Initial approach to Epidermal Growth Factor in SARS-CoV-2 infection

Aproximación inicial al factor de crecimiento epidérmico en la infección por SARS-CoV-2

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ABSTRACT

Introduction: Epidermal growth factor (EGF) receptor plays a critical role in lung inflammation. Data exploring the role of its canonical ligand are scarce. Exploring potential and new biomarkers expands diagnostic and therapeutic options, providing resilience in complex healthcare contexts.

Objective: To describe the behavior of serum epidermal growth factor levels and evaluate its possible impact in the context of patients hospitalized with COVID-19.

Methods: Controlled exploratory study with quota sampling, in patients with COVID-19 admitted at the "Saturnino Lora Hospital", and 23 apparently healthy subjects, active donors of Blood Bank "Renato Guitar Rosell". For EGF determinations, the commercial UMELISA EGF kit from the Cuban Immunoassay Center was used. Summary measures: absolute frequency, percentage, and the arithmetic mean were used. The statistical significance of observable differences between groups was explored with the chi-square test or Welch's t test with $\alpha = 0.05$.

Results: 46 subjects enrolled in the study, (23) 50% positive for SARS-CoV-2 by RT-PCR. Between COVID-19 vs. control, general differences were observed regarding epidermal growth factor (g=1.4465; p= 0.0000*), similar behavior was observed with respect to sex and age. In COVID-19 regarding

severity, slight differences were generally observed depending on severity (g= 0.2152), a trend that was accentuated in the case of males (g= 1.1677) and females (g= 0.7533), the latter comparatively minor.

Conclusions: Determining serum EGF in patients infected by SARS-CoV-2 could have a predictive value for severity in patients with COVID-19.

Keywords: COVID-19; epidermal growth factor; inflammation; serum biomarkers.

RESUMEN

Introducción: El receptor de factor de crecimiento epidérmico (EGF) juega un rol crítico en la inflamación pulmonar. Son escasos los datos referentes a los niveles séricos de su ligando principal.

Objetivos: Describir el comportamiento de los niveles séricos del EGF y evaluar su posible repercusión en el contexto de pacientes hospitalizados por COVID-19.

Métodos: Estudio exploratorio controlado, con muestreo por cuotas, en pacientes con COVID-19, ingresados en el Hospital "Saturnino Lora" y 23 sujetos aparentemente sanos, donantes activos del Banco de Sangre Renato "Guitar Rosell". Para las determinaciones de EGF se empleó el kit comercial UMELISA EGF del Centro de Inmunoensayo de Cuba. Se utilizaron medidas de resumen: frecuencia absoluta, porcentaje y media aritmética. La significación estadística de las diferencias observables entre grupos se exploró con la prueba de *ji* cuadrado de Pearson, o la prueba t de Welch con α= 0,05.

Resultados: De 46 sujetos inscritos en el estudio, 50 % fueron positivos para el SARS-CoV-2 mediante RT-PCR. Entre los casos de COVID-19 y los controles, se observaron diferencias generales respecto al EGF (g= 1,4465; p= 0,0000*), con similar comportamiento en el sexo y la edad. En cuanto a la gravedad de la enfermedad, se observaron diferencias ligeras (g= 0,2152), tendencia que se acentuó en el sexo masculino (g= 1,1677) y las femenino (g= 0,7533), este último comparativamente menor.

Conclusiones: Determinar EGF sérico en pacientes infectados por SARS-CoV-2, pudiera tener un valor predictivo de la gravedad en pacientes con la COVID-19.

Palabras clave: COVID-19; factor de crecimiento epidérmico; inflamación; marcadores séricos.

INTRODUCTION

The discovery in January 2020 of what would be called severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) marked a before and after in the international health scenery.[1] This virus is responsible for an atypical form of pneumonia called COVID-19.

Coronaviruses in general are encapsulated positive single-stranded RNA viruses (positive ssRNA), betacoronaviruses specifically, in some cases they can cause adult respiratory distress (ARDS), as is the case with SARS-CoV-2.[2] One of the critical proteins is the Spike (S) protein, responsible for binding to surface receptors, preferentially through the receptors for the angiotensin II converting enzyme,[3] which causes a rearrangement of cellular metabolism, the production of new viruses and progressively alters the infected cells functionally and structurally, leading to programmed cell death.[4]

Associated with the severity of COVID-19, a series of molecular phenomena have been identified, colloquially called cytokine storm. The evidence regarding the role of proinflammatory molecules, such as IFN-γ, TNF-a, IL-1β, IL-6 and IL-8, among others, in the evolution of the severity of SARS-CoV-2 infection is robust.[5]

Although a critical role in SARS-CoV-2 infection has been reported for Epidermal Growth Factor Receptor (EGFR),[6,7] and it has been observed that the modulation of its signals is associated with an effective therapeutic response in the disease,[8,9,10,11] data regarding the behavior of its canonical ligand are scarce in the published literature.

Cuba has a solid technological platform for the determination of serum EGF with a high degree of analytical performance.[12] Cuban biotechnology is a pioneer in the introduction into the clinical setting of a powerful and safe EGF depleting therapy: CIMAvax-EGF®.[13] A better understanding of the biology of EGF in the health-disease process paves the way towards evaluating the positioning of this innovative molecule in new therapeutic niches that link pneumoinflammation with EGF-dependent signaling.

The objective of this study is to describe the behavior of serum EGF levels and evaluate its possible impact in the context of patients hospitalized with SARS-CoV-2.

METHODS

Controlled analytical cross-sectional exploratory study with quota sampling, with randomized selection, which recruited 46 subjects, 23 patients with COVID-19, treated in the Intensive Surveillance Service of the "Saturnino Lora" Hospital, between the months of August-September 2021 (n= 67), and 23 apparently healthy subjects, active donors of the Blood Bank "Renato Guitar Rosell".

The diagnostic criteria used were those declared by the Ministry of Public Health of Cuba (Minsap) in version 1.7 of the National Action Protocol for COVID-19, which came into force in June 2021, based on World Health Organization recommendations.[14] COVID-19 diagnoses were made by experienced certified professionals, included chest X-ray evaluations (determine inflammatory lung lesions) and virologic diagnoses by reverse transcriptase polymerase chain reaction technique (RT-PCR). In the case of healthy donors, the exhaustive and periodic medical check-up certified their status as apparently healthy subjects.

The information used was collected from medical records and included: age, sex, serum epidermal growth factor value, and reporting status. It was verified that the acquisition of the analytical parameters was carried out under strict compliance with the standardized procedures of the clinical laboratory of the institutions and in accordance with the current (*Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos*) CECMED regulations.[15]

Detection of serum EGF was performed using the commercial UMELISA-EGF kit from the Cuban Immunoassay Center. In all cases, 5 mL of blood was collected by puncture of the cephalic vein in the flexure of the arm using disposable syringes of 10 mL capacity, with 21 G hypodermic needles, deposited in a dry test tube, obtaining the serum by the technique clot retraction for 4 hours and centrifugation (according to manufacturer's recommendations at 1500 rpm for 10 minutes at 24 ^{0}C). The serum obtained was dispensed using Eppendorf micro-pipettes into 1.5 mL Eppendorf vials, after which they were stored

frozen at -20 ^{0}C, until processing in the SUMA laboratory, certified by CECMED, at the Juan Bruno Zayas Hospital. The results were expressed in picograms per milliliter (pg/mL).

For the alternative procedure, serum processing guidelines were modified, according to the recommendations for obtaining platelet-rich serum, and lysis was carried out using the freeze/thaw procedure.

A digital database created using the technical facilities of the Excel software of the Microsoft office 2010 platform (Microsoft, USA) was used to record data, on a laptop computer from the Hewlett-Packard company. Data processing was carried out on the same technological platform. In the statistical analysis, measures of central tendency (arithmetic mean), dispersion (standard deviation and confidence interval) and the Pearson correlation coefficient were used as synthesis parameters. The QQ graphical normality tests and the Jarque-Bera (JB) statistic were performed. In addition, the statistical significance of the observable differences between the groups was explored with the chi-square test (categorical variables) or the Welch t test (continuous variables), the effect size was estimated using Hedge 's g formula.

In general, in relation to p values, whenever the results were more than four decimal zeros, they were represented as p= 0.0000*.

The results of the study are part of the project: Role of the Epidermal Growth Factor in the etiopathogenesis and pathophysiology of inflammatory lung disease in the context of the SARS-CoV-2 pandemic (PS24SC1223).

The study was designed and conducted by the general principles established in the documents adopted by the international community in relation to biomedical research in human beings, included in the Declaration of Helsinki (update of the World Medical Assembly held in Brazil, 2013),[16] with the current state regulations according to the requirements of the national regulatory authority (Regulation M83-15 of the CECMED, approved by Resolution 165/2000 of the Minsap),[15] as well as in the Guide to Good Clinical Practices of the International Conference of Harmonization (ICH E6-R3).[17] The research was approved by the Research Ethics Committee of the "Saturnino Lora" Hospital, and the corresponding certification by the Regional Ethics Committee of the southeastern region of Cuba. Prior to the inclusion of each subject in the study, Informed Consent was requested and obtained.

RESULTS

Forty-six subjects enrolled with an average age of 60.30 ± 6.9 years (JB= 0.5717; p= 0.7513), 52.1% male, with a prevalence of comorbidities of 85.1%, 62.3% with more than one NCD; In the particular case of hypertension the prevalence was 68.5%, followed by ischemic heart disease with 42% and diabetes type 2 with 31.2%. Regarding age, marginally significant differences between groups were observed (g= 0.4015, p= 0.0516). Specific data regarding the subjects who served as controls are seen in table 1.

Table 1 - General parameters according to group

Parameters	General	Control
Age	60.3 ± 6.90 years	52.78 ± 2.12 years
Sex		
Men	52.1%	43.47%
Women	47.8%	56.52%
EGF*	166.89 ± 23.88 pg/mL	641.29 ± 129.53 pg/mL

*p= 0.0342×10^{-7}

Between groups, large general differences were observed between the EGF means (g= 1.4465; p= 0.0000*). Similar behavior was observed with respect to sex and age, as reflected in table 2.

Table 2 - Behavior of EGF according to history, age and sex

Subgroup	General	Control	p
Male sex	165.75 ± 33.06	501.95 ± 193.21	0.0072
Female sex	168.13 ± 36.19	748.48 ± 156.30	0.0000*
< 55 years	184.91 ± 40.02	616.53 ± 197.61	0.0012
> 55 years	150.37 ± 25.52	659.86 ± 158.42	0.0001

Specifically, in patients with COVID-19, no differences were observed with respect to age. As can be seen in table 3, slight differences were generally observed depending on the severity (g= 0.2152), a trend

that was accentuated in the case of the male sex (g= 1.1677) and reversed in the case of the female sex (g= 0.7533).

Table 3 - Behavior of EGF according to severity, age and sex

Subgroup	Serious	Of care	p
Age	60.81 ±8.54	59.14 ±12.50	0.5576
EGF	161.45 ±30.01	179.32 ±39.76	0.5636
Male sex	140.55 ±35.09	216.15 ±37.42	0.0202
Female sex	182.35 ±46.36	130.21 ±12.64	0.0661

In the samples that were subjected to platelet lysis before proceeding to the determination of EGF, differences were observed in both groups. In general, and comparatively with respect to the controls, the previously observed trends were replicated (g= 1.1125, p= 0.0006). Notable differences were observed between EGF values depending on platelet lysis, particularly intense in healthy controls (g= 3.1812, p= 0.0000*) compared to COVID-19 patients (g= 1.0094, p= 0.0013).

In the context of COVID-19, depending on the severity, variable differences are observed depending on platelet lysis, notably intense in the subset of severely ill patients (g= 1.5619, p= 0.0015), and mild in the subset of patients reported for care (g= 0.4862, p= 0.2951). With platelet lysis, important differences are observed between serum EGF values in favor of severely ill patients (g=0.8470, p=0.0436). Figures 1 and figure 2 are illustrative in this regard.
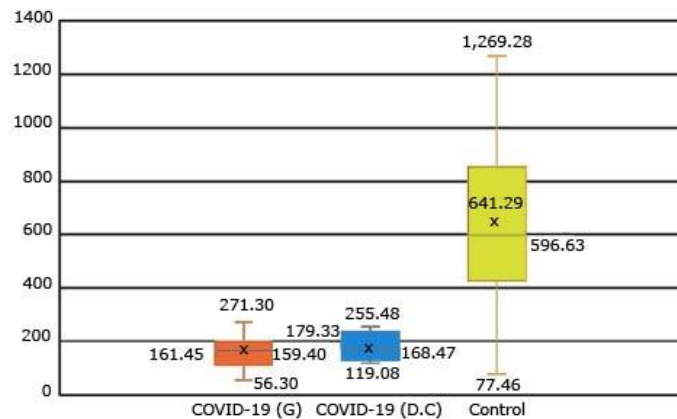

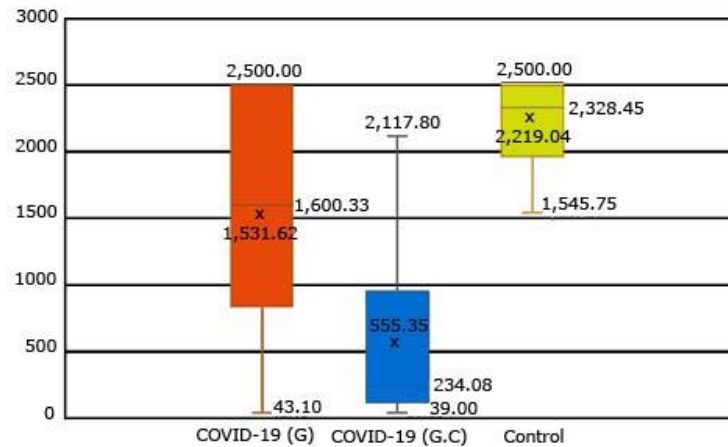**Fig. 1 -** Serum EGF concentrations in COVID-19 according to severity vs. control, unlysed samples.

Fig. 2 - Serum EGF concentrations in COVID-19 according to severity vs. control, lysed samples.

DISCUSSION

This study describes the behavior of serum EGF levels in the context of SARS-CoV-2 infection, as well as make an initial approach to the possible impact on the severity of COVID-19, observing notable differences with respect to controls, but not with respect to severity in general, based on their serum concentrations. Likewise, in a pioneering way, what would be defined as platelet reserve, and its implications in COVID-19, are experimentally approached.

The platelet reserve would be the difference in serum concentrations of EGF based on the values determined in serum compared to those determined in serum rich in lysed platelets. In this way, this concept particularly differentiates the platelet contribution from the total balance of EGF in peripheral blood.

No published data were found in the main databases where an experimental approach is made to the differences that have been observed in this study, when differentially analyzing serum samples with respect to serum rich in lysed platelets.

Inflammation as an innate response mechanism is transversally related to the response to all pathogens.[18] Likewise, the direct stimulation of the S proteins of the virus,[19] together with intracellular replication[20]

determine a powerful mechanism of amplification of the inflammatory response. An exacerbated release of cytokine marks the decline in clinical status of COVID-19 patients.[21,22]

The pathogenesis of SARS-CoV-2 infection in humans manifests from mild symptoms to severe respiratory failure. By binding to the epithelial cells of the respiratory tract, SARS-CoV-2 begins to replicate and migrate into the airways and enters the alveolar epithelial cells of the lungs. The rapid replication of SARS-CoV-2 in the lungs can trigger a strong immune response. Cytokine storm syndrome causes acute respiratory distress syndrome and respiratory failure, which is considered the leading cause of death in patients with COVID-19.[23,24]

Although SARS-CoV-2 uses the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2),[25,26] other molecules are closely related to its internalization and pathogenesis.[27] Notable is the case of the transmembrane protease serine protease 2 (TMPRSS2) necessary in the proteolytic processing of the S protein to activate the endocytic pathway, activating the entry of SARS-CoV-2.[28,29,30]

In the context of chronic inflammation associated with cancer, a complex molecular relationship between ACE2, TMPRSS2 and EGFR has been demonstrated, observing the effect of ACE2 on lung cancer metastasis and that TMPRSS2 can induce resistance to EGFR-TKI, a standard first-line therapy for ,patients with advanced NSCLC harboring the EGFR mutation[31,32] that maintain a phosphorylation state of the tyrosine residues independent of the heterodimerization of the receptor.

The relationship between ACE2 expression dependent on EGFR activity in the acute and chronic inflammatory context is known.[33,34] In the inflammatory environment, ACE2 and EGFR are overexpressed with a direct relationship to the presence of TNF-α, IL-1 and IL-6.[35,36,37] The activation of EGFR itself stimulates the positive regulation of pro-inflammatory cytokines.[38]

Although differentially at the lung tissue, the expression of these proteins is differential, observed in the RNA-seq analyzes values for EGFR in type I pneumocytes (154.1 nTPM) significantly higher than those of ACE2 (0.3 nTPM).[39,40] Therefore, the role of the EGF is not negligible.

Although differences in biological sex were observed in the control group, these are not evident in the case of patients with COVID-19. The differences observed in the controls are consistent with existing reports in the literature.[41] The general differences observed with respect to age between the groups are consistent with the reported trends,[42] which are not observed taking the classification age as 55 years.

Although traditionally there is a strong association between serum EGF and platelet intake, the evidence is not conclusive,[43,44,45,46] and there are many studies that uncritically carry this postulate as a statement, in the absence of robust evidence.

Despite the sample size being a limitation of the study, the observed differences are statistically supported, which is why this study constitutes a valid initial approach and serves as a reference for the design of subsequent interventions, which achieve a higher degree of robustness with respect to the identified trends.

The pioneering definition of the concept of platelet reserve with respect to EGF values may contribute to a better understanding of the role of platelets in the biology of EGF, with translation to the clinical context.

Conclusive, notable differences were observed between EGF values in COVID-19 vs. controls, as well as with respect to sex and age, with higher values in healthy subjects. In addition, slight differences in severity were observed in patients with COVID-19, a trend that was differentially accentuated in the analysis by sex, but not with respect to age. Besides determining serum EGF in patients infected with SARS-CoV-2 could have a predictive value for severity in patients with COVID-19.

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Conflict of interests

No conflicts of interest are declared.

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Authorship contribution

Sole author.

Data availability statement

The study data are confidential. To access them, authorization is required from the General Management of the "Saturnino Lora" Provincial Hospital.