cell adhesion into the hydrogels can be controlled via selection of carbohydrates with defined physical properties (hydrophilicity, charge) and biological properties [63]. For example, a chiral hydrogel accelerates re-epithelialization in chronic wounds and facilitates keratinocyte adhesion, proliferation, and migration, which accelerates re-epithelialization [64].

The swelling behavior of hydrogels allows them to absorb, retain, and release active substances under controlled conditions. The high water content makes them compatible with most living tissues [45]. Mater *et al.* [65] mentioned in their patent the development of a polyethylene glycol hydrogel with adjustable swelling indices to release silver ions as an antimicrobial agent in biomedical applications.

Hydrogels, as a means of drug delivery, should allow for continuous drug administration at the necessary

concentration level, achieving optimal performance during therapeutic action. The concentration must be less than the toxic level and greater than the minimum efficiency to be considered optimal. The main problem with conventional administration systems is the harmfulness of treatments due to the use of higher doses to attain the desired outcomes. The challenge for existing therapies is to achieve optimal concentration control in a single dose of a more significant volume, thereby eliminating the need for daily doses. In this sense, hydrogels are promising treatments [5].

Hydrogels offer numerous benefits as drug delivery and release agents compared to traditional techniques. Short-term drug administration frequencies can lead to better patient reactions to the treatment, which is more practical. In addition, there is a decrease in the fluctuation of plasma concentrations, especially with rapidly absorbed drugs, which causes a reduction in high plasma peaks, minimizing adverse effects and, in turn, avoiding subtherapeutic plasma levels that lead to the loss of efficacy [66]. Additionally, hydrogels can protect drugs against environmental and enzymatic degradation and can transition from a liquid state to a gel state for *in vivo* injection, resulting in improved drug utilization and a reduced need for frequent dosing [67].

Typically, the active substance is chemically attached to the hydrogel in these drug delivery systems. However, the most common method is to swell the hydrogel with the drug solution to prevent denaturation of the drug and physically bond it to the hydrogel. The hydrophilic properties of the hydrogel trap the drug in solution form, acting as a storage and dosage support [11]. For example, Malik *et al.* [68] developed a carboxymethylcellulose hydrogel cross-linked with β-cyclodextrin to control the release of acyclovir. The hydrogels were dried and immersed in the acyclovir solution to add the drug, then frozen for subsequent freeze-drying.

In some cases, the drug is chemically attached to the polymer chains and subsequently released through hydrolytic or enzymatic degradation [11]. The degradation rate and gelation of the hydrogel are important factors to consider for therapeutic applications, particularly in tissue regeneration. For instance, when a hydrogel is used for tendon regeneration, its gelation and degradation rates can impact its mechanical and biological properties and must align with tissue remodeling [69]. Kuo *et al.* [70] developed a xanthan gum/gellan gum/hydrogel to reduce tendon adhesion without compromising tendon strength. The material's degradation rate increased, and the membrane acted as a barrier for an extended period of time. Due to their characteristics and design, hydrogels have been shown to overcome the limitations of conventional drug administration routes and offer advantages in treating tendinopathy. Therefore, hydrogels represent a promising treatment with a lower probability of producing adverse effects compared to conventional routes.

Mechanisms of drug release in hydrogels

Hydrogels can release drugs through diffusion, swelling, or chemical erosion (Figure 2). From a biomaterial perspective, the goal is to develop systems loaded with the active ingredient/substance and respond by releasing their load at the desired place, time, and rate. For this reason, hydrogels have gained popularity as they can be tailored to meet the specific needs of patients and pathologies [18]. Hsiao *et al.* [71] developed a hyaluronic acid hydrogel as a drug carrier for early intervention in tendinopathy. The hydrogel demonstrated an initial drug release burst of 51.5 % during the first 24 h, followed by a steady release of 40.8 % over 1-10 days.

Release by diffusion: This is the most common mechanism, which allows molecules to move from a higher solute concentration zone to a lower concentration zone when separated by a polymeric membrane. It is essential to consider the size of the hydrogel pores. When the pores are larger than the drug, the speed of dissemination is related to the hydrogel's porosity.

However, when the pore size is similar to the drug, the speed decreases, resulting in reduced volume available for mobility and increased path length for drug dissemination [72]. Freedman *et al.* [73] report adhesive hydrogels that facilitate the diffusion of a drug from the hydrogel drug reservoir into the target tissue rather than in the adjacent tissues by increasing the direct contact surface area and reducing the diffusion barrier.

Release by swelling: The influx of solvent molecules that swell the hydrogel controls the release. In these systems, the drug is dissolved or dispersed in the polymers in either a crystalline or vitreous state. There is a transition from the crystalline form, where the molecules are immobile, to a gel-like state, where the molecules can quickly disseminate [11]. For example, Pourjavadi and Doroudian [74] synthesized an electro-responsive hydrogel containing biodegradable and hydrolyzed collagen polypeptide. The drug release was achieved through hydrogel swelling.

Release by chemical degradation: Chemical erosion can be classified into homogeneous and heterogeneous erosion, determined by the polymer's morphology and hydrophobicity. Homogeneous erosion occurs throughout the hydrogel, while heterogeneous erosion occurs only on the surface. The more hydrophilic the polymer, the more homogeneous the erosion, as it can absorb more water. Conversely, the more crystalline the polymer, the more heterogeneous the erosion, as the crystalline regions exclude water. Drug release is generated through enzymatic degradation or hydrogel swelling, exposing the drug to the surrounding medium. In systems with lateral chains, the drug is chemically bound to the polymer chains and later released through hydrolytic or enzymatic breaking of the linkages [11]. Zheng *et al.* [75] developed sequentially degradable injectable hydrogel microspheres for synergistic local chemotherapy. Combretastatin A-4 was released from the hydrogel with more rapid degradation, perturbing the vascular structure of the tumor and reducing the exchange between the tumor and adjacent tissues.

As has been observed, hydrogels can be tailored to deliver drugs based on the specific needs of tendon pathologies. Therefore, their characteristics and design can be modified to ensure proper drug dosing and distribution within the damaged tissue.

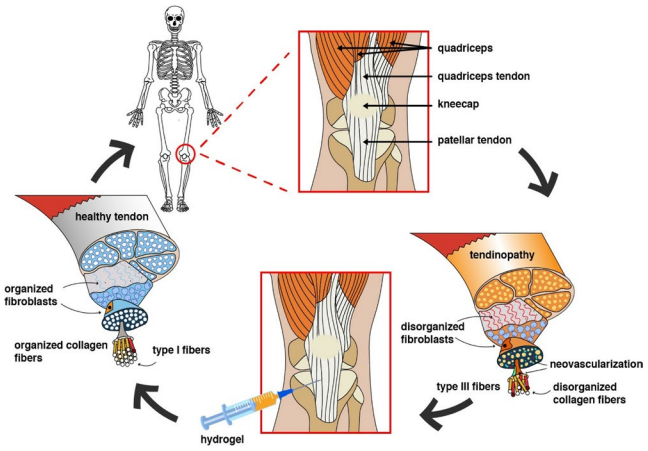

FIGURE 2. Mechanisms of hydrogel drug release. a) Chemically by homogeneous erosion, b) chemically by heterogeneous erosion, c) Dissemination from a matrix system, d) dissemination from a reservoir system, e) Diffusion by swelling.

Hydrogels used in tendinopathy

In the pathology of tendons, no treatment has obtained long-term results, and the tendons do not regain their original strength and function. Thus, it is essential to develop materials that mimic tissue characteristics, transport cells, growth factors, and drugs to the damaged area, and aid in tissue regeneration without causing inflammatory reactions or adhesions [19][76][77]. In addition, these materials must be stable and possess good mechanical properties, biocompatibility, and biodegradability [78]. Farnebo *et al.* [79] developed a tendon-derived extracellular matrix hydrogel to enhance tendon healing *in vivo*. The hydrogel was infused with fibroblast growth factor, insulin-like growth factor-1, and platelet-derived growth factor-BB, which stimulated cell proliferation.

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Hydrogels must be biocompatible materials due to potential immunological reactions in the body. These materials have the ability to mimic the composition and structure of the tissue's extracellular matrix, thereby reducing the immune responses and the risk of rejection by the patient [20].

Hydrogels serve as an excellent tool for controlling regeneration, acting as cellular support for the development of engineered tissue *in vitro* or as a delivery vehicle for *in vivo* therapeutic agents, such as cells or biomolecules. Hydrogels provide temporary scaffolds composed of the tendon's extracellular matrix. For instance, tendons can be engineered using hydrogels loaded with cultured cells in bioreactors under mechanical conditions to stimulate tenogenesis and generate tissues *in vitro* prior to implantation [21]. Another example involves the use of hydrogel microspheres to deliver drugs, cells, or bioactive factors, with the encapsulated contents exhibiting long-acting and sustained release effects that extend degradation time [11]. In another report, composite scaffolds formed by combining hydrogels with other materials facilitated viable cells and growth factors with improved mechanical properties, such as collagen gels combined with poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) tubes. The tissue compatibility of the polyester and its delayed biodegradability promoted cell migration, organization, and function in a murine model of achilles tendon repair [80].

Delivery vehicles: Hydrogels that deliver therapeutic agents into the tendon can enhance tissue healing or regeneration. An example of this is a sustained-release hydrogel-based Rhynchophylline delivery system used to repair injured tendons [22]. Xu *et al.* [81] developed an injectable fibromodulin-releasing hydrogel for tendon healing that significantly improved the histological results of tendon wound healing and led to the recovery of mechanical properties. Various cell delivery methods, such as hydrogel-based cell delivery, which delivers dermal fibroblasts into the tendon, can enhance and stimulate this process compared to adipose-derived stem cells [82].

Injectables: The production of injectable hydrogels for repairing and regenerating tendons uses natural and synthetic biomaterials since it is necessary to consider biological parameters, such as cell adhesion and material degradation, as well as physical parameters, like mechanical properties. Due to their advantages over synthetic materials, the most commonly used natural materials include collagen, fibrin, gelatin, chitosan, and hyaluronic acid. However, these natural materials degrade quickly, and their mechanical properties are insufficient. Injectable hydrogels have gained relevance in numerous applications. Injuries to the musculoskeletal system, especially tendons, present a significant challenge as they do not respond adequately to conventional treatments, and damaged tissue is slow to repair, rarely achieving full recovery [80]. In situ injection can treat tissue with minimal damage and side effects [15]. Most hydrogels can be injected *in situ* into custom-shaped molds or scaffolds to form composite structures (Figure 3) [21].

A patent has been proposed for an extracellular matrix hydrogel obtained from mammalian connective tissue to facilitate the infiltration of fibroblasts, tenoblasts,

and tenocytes and promote the repair and regeneration of tendons [83]. Likewise, a biocompatible hydrogel comprised of a human tendon extracellular matrix (ECM) allowed the creation of a tendon graft through the photocrosslinking of stacked scaffold sheets [84]. In this regard, cellulose hydrogels have been increasingly studied for tissue regeneration due to their similarity to ECM [85].

However, the progress of injectable hydrogels, whether derived from natural or synthetic polymers, for tendon repair highlights the need to develop hydrogels with better mechanical properties, specific binding to tissue damage, and disease response to achieve personalized treatment [86]. Current treatments using hydrogels as supports or delivery vehicles are suitable for use in tendinopathies, despite their limitations [21]. For instance, Kim *et al.* [87] reported on a hyaluronic acid-based injectable hydrogel for tendinopathy treatment, using vitamin D on damaged tenocytes as a new regeneration technique and demonstrating its capability to repair tendinopathy based on tendon restoration properties *in vitro* and *in vivo*. However, a more advanced delivery system could be developed with sophisticated scaffolds such as hydrogels and nanofibers.

The main purpose of using hydrogels in tendinopathy is to deliver the drug to the specific site of the lesion due to the limited capacity of the tissue for self-repair.

Hydrogels function as supports and delivery systems for the active agents in the damaged area. Overall, the progress made in the use of hydrogels for tendon repair highlights the potential for developing more advanced delivery systems in the future.

To quantify the effectiveness of hydrogels as a tendinopathy treatment, the Bonar Score has been designed to assess tendon morphology and histological changes such as cell morphology, collagen arrangement, cellularity, vascularity, and ground substance [88]. Alternatively, the Victorian Institute of Sport Assessment (VISA) scale can be used to analyze the results in the patient's clinic. Alternatively, the Victorian Institute of Sport Assessment (VISA) scale can be used to analyze the results in the patient's clinic. It is useful for assessing pain, stiffness, body structure or function, activity limitation, and restriction of the patient's participation in daily living activities or sports [6].

Finally, Table 1 summarizes the data corresponding to the hydrogels reported in this document that have been directly applied to tendon pathologies.

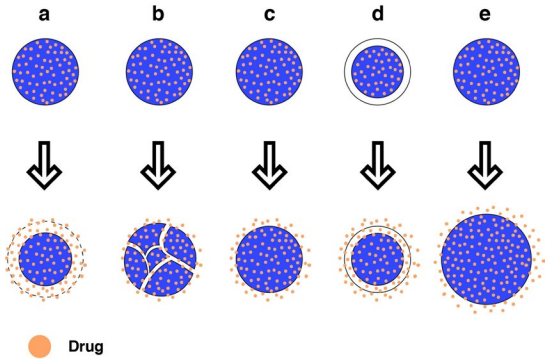

FIGURE 3. **Administration of injectable hydrogels as a cure for degenerative tendinopathy.**

CONCLUSIONS

The approach to tendinopathy through multidisciplinary health sciences and technologies has made it possible to break down the barriers of conventional treatments, ranging from physiotherapy, drugs, and surgery to tissue limitations. The high incidence and poor management of tendinopathy have generated greater interest and research. In this sense, natural or synthetic polymer hydrogels are promising smart materials that offer multiple advantages. Their improved mechanical properties allow the restoration of injured tendon tissue and also act as supports and controlled drug-releasing systems in low-irrigated tissues such as tendons, accelerating their recovery. Hydrogels, as drug carriers, hold promise for treating tendinopathy and continue to be incorporated into new

treatment strategies. For future applications, it is necessary to evaluate hydrogel release systems in a clinical environment and assess their long-term effectiveness *in vivo*.

Future directions

The future directions of hydrogels are based on the modulation of macrophages and immune cells, controlling their reprogramming and plasticity to regenerate tissues. Additionally, designing intelligent regenerative hydrogels as tissue engineering tools to guide the growth, differentiation of cells, and spatial organization [20]. Developing hydrogels with mechanical properties specific to tissue damage and responsive to the disease is necessary. In the same vein, the advantages of various biological materials should be combined to achieve personalized therapy [59]. Furthermore, it is necessary that hydrogels as drug delivery systems be further studied to improve their sustained release properties, ensuring the correct doses of the drug are stored to maintain an optimal drug concentration over time. Finally, the application frequency on the human body should be optimized [89][25].

AUTHOR CONTRIBUTIONS

L.S.O conceptualized the project, contributed to the writing of the original manuscript, performed investigation, and carried out formal analyses. M.V.I. conceptualized the project, contributed to the writing of the original manuscript and the writing, editing, and reviewing the different stages of the manuscript, performed the analyses and oversaw the project. B.E.J.L. contributed to the writing, editing and reviewing of the manuscript, performed formal analyses and oversaw the project. R.B.P. performed the formal analyses and oversaw the project. All authors reviewed and approved the final version of the manuscript.

ETHICAL STATEMENT

The authors declare that they have no conflict of interest directly related to the content of this article.

TABLE 1. Advances in the treatment of tendons with hydrogels

System	Application	Properties/results	Ref.
ADN Hydrogel	Delivery system for tendon stem/progenitor cells	Hydrogel promotes cell proliferation and protection	[12]
3D printed hydrogel particles containing PRP	Tendon postinjury repair	Hydrogel promotes tendon differentiation in tendon-derived stem cell and reduces inflammatory response	[16]
Gelatin/Fe_3O_4/Celecoxib hydrogel	Repair the later stage in tendinopathy	Hydrogel reduced inflammatory reaction of macrophage response	[19]
Chitosan-collagen HG with poly-L-lactide fibers	To mimic the glycosaminoglycans of sheath extracellular matrix for tendon regeneration	Good cell proliferation was observed, tenocytes showed proper attachment and spreading on the scaffolds, indicating that they would be suitable for flexor tendon regeneration	[38]
Collagen I hydrogels	Bioengineered Tissue microenvironments	Scaffolds for engineered tissues with a diffusion capacity	[43]
Thermo-responsive in-situ HG based on poly (N-isopropylacrylamide)	Prevent post-operative peritendinous adhesion	Hydrogels were feasible as injectable barrier materials to prevent post-operative peritendinous adhesion and maintain the intra-tendinous strength or repaired tendons	[44]
Synthetic Polymer, Natural polymer-based hydrogels	Wound healing, adsorbents, drug delivery	CMCN can absorb large amounts of water and form superabsorbent hydrogels depending on the crosslinking agent used	[48]
Photocrosslinkable magnetic responsive HG made of methacrylate chondroitin sulfate with platelet lysate	Application in tendon-to-bone interface	In addition to swelling and electromagnetic fields, degradation could modulate the release profile of growth factors, and therefore could be used as a delivery strategy	[57]
Xanthan gum/gellan gum/hyaluronan HG membranes	Prevent the adhesion of post-repaired tendons	The HG membranes degraded slowly, reducing tendon adhesion without compromising tendon strength	[70]
Drug-loaded hyaluronic acid hydrogels	Sustained release in early intervention of tendinopathy	Better recovery of the tissues and faster healing promoting oxidative stress migration	[71]
A tough adhesive HG, termed Janus Tough Adhesive	Drug delivery for tendon	HG adheres to tendons, is biocompatible, promotes tendon healing, and enables high drug loading and sustained drug release *in silico* and *in vitro*	[73]
Polyvinyl-alcohol and hyaluronic acid hydrogel for controlled drug release	Promote tendon healing	Hydrogel alleviated inflammation enhancing tendon wound regeneration	[76]
Sustained-Release hyaluronic acid hydrogel-based delivery system	Prevent adhesions as treatment for injured tendons	Local release inhibits the formation of tendon adhesion and help the injured tendon to structural healing	[77]
2-methacryloyloxyethyl phosphorylcholine HG	Prevent the formation of adhesions in the tendon	The HG prevented tissue adhesion to the tendon with no adverse effects on the healing process of the injured tendon	[78]
Tendon-derived extracellular matrix HG	Tendon healing *in vivo*	The extracellular matrix hydrogel with growth factors stimulates cell proliferation, and infiltration of host cells into the gel increases with an optimal concentration of growth factors *in vivo*	[79]
Injectable granular hyaluronic acid HG	Tendon healing and recovery of functions	The tendon strength of the treated rats and their gait performance returned to normal, similar to the healthy controls	[81]
HG- cadaver tendon	Delivers dermal fibroblasts into the tendon	It enhances and stimulates this process compared to adipose-derived stem cells	[82]
Decellularized extracellular matrix HG derived from mammalian connective tissue	*In-situ* repair and regeneration of an injured ligament or tendon in mammalian subject	It facilitates fibroblast, tenoblast, and tenocyte infiltration and promote ligament or tendon repair and regeneration	[83]
A biocompatible HG consisting of extracellular matrix (ECM) from human tendons	Tendon tissue engineering	Decellularized tendons were milled and enzymatically digested to form an ECM solution, which offers a promising alternative in tendinopathies	[84]
Injectable hyaluronic acid-based HG	Restoration of tendinopathy	The hydrogel facilitated anti-apoptosis, tenocyte proliferation, tendon-related protein production, and tissue alignment during the regenerating tendon process	[87]

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Análisis de Variables Antropométricas y su Relación con la Fuerza Pinch

Analysis of the Anthropometric Variables and their Relationship with the Pinch Force

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RESUMEN

La evaluación de la fuerza en la mano es utilizada en ámbitos de salud y laborales, está compuesta por la fuerza de agarre y la fuerza de pellizco o fuerza pinch (Palmar Pinch - PP y Key Pinch - KP). La fuerza pinch ha sido poco estudiada y relacionada con variables antropométricas. El objetivo del presente trabajo fue determinar la relación entre la fuerza PP y KP con el género, la dominancia, la edad y variables antropométricas. Haciendo uso de un dinamómetro Jamar y con la participación de 681 sujetos (48,9 % F y 51.1 % M) aparentemente sanos de la Ciudad de Bogotá (Colombia), quienes desempeñaban diferentes actividades ocupacionales, se encontró que las fuerzas PP y KP fueron significativamente más altas en los hombres que en las mujeres tanto en la mano no dominante (8.27 Kgf Vs 6.0 Kgf) como en la mano dominante (8.57 Kgf Vs 6.27 Kgf). Se propusieron modelos predictivos que definieron como variables principales la edad, espesor, circunferencia y circunferencia máxima de la mano. En el género femenino se estableció como variable primordial la edad, mientras que en el masculino en dos modelos se define la circunferencia de la mano y en otros dos la circunferencia máxima de la mano.

PALABRAS CLAVE: dinamometría, fuerza Pinch, mano dominante, mediciones antropométricas

ABSTRACT

The evaluation of the force in the hand is used in health and labor fields; it is composed of the grip force and the pinch force (Palmar Pinch - PP and Key Pinch - KP). The pinch force has not had significant amount of studies and connections with anthropometric variables. This work aimed to determine the relationship between the PP and KP strength with gender, dominance, age, and anthropometric variables. Using a Jamar dynamometer and with the participation of 681 subjects apparently healthy (48.9 % F and 51.1 % M) from the City of Bogotá (Colombia), who performed different occupational activities, it was found that the PP and KP forces were significantly higher in men than in women both in the non-dominant hand (8.27 Kgf Vs. 6.0 Kgf) and in the dominant hand (8.57 Kgf Vs 6.27 Kgf). The predictive models proposed in this study defined age, thickness, circumference, and maximum circumference of the hand as the main variables. In the female gender, age was established as the primary variable. At the same time, in the male, the circumference of the hand was defined in two models, and the maximum circumference of the hand in another two.

KEYWORDS: anthropometric measurements, dominant hand, dynamometry, pinch force

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INTRODUCCIÓN

La fuerza para agarrar y manipular objetos influye en las funciones de la mano, su deterioro afecta las labores cotidianas. La fuerza Manual de Agarre *(HGS-Handgrip Strength)* y de Pellizco *(PS-Pinch Strength)* influyen al momento de realizar funciones manuales prensiles con un alto grado de demanda y para la ejecución de actividades musculares diarias en las cuales intervengan el uso de músculos de potencia y precisión, dispuestos a manipular los dedos de la mano de forma constante [1][2]. La medición de HGS y PS se efectúa con dinamómetros especializados y en diferentes posturas.

Existen tres pruebas estándar utilizadas para realizar un estudio de fuerza PS: Pellizco palmar *(palmar pinch - PP)*, Pellizco de la llave *(key pinch - KP)* y Pellizco de punta *(tip pinch -TP)*. La fuerza PP es un apriete intermedio entre la yema del dedo pulgar y la yema de los dedos medio e índice [3]. Esta fuerza requiere la acción de los músculos flexores superficiales de los dedos índice y medio, juntamente con los músculos tenares para estabilizar las falanges media y proximal del pulgar en flexión, respectivamente [4]. El PP Se usa en el 60 % de las actividades de la vida diaria, un ejemplo de este tipo de fuerza es cuando se utiliza un bolígrafo [5].

La fuerza *KP* se realiza entre la yema del dedo pulgar y la cara lateral de la falange media del dedo índice, como si se metiera una llave en una cerradura [4][5]. Este pellizco requiere la utilización de la musculatura aductora del pulgar. La fuerza TP es la más fina y precisa de los pellizcos realizados por los dedos, se logra utilizando la yema de los dedos pulgar e índice y se utiliza para agarrar objetos pequeños [4].

Los estudios de fuerza en miembros superiores se han especializado en la medición de fuerza de agarre y fuerza pinch, encontrando menor número de reportes de esta última. Los reportes muestran la posible correlación de la fuerza de agarre con diferentes variables: género [6], edad [7], dominancia de la mano [8], actividad física diaria [9][10], ocupación [11], estado de salud [12], factores antropométricos [13][14], postura [15], y estado nutricional de la persona [16].

En Colombia, se han realizado reportes en publicaciones arbitradas y no arbitradas que han desarrollado diferentes diseños metodológicos encaminados a determinar la relación de la fuerza manual de agarre asociándolas a variables como la talla, peso, edad, género y dominancia manual [10][17][18][19][20][21][22]. Sin embargo, son estudios aislados, de diferentes regiones del país, y que adicionalmente utilizan diferentes metodologías y equipos para dimensionar la fuerza lo cual no permite una unificación ni generalización de resultados en el momento de pensar en la población colombiana a nivel general ni tampoco a nivel específico.

Objetivo

En cuanto a la fuerza pinch, existe escasez de datos y análisis en población colombiana. El objetivo del presente estudio fue determinar la influencia de las covariables género, edad, altura, peso, índice de masa corporal (IMC), dominancia y medidas antropométricas de la mano durante la realización de fuerza de pellizco palmar (PP) y de llave (KP).

MATERIALES Y MÉTODOS

Los participantes provinieron de una convocatoria abierta en diferentes centros empresariales y oficinas en Bogotá, Colombia. La característica de los sujetos del estudio fue finita y discreta. El total de los incorporados fue de 681 personas durante el lapso de enero a junio de 2022, de los cuales 333 pertenecieron al género femenino y 348 al masculino. Fueron excluidos de la investigación los participantes que presentaran antecedentes de desórdenes músculo esqueléticos, diagnósticos médicos en miembros superiores y entrenamiento físico en miembros superiores. Los inscritos fueron todos colombianos y con las características descritas en la Tabla 1.

La recolección de la información en campo se realizó mediante dos formularios. El Formulario (1) de Consentimiento Informado, aprobado por el Comité de Ética de la Facultad de Ingeniería de la Pontifica Universidad Javeriana Nro. 12. El formulario 2 de Recolección de Información que incluye los datos demográficos y condiciones de salud auto reportadas. Adicionalmente este formulario se registraban los resultados la fuerza PP y KP. Estos instrumentos no presentaron estudios psicométricos y fueron creados por el equipo de investigación del Centro de Estudios de Ergonomía de la Pontifica Universidad Javeriana Bogotá.

TABLA 1. Información demográfica de los participantes.

Género	Femenino (48.9 %) Masculino (51.1 %)
Mano dominante	Derecha (89.1 %) Izquierda (7.5 %) Ambas (3.4 %)
(IMC)	24.661, DS=3.805
Edad	Femenino 35.641, DS 12.790 Masculino 32.327, DS 11.704
Altura (cm)	Femenino 160.14, DS 6.189 Masculino 171.88, DS 6.857
Peso (Kg)	Femenino 62.93, DS 11.23. Masculino 74.10, DS 11.55

Dimensionamiento Antropométrico y Postura

Las dimensiones antropométricas de las manos de los participantes se realizaron con cinta métrica, calibrador pie de rey y un cono antropométrico. Las técnicas de medición antropométricas fueron seguidas de acuerdo con estudios similares [11][23][24][25][26]; establecidas por NASA 1024 (Anthropometric Source Book II - 1978) [27].

El dimensionamiento sigue la metodología reportada por Mohammad [26] y señala los pasos para realizar el dimensionamiento antropométrico: i) dos longitudes (longitud máxima de mano (1) y longitud palmar (2)), ii) dos anchos (ancho de la mano (3) y ancho máximo de la mano (4)), iii) el espesor de la mano (5), iv) el diámetro de agarre (6) y v) dos dimensiones de circunferencia (circunferencia máxima de la mano (7) y circunferencia de la mano (8)). En la Figura 1 se muestra la forma en la cual se realizó el dimensionamiento de la mano.

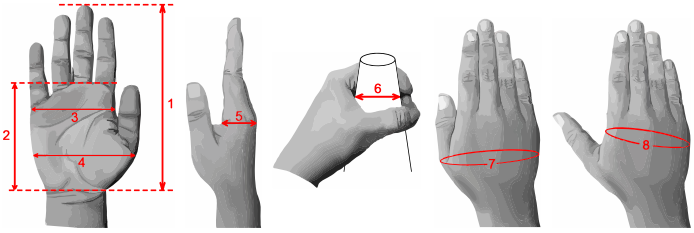


FIGURA 1. Dimensionamiento antropométrico de la mano.

La postura para realizar la medición de la fuerza PP y KP fue definida de acuerdo a las indicaciones dadas por la ASTH (American Society of Hand Therapists) y que ha sido utilizada por otros estudios [3][6][8]: Las pruebas se deben realizar con la persona sentada, utilizando una silla que permita tener soporte lumbar y los pies deben estar totalmente apoyados en el piso, por otro lado, el brazo debe estar cercano al cuerpo y el antebrazo y codo flexionado a noventa grados, pero sin tener ningún tipo de apoyo que interfiera con las extremidades corporales, en esa misma dirección, se debe encontrar las muñeca.

Dimensionamiento de las Fuerzas

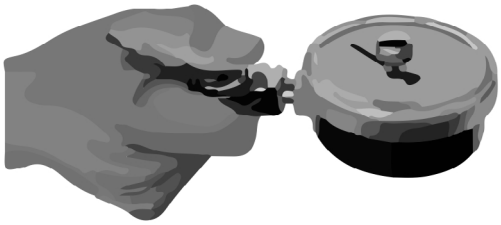
La medición de la fuerza PP y KP fueron realizadas con un dinamómetro de pinch marca Jamar, calibrado antes de iniciar las mediciones bajo la Norma ABNT-NBR-8197:2012. Para cada una de las fuerzas los participantes realizaron tres mediciones con la mano derecha y tres con la mano izquierda. El primer intento se realizaba con la mano derecha e inmediatamente después se realizaba con la mano izquierda y así sucesivamente hasta completar las tres mediciones en cada mano. La persona debía sostener la fuerza durante tres segundos y el tiempo de descanso para cada medición de fuerza era de cinco segundos. En la Figura 2 se observa la forma en la cual las personas manipularon el dinamómetro.

Análisis Estadísticos

Los datos recolectados fueron almacenados en Excel,

luego procesados en SPSS versión 28 y analizados bajo la segmentación del género, para PP y KP; tanto para mano dominante y no dominante. Los análisis incluyeron tres fases: (a) descriptiva, (b) bivariada (ANOVA y t de student) y (c) multivariante a través de una regresión lineal.

a)
Medición de fuerza PP (Palmar Pinch)



b)
Medición de fuerza KP (Key Pinch)

FIGURA 2. **Medición de fuerza PP y KP.**

RESULTADOS Y DISCUSIÓN

Teniendo en cuenta la escritura como mano dominante, el 90.1 % de los participantes femeninos y el 88.2 % de los masculinos fueron diestros, el 5.4 % de las mujeres y el 1.5 % de los hombres fueron zurdos, el 4.5 % de las mujeres y el 2.3 % de los hombres fueron ambidiestros. Esta última condición fue considerada y medida para este estudio como diestros para todos los sujetos.

Características Antropométricas

Las siguientes son las características antropométricas de los participantes de acuerdo al género. El promedio de estatura en los hombres es mayor que el de las mujeres (M= 171.81 cm, DS= 6.85 vs M= 160.14 cm, DS= 6.18). Respecto al peso se observa mayor valor entre los hombres (M= 74.10 kg, DS= 12,1 vs M= 62.93 kg, DS= 11,9;). Con relación a la circunferencia de la mano se presenta menor valor en las mujeres (18.42 cm, DS= 1.58 VS 21.11 cm, DS= 1.88), igual sucede en cuanto a la circunferencia máxima de la mano (21.77 cm, DS= 1.42 vs 24.77 m, DS= 1.58). Así mismo, se observó valores menores en las mujeres respecto a los hombres en cuanto a: espesor de la mano (2.59 cm, DS= 0.5 vs 2.97 cm, DS= 0.5), ancho de la mano (7.67 cm, DS = 1.10 vs 8.55 cm, DS= 1.05), ancho máximo de la mano (9.02 cm, DS= 1.26 vs 10.13 cm, DS= 1.18), longitud palmar (10.12 cm, DS= 1.83 vs 11.20 cm, DS= 2.02) y longitud máxima palmar (16.94 cm, DS= 1.31 vs 18.44 cm, DS= 1.31).

Desarrollo del Protocolo de Estudio

El análisis de los datos y productos de esta investigación se realizaron teniendo en cuenta la dominancia de la mano y el género:

FPPD: Fuerza Palmar Pinch en mano dominante en género femenino.
MPPD: Fuerza Palmar Pinch en mano dominante en género masculino.
FPPND: Fuerza Palmar Pinch en mano no dominante en género femenino.
MPPND: Fuerza Palmar Pinch en mano no dominante en género masculino.
FKPD: Fuerza key Pinch en mano dominante en género femenino.
MKPD: Fuerza key Pinch en mano dominante en género masculino.
FKPND: Fuerza key Pinch en mano no dominante en género femenino.
MKPND: Fuerza key Pinch en mano no dominante en género masculino.

En cuanto al género, los resultados indican que existe mayor fuerza PP no dominante (kgf) en el género masculino (M=8.27, DS=1.42) vs el género femenino

(M=6.0, DS=1.42). Sucede lo mismo para la fuerza PP dominante (kgf) ($M_{masculino}$= 8.57, DS=1.48) ($M_{femenino}$ =6.27, DS=1.44). Respecto a la fuerza KP (kgf), también existen mayores valores en el género masculino vs el femenino, tanto para la mano dominante como para la no dominante: Mano no dominante ($M_{masculino}$ =9.42, DS=1.60) ($M_{femenino}$ =6.62, DS=1.22) y mano dominante ($M_{masculino}$ =8.82, DS=1.51) ($M_{femenino}$ =6.19, DS=1.22) (Tabla 2).

La correlación entre la fuerza y todas las variables independientes se exploró con base en un análisis bivariado de Pearson y se cumplieron todos los supuestos de independencia de observaciones, relación lineal entre las variables, ausencia de valores atípicos, homocedasticidad, normalidad de los residuos, colinealidad a través de VIF y Durbin-Watson (Tabla 2).

Fuerza Palmar Pinch (PP)

En referencia al grupo PP no dominante en el género femenino no se encontraron relaciones estadísticamente significativas con: IMC, peso corporal, circunferencia de la mano, circunferencia máxima de la mano, espesor de la mano, ancho de la mano, ancho máximo de la mano y longitud máxima palmar. Se encontraron asociaciones con las variables género, longitud palmar R^2=3.6 %, altura R^2=2.4 %, Edad R^2=10.1 % (Figura 3) y ancho máximo palmar R^2=0.6 % (Tabla 2).

En cuanto al género masculino se encontraron diferencias significativas y modelos explicativos en el modelo de regresión lineal con respecto a: IMC R^2=1.8 %, ancho máximo de la mano R^2=0.8 %, circunferencia de la mano R^2=4.2 %, circunferencia máxima de la mano R2=3.6 %, espesor de la mano R2=2.4 % y peso corporal R2 =2.2 %. No se reportan relaciones con la edad, altura, ancho de la mano, longitud palmar y longitud máxima palmar.

En lo correspondiente al grupo PP dominante en el género femenino no se encontraron asociaciones con la variable mano dominante, IMC, circunferencia de la mano, circunferencia máxima de la mano, espesor de la mano, ancho máximo de la mano y longitud máxima palmar. Sin embargo, se reportan relaciones con: edad R^2 =9.4 % (Figura 3), la longitud palmar R^2=4.5 %, la Altura reporta R^2=2.6 % y el ancho de la mano R^2=1.4 %.

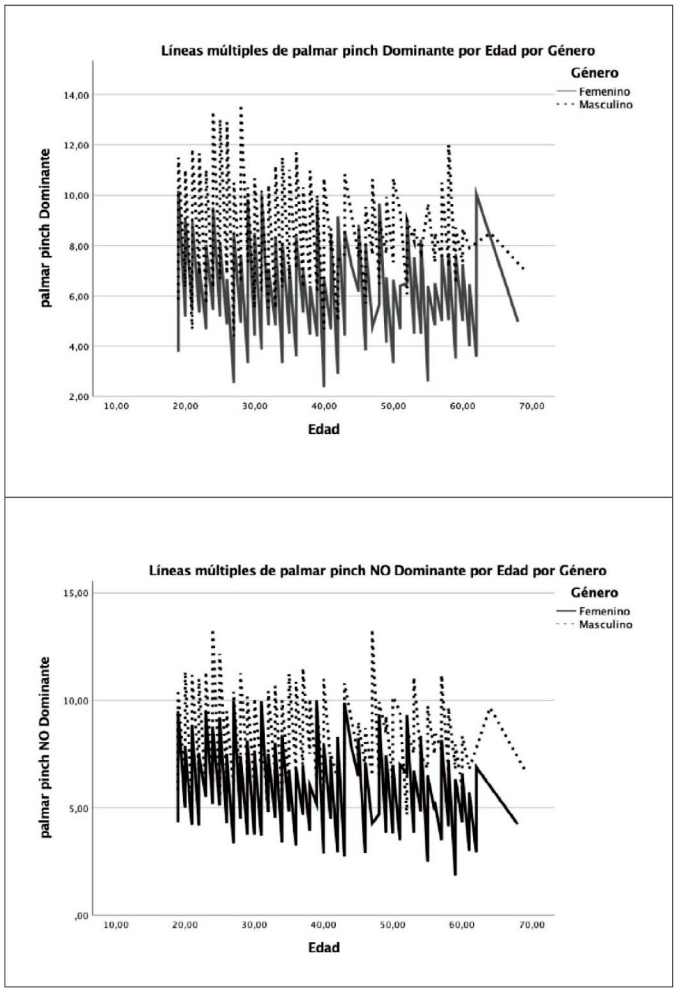


FIGURA 3. Fuerza PP en mano dominante y no dominante Vs edad.

Respecto al género masculino no se reportan relaciones con la mano dominante, IMC, altura, peso corporal, ancho de la mano y longitud máxima palmar. Por otro lado, se presentan relaciones con las siguientes variables de acuerdo al modelo de regresión lineal: circunferencia de la mano R^2 = 3.5 %, espesor de la mano R^2 = 3 %, circunferencia máxima de la mano R^2= 2.2 %, edad R2= 1.5 %, longitud palmar R^2 =1.16 % y ancho máximo de la mano R^2=0.1 % (Tabla 3).

TABLA 2. Correlaciones entre variables.

Variables		PPND	P	PPD	P	KPD	P	KPND	P
IMC (kg/m²)	M	0.133*	0.013	0.041	0.449	0.198**	<.001	0.238**	<.001
	F	-0.013	0.854	0.190	0.727	0.179**	0.001	0.018**	<.001
Edad	M	-0.007	0.895	-0.123	0.021	0.106	0.049	0.040	0.453
	F	-0.318**	<.001	0.307**	<.001	0.158**	<.001	0.173**	<.001
Altura (cm)	M	0.061	0.253	0.093	0.085	0.082	0.129	0.044	0.416
	F	0.155**	0.005	0.162**	0.003	0.129*	0.019	0.124**	0.002
Peso (Kg)	M	0.150**	0.005	0.080	0.136	0.220**	<.001	0.240**	<.001
	F	0.590	0.283	0.032	0.557	0.220**	<.001	0.222**	<.001
Circunferencia de la mano (cm)	M	0.206**	<.001	0.186**	<.001	0.334**	<.001	0.329**	<.001
	F	0.003	0.962	0.019	0.727	0.160**	0.004	0.199**	<.001
Circunferencia máxima de la mano (cm)	M	0.189**	<.001	0.150**	0.006	0.367**	<.001	0.367**	<.001
	F	0.047	0.397	0.110	0.838	0.156**	0.004	0.165**	0.003
Espesor de la mano (cm)	M	0.155**	0.005	0.173**	0.002	0.280**	<.001	0.285**	<.001
	F	0.001	0.979	0.180	0.738	0.117*	0.033	0.111**	0.043
Ancho de la mano (cm)	M	0.105	0.055	0.060	0.272	0.180**	<.001	0.177**	0.001
	F	-0.105	0.057	-0.011	0.003	0.023	0.680	0.046	0.405
Ancho máximo de la mano (cm)	M	0.087	0.111	0.033	0.546	0.143**	0.009	0.137*	0.012
	F	-0.075	0.171	-0.080	0.147	0.060	0.274	0.035	0.524
Longitud palmar (cm)	M	0.107	0.051	0.125**	0.022	-0.108*	0.049	-0.122*	0.040
	F	0.194**	<.001	0.212**	<.001	0.051	0.359	0.111**	0.004
Longitud máxima palmar (cm)	M	0.067	0.224	0.076	0.164	0.149**	0.006	0.051	0.348
	F	0.50	0.354	0.034	0.533	0.106	0.053	0.137	0.001

Correlación de Pearson, (*) significativa a nivel de 0.01 y (**) significativa a nivel de 0.001.

TABLA 3. Relaciones entre variables.

Variables		PPND (Media)	Significancia estadística	PPD (Media)	Significancia estadística	KPD (Media)	Significancia estadística	KPND (media)	Significancia estadística
Género	M	8.278	t de Student -20.783 (p<0.001)	8.577	t de Student -20.493 (p<0.001)	9.272	t de Student -25.696	8.823	t de Student -24.803 (p<0.001)
	F	6.000		6.277		6.624	(p<0.001)	6.192	
IMC (kg/m2)	M	8.285	F 6.212 p=(0.013)		Sin relación	9.430	F 19.923 p=(0.001)	8,83	F 11.117 p=(0.001)

TABLA 3. Relaciones entre variables (continuación de la pag. 61).

	F	6.000		6.277		6.624	(p<0.001)	6.192	
IMC (kg/m2)	M	8.285	F 6.212 p=(0.013)		Sin relación	9.430	F 19.923 p=(0.001)	8,83	F 11.117 p=(0.001)
	F		Sin relación			6.626	F 13.986 p=(0.001)	6.195	F 20.655 p=(0.001)
Edad	M		Sin relación	8.577	F 5.356 p=(0.001)	9.429	F 3.901 p=(0.049)		Sin relación
	F	6.000	F 37.252 p=(0.001)	6.275	F 34.276 p=(0.001)	6.626	F 8.494 p=(0.004)	6.195	F 10.172 p=(0.002)
Altura (cm)	M		Sin relación		Sin relación		Sin relación		Sin relación
	F	6.010	F 8.126 p=(0.005)	6.286	F 8.920 p=(0.003)	6.630	F 5.586 p=(0.019)	6.193	F 5.185 p=(0.023)
Peso (Kg)	M	8.285	F 7.900 p=(0.005)		Sin relación	9.430	F 17.416 p=(0.001)	8.830	F 17.013 p=(0.001)
	F		Sin relación		Sin relación	6.626	F 16.798 p=(0.001)	6.195	F 20.972 p=(0.001)
Circunferencia de la mano (cm)	M	8.759	F 14.711 p=(0.001)	8.550	F 11.970 p=(0.001)	9.442	F 40.500 p=(0.001)	7.400	F 41.900 p=(0.001)
	F		Sin relación		Sin relación	6.190	F 9.170 p=(0.001)	5.830	F 8.610 p=(0.001)
Circunferencia máxima de la mano (cm)	M	8.795	F 12.320 p=(0.001)	8.555	F 7.644 p=(0.001)	9.442	F 7.640 p=(0.001)	7.850	F 51.830 p=(0.001)
	F		Sin relación		Sin relación	6.190	F 13.510 p=(0.001)	6.111	F 8.200 p=(0.001)
Espesor de la mano (cm)	M	8.797	F 8.140 p=(0.001)	8.554	F 10.230 p=(0.001)	9.493	F 29.240 p=(0.001)	8.610	F 28.250 p=(0.001)
	F		Sin relación		Sin relación	6.190	F 4.110 p=(0.001)	6.340	F 4.577 p=(0.001)
Ancho de la mano (cm)	M		Sin relación		Sin relación	9.442	F 10.760 p=(0.001)	8.410	F 11.090 p=(0.001)
	F			6.266	F 4.588 p=(0.001)		Sin relación		Sin relación

TABLA 3. **Relaciones entre variables (continuación de la pag. 63).**

Ancho máximo de la mano (cm)	M	8.795	F 51.874 p=(0.001)	8.554	F 7.645 p=(0.006)	9.442	F 51.833 p=(0.001)	8.250	F 12.328 p=(0.001)
	F	6.190	F 13.512 p=(0.001)		Sin relación	6.621	F 8.280 p=(0.004)		Sin relación
Longitud palmar (cm)	M		Sin relación	8.555	F 5.310 p=(0.001)	9.442	F 4.260 p=(0.001)	8.795	F 3.890 p=(0.001)
	F	6.000	F 3.833 p=(0.001)	6.000	F 15.555 p=(0.001)	6.180	F 4.088 p=(0.004)	6.372	F 4.081 p=(0.044)
Longitud máxima palmar (cm)	M		Sin relación		Sin relación	9.442	F 7.566 p=(0.006)	8.260	F 7.560 p=(0.001)
	F					6.18	F 6.260 p=(0.004)		Sin relación

Fuerza de Pellizco de Llave (KP)

En razón al grupo KP no dominante se encontraron diferencias respecto al género. En lo que respecta en particular al género femenino, no se reportan relaciones con la mano dominante, ancho de la mano, y longitud máxima palmar. Los resultados indican relaciones con las variables: IMC R2= 4.9 %, circunferencia máxima de la mano R2=2.4 %, circunferencia de la mano R2= 2.6 %, edad R2= 2.5 %, altura R2 = 1.7 %, espesor de la mano R2= 1.4 % y longitud palmar R2= 1.2 % (Tabla 3).

En lo concerniente al género masculino no se encontraron asociaciones con la mano dominante, edad y altura. Por otro lado, sí se encontraron asociaciones con circunferencia máxima de la mano R^2 =13.5 %, circunferencia de la mano R^2= 11.2 %, espesor de la mano R^2 =8.01 %, IMC R^2= 4.8 %, ancho de la mano R^2= 3.2 %, ancho máximo de la mano R^2= 2.2 %, longitud máxima palmar R^2= 2.2 %, longitud palmar R^2=1.12 % y edad R^2=1.10 % (Tabla 3). El comportamiento de la fuerza KP de acuerdo al género y la edad se puede ver en la Figura 4.

Finalmente, el grupo KP dominante reporta al igual que en el grupo no dominante diferencias en cuanto al género. El género femenino presentó relación con circunferencia máxima de la mano R2= 4 %, IMC R2= 3.2 %, edad R2= 2.5 %, circunferencia de la mano R2= 2.7 %, longitud máxima palmar R2=1.9 %, altura R2=1.5 %, espesor de la mano R2=1.2 %, longitud palmar R2=1.2 % y ancho máximo de la mano R2=0.4 %. No se reportan asociaciones respecto a la mano dominante, IMC, rangos de edad, ancho de la mano y ancho máximo de la mano.

Respecto al género masculino se encontraron asociaciones con espesor de la mano R2=8.01 %, ancho de la mano R2= 3.10 %, longitud palmar máxima R2=2.2 %, circunferencia máxima de la mano R2=1.30 %, ancho máximo de la mano R2= 1.9 %, longitud palmar R2= 1.13 %, la circunferencia de la mano R2= 1.08 % y edad R2= 0.8 %. Las demás variables altura y mano dominante no presentan relación alguna.

Resultados Predictivos

Las siguientes ecuaciones (1 a 8) muestran los efectos de las variables independientes que influyen en cada una de las fuerzas de estudio dependiendo del género; fueron realizadas con base en un modelo de regresión lineal. Estas ecuaciones permiten estimar un valor específico para cada caso de las variables dependientes y tienen su fuente en la recolección de los datos

entre los sujetos de esta investigación. Los valores de R2 se encuentran entre 4 % y 18.2 %, con características significantes p<=0.05.

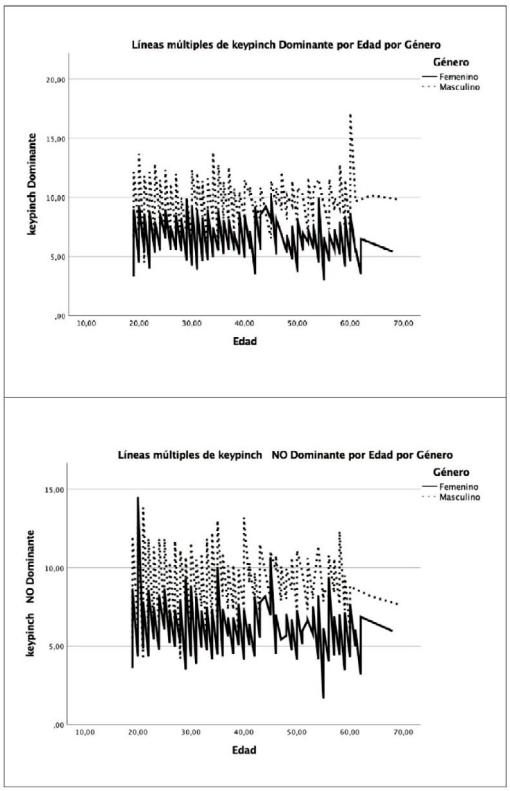


FIGURA 4. Fuerza KP en mano dominante y no dominante Vs edad.

$$F(PPD)_{femenino} = 2.203 - (0.029)Edad + (0.026)Altura + (0.094)Longitud\ Palmar, \quad p = 0.01\ y\ R^2 = 12.4\ \% \tag{1}$$

$$M(PPD)_{masculino} = 2.887 + (0.146)Longitud\ palmar + (0.133)Circunferencia\ de\ la\ mano + (0.410)Espesor\ de\ la\ mano, \quad p = 0.01\ y\ R^2 = 8.90\ \% \tag{2}$$

$$F(PPND)_{femenino} = 3.024 - (0.034)Edad + (0.026)\ Altura \quad p = 0.001\ y\ R^2 = 11.6\ \% \tag{3}$$

$$M(PPND)_{masculino} = 5.060 + (0.151)circunferencia\ de\ la\ mano, \quad p < .0\ \ y\ R^2 = 4\ \% \tag{4}$$

$$F(KPD)_{femenino} = 4.002 - (0.025)Edad + (0.030)Peso + (0.089)Circunferencia\ de\ la\ mano, \quad p = 0.001\ y\ R^2 = 12.40\ \% \tag{5}$$

$$M(KPD)_{masculino} = 0.030 + (0.319)_{circunferencia\ máxima\ de\ la\ mano} + (0.504)Espesor\ de\ la\ mano, \quad p < .0\ y\ R^2 = 16.70\ \% \tag{6}$$

$$F(KPND)_{femenino} = 2.614 - (0.028)Edad + (0.028)Peso + (0.130)_{circunferenia\ máxima\ de\ la\ mano}, \quad p < .0\ y\ R^2 = 13.7\ \% \tag{7}$$

$$M(KPND)_{masculino} = -0.339 + (0.256)Circunferencia\ de\ la\ mano + (0.444)Espesor\ de\ la\ mano + (0.059)\ IMC, \quad p < .001\ y\ R^2 = 18.2\ \% \tag{8}$$

Discusión

El presente estudio se realizó con el fin de determinar la influencia de las covariables género, edad, altura, peso, índice de masa corporal, dominancia, ocupación y medidas antropométricas de la mano respecto al pellizco palmar (PP) y de llave (KP) en una población que desempeña diferentes actividades laborales en la ciudad de Bogotá.

Los principales hallazgos se encuentran representados en que los esfuerzos PP y KP fueron significativamente más altos en los hombres que en las mujeres. Adicionalmente, los resultados de la fuerzas PP y KP, son congruentes con los encontrados por Dianat [1] y Gachette [14], ya que las fuerzas fueron mayores en la mano dominante al compararlos con la mano no dominante.

Con respecto a la edad y al género, en los hombres, la mayor fuerza PP en mano dominante se realiza en entre los 25 y 30 años y a partir de esa edad, comienza a decrecer, en cuanto a la fuerza PP en la mano no dominante los mayores valores de fuerza máxima ocurren entre los 20 a 25 años. En cuanto a la fuerza KP en

mano dominante los mayores valores de fuerza se encuentran entre los 30 a los 35 años y en la fuerza KP no dominante se encuentran entre los 20 a los 25 años. El estudio realizado por Werle [7] reporta que la mayor fuerza pinch KP en los hombres sucede entre los 25 a 29 años y entre los 40 y 44 años en mano dominante, en la mano no dominante se encuentra entre los 35 a 44 años.

En las mujeres, los mayores valores de fuerza PP en mano dominante y PP en mano no dominante ocurren entre los 25 y 30 años. Los mayores valores de fuerza KP en mano dominante ocurren entre los 27 y 30 años, mientras que para la fuerza KP en mano no dominante los mayores valores fueron registrados entre los 20 y 30 años. En el mismo estudio de Werle [7] menciona que en las mujeres, la mayor fuerza KP en mano dominante ocurre entre los 35 y 39 años, mientras que en la mano no dominante ocurre entre los 30 y 39 años.

El desarrollo de esta investigación determinó que la fuerza pinch PP y KP en mano dominante y no dominante en el género femenino tiene correlación con la edad y la altura. Este hallazgo se encuentra acorde con el reporte realizado por Rostamzadeh [2] quien en el estudio realizado para población adolescente también reporta correlaciones con la edad y la altura de las personas en los mismos tipos de fuerza; Aunque Gachette [14] no discrimina el tipo de la fuerza pinch, también determina correlación para la edad y la altura.

Por otro lado, las variables que guardan correlación en el género masculino son el espesor de la mano y la fuerza pinch PP y KP en mano dominante y no dominante. Aunque el estudio de Rostamzadeh [2] no reporta directamente resultados respecto al espesor de la mano, si reporta valores de profundidad de mano que podrían compararse y menciona que no existe correlación entre la profundidad y ninguno de los dos tipos de fuerza pinch dimensionados.

De acuerdo con la revisión literaria realizada hasta 2021, esta es una primera aproximación que buscó caracterizar esfuerzos de pellizco teniendo en cuenta diferentes poblaciones laborales en la ciudad de Bogotá. Sin embargo, es indispensable tener cuidado al aplicarlos en un caso de estudio debido a que los resultados solo se pueden generalizar a la población estudiada. Es pertinente adelantar otros estudios complementarios en los cuales se pueda tener en cuenta otro tipo de variables como por ejemplo el pellizco de punta (tip-pinch) y variables antropométricas que pertenezcan al brazo y al antebrazo.

CONCLUSIONES

El presente estudio tuvo en cuenta el dimensionamiento de 7 variables antropométricas de la mano, adicionalmente se incluyó la estatura, el peso corporal, el IMC asociado a cada persona y la edad con el fin de determinar su relación en el desarrollo de las fuerzas PP y KP en mano dominante y mano no dominante, lo que permitió el planteamiento de 8 modelos predictivos divididos por tipo de fuerza, género y dominancia.

De los modelos predictivos descritos, se pudo observar que en ninguno se encuentra el uso de las variables IMC, ancho de mano, ancho máximo de mano y longitud máxima palmar. Las variables que más se repiten, en su orden son: edad, circunferencia de la mano, circunferencia máxima de la mano y el espesor de la mano, mientras que las que menos se repiten son altura, longitud palmar y peso.

En futuros estudios de fuerza de pellizco se sugiere adicionar la fuerza TP (Tip pinch), determinar la fuerza en los diferentes tipos de pellizco como por ejemplo PP (palmar pinch), KP (key pinch) y TP (Tip pinch) debido a que los valores de fuerza presentan diferentes asociaciones entre la postura, el género, la edad, el peso y la ocupación que desempeñe la persona. Adicionalmente se sugiere evaluar personas en un mayor número de actividades con lo cual se podrían proponer ecuaciones predictoras para poblaciones generales y específicas. La medición, caracterización y

predicción de la fuerza de pellizco determinaría la posible pérdida de fuerza y adicional permitiría cuantificarla de manera adecuada teniendo en cuenta las variables mencionadas.

AGRADECIMIENTOS

Los recursos utilizados en el proyecto se establecieron de la siguiente forma: a) Equipos y personal que hacen parte del Centro de Estudios de Ergonomía de la Pontificia Universidad Javeriana y b) recursos económicos y personal de la Universidad Santo Tomás asignados al proyecto por medio de la convocatoria FODEIN - Fondo de Investigación Universidad Santo Tomás.

CONTRIBUCIÓN DE AUTORES

C.R.Z.F. y M.V.M.S conceptualizaron el proyecto, diseñaron y desarrollaron la metodología, realizaron los análisis formales, proporcionaron recursos materiales e informáticos, obtuvieron el financiamiento, participaron en todas las etapas de redacción del manuscrito y supervisaron el proyecto. M.M.L y N.V.M.A. participaron en la recopilación y curación de datos, llevaron a cabo análisis formales, participaron en el desarrollo de la metodología y contribuyeron a la redacción, edición y revisión del manuscrito. Todos los autores revisaron y aprobaron la versión final del

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