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Clinical monitored in subjects metabolically healthy and unhealthy before and during a SARS-CoV-2 infection– A cross-sectional study in Mexican population

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ABSTRACT

The COVID-19 disease has forced us to consider the physiologic role of obesity and metabolically healthy and unhealthy status in response to SARS-CoV-2 infection. Hematological, coagulation, biochemical, and immunoinflammatory changes have been informed with a disparity in morbidity and mortality. Therefore, we aimed to investigate the influence of metabolic health on clinical features in a cross-sectional study in Mexican subjects with and without SARS-CoV-2 infection in non-severe stages after a rigorous classification of obese and non-obese subjects who were metabolically healthy and unhealthy. Four groups were formed: 1) metabolically healthy with normal BMI (MHN); 2) metabolically unhealthy with normal BMI (MUN); 3) metabolically healthy obese (MHO); 4) metabolically unhealthy obese (MUO). Serum proinflammatory (TNF-α, MCP-1, IL-1β, and IL-6) and anti-inflammatory (TGF-β, IL-1Ra, IL-4, and IL-10) cytokines, hematological parameters, coagulation, and acute phase components were evaluated. Our results showed that MHO people live with inflammaging. Meanwhile, MUN and MUO subjects develop metaflammation. Both inflammaging and metaflammation cause imperceptible modifications on hematological parameters, mainly in leukocyte populations and platelets, as well as acute phase and coagulation components. The statistical analysis revealed that many clinical features are dependent on metabolic health. In conclusion, MHO subjects seem to be transitioning from metabolically healthy to unhealthy, which is accelerated in acute processes, such as SARS-CoV-2 infection. Meanwhile, metabolically unhealthy subjects independently of BMI have a deteriorating immunometabolic status associated with a hyperinflammatory state leading to multi-organ dysfunction, treatment complications, and severe COVID-19 disease.

1. Introduction

In late December 2019, Wuhan Municipal Health Commission notified the public of a pneumonia outbreak of an unidentified cause and informed the World Health Organization (WHO) [1]. With metagenomic RNA sequencing and virus isolation from bronchoalveolar lavage fluid samples from patients with severe pneumonia, the virus was identified, and on 30 January, the WHO declared the novel coronavirus outbreak a public health emergency of international concern [2]. On 11 February, the International Committee on Taxonomy of Viruses named the novel coronavirus SARS-CoV-2, and the WHO named the disease "COVID-19". Since then, the rapid worldwide spread of COVID-19 has been observed [3].

Clinical manifestations of patients with COVID-19 have included

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fever, fatigue, dry cough, shortness of breath, olfactory and taste disorders, and acute respiratory distress syndrome. Less common symptoms include sputum production, headache, hemoptysis, diarrhea, anorexia, sore throat, chest pain, chills, nausea, and vomiting [4,5]. Most people showed signs of disease after an incubation period of 1–14 days, and dyspnoea and pneumonia developed within a median of 8 days from illness onset [1]. Additionally, laboratory studies confirmed that COVID-19 patients presented lymphopenia and cytokine storm associated with disease severity. It appears that all ages of the population are susceptible to SARS-CoV-2 infection [6]. However, clinical manifestations differ with age and the presence of co-morbidities (diabetes, hypertension, obesity, asthma, etc.). The subjects with co-morbidities independently of age are more likely to develop a severe respiratory disease that requires hospitalization or even die [7].

The Center for Disease Control and Prevention (CDC) has issued a list of risk factors for severe COVID-19 disease [8]. Body-mass index (BMI) greater than 30, is considered a strong predictor. In Mexico, obesity, diabetes, and hypertension are substantial risk factors for acquiring SARS-CoV-2 infection and developing severe disease [9]. Elevated glycosylated hemoglobin (HbA1c) levels, which is a marker for long-term blood glucose control in diabetic subjects, have been linked to inflammation, hypercoagulation, and high mortality [10]. COVID-19 fatality rates were highest for cardiovascular disease (27.7%) compared with diabetes and hypertension (10.5%) [11]. In contrast, patients without pre-existing conditions had a fatality rate of $< 1\%$ [11]. These comorbidities have effects on glucose and lipid metabolism in common. However, not all obese people are metabolically dysregulated, nor are all lean people metabolically healthy.

Some studies have evidenced obese people without metabolic abnormalities as having a low risk of cardiovascular complications are labeled as metabolically healthy obese (MHO) [12]. MHO could represent a unique subset of people transitioning to developing metabolically unhealthy obesity (MUO) because excessive adiposity involves metabolic defects and impairment of immune response [13]. Some studies show that individuals in long-term obesity treatment programs may undergo cycles of weight loss and weight regain accompanied by their phenotype changing from MUO to MHO and back to MUO [14,15]. The transitions between metabolic status are not specific to obesity, age, or sex [16–20]. This finding is supported by a *meta*-analysis of 12 studies including more than 5900 individuals with 3–10-year follow-up, demonstrating that almost half of the participants classified as MHO developed at least one metabolic abnormality [21]. Among participants of a prospective study, ~30% of individuals diagnosed with MHO at baseline converted to MUO in the 6-year follow-up investigation [22]. Notably, the transition from MHO to MUO is not necessarily a one-way road [23]. Data from 3743 women (51%) and men $\geq$ 18 years of age in the North West Adelaide Health Study show that conversion from MUO to MHO occurred without significant gender differences in 16% of the participants in up to 10-year recall visits [19].

Addionally, obesity is typically associated with metaflammation and inflammaging [24]. Metaflammation refers to metabolic inflammation caused by nutrient excess or overnutrition, which exists in chronic age-related metabolic diseases. Metaflammation is the most convincing mechanism linking nutritional disorders to inflammaging, indicating that the inflammatory milieu of metabolic cells, tissues, and organs is altered due to the high nutrient intake. Meanwhile, the term inflammaging describes the condition of chronic sterile low-grade inflammation observed in older organisms. Inflammaging is the long-term result of chronic physiological stimulation of the immune system. It possesses various cellular and molecular mechanisms, including cellular senescence, immunosenescence, mitochondrial dysfunction, defective autophagy, metaflammation, and gut microbiota dysbiosis [25]. The inflammaging needs to be counterbalanced by anti-inflammatory mechanisms. Chronically, inflammaging impairs anti-inflammatory mechanisms, inducing cellular senescence. Cellular senescence and the acquisition of the senescence-associated secretory phenotype (SASP) by fibroblasts, endothelial, and immune cells has also been pinpointed as a significant contributor to inflammaging. Cell senescence induces the accumulation of differentiated B, T, and NK cells with dysregulated function [26,27], which in acute infections as SARS-CoV-2 can generate cytokine hyperresponse, severe clinical manifestations, and laboratory test alterations associated with COVID-19. In this study, we aimed to investigate the cytokine levels and clinical biomarkers of inflammation, coagulation, and biochemistry in obese and non-obese subjects who are metabolically healthy and unhealthy, with and without SARS-CoV-2 infection in non-severe stages.

2. Subjects and methods

2.1. Study design and setting

We undertook a prospective study (January 2020 to May 2021) with collected data from the Clinical Specialized Laboratory “Los Angeles” database, which contains computerized records of primary metabolic care subjects from Puebla, Mexico. The database contains records of anthropometric measurements (e.g., height, weight, body mass index, body mass fat percentage, body lean mass percentage) and clinical parameters (e.g., glucose, insulin, insulin resistance indexes, triglycerides, cholesterol and its fractions, free fatty acids, leptin, and adiponectin). These measurements were recorded at patient registration by primary care physicians. Then, the patients were informed about COVID-19 symptoms, and they were evaluated by quantitative real-time polymerase chain reaction (qRT-PCR) viral assay when they had any symptoms. When the test was positive for SARS-CoV-2, blood samples were collected for a complete clinical evaluation. Positive patients and their records were referred to health services for intervention and treatment. For this study, written informed consent was obtained from every subject before data collection. The Scientific Review Committee of the Benemeritous Autonomous University of Puebla granted approval. The study complied with the ethical standards of the Helsinki Declaration.

2.2. Study population

This study included 1578 subjects from the metropolitan area of Puebla, Mexico. The age range was 25–50 years old, and similar gender distribution between study groups. This study excluded menopausal women, diabetic subjects, patients with non-controlled endocrine disorders, chronic degenerative diseases, cardio- and cerebrovascular diseases, previous diagnoses of atherosclerosis, and patients with infections that differ from SARS-CoV-2, as well as current medications. All participants answered the standardized questionnaire administered by well-trained investigators.

2.3. Measurements of anthropometric parameters

After the interview, all subjects underwent anthropometric measurements according to a standardized protocol. Briefly, body weight, body mass index, body fat percentage, and lean body weight were measured at standing position without shoes, in light clothing using an InBody 570 body composition analyzer (Biospace, Inc. Seoul, Korea). Height was measured using a standard right-angle device and a fixed measurement tape. Waist circumference (WC) was defined as mid-way between the lowest rib and iliac crest and measured under steady breaths using a cloth tape directly on the participant’s skin. Hip circumference (HC) was defined as the distance around the largest part of the hips and the widest part of the buttocks. Then, waist to hip ratio (WHR) was calculated.

2.4. Measurements of biochemical parameters

Ten milliliters of blood sample was collected in two BD Vacutainer®

Venous Blood Collection systems, with and without anticoagulant. Phlebotomy was carried out the morning (7:30 – 9:30 a.m.) after 8-h fasting. The hemoglobin A1C test was performed using anticoagulated samples and an I-Chroma Analyzer certified by the NGSP and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Samples without anticoagulant were centrifuged at 400 × g for 10 min; the serum was separated and frozen at − 70 °C until analysis.

The serum concentrations of glucose, triglycerides, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) were determined using autoanalyzer A15 (BioSystems, Guadalajara, Mex.). The concentration of free fatty acid (FFA) was determined according to the method described by Brunk and Swanson, 1981 [28]. Serum levels of insulin (Detection limits [DL] = 0.2 – 1000 μIU/mL; inter-assay variation = 2.18%), leptin (DL = 0.6 – 400 ng/mL; inter-assay variation = 6.9%), and adiponectin (DL = 0.3 – 1500 μg/mL; inter-assay variation = 3.1%) were quantified in a Stat fax 2600 plate reader at 415 nm (WinerLab Group, Buenos Aires, Argentina). The homeostatic model assessment insulin resistance (HOMA-IR) and sensitivity (HOMA-S%) were calculated by standard formulas. The adipocyte insulin resistance index was calculated as follows adipocyte-IR= (fasting plasma insulin)* $_{log}$(fasting plasma FFA) [29].

2.5. Definitions of obesity, healthy and unhealthy metabolism

Obesity was defined by the body mass index (BMI) criteria of the world health organization. BMI was calculated as body weight in kilograms divided by the square of height in meters. Subjects were classified according to BMI as normal weight (18.5–24.9 kg/m^2) and obese (≥30.0 kg/m^2) [12]. Meanwhile, metabolically healthy and unhealthy subjects were classified by anthropometric and biochemical parameters [13,30]. The subjects who entered the study met at least 10 of the 13 criteria. **a)** Body fat percentage (healthy: Female 25–31%, Male 18–25%; unhealthy: Female ≥ 32%, Male ≥ 26%); **b)** WC (healthy: Female ≤ 80 cm, Male ≤ 90 cm; Central obesity (unhealthy): Female ≥ 88 cm, Male ≥ 102 cm); **c)** WHR (healthy: Female ≤ 0.8, Male ≤ 0.95; unhealthy: Female ≥ 0.85, Male ≥ 1); **d)** FFA (healthy: 450–900 μmol/L; unhealthy: ≥ 1000 μmol/L); **e)** Fasting triglycerides (healthy: ≤ 95 mg/dL; unhealthy: ≥ 150 mg/dL); **f)** Total cholesterol (healthy: ≤ 200 mg/dL; unhealthy: ≥ 240 mg/dL); **g)** LDL-C (healthy: ≤ 100 mg/dL; unhealthy: ≥ 190 mg/dL); **h)** HDL-C (unhealthy: Female ≤ 50 mg/dL, Male ≤ 40 mg/dL); **i)** Hb-A1C (unhealthy: ≥ 5.7 %); **j)** Fasting glucose (unhealthy: ≥ 100 mg/dL); **k)** HOMA-IR (unhealthy: ≥ 2.5); **l)** HOMA-S % (unhealthy: ≤ 60%); **m)** Adipocyte-IR (unhealthy: ≥ 30); and **n)** adiponectin/leptin ratio (healthy: ≥ 1; unhealthy: ≤ 0.5). According to measurements, four groups were conformed: **1)** metabolic healthy with normal BMI (MHN); **2)** metabolic unhealthy with normal BMI (MUN); **3)** metabolic healthy obese (MHO); **4)** metabolic unhealthy obese (MHO).

2.6. qRT-PCR detection

The subjects were monitored, and when they presented viral respiratory illness symptoms (dry cough, sore throat, headache, mild fever, dyspnea, anosmia, ageusia (or dysgeusia), musculoskeletal symptoms (e.g., arthralgias or myalgias), fatigue, rhinitis, and/or diarrhea), a qRT-PCR test for SARS-CoV-2 was performed. Subjects with symptoms but negative for SARS-CoV-2, asymptomatic, acute respiratory distress syndrome, pulmonary embolism, or pulmonary bacterial infection were not included. The presence of SARS-CoV-2 in nasopharyngeal swab specimens was detected by qRT-PCR (MIC-4 RidaClycler; R-Biopharm AG, Darmstadt, Germany) amplification of SARS-CoV-2 for envelope (E) and nucleocapsid protein (N) gene fragments using kits provided by R-Biopharm AG (Darmstadt, Germany). Conditions for amplification were 58 °C for 10 min, 95 °C for 1 min, followed by 45 cycles of 95 °C for 10 s and 60 °C for 30 s. When two targets (E, N) tested positive for specific qRT-PCR, the case was considered laboratory-confirmed. A cycle threshold value (Ct-value) of less than 17 was defined as a positive test, and a Ct-value of 20 or more was defined as a negative test. A medium load, defined as a Ct-value of 17 to less than 20, required confirmation by retesting.

2.7. Cytokines and laboratory testing

A total of 360 blood samples from patients testing positive for SARS-CoV-2 and 384 blood samples from patients testing negative for SARS-CoV-2 without symptoms were collected. The samples were used to analyze a cytokine profile and clinical parameters. Proinflammatory cytokines [TNF-α (ab181421; DL = 0.31 – 500 pg/mL; inter-assay variation = 7.4%), MCP-1 (ab179886; DL = 15.6 – 1000 pg/mL; inter-assay variation = 8.7%), IL-1β (ab217608; DL = 1.9 – 250 pg/mL; inter-assay variation = 6.6%), and IL-6 (ab178013; DL = 0.56 – 150 pg/mL; inter-assay variation = 5.2%)], and anti-inflammatory cytokines [TGF-β (ab100647; DL = 30 – 4000 ng/mL; inter-assay variation = 4.9%), IL-1Ra (ab211650; DL = 31.2 – 2000 pg/mL; inter-assay variation = 6.1%), IL-4 (ab215089; DL = 1.8 – 500 pg/mL; inter-assay variation = 5.6%), and IL-10 (ab185986; DL = 1.15 – 200 pg/mL; inter-assay variation = 5.6%)] were carried out with commercial kits (Abcam; Cambridge, MA, USA) in a Stat fax 2600 plate reader at 415 nm (WinerLab Group, Buenos Aires, Argentina). Laboratory testings: Hematological parameters such as white blood cell (WBC), basophil, eosinophil, neutrophil, lymphocyte and monocyte count, red blood cell (RBC), hemoglobin, hematocrit, and platelets (PLT) counts were taken in an automatized cell counter (5Diff 5H+; DESEGO, Morelia, Mex.); markers for inflammatory conditions such as high sensitive C-reactive protein (hs-CRP) and procalcitonin (PCT) (iChroma II; DESEGO, Morelia, Mex.) were observed; tests for coagulation such as prothrombin (PT) and activated partial thromboplastin times (APTT), fibrinogen (FIB) (Cuatron A4; Licon, CDMX, Mex.), and D-dimer (iChroma II; DESEGO, Morelia, Mex.) were carried out; and complementary indicators such as lactate dehydrogenase (LDH), and ferritin were performed with commercial kits (BioSystems, Guadalajara, Mex.).

2.8. Statistical analysis

Results are expressed as the mean ± standard error of the mean (SEM). A two-way ANOVA analyzed groups were evaluated with a Bonferroni post hoc test using GraphPad Prism 5, comparing healthy metabolism interaction on SARS-CoV-2 infection as independent variables, with a significance level of $p \leq 0.05$; only significant F statistics were discussed.

3. Results

1578 subjects (888 women and 690 men) with a mean age of 37.2 years old (37.6 women and 36.8 men) participating in this study were classified according to their anthropometric parameters in normal and obese BMI. Then, depending on anthropometric and biochemical features defined in the subjects and methods section they were subdivided into four groups, metabolically healthy with normal BMI (MHN), metabolically healthy obese (MHO), metabolically unhealthy with normal BMI (MUN), and metabolically unhealthy obese (MUO) (Table 1). The results suggest a greater amount of subcutaneous adipose tissue than visceral fatty tissue in the metabolically healthy groups, both in women and men. Conversely, in metabolically unhealthy groups, the visceral adipose tissue prevails.

Proinflammatory cytokine response was analyzed in the groups with and without SARS-CoV-2 infection. A strong interaction between the independent variables was observed. In subjects without SARS-CoV-2 infection, the serum concentrations of TNF-α, IL-6, IL-1β, and MCP-1 were different among the groups, being significantly higher in unhealthy groups and in the MHO group than the MHN group, which suggests that unhealthy and / or obese subjects have low-grade inflammation (Fig. 1). Infected SARS-CoV-2 subjects had a

Table 1
Metabolically healthy and unhealthy population classification.

	MHN	MHO	MUN	MUO
	n = 350 (**M** = 150/**F** = 200)	n = 367(**M** = 170/**F** = 197)	n = 361(**M** = 140/**F** = 221)	n = 500 (**M** = 230/**F** = 270)
Anthropometric Parameters:				
Age	**M:** 36.7 ± 1.3**F:** 38.2 ± 1.1	**M:** 37.6 ± 1.6**F:** 38.6 ± 1.4	**M:** 36.2 ± 1.3**F:** 37.7 ± 1.4	**M:** 36.6 ± 1.2**F:** 35.9 ± 1.2
Weight (kg)	**M:** 75.5 ± 1.3**F:** 56.5 ± 1.0	**M:** 106 ± 1.8**F:** 87.5 ± 1.2	**M:** 76.8 ± 1.3**F:** 57.5 ± 0.8	**M:** 113.6 ± 2.5**F:** 91.1 ± 1.2
Height (cm)	**M:** 178 ± 1.4**F:** 156.3 ± 0.9	**M:** 178.2 ± 1.2**F:** 159.1 ± 1	**M:** 178.6 ± 1.3**F:** 157.5 ± 1	**M:** 181.2 ± 1.4**F:** 156.9 ± 1.1
Body mass index (kg/m^2)	**M:** 23.8 ± 0.1**F:** 23.1 ± 0.3	**M:** 33.3 ± 0.3**F:** 34.5 ± 0.2	**M:** 24.0 ± 0.1**F:** 23.2 ± 0.2	**M:** 34.8 ± 0.9**F:** 36.9 ± 0.4
Body fat (%)	**M:** 23.8 ± 0.2**F:** 27.3 ± 0.4	**M:** 29.5 ± 0.5**F:** 34.9 ± 0.5	**M:** 24.0 ± 0.1**F:** 28.5 ± 0.2	**M:** 36.5 ± 0.2**F:** 35.7 ± 0.5
Lean body weight (%)	**M:** 57.6 ± 1.1**F:** 41.1 ± 0.8	**M:** 74.8 ± 1.6**F:** 57 ± 0.9	**M:** 58.3 ± 1.0**F:** 41.1 ± 0.6	**M:** 72.1 ± 1.6**F:** 58.6 ± 1.3
Waist circumference (cm)	**M:** 87.9 ± 0.6**F:** 70.2 ± 0.6	**M:** 111.8 ± 1.2**F:** 90.9 ± 1.3	**M:** 88.7 ± 0.8**F:** 74.1 ± 0.5	**M:** 147.1 ± 1.0**F:** 96.4 ± 1.3
Hip circumference (cm)	**M:** 98.1 ± 0.4**F:** 89.9 ± 0.9	**M:** 126.2 ± 1.0**F:** 110 ± 1.5	**M:** 98.8 ± 0.4**F:** 91.9 ± 0.7	**M:** 146.8 ± 0.6**F:** 107.6 ± 1.2
Waist / hip ratio	**M:** 0.9 ± 0.01**F:** 0.78 ± 0.01	**M:** 0.89 ± 0.01**F:** 0.83 ± 0.01	**M:** 0.9 ± 0.01**F:** 0.81 ± 0.02	**M:** 1.0 ± 0.01**F:** 0.9 ± 0.01
Biochemical parameters:				
FFA (μmol/L)	739 ± 20	634 ± 24	2066 ± 128	4399 ± 340
Triglycerides (mg/dL)	77.9 ± 1.9	81.6 ± 1.8	254 ± 10.7	553 ± 33
Total cholesterol (mg/dL)	167.9 ± 3.2	170 ± 3.4	300 ± 6.2	318 ± 8.8
LDL-C (mg/dL)	82.1 ± 3.5	92.8 ± 3.7	211 ± 6.9	175 ± 13
HDL-C (mg/dL)	70.1 ± 2.0	60.7 ± 1.5	37.8 ± 0.8	32.8 ± 0.7
Hb-A1C (%)	5.2 ± 0.05	5.1 ± 0.1	6.0 ± 0.1	6.5 ± 0.1
Fasting glucose (mg/dL)	82.1 ± 1.5	84.4 ± 1.7	107.5 ± 1.9	144.4 ± 1.5
Fasting insulin (mUI/mL)	7.6 ± 0.2	8.0 ± 0.3	20.3 ± 1.0	32 ± 1.3
HOMA-IR	1.53 ± 0.05	1.66 ± 0.06	5.33 ± 0.24	9.02 ± 0.35
HOMA-S%	67.3 ± 2.2	62.8 ± 2.44	20 ± 0.96	11.7 ± 0.55
Adipocyte-IR	21.7 ± 0.6	22.7 ± 0.7	66.9 ± 3.44	114.6 ± 4.5
Leptin (ng/mL)	14.3 ± 0.94	15.4 ± 0.92	21.2 ± 2.01	35 ± 1.71
Adiponectin (μg/mL)	19.03 ± 1.44	16.3 ± 0.71	12.5 ± 1.02	8.83 ± 0.63
Adiponectin/Leptin ratio	1.48 ± 0.15	1.18 ± 0.09	0.88 ± 0.15	0.27 ± 0.03

Data are reported as mean ± standard error of the mean (SEM). **MHN**: metabolic healthy normal BMI; **MUN**: metabolic unhealthy normal BMI; **MHO**: metabolic healthy obese; **MUO**: metabolic unhealthy obese; **FFA**: free fatty acid; **LDL-C**: low-density lipoprotein-cholesterol; **HDL-C**: high-density lipoprotein-cholesterol; **Hb-A1C**: hemoglobin A1C; **HOMA-IR**: homeostatic model assessment insulin resistance; **HOMA-S%**: homeostatic model assessment insulin sensitivity; **Adipocyte-IR**: adipocyte insulin resistance index.

proinflammatory cytokine hyperresponse in metabolically unhealthy and / or obese subjects. The statistical analysis demonstrated that unhealthy metabolism has an important influence on the hyperresponse of cytokine in subjects with SARS-CoV-2 infection. For TNF-α, the unhealthy metabolism generated 41.7% of the total variance ($F = 1126$, $p < 0.0001$), and SARS-CoV-2 infection generated 17.9% of the total variance ($F = 116.4$, $p < 0.0001$) (Fig. 1A). For MCP-1, a similar interaction was generated by the unhealthy metabolism and SARS-CoV-2 infection, 28.9% and 26.9% of the total variance, respectively, with an $F = 527.7$ ($p < 0.0001$) and $F = 163.5$ ($p < 0.0001$) (Fig. 1D). Meanwhile for IL-1β and IL-6, most important interaction was generated by SARS-CoV-2 infection, 35.3% and 30.1% of the total variance ($F = 159.6$, $p < 0.0001$and $F = 216.6$, $p < 0.0001$), compared to unhealthy metabolism, 8.1% and 23.1% of the total variance ($F = 110.1$, $p < 0.0001$and $F = 497.8$, $p < 0.0001$) (Fig. 1B-C).

The anti-inflammatory cytokine response also was analyzed in the groups with and without SARS-CoV-2 infection. A strong interaction between the independent variables was observed. In subjects without SARS-CoV-2 infection, the serum concentrations of TGF-β and IL-4 were significantly higher in unhealthy and MHO groups than in the MHN group (Fig. 2A-C). Meanwhile, serum concentrations of IL-10 and IL-1Ra were significantly lower in unhealthy and MHO groups than in the MHN group (Fig. 2B-D). Data suggest an impairment anti-inflammatory cytokine response in unhealthy and/or obese subjects. On the other hand, metabolically unhealthy and/or obese subjects infected with SARS-CoV-2 had a TGF-β hyper response (MHO = 3.8-folds, MUN = 2-folds, and MHU = 5-folds) (Fig. 2A). Only the MHO group maintained a similar or greater anti-inflammatory response than the MHN group in IL-10, IL-1Ra, and IL-4 concentrations. Meanwhile, metabolically unhealthy groups (MUN and MUO) had lower concentrations of IL-10, IL-4, and IL-1Ra (Fig. 2B-D). Statistical analysis suggest that an unhealthy metabolism impairs the anti-inflammatory cytokine response in subjects with SARS-CoV-2 infection. For TGF-β, IL-4 and, IL-1Ra, the unhealthy metabolism generated 36.9% ($F = 837.7$, $p < 0.0001$), 22.1% ($F = 336.7$, $p < 0.0001$) and 55.3% ($F = 1540$, $p < 0.0001$) of the total variance, respectively; while SARS-CoV-2 infection generated 21% ($F = 159.2$, $p < 0.0001$), 13.8% ($F = 70.5$, $p < 0.0001$), and 12% ($F = 111.5$, $p < 0.0001$) of the total variance. For IL-10, the most important interaction was generated by SARS-CoV-2 infection, 27.3% ($F = 122.9$, $p < 0.0001$) of the total variance, compared to unhealthy metabolism, 11.6% ($F = 156.3$, $p < 0.0001$) of the total variance.

In the groups without SARS-CoV-2 infection, hematological parameters were within the biological reference interval. However, statistical differences were observed between groups (Table 2). The red series showed a significant difference in the RBC count and hemoglobin concentration. Metabolically unhealthy and obese subjects showed a trend to diminish these parameters. The leukocytes also showed interesting behavior. Basophils and eosinophils showed differences between MHO, MUN, and MUO groups, significantly increasing in the last behavior. Neutrophils showed a significant diminishing according to metabolic worsening. Lymphocytes significantly increased in obese subjects, while monocyte increased in unhealthy people. Platelets showed a diminishing trend mainly in obese subjects. Meanwhile, in SARS-CoV-2 infected subjects, the most important results were observed in leukocytes. The metabolically unhealthy and/or obese subjects did not show a correct response to acute inflammation. They showed a significantly lower platelet and WBC count than the MHN group; particularly, in neutrophils, basophils, eosinophils and, monocytes (except in the MUN group). Conversely, the lymphocyte count significantly increased in MHO, MUN, and MUO groups compared to the MHN group (Table 2). Unhealthy metabolism and/or obesity had a low interaction on hematological red line parameters. The RBC count presented 5.9% ($F = 53.3$, $p < 0.0001$) and hemoglobin 2.8% ($F = 25.8$, $p < 0.0001$) of the total variance, while hematocrit did not show interaction (0.5%, $F = 4.2$, $p = 0.071$). The interaction between variables in infected SARS-CoV-2 subjects was not significant to the red line parameters. Conversely, white cell lineage showed a great dependency on SARS-CoV-2 infection more than that for unhealthy metabolism, leukocyte 31.1% and 9.5% ($F = 215.3$, $p < 0.0001$; $F = 197.7$, $p < 0.0001$), neutrophil 45.7% and 12.4% ($F = 544.3$, $p < 0.0001$; $F = 442.2$, $p < 0.0001$), lymphocyte 13.3% and 3.6% ($F = 42.7$, $p < 0.0001$; $F = 34.6$, $p < 0.0001$), and eosinophil 11.7% and 1.4% ($F = 48.1$, $p < 0.0001$; $F = 17.1$, $p < 0.0001$) of the total variance. Basophils showed a low interaction with SARS-CoV-2 infection, 8.03% ($F = 26.01$, $p < 0.0001$) of the total variance, but not with health metabolism 0.25% ($F = 2.41$, $p = 0.121$). Monocyte presented 8.4% ($F = 81.1$, $p < 0.0001$) of the total variance related to unhealthy

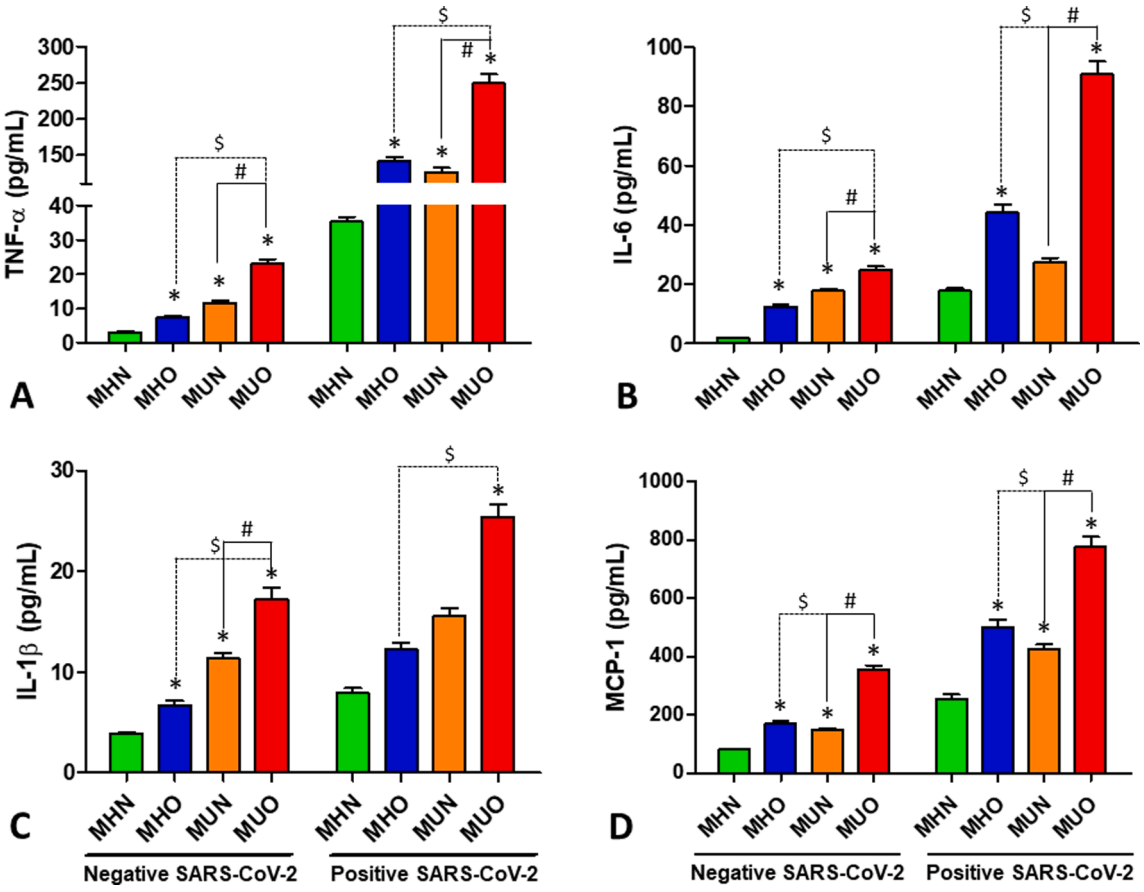

Fig. 1. Proinflammatory cytokine profile of the metabolically healthy and unhealthy population, negative and positive to SARS-CoV-2 infection. A) TNF-α; B) IL-6; C) IL-1β; D) MCP-1. Data are reported as mean ± standard error of the mean (SEM). Differences were tested using a two-way ANOVA with a Bonferroni post hoc test. (*) Indicates significant differences from the MHN group. ($) Indicates significant differences between obese groups. (#) Indicates significant differences between metabolic unhealthy groups.

metabolism and barely 5.3% ($F = 16.96$, $p < 0.0001$) with SARS-CoV-2 infection. Finally, platelets showed 22.9% ($F = 118$, $p < 0.0001$) of the total variance related to SARS-CoV-2 infection and 14.3% ($F = 217.1$, $p < 0.0001$) with the unhealthy metabolism.

On the other hand, clinical parameters were measured in the groups without SARS-CoV-2 infection (Table 3). the hs-CRP significatively increased in metabolically unhealthy and/or obese subjects, but only in the MUN and MUO groups that were above the reference interval. In the same way, the FIB and LDH showed a significant increase, although only the MUO group was above the biological range. PCT, D-dimer, and ferritin also observed increased behavior, but these were in reference intervals. Meanwhile, PT, INR, and APTT were in the biological reference range, but significatively decreased in metabolically unhealthy and/or obese groups. Meanwhile, in SARS-CoV-2 infected subjects, only PCT significatively increased, but it was maintained within the reference range. APTT also significatively increased in metabolically unhealthy and/or obese subjects, but it was only above the clinical range in the MUO group. PT, INR, D-dimer, LDH, and ferritin had the same behavior, although only metabolically unhealthy groups were above the reference range. Fibrinogen concentration significantly increased above clinical range in metabolically unhealthy and/or obese groups. Finally, hs-CRP significatively increased above the biological interval in all SARS-CoV-2 infected subjects. The two-way analysis showed that healthy metabolism has a greater impact than that SARS-CoV-2 infection in the INR 53% and 5.6% ($F = 2402$, $p < 0.0001$; $F = 82.5$, $p < 0.0001$), hs-CRP 45.3% and 17.2% ($F = 1295$, $p < 0.0001$; $F = 163.9$, $p < 0.0001$), and D-dimer 40.2% and 18.3% ($F = 1104$, $p < 0.0001$; $F = 18.3$, $p < 0.0001$) of the total variance. Similar interaction between healthy metabolism and SARS-CoV-2 infection in the FIB 32.4% and 27.6% ($F = 734.1$, $p < 0.0001$; $F = 208.2$, $p < 0.0001$), ferritin 28.6% and 32.4% ($F = 1168$, $p < 0.0001$; $F = 440.8$, $p < 0.0001$), PT 27% and 36.3% ($F = 25850$, $p < 0.0001$; $F = 11568$, $p < 0.0001$), and PCT 6.2% and 9.6% ($F = 56.8$, $p < 0.0001$; $F = 29.24$, $p < 0.0001$) of the total variance. And a high interaction with SARS-CoV-2 infection compared to health metabolism in LDH 41.8% and 20.1% ($F = 329$, $p < 0.0001$; $F = 476$, $p < 0.0001$) and APTT 18% and 1% ($F = 124.7$, $p < 0.0001$; $F = 19.9$, $p < 0.0001$) of the total variance.

4. Discussion

In this study, first, we classified obese and non-obese subjects based on BMI, body fat content, waist and hip circumference, waist/hip ratio, and their combination with 10 criteria of a healthy metabolism to define the different phenotypes (Table 1). With these data, four groups were conformed, metabolically healthy with normal BMI (MHN), metabolically unhealthy with normal BMI (MUN), metabolically healthy obese (MHO), and metabolically unhealthy obese (MHO). The complete anthropometric measurements provide evidence to distinguish between fat and lean tissue, as well as fat distribution, because visceral fat accumulation is associated with an increased risk of type 2 diabetes, hypertension, dyslipidemia, and cardiometabolic diseases, reducing life expectancy [31]. However, not all obese people have metabolic complications, raising the question of whether those who are metabolically healthy represent a unique subset of people with obesity or are a group in transition to developing later MUO. These patients circumvented the classic models of metabolic and cardiovascular risk. Likewise,

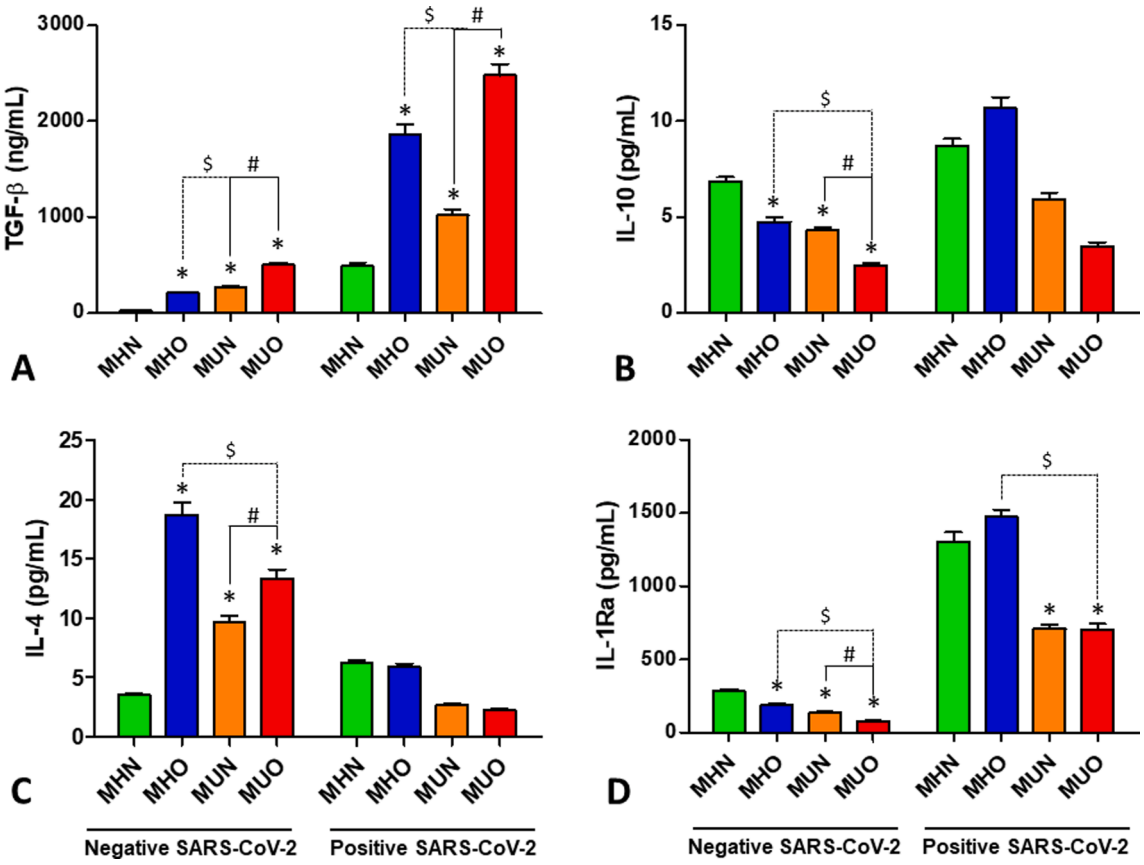

Fig. 2. Anti-inflammatory cytokine profile of the metabolically healthy and unhealthy population, negative and positive to SARS-CoV-2 infection. A) TGF-β; B) IL-10; C) IL-4; D) IL-1Ra. Data are reported as mean ± standard error of the mean (SEM). Differences were tested using a two-way ANOVA with a Bonferroni post hoc test. (*) Indicates significant differences from the MHN group. ($) Indicates significant differences between obese groups. (#) Indicates significant differences between metabolic unhealthy groups.

Table 2
Hematological parameters of the metabolically healthy and unhealthy population negative and positive to SARS-CoV-2 infection.

	Negative SARS-CoV-2				Positive SARS-CoV-2			
	MHN	MHO	MUN	MUO	MHN	MHO	MUN	MUO
	n = 96	n = 96	n = 96	n = 96	n = 90	n = 90	n = 90	n = 90
Hematological parameters:								
RBC count (4.1–6.1 x10^{12}/L)	5.06 ± 0.07	4.38 ± 0.05*	4.65 ± 0.05*#	4.2 ± 0.04*#	5.17 ± 0.08	4.79 ± 0.06*	4.84 ± 0.07*	4.79 ± 0.06*
Hemoglobin (13 – 17 g/dL)	14.8 ± 0.1	14.3 ± 0.07*$	13.9 ± 0.05*	13.8 ± 0.06*$	15.1 ± 0.12	14.4 ± 0.1*	14.2 ± 0.1*	14.4 ± 0.1*
Hematocrit (37 – 52%)	43.4 ± 0.49	44 ± 0.57	43.9 ± 0.56	42.7 ± 0.59	43.3 ± 0.58	42 ± 0.52	43.5 ± 0.59	42 ± 0.52
WBC count (4.2 – 10.8 x10^{9}/L)	6.53 ± 0.09	6.5 ± 0.14	5.01 ± 0.05*#	6.3 ± 0.2#	12.6 ± 0.28	6.9 ± 0.21*$	6.47 ± 0.15*#	5.27 ± 0.16*#$
Basophil (0 – 0.2 x10^{9}/L)	0.03 ± 0.003	0.04 ± 0.004$	0.05 ± 0.004#	0.1 ± 0.01*#$	0.13 ± 0.01	0.04 ± 0.004*	0.02 ± 0.004*#	0.06 ± 0.01*#
Eosinophil (0 – 0.55 x10^{9}/L)	0.06 ± 0.01	0.1 ± 0.01$	0.08 ± 0.01#	0.14 ± 0.01*#$	0.32 ± 0.02	0.11 ± 0.009*$	0.06 ± 0.01*	0.02 ± 0.003*$
Neutrophil (1.6 – 9.35 x10^{9}/L)	4.6 ± 0.08	4.2 ± 0.09*$	2.9 ± 0.05*	3.1 ± 0.1*$	10.5 ± 0.23	4.71 ± 0.16*$	4.0 ± 0.13*#	2.95 ± 0.1*#$
Lymphocyte (0.8 – 4.4 x10^{9}/L)	1.7 ± 0.04	2.0 ± 0.07*$	1.8 ± 0.04#	2.6 ± 0.1*#$	1.27 ± 0.04	1.82 ± 0.09*	1.95 ± 0.07*	1.92 ± 0.07*
Monocyte (0.08 – 0.77 x10^{9}/L)	0.14 ± 0.01	0.17 ± 0.01$	0.19 ± 0.01*#	0.35 ± 0.02*#$	0.41 ± 0.04	0.22 ± 0.02*$	0.47 ± 0.03#	0.32 ± 0.02#$
PLT count (150 – 450 x10^{9}/L)	345 ± 6	323 ± 5*	331 ± 4	318 ± 4*	355 ± 6	308 ± 8*$	242 ± 4*#	191 ± 4*#$

Data are reported as mean ± standard error of the mean (SEM). Differences were tested using a two-way ANOVA with a Bonferroni post hoc test. (*) Indicates significant differences from the MHN group. ($) Indicates significant differences between obese groups. (#) Indicates significant differences between metabolic unhealthy groups. **MHN**: metabolic healthy with normal BMI; **MHO**: metabolic healthy obese; **MUN**: metabolic unhealthy with normal BMI; **MUO**: metabolic unhealthy obese; **RBC**: Red blood cell; **WBC**: White blood cell; **PLT**: Platelets.

individuals with normal weight or obesity but with metabolic disorders (MUN and MUO, respectively) increase the risks of developing chronic degenerative diseases. Therefore, accurate classification and mechanistic understandings are required based on anthropometrical and biochemical measurements for individuals with these conditions that ensure the best healthcare, appropriate treatments, and decrease healthcare costs [13,32,33]. There are more than 30 different definitions for MHO [13,23,34–39]; however, more rigorous criteria are necessary to generate a universally accepted definition In the present work, the criteria identify checkpoints of carbohydrate and lipid metabolism that permit differentiation between healthy and unhealthy metabolism. Results showed that carbohydrate and lipid metabolism and hormones involved are secreted adequately in healthy people, independently of their BMI. Meanwhile, in metabolically unhealthy subjects, WHR is close to or above 1, which is indicative of a greater visceral fat mass that secretes more leptin and less adiponectin, affecting insulin sensitivity, impairing glycemia, and developing dyslipidemia (Table 1) [40,41].

In particular, visceral adipose tissue expansion in cell number and

Table 3
Clinical parameters of the metabolically healthy and unhealthy population negative and positive to SARS-CoV-2 infection.

	Negative SARS-CoV-2				Positive SARS-CoV-2			
	MHN	MHO	MUN	MUO	MHN	MHO	MUN	MUO
	n = 96	n = 96	n = 96	n = 96	n = 90	n = 90	n = 90	n = 90
Inflammation:								
hs-CRP (<1 mg/L)	0.33 ± 0.01	0.71 ± 0.02$^{*\$}$	1.08 ± 0.03$^{*\#}$	1.44 ± 0.04$^{*\#\$}$	2.66 ± 0.07	5.67 ± 0.23$^{*\$}$	9.3 ± 0.36$^{*\#}$	12.34 ± 0.59$^{*\#\$}$
PCT (<0.5 ng/mL)	0.1 ± 0.003	0.12 ± 0.01$^{*\$}$	0.13 ± 0.01$^{*\#}$	0.15 ± 0.01$^{*\#\$}$	0.12 ± 0.005	0.15 ± 0.01$^{*\$}$	0.19 ± 0.006$^{*\#}$	0.22 ± 0.01$^{*\#\$}$
Coagulation:								
PT (12.5 – 14.5 seg)	14 ± 0.03	13.9 ± 0.03$^{*\$}$	13.5 ± 0.03$^{*\#}$	13.2 ± 0.02$^{*\#\$}$	14.3 ± 0.03	15.1 ± 0.04$^{*\$}$	15.2 ± 0.04$^{*\#}$	16.6 ± 0.08$^{*\#\$}$
INR (1; ISI 1.26)	1 ± 0.003	0.99 ± 0.003$^{*\$}$	0.96 ± 0.003$^{*\#}$	0.93 ± 0.002$^{*\#\$}$	1.03 ± 0.003	1.1 ± 0.002$^{*\$}$	1.13 ± 0.004$^{*\#}$	1.24 ± 0.01$^{*\#\$}$
APTT (29 – 42 seg)	40 ± 0.12	38.9 ± 0.12$^{*\$}$	38.2 ± 0.12$^{*\#}$	36.9 ± 0.12$^{*\#\$}$	31.4 ± 0.21	35 ± 0.3$^{*\$}$	39.1 ± 0.35$^{*\#}$	44.9 ± 0.58$^{*\#\$}$
FIB (150 – 300 mg/dL)	218.7 ± 3.5	232.5 ± 5.1$^{\$}$	262 ± 3.7$^{*\#}$	306 ± 4.8$^{*\#\$}$	268.3 ± 4.04	364.5 ± 7.8$^{*\$}$	402.9 ± 6.4$^{*\#}$	525.7 ± 14.4$^{*\#\$}$
D-dimer (≤500 ng/mL)	125.8 ± 4.2	146.9 ± 5.9$^{*\$}$	181.4 ± 4.1$^{*\#}$	200.6 ± 4.9$^{*\#\$}$	421.3 ± 11.0	483.1 ± 15.6$^{\$}$	867.1 ± 38.2$^{*\#}$	1432 ± 63$^{*\#\$}$
Biochemical:								
LDH (230 – 460 U/L)	301.4 ± 3.4	379.4 ± 6.3$^{*\$}$	398.6 ± 6.0$^{*\#}$	467.8 ± 4.7$^{*\#\$}$	355.4 ± 6.7	453.5 ± 9.4$^{*\$}$	554.6 ± 9.2$^{*\#}$	697.3 ± 15$^{*\#\$}$
Ferritin (15 – 290 ng/mL)	65.2 ± 3.4	176.7 ± 6.8$^{*\$}$	194.1 ± 5.5*	206.1 ± 4.9$^{*\$}$	205.3 ± 5.9	251.6 ± 6$^{\$}$	536.9 ± 12$^{*\#}$	1025 ± 36$^{*\#\$}$

Data are reported as mean ± standard error of the mean (SEM). Differences were tested using a two-way ANOVA with a Bonferroni post hoc test. (*) Indicates significant differences from the MHN group. ($) Indicates significant differences between obese groups. (#) Indicates significant differences between metabolic unhealthy groups. **MHN**: metabolic healthy with normal BMI; **MHO**: metabolic healthy obese; **MUN**: metabolic unhealthy with normal BMI; **MUO**: metabolic unhealthy obese; **hs-CRP**: High sensitive C-reactive protein; **PCT**: Procalcitonin; **PT**: Prothrombin time; **INR**: International normalized ratio; **ISI**: International sensitivity index; **APTT**: Activated partial thromboplastin time; **FIB**: fibrinogen; **LDH**: Lactate dehydrogenase.

size increases the WC and triglyceride storage and diminishes the adiponectin/leptin ratio [41,42]. Due to cell and tissue expansion limitations, the adipocytes inevitably reach a limit of excessive anabolic pressure, which initiates a low-grade chronic inflammatory response [43]. Proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 accelerate adipose tissue fibrosis and insulin resistance, a tissue adaptation with redundancies in hypertrophy and lipolysis [44]. IL-1β and IL-6 increase MCP-1 levels and recruit M1 macrophages while M2 macrophages are reduced, establishing inflammaging conditions [45,46]. Inflammaging can coexist in metabolically healthy subjects; in fact, several studies have suggested this "favorable" inflammatory profile in MHO development because it prepares adipose tissue for high triglyceride storage [47,48]. However, the anti-inflammatory response is poorly studied. Our results showed a significant increase in serum concentrations of proinflammatory cytokines TNF-α, IL-1β, IL-6, and MCP-1 in the MHO group without SARS-CoV-2 infection (Fig. 1A-D). These concentrations were in the biological range. However, the anti-inflammatory cytokines TGF- β and IL-4 were clinical and statistically increased significantly, which explains, at least in part, the inflammaging in these subjects (Fig. 2A, C). IL-10 and IL-1Ra plasma levels and hematological parameters such as platelets, RBC count, and hemoglobin concentration were within a biological range but statistically diminished (Fig. 2B, 2D, and Table 2). Likewise, the neutrophil count statistically decreases in the white linage, while the lymphocyte count increases (Table 2). The results suggest imperceptible changes that in an acute injury can impair immune response. In the same way, clinical biomarkers of inflammation, coagulation, and biochemistry were in the biological range. Still, hs-CRP, PCT, D-dimer, LDH, and ferritin significantly increased, while PT, INR, and APTT diminished (Table 3).

Inflammaging can progress to metaflammation (the metabolic inflammation accompanying metabolic diseases) that is thought to be the form of chronic inflammation driven by nutrient excess or overnutrition; metaflammation is characterized by the same mechanisms underpinning inflammaging with deteriorating physiological responses [49–51]. The uninfected metabolically unhealthy obese and non-obese subjects SARS-CoV-2 showed a serum increase of TNF-α, IL-1β, IL-6, and MCP-1, TGF-β, and IL-4 (Fig. 1A-D and 2A, C). Meanwhile, IL-10 and IL-1Ra plasma levels were clinical and statistically low (Fig. 2B, D). A phenotype previously manifested in obese and non-obese diabetic subjects [52,53]. However, RBC count, hemoglobin concentration, and neutrophil count were statistically diminished, while monocyte count increased. Only MUO subjects had a greater basophil, eosinophil, and lymphocyte count and diminishing platelets (Table 2). In both groups, hs-CRP increased above the biological range, coinciding with proinflammatory cytokine levels. Only MUO subjects increased FIB and LDH levels, while in MUN subjects, these parameters were in the reference interval but statistically increased. PCT, D-dimer, and ferritin were in the biological range but significantly increased in both groups. Meanwhile, PT, INR, and APTT were within clinical values but statistically diminished (Table 3). The results suggest that metaflammation deteriorates hematological, inflammation, coagulation, and biochemical homeostasis, obese subjects being more affected.

Metaflammation might precede and contribute to inflammaging and vice versa, and age-related metabolic diseases could be considered manifestations of the acceleration of aging or senescence [49]. When cells reach senescence, they produce cytokines, chemokines, growth factors, proteases, and angiogenic factors that characterize a senescence-associated secretory phenotype (SASP). As senescent cells accumulate, SASP may also contribute to inflammaging and metaflammation, resulting from a complex interplay between SASP, lifestyle factors, and dysregulated innate immune cell functions [54,55]. In a metabolically unhealthy population, these conditions are often presented with multimorbidity and may finally lead to organ failure. Therefore, subjects with metaflammation are the ones with heightened risk for developing severe COVID-19 and dying [56,57].

Inflammaging (in MHO) or metaflammation (in MUN and MUO) infected SARS-CoV-2 subjects showed a proinflammatory cytokine hyperresponse combined with obesity, unhealthy metabolism, and immune response against the virus, as shown in the statistical analysis. However, MUO subjects were more affected. TNF-α concentration was mostly influenced by obesity and unhealthy metabolism, while IL-1β and IL-6 response is affected by SARS-CoV-2 infection, and MCP-1 is equally modulated. Our results correlate with the reported literature, where severe cases of COVID-19 presented cytokine storm, which is the release of large amounts of cytokines and chemokines by effector cells of the immune system. The cytokines most associated with the cytokine storm are IL-1β, IL-6, IL-12, and TNF-α [58,59]. Patients with COVID-19 observe a shift in proinflammatory monocyte populations in circulation that coincides with increased cytokine and chemokine [60]. Proinflammatory circulating monocyte and macrophage populations are associated with many chronic diseases, including obesity, metabolic disorders, and metaflammation [45,61,62]. Increased BMI also correlates with an increase of several cytokines, including IL-6, IL-8, IL-1β, and TNF-α. Particularly, MUO subjects have an increase in chemokines such as CCL14 and MCP-1, furthering the overall inflammation in COVID-19 disease [63,64]. In addition, TGF-β, IL-4, and IL-1Ra of the anti-inflammatory response are mostly influenced by unhealthy metabolism and obesity, while IL-10 is affected by SARS-CoV-2 infection.

This anti-inflammatory pattern impairs the response against viral infection from macrophages, naive T cells, T helper (Th)1, and Th2 that decreased the ability to clear intracellular pathogens [65]. The substantial diminishing of IL-10, IL-4, and IL-1Ra in SARS-CoV-2 infected subjects breaks the inflammation homeostasis and modifies acute phase response, hematological parameters, endothelial function, and hepatic activity.

SARS-CoV-2 infection positively influenced leukocyte response. Interestingly, MHU, MUN, and MUO patients did not show leukocytosis; neutrophilia with lymphopenia percentual was observed, although absolute values of these parameters were found within biological limits. Likewise, the basophil and eosinophil linages showed low counts. This leukocyte pattern has been described in patients infected with SARS-CoV-2. Some authors have proposed neutrophil-to-lymphocyte ratio (NLR) as an independent risk factor for severe disease associated with an increased risk of death during hospitalization of COVID-19 patients [66]. In addition, monocyte variation was considerably influenced by obesity and/or unhealthy metabolism. Macrophages from obese animals and humans have been described as metabolically active, M1 polarized, and proinflammatory with both regulatory and detrimental activity [67]. Platelet count was mostly influenced by SARS-CoV-2 infection. The thrombocytopenia observed in COVID-19 patients is associated with the progression and prognosis of the disease [68]. Thrombocytopenia can result from the change of levels and types of cytokine that act on hematopoietic cells or bone marrow stromal cells, leading to hematopoietic inhibition and lung injury that increased platelet consumption [69].

Pulmonary microthrombosis and disseminated intravascular coagulation are common complications of COVID-19 disease, resulting from an inflammatory and hypercoagulable state [4–6,70]. SARS-CoV-2 also includes infection-related dysfunction of endothelial cells, which causes an increased production of thrombin and inhibition of fibrinolysis [71,72]. Obese subjects with insulin resistance and low adiponectin levels are susceptible to vascular complications, including thrombosis and atherogenesis [73]. Additionally, the hypoxemia observed in COVID-19 patients can promote thrombosis by increasing blood viscosity. Liver dysfunction is associated with unhealthy metabolism, and also could impair the production of coagulation factors, LDH, and ferritin [74,75]. Together, these events may significantly contribute to an increased risk of thrombotic events in COVID-19 patients [76]. Clinically, increased D-dimer levels found in COVID-19 patients reflect the coagulation alterations [77]. It is noteworthy that D-dimer levels are associated with a poor outcome defined as an increased risk of acute respiratory distress syndrome [78]. Also, increased fibrinogen, fibrin degradation product (FDP) levels, PT, and APTT during the early phase of COVID-19 have been associated with severe disease [79]. Our results showed that the increase of INR, hs-CRP, and D-dimer are dependent on obesity and healthy metabolism, more than SARS-CoV-2 infection. Meanwhile, FIB, ferritin, PT, and PCT had a similar dependency between healthy metabolism and SARS-CoV-2 infection. Finally, SARS-CoV-2 infection influences the increase of LDH and APTT. MHO subjects showed the most significant alterations in all clinical parameter measurements.

In summary, due to considerable heterogeneity in the metabolic complications associated with obesity, defining metabolic health with rigorous clinical parameters in obese and non-obese subjects can help us understand the mechanisms leading to chronic-degenerative diseases. In this sense, our findings showed that MHO people live with a chronic-non resolutive low-grade inflammation called inflammaging. Meanwhile, MUN and MUO subjects develop metaflammation. Both inflammaging and metaflammation cause imperceptible modifications on acute phase response, hematological parameters, mainly in leukocyte populations, and coagulation components. Together, they impair immunoinflammatory response in SARS-CoV-2 infection, condition a poor resolution, and patients advance to severe COVID-19 symptomatology. Therefore, in MHO, MUN, and MUO subjects it is necessary to stratify or stake out reference values of each biological parameter to increase diagnostic sensibility in response to acute inflammations. In conclusion, MHO subjects seem to be transitioning from metabolically healthy to unhealthy, which is accelerated in acute processes, such as SARS-CoV-2 infection. Meanwhile, metabolically unhealthy subjects apart from BMI have a deteriorating immunometabolic status associated with a hyper-inflammatory state leading to multi-organ dysfunction, treatment complications, and severe COVID-19 disease.

CRediT authorship contribution statement

Samuel Treviño: Conceptualization, Writing – review & editing. **Steffany Cortezano-Esteban:** Methodology. **Hugo Hernández-Fragoso:** Methodology. **Alfonso Díaz:** Conceptualization. **Rubén Vázquez-Roque:** . **Victor Enrique Sarmiento-Ortega:** Methodology. **Diana Moroni-González:** Methodology. **Rosana Pelayo:** Methodology, Validation. **Eduardo Brambila:** Conceptualization, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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