

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 July 16; 9(20): 5352-5753



## Contents

Thrice Monthly Volume 9 Number 20 July 16, 2021

## EDITORIAL

- 5352 COVID-19: Considerations about immune suppression and biologicals at the time of SARS-CoV-2 pandemic

*Costanzo G, Cordeddu W, Chessa L, Del Giacco S, Firinu D*

## REVIEW

- 5358 Obesity in people with diabetes in COVID-19 times: Important considerations and precautions to be taken
- Alberti A, Schuelter-Trevisol F, Iser BPM, Traebert E, Freiberger V, Ventura L, Rezin GT, da Silva BB, Meneghetti Dallacosta F, Grigollo L, Dias P, Fin G, De Jesus JA, Pertille F, Rossoni C, Hur Soares B, Nodari Junior RJ, Comim CM*

- 5372 Revisiting delayed appendectomy in patients with acute appendicitis

*Li J*

## MINIREVIEWS

- 5391 Detection of short stature homeobox 2 and RAS-associated domain family 1 subtype A DNA methylation in interventional pulmonology

*Wu J, Li P*

- 5398 Borderline resectable pancreatic cancer and vascular resections in the era of neoadjuvant therapy

*Mikulic D, Mrzljak A*

- 5408 Esophageal manifestation in patients with scleroderma

*Voulgaris TA, Karamanolis GP*

- 5420 Exploration of transmission chain and prevention of the recurrence of coronavirus disease 2019 in Heilongjiang Province due to in-hospital transmission

*Chen Q, Gao Y, Wang CS, Kang K, Yu H, Zhao MY, Yu KJ*

- 5427 Role of gastrointestinal system on transmission and pathogenesis of SARS-CoV-2

*Simsek C, Erul E, Balaban HY*

## ORIGINAL ARTICLE

## Case Control Study

- 5435 Effects of nursing care in fast-track surgery on postoperative pain, psychological state, and patient satisfaction with nursing for glioma

*Deng YH, Yang YM, Ruan J, Mu L, Wang SQ*

## Retrospective Study

- 5442 Risk factors related to postoperative recurrence of dermatofibrosarcoma protuberans: A retrospective study and literature review

*Xiong JX, Cai T, Hu L, Chen XL, Huang K, Chen AJ, Wang P*

- 5453** Prediction of presence and severity of coronary artery disease using prediction for atherosclerotic cardiovascular disease risk in China scoring system

*Hong XL, Chen H, Li Y, Teeroovengadum HD, Fu GS, Zhang WB*

- 5462** Effects of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors on COVID-19

*Li XL, Li T, Du QC, Yang L, He KL*

- 5470** Prognostic factors and its predictive value in patients with metastatic spinal cancer

*Gao QP, Yang DZ, Yuan ZB, Guo YX*

### Clinical Trials Study

- 5479** Prospective, randomized comparison of two supplemental oxygen methods during gastro-scopy with propofol mono-sedation in obese patients

*Shao LJZ, Hong FX, Liu FK, Wan L, Xue FS*

### SYSTEMATIC REVIEWS

- 5490** Herb-induced liver injury: Systematic review and meta-analysis

*Ballotin VR, Bigarella LG, Brandão ABM, Balbinot RA, Balbinot SS, Soldera J*

### META-ANALYSIS

- 5514** Type 2 diabetes mellitus increases liver transplant-free mortality in patients with cirrhosis: A systematic review and meta-analysis

*Liu ZJ, Yan YJ, Weng HL, Ding HG*

### CASE REPORT

- 5526** Duplication of 19q (13.2-13.31) associated with comitant esotropia: A case report

*Feng YL, Li ND*

- 5535** Multiple left ventricular myxomas combined with severe rheumatic valvular lesions: A case report

*Liu SZ, Hong Y, Huang KL, Li XP*

- 5540** Complete pathological response in locally advanced non-small-cell lung cancer patient: A case report

*Parisi E, Arpa D, Ghigi G, Micheletti S, Neri E, Tontini L, Pieri M, Romeo A*

- 5547** Successful reversal of ostomy 13 years after Hartmann procedure in a patient with colon cancer: A case report

*Huang W, Chen ZZ, Wei ZQ*

- 5556** Delayed papillary muscle rupture after radiofrequency catheter ablation: A case report

*Sun ZW, Wu BF, Ying X, Zhang BQ, Yao L, Zheng LR*

- 5562** Temporary coronary sinus pacing to improve ventricular dyssynchrony with cardiogenic shock: A case report

*Ju TR, Tseng H, Lin HT, Wang AL, Lee CC, Lai YC*

- 5568** Hemoglobin Fukuoka caused unexpected hemoglobin A<sub>1c</sub> results: A case report  
*Lin XP, Yuan QR, Niu SQ, Jiang X, Wu ZK, Luo ZF*
- 5575** Giant androgen-producing adrenocortical carcinoma with atrial flutter: A case report and review of the literature  
*Costache MF, Arhirii RE, Mogos SJ, Lupascu-Ursulescu C, Litcanu CI, Ciunanghel AI, Cucu C, Ghiciuc CM, Petris AO, Danila N*
- 5588** Can kissing cause paraquat poisoning: A case report and review of literature  
*Ly B, Han DF, Chen J, Zhao HB, Liu XL*
- 5594** Spinal dural arteriovenous fistula 8 years after lumbar discectomy surgery: A case report and review of literature  
*Ouyang Y, Qu Y, Dong RP, Kang MY, Yu T, Cheng XL, Zhao JW*
- 5605** Perianal superficial CD34-positive fibroblastic tumor: A case report  
*Long CY, Wang TL*
- 5611** Low-dose clozapine-related seizure: A case report and literature review  
*Le DS, Su H, Liao ZL, Yu EY*
- 5621** Rapid diagnosis of disseminated *Mycobacterium mucogenicum* infection in formalin-fixed, paraffin-embedded specimen using next-generation sequencing: A case report  
*Liu J, Lei ZY, Pang YH, Huang YX, Xu LJ, Zhu JY, Zheng JX, Yang XH, Lin BL, Gao ZL, Zhuo C*
- 5631** Cytomegalovirus colitis induced segmental colonic hypoganglionosis in an immunocompetent patient: A case report  
*Kim BS, Park SY, Kim DH, Kim NI, Yoon JH, Ju JK, Park CH, Kim HS, Choi SK*
- 5637** Primary extra-pancreatic pancreatic-type acinar cell carcinoma in the right perinephric space: A case report and review of literature  
*Wei YY, Li Y, Shi YJ, Li XT, Sun YS*
- 5647** Muscular atrophy and weakness in the lower extremities in Behçet's disease: A case report and review of literature  
*Kim KW, Cho JH*
- 5655** Novel technique of extracorporeal intrauterine morcellation after total laparoscopic hysterectomy: Three emblematic case reports  
*Macciò A, Sanna E, Lavra F, Calò P, Madeddu C*
- 5661** Rare isolated extra-hepatic bile duct injury: A case report  
*Zhao J, Dang YL, Lin JM, Hu CH, Yu ZY*
- 5668** Gelfoam embolization for distal, medium vessel injury during mechanical thrombectomy in acute stroke: A case report  
*Kang JY, Yi KS, Cha SH, Choi CH, Kim Y, Lee J, Cho BS*



- 5675** Oncocytic adrenocortical tumor with uncertain malignant potential in pediatric population: A case report and review of literature  
*Chen XC, Tang YM, Mao Y, Qin DR*
- 5683** Submucosal hematoma with a wide range of lesions, severe condition and atypical clinical symptoms: A case report  
*Liu L, Shen XJ, Xue LJ, Yao SK, Zhu JY*
- 5689** Chorioamnionitis caused by *Serratia marcescens* in a healthcare worker: A case report  
*Park SY, Kim MJ, Park S, Kim NI, Oh HH, Kim J*
- 5695** Endoscopic management of biliary ascariasis: A case report  
*Wang X, Lv YL, Cui SN, Zhu CH, Li Y, Pan YZ*
- 5701** Role of ranulas in early diagnosis of Sjögren's syndrome: A case report  
*Chen N, Zeng DS, Su YT*
- 5709** Sacral chondroblastoma — a rare location, a rare pathology: A case report and review of literature  
*Zheng BW, Niu HQ, Wang XB, Li J*
- 5717** Primary liver actinomycosis in a pediatric patient: A case report and literature review  
*Liang ZJ, Liang JK, Chen YP, Chen Z, Wang Y*
- 5724** Splenosis masquerading as gastric stromal tumor: A case report  
*Zheng HD, Xu JH, Sun YF*
- 5730** Hemorrhagic transformation of ischemic cerebral proliferative angiopathy: A case report  
*Xia Y, Yu XF, Ma ZJ, Sun ZW*
- 5737** Multidisciplinary team therapy for left giant adrenocortical carcinoma: A case report  
*Zhou Z, Luo HM, Tang J, Xu WJ, Wang BH, Peng XH, Tan H, Liu L, Long XY, Hong YD, Wu XB, Wang JP, Wang BQ, Xie HH, Fang Y, Luo Y, Li R, Wang Y*
- 5744** Histopathology and immunophenotyping of late onset cutaneous manifestations of COVID-19 in elderly patients: Three case reports  
*Mazzitelli M, Dastoli S, Mignogna C, Bennardo L, Lio E, Pelle MC, Trecarichi EM, Pereira BI, Nisticò SP, Torti C*

**CORRECTION**

- 5752** Corrigendum to "Probiotic mixture VSL#3: An overview of basic and clinical studies in chronic diseases"  
*Sang LX*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Fan-Zheng Meng, MD, PhD, Director, Professor, Department of Pediatrics, The First hospital of Jilin University, Changchun 130021, Jilin Province, China. mengfanzheng1972@163.com

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Jia-Hui Li; Production Department Director: Yu-Jie Ma; Editorial Office Director: Jin-Lei Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

July 16, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Obesity in people with diabetes in COVID-19 times: Important considerations and precautions to be taken

Adriano Alberti, Fabiana Schuelter-Trevisol, Betine Pinto Moehlecke Iser, Eliane Traebert, Viviane Freiburger, Leticia Ventura, Gislaine Tezza Rezin, Bruna Becker da Silva, Fabiana Meneghetti Dallacosta, Leoberto Grigollo, Paula Dias, Gracielle Fin, Josiane Aparecida De Jesus, Fabiane Pertille, Carina Rossoni, Ben Hur Soares, Rudy José Nodari Júnior, Clarissa Martinelli Comim

**ORCID number:** Adriano Alberti 0000-0003-0313-0380; Fabiana Schuelter-Trevisol 0000-0003-0997-1594; Betine Pinto Moehlecke Iser 0000-0001-6061-2541; Eliane Traebert 0000-0001-9667-7216; Viviane Freiburger 0000-0003-2247-5157; Leticia Ventura 0000-0002-0912-6801; Gislaine Tezza Rezin 0000-0002-1352-0369; Bruna Becker da Silva 0000-0001-7190-4646; Fabiana Meneghetti Dallacosta 0000-0003-3515-9225; Leoberto Grigollo 0000-0002-7838-9197; Paula Dias 0000-0002-4145-9673; Gracielle Fin 0000-0001-7860-4451; Josiane Aparecida De Jesus 0000-0002-2345-2259; Fabiane Pertille 0000-0001-3117-2637; Carina Rossoni 0000-0002-6494-4639; Ben Hur Soares 0000-0001-6762-4799; Rudy José Nodari Júnior 0000-0002-8375-657X; Clarissa Martinelli Comim 0000-0003-4991-042X.

**Author contributions:** Alberti A conceived and designed the study; Schuelter Trevisol F, Iser BPM, Traebert E, Freiburger V, Ventura L, Rezin GT, Da Silva BB, Dalacosta F, Dias P, Jesus J, Pertile F, Rossoni C, and Hur Soares B researched the material to support and write the article; Nodari Júnior RJ and Comim CM reviewed the manuscript; All authors approved the final version of this manuscript.

**Adriano Alberti, Viviane Freiburger, Leticia Ventura, Leoberto Grigollo, Paula Dias, Clarissa Martinelli Comim**, Research Group in Neurodevelopment of Childhood and Adolescence, Laboratory of Experimental Neuroscience, Postgraduate Program in Health Sciences, University of South Santa Catarina (Unisul), Palhoça, 88137-270, Santa Catarina, Brazil

**Fabiana Schuelter-Trevisol, Betine Pinto Moehlecke Iser, Gislaine Tezza Rezin**, Brazil Clinical Research Center, Postgraduate Program in Health Sciences, University of Southern Santa Catarina at Tubarão, Tubarão, 88704 -900, Santa Catarina, Brazil

**Eliane Traebert, Bruna Becker da Silva**, Postgraduate Programme in Health Sciences, University of Southern Santa Catarina, Palhoça, 88137-270, Santa Catarina, Brazil

**Fabiana Meneghetti Dallacosta, Josiane Aparecida De Jesus, Fabiane Pertille**, Postgraduate Program in Biosciences and Health, University of the West of Santa Catarina, Joaçaba, 89600-000, Santa Catarina, Brazil

**Gracielle Fin**, Department of Physical Education, University of the West of Santa Catarina, Joaçaba, 89600-000, Santa Catarina, Brazil

**Carina Rossoni**, Environmental Health Institute of the Faculty of Medicine of the University of Lisbon, Lisboa, 1649-029, Portugal

**Ben Hur Soares**, Health Science, University of Passo Fundo, Passo Fundo, 99052-900, Rio Grande do Sul, Brazil

**Rudy José Nodari Júnior**, Research department, Salus Dermatoglifia, Luzerna, 89609-000, Santa Catarina, Brazil

**Corresponding author:** Adriano Alberti, MSc, PhD, Professor, Research Group in Neurodevelopment of Childhood and Adolescence, Laboratory of Experimental Neuroscience, Postgraduate Program in Health Sciences, University of South Santa Catarina (Unisul), Avenida José Acácio Moreira 787, Palhoça, 88137-270, Santa Catarina, Brazil.  
[adrianoalberti90@hotmail.com](mailto:adrianoalberti90@hotmail.com)

### Abstract

At the end of 2019, a new disease with pandemic potential appeared in China. It

**Conflict-of-interest statement:** The authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Specialty type:** Health care sciences and services

**Country/Territory of origin:** Brazil

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

**Received:** January 20, 2021

**Peer-review started:** January 20, 2021

**First decision:** May 3, 2021

**Revised:** May 4, 2021

**Accepted:** June 4, 2021

**Article in press:** June 4, 2021

**Published online:** July 16, 2021

**P-Reviewer:** Feng X

**S-Editor:** Zhang H

**L-Editor:** Filipodia

**P-Editor:** Li JH



was a novel coronavirus called coronavirus disease 2019 (COVID-19). Later, in the first quarter of 2020, the World Health Organization declared the outbreak of this disease a pandemic. Elderly people, people with comorbidities, and health care professionals are more vulnerable to COVID-19. Obesity has been growing exponentially worldwide, affecting several age groups. It is a morbidity that is associated with genetic, epigenetic, environment factors and/or interaction between them. Obesity is associated with the development of several diseases including diabetes mellitus, mainly type 2. Diabetes affects a significant portion of the global population. Obesity and diabetes are among the main risk factors for the development of severe symptoms of COVID-19, and individuals with these conditions constitute a risk group. Based on a literature review on obesity in people with diabetes in the framework of the COVID-19 pandemic, this study presents updated important considerations and care to be taken with this population.

**Key Words:** Obesity; Diabetes; COVID-19; Population; World; Disease

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** This article addresses obesity in people with diabetes in coronavirus disease 2019 (COVID-19) times, addressing the main points of the diseases and the interaction between them. Based on a literature review on obesity in people with diabetes in the framework of the COVID-19 pandemic, this study presents updated important considerations and care to be taken with this population.

**Citation:** Alberti A, Schuelter-Trevisol F, Iser BPM, Traebert E, Freiburger V, Ventura L, Rezin GT, da Silva BB, Meneghetti Dallacosta F, Grigollo L, Dias P, Fin G, De Jesus JA, Pertille F, Rossoni C, Hur Soares B, Nodari Júnior RJ, Comim CM. Obesity in people with diabetes in COVID-19 times: Important considerations and precautions to be taken. *World J Clin Cases* 2021; 9(20): 5358-5371

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i20/5358.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i20.5358>

## INTRODUCTION

Obesity affects people of different age groups, with a significant increase in its prevalence in the last three decades, with worldwide prevalence rates of 27.5% in adults and 47.1% in children[1]. Obesity is associated with the occurrence of several diseases, including diabetes mellitus (DM)[2]. Obesity is involved not only in the etiopathogenesis of the most common type of diabetes, type 2 DM but also in its complications. There is also a growing scientific evidence on the role of obesity in type 1 diabetes[3].

Diabetes affects more than 422 million adults worldwide, which is predicted to increase to 640 million by 2040[4,5]. It is one of the major causes of mortality and reduced life expectancy worldwide[6]. Among the types of diabetes, type 1 is an autoimmune disease mediated by T cells, marked by an insulin defect resulting from the destruction of the pancreatic  $\beta$  cells[7], with an estimated prevalence of 9.5% worldwide[8]. Type 2 diabetes is a condition that involves resistance to the effects of insulin or an inefficient production of insulin to maintain a normal blood glucose level [8]. Corresponding to more than 90% of diabetes cases, type 2 diabetes has an estimated prevalence of 9.3% and is growing exponentially, in parallel with the increase in obesity[9].

In March 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a pandemic after the virus had infected more than 381000 people in 195 countries[10]. The course of the disease is varied, depending on individual immunological factors, age, and existing comorbidities. Individuals with obesity and diabetes need greater care in times of coronavirus disease 2019 (COVID-19), since they are part of the risk groups[11] and the subsequent development of the infection has been highly associated with



morbidity and mortality in these individuals[12-14].

Based on a literature review on obesity in people with diabetes in times of the COVID-19 pandemic, this study presents updated important considerations and care to be taken with this population.

## OBESITY

Obesity is one of the most serious public health problems of the 21<sup>st</sup> century[15]. It is a complex multifactorial disease that affects individuals of all age groups in low- and middle-income countries in urban areas[15,16]. Many studies have shown that the main cause of obesity is calorie consumption greater than energy expenditure, resulting in high energy storage in the form of fat, especially in the abdominal region, associated with disorders such as type 2 DM[17], metabolic syndrome[18], obstructive sleep apnea[19], and increased risk of cardiovascular disease[18], conditions that decrease life expectancy.

The worldwide prevalence of overweight and obesity has doubled since 1980, so that almost one-third of the world population is classified as overweight or obese. The significant increase in the incidence of obesity in recent years makes this disease an epidemic[20,21]. According to data from the Global Burden of Disease[20,21], obesity rates increased at all ages and in both genders, regardless of geographic location, ethnicity or socioeconomic status, although the prevalence of obesity is generally higher in the elderly and in women. This trend was similar in all regions and countries, although the rates of absolute prevalence of overweight and obesity varied widely. In some developed countries, prevalence rates appear to have stabilized in recent years. However, in the United States, according to 2019[5] data from the Centers for Disease Control and Prevention, six states had a 35% or more obesity prevalence among non-Hispanic white adults; 15 states had a prevalence of 35% or more among Hispanic adults and in 34 states and the District of Columbia, the prevalence of obesity was 35% or more among non-Hispanic black adults[22].

Recent data from the WHO[23] showed that in the past four decades, the number of children and adolescents with obesity has increased considerably worldwide. While just under 4% of children and adolescents aged 5 to 19 years were obese in 1975, more than 124 million were classified as obese in 2016 that is, the prevalence that was 4% in 1975 increased to 18% in about 40 years. This is critical, since the probability of an obese child remaining obese in adulthood ranges from 20% to 50%. For an adolescent with obesity, this probability increases even more[24,25].

In view of the complexity of obesity, its pathophysiological aspects and also the importance of this chronic disease as a public health problem, there has been a growing number of studies aimed at understanding the pathophysiology of this disease and associated events. In this connection, it is important to note that the white adipose tissue (WAT) is the main secretory site of leptin, an adipokine, which upon reaching the central nervous system (CNS), acts on the hypothalamic receptors and reduces appetite. However, high levels of leptin in individuals with obesity, cause a process of central resistance of this hormone, impairing the signs of satiety[26]. In addition, another hormone present in the metabolic homeostasis is insulin, which is stimulated by increased glucose in the bloodstream. However, changes in eating behavior can be associated with an imbalance of this hormone. For example, the excess of free fatty acids directly affects cellular metabolism, triggering the activation of inflammatory pathways, and therefore, the development of insulin resistance[27].

In contrast, the high consumption of nutrients, exceeding the body's energy needs, can generate adipocytes hypertrophy and hyperplasia[28,29], and consequently, the compression of blood vessels, hindering adequate oxygen supply, generating hypoxia[30,31]. Hypoxia is related to the recruitment of macrophages for this tissue[32-36]. The infiltrated macrophages form crown-like structures surrounding the adipocytes, which leads to excessive adipokine production, which includes pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-6, C-reactive protein (CRP), and adipokines[37-44].

Thus, obesity is characterized by a low-grade chronic inflammation, detected by the elevation of pro-inflammatory mediators and by the presence of macrophages infiltrated in WAT[45,46]. This inflammation in WAT turns into systemic inflammation and contributes to the onset and progression of associated metabolic diseases[47-49]. In addition, studies conducted in the last decade have shown that obesity and its comorbidities are not limited to peripheral tissues, but also involve the CNS[50-53].

## DM

DM is defined as a disorder in the glucose metabolism, in which the serum glucose concentration is abnormally high, as the body does not release or use glucose properly [54]. The two most common forms of diabetes are type 1 and type 2. Type 1 diabetes results from the autoimmune destruction of the pancreatic beta cells, which produce insulin, and type 2 diabetes is caused mainly by a combination of insulin resistance and relative insulin deficiency [55].

DM, as well as obesity, is also considered one of the major public health problems of the 21<sup>st</sup> century. In 2019, there were 463 million people with diabetes in the world, expected to increase to 700 million by 2045 [56]. This increase in the prevalence of diabetes is due to the epidemiological and nutritional transition, population aging, physical inactivity, overweight and obesity, and further to the greater survival of individuals with diabetes [54].

The countries with the highest prevalence of DM in adults aged 20 to 79 years in the world are China, India and the United States. The region of Central and South America ranks fifth, with 32 million people with the disease. Brazil appears in the sixth place, with 16.8 million people with DM in 2019 and an estimate to reach 26 million by 2045 [56].

The prevalence of DM in this country varies according to the survey carried out, and according to the region and age group assessed: In the Social Dimensions of Inequalities Survey, carried out in 2008 with the representation of macro-regions, a national prevalence of 7.5% self-reported DM was observed [57]. The National Health Survey (NHS), carried out in 2013, indicated a 6.2% prevalence of self-reported diabetes, that is, the previous diagnosis of the disease was reported by more than 9 million Brazilians aged 18 or over [58]. In a subsample of the NHS with collection of biochemical tests, carried out in 2014/2015, the prevalence of DM based on glycated hemoglobin data was 6.6% and, even considering the use of medication, 8.4% [59]. Data indicated a progressive increase in this morbidity reported in the adult population, from 1980 to 2015, in both men and women [60]. In different analyses, diabetes is associated with older age, less education, and overweight/obesity [58,59].

Diabetes is a chronic condition that requires constant care, including weight control through healthy habits, such as low carbohydrate diet, regular physical activity and, in some cases, help with hypoglycemic medication. Adequate glycemic control can delay or prevent the occurrence of microvascular and macrovascular complications of the disease, especially in patients diagnosed at an earlier age, with repercussions on the patient's quality of life and general health, such as retinopathy, nephropathy, neuropathy, coronary disease, cerebrovascular disease and peripheral arterial disease [54].

One of the problems associated with DM is the increased susceptibility to infections, due to several factors, directly or indirectly related to chronic hyperglycemia such as reduced vascular response to inflammatory mediators such as histamine and bradykinin, decreased activity of neutrophil polymorphonuclear cells, alteration in adherence, chemotaxis and leukocyte opsonization, peripheral and autonomic neuropathy, decreased protein binding with consequent edema, inefficient and delayed cellular immune response to harmful agents, change of antioxidant systems and reduced production of interleukin-2, vascular failure, reduction of mast cell degranulation, and worsening of tissue oxygenation [61].

Diabetes contributes to a worse prognosis of an infection, with higher morbidity and mortality from sepsis compared to the general population [62]. Some studies on the biochemical characteristics of diabetic patients have found that the lymphocyte count is lower than in individuals without diabetes, while that of neutrophils is higher, in addition to a higher proportion of highly sensitive CRP and procalcitonin [63,64]. Inflammation-related biomarkers were also elevated in diabetics. All of these effects form an inflammatory storm, which leads to rapid deterioration in the framework of diseases like COVID-19 [62].

Diabetes and associated complications can increase the risk of morbidity and mortality during acute infections due to the suppression of innate and humoral immune functions. Thus, diabetes is an important comorbidity to be considered in infectious processes, such as those triggered by COVID-19, especially when it accrues to other risk factors with inflammatory potential, including obesity. Both obesity and diabetes have deleterious effects on the host's immunity, increasing the risk of infectious susceptibility and severity [62].

## COVID-19

COVID-19 is an infectious disease caused by the SARS-CoV-2. SARS-CoV-2 is the third coronavirus identified to cause severe disease in humans. The first one was SARS-CoV, also from China, which caused a pandemic between 2002 and 2003. The second was the cause of the severe acute respiratory syndrome of the Middle East, called Middle East respiratory syndrome coronavirus (MERS-CoV), which was initially identified in the Arabian Peninsula in 2012[65]. Coronaviruses have the bat as their natural host and through recombination and genetic variation, adaptation and infection in other species was made possible. In the case of humans, possibly other mammals were the intermediate hosts, which is why COVID-19 is considered a zoonosis[66].

Coronaviruses have four structural proteins; spike (S), membrane (M), envelope (E) and nucleocapsid (N). Spike is composed of a trimetric glycoprotein transmembrane protruding from the viral surface, which determines the diversity of coronavirus and tropism in the host. The spike protein comprises two functional subunits: The S1 subunit is responsible for binding to the host cell receptor and the S2 subunit for fusion among viral and cellular membranes[67].

The SARS-CoV-2 infection is due to a highly transmissible virus among humans; the disease can be asymptomatic or oligosymptomatic, with a varied spectrum that can culminate in a condition of viral pneumonia, respiratory failure, involvement of other organs and systems, and death can be the outcome. The declared global pandemic, which affected 84233579 people and caused 1843293 deaths by the beginning of 2021, remains a challenge for public health, given its heterogeneity in the clinical conditions and the number of people affected[68].

The transmission of SARS-CoV-2 occurs directly between an infected and a susceptible individual by the inoculation of droplets expelled from the respiratory tract or saliva in the nasal, oral or conjunctiva mucosa during speech, coughing or sneezing. Transmission can also be indirect by sharing contaminated objects or surfaces or by aerosols[69]. The incubation time varies from 2 to 14 d, with an average of 5 d, in symptomatic cases. In the mild disease, the upper respiratory tract is usually affected, with the occurrence of fever, fatigue, myalgia, cough, odynophagia, nasal discharge and sneezing. There is a possibility of gastrointestinal symptoms, due to the presence of hemagglutinin esterase protein, with abdominal pain, vomiting and diarrhea. There are also many records of anosmia and ageusia as important symptoms in the diagnosis of suspected COVID-19[69].

In moderate disease, there is involvement of the lower respiratory tract, characterized by viral pneumonia, with fever and cough, and the pulmonary involvement is visualized by radiography or chest tomography. The presence or absence of hypoxia determines the severity criterion and the assistance to be provided. In cases where saturation is less than 92%, hospital monitoring with non-invasive oxygen supplementation is required. In some situations, failure to resolve hypoxia requires orotracheal intubation and monitoring in an intensive care unit[70].

In the initial stage of infection, SARS-CoV-2 binds to target cells in the nasal tract, bronchial epithelial cells, or pneumocytes, by tying the spike (S) protein to the angiotensin converting enzyme-2 (ACE-2) receptor. The transmembrane serine protease type 2 (TMPRSS2), present in the host cell, causes the viral withdrawal through the cleavage of ACE-2 and activation of the SARS-CoV-2 protein S, which mediates the entry of the coronavirus into the host cells. ACE-2 and TMPRSS2 are present mainly in alveolar cells. After the viral adsorption, viral replication is activated. This process damages the host cell and causes proptosis due to damage caused by ATP, nucleic acids and ASC oligomers. The neighboring cells of the endothelium recognize cellular changes, initiating the signaling of the inflammatory process. The presence of alveolar macrophages and endothelial cells that trigger the generation of pro-inflammatory cytokines and chemokines (IL-6, interferon gamma (INTg)-induced protein 10, macrophage inflammatory protein-1 alpha (MIP-1α), MIP-1β, and mitochondrial pyruvate carrier-1), which attract macrophages, T cells, and INTγ creating a pro inflammatory feedback loop. In the production of neutralizing antibodies, the infection resolves; but there may be production of non-neutralizing antibodies generating the cytokine storm. This inadequate and exacerbated inflammatory response allows viremia to cause sepsis and shock, coagulation disorders, with damage to other target cells of vital organs such as the brain, heart and kidneys[70]. This inflammatory dysregulation, the main damage resulting from COVID-19, has been more common in patients with comorbidities and risk factors, probably due to low immunogenicity. In addition, diabetic and hypertensive patients have more ACE-2 receptors, as well as a greater number of these receptors in adipocytes due to the fact

that obesity generates a low-grade inflammatory process[71-73] (Figure 1).

The development of severe acute respiratory syndrome is seen more frequently in elderly patients with COVID-19 pneumonia and with underlying chronic diseases, such as systemic arterial hypertension, cardiovascular diseases, type 2 diabetes, chronic obstructive pulmonary disease or neoplasms[73]. All age groups are affected by COVID-19; however, individuals above 60 years of age present with the worst conditions, leading towards a death outcome[74].

---

## DM, OBESITY, AND COVID-19

---

Infection by COVID-19 has highly impacted daily clinical practice, since practically all organs and biological systems suffer from this new infection, either because the virus directly affects specific tissues or because of indirect effects[75]. Due to the high prevalence of diabetes and obesity worldwide, it is important to understand aspects of coronavirus infection and the impact of multiple epidemics co-existence on health systems, as pre-existing conditions contribute to a worse prognosis, due to the immune system impairment[75].

---

## DIABETES AND COVID-19

---

During previous SARS pandemics, the rate of admission to the intensive care units (ICUs), the need for mechanical ventilation and the mortality of diabetic patients was 3.1 times higher than that of non-diabetic patients[76]. During the 2012 (MERS-CoV) outbreak, diabetes was prevalent in almost 50% of the population and the odds ratio (OR) for severe or critical MERS-CoV ranged from 7.2 to 15.7 in the cohort of individuals with DM compared to the general population[76].

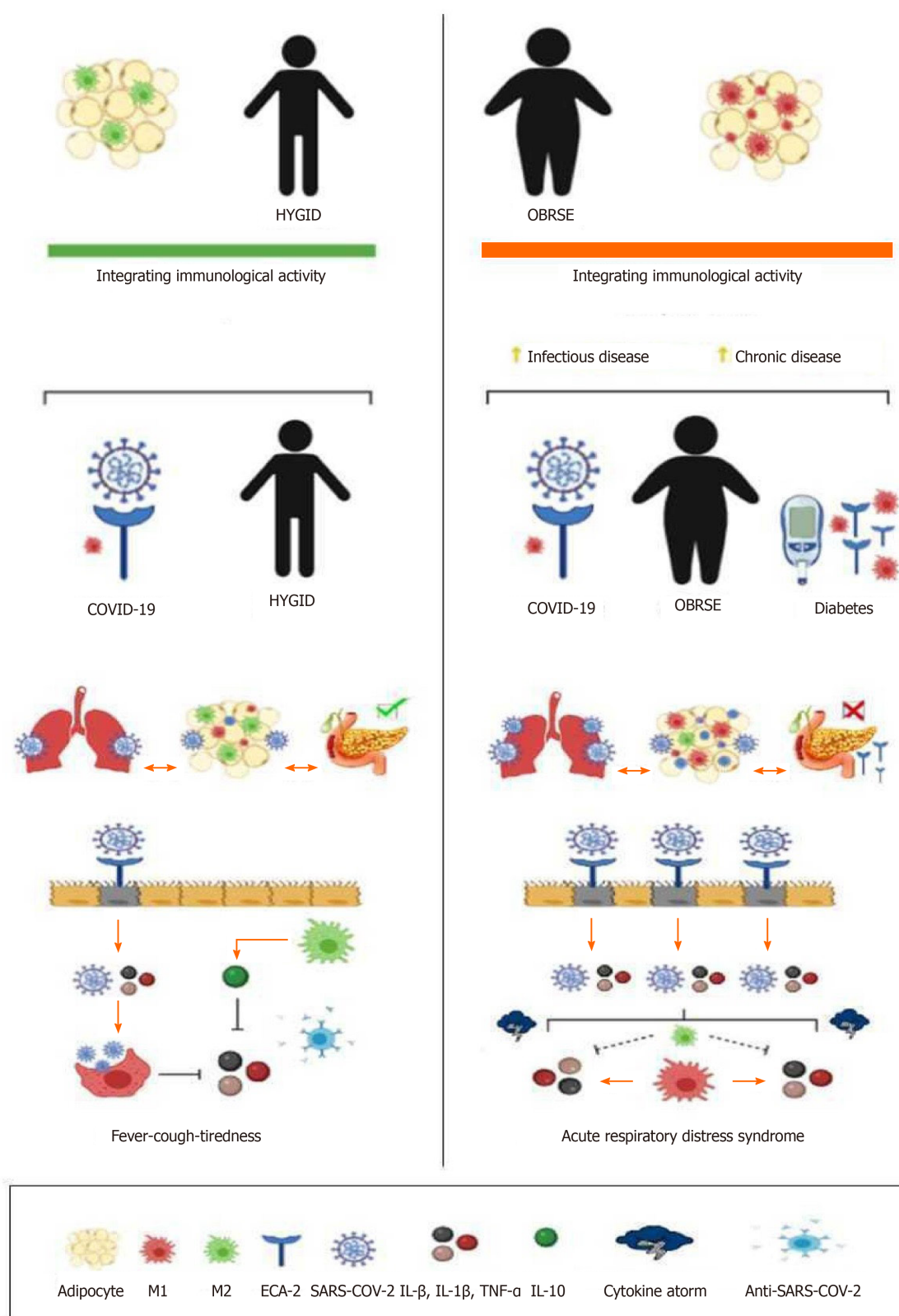
Recent studies have also shown a relationship between SARS-CoV-2 infection and the presence of diabetes: 34% to 58% COVID-19 patients had diabetes. Other reports suggest that patients with both COVID-19 and diabetes are more often associated with severe or critical cases. In a study with 138 patients with COVID-19, Wang *et al*[77] observed that 72% of patients with comorbidities, including diabetes, required admission to the ICU, compared with 37% of patients without comorbidities. Wu *et al* [78] evaluated 201 patients with COVID-19 and found that diabetic patients had a risk ratio of 2.34 (95% confidence interval [CI]: 1.35 to 4.05;  $P = 0.002$ ) for acute respiratory syndrome. Diabetic patients usually exhibit a worse infection prognosis, with higher sepsis morbidity and mortality compared to the general population[79].

In addition to the presence of diabetes, the individual's hyperglycemic state has been associated with greater severity of COVID-19 and unfavorable outcome in infected patients, especially when micro and macrovascular complications are present [80]. In addition, SARS-CoV-2 infection has been associated to the onset of hyperglycemia, and the need to use insulin, especially in patients requiring ICU admission[81]. Diagnosis of diabetes can occur on admission and in a frequency similar to that of already known cases (about 15%), and can be a greater risk factor for severity of COVID-19 than pre-existing disease[77-81].

In addition, some medications used to treat COVID-19 patients can alter glycemic homeostasis in different ways, suggesting that infected patients are more susceptible to the worsening of the disease. However, there is still insufficient evidence to state that COVID-19 can also accelerate the onset of diabetes complications in diabetic patients who have been infected[80].

Adequate glycemic control is essential to reduce the severity of the clinical condition of infected patients. Considering poor control when glycated hemoglobin (HbA1c) levels were greater than 8%, a study of 80 patients with type II diabetes in India showed that patients with worse glycemic control had: Severe clinical manifestation of COVID-19, such as cough and shortage of breath, more severe inflammatory responses with high serum levels contents of fibrin degradation products, indicating hypercoagulability, D-dimer and interleukin IL-6, in addition to greater pulmonary impairment found in radiographic findings. Still, those patients needed more frequently intensive treatment, non-invasive ventilation, had longer hospitalization and higher mortality[82]. Such conditions had already been described in patients with diabetes during the Influenza pandemic in 2009. HbA1c levels > 9% were associated with a 60% increased risk of hospitalization and pneumonia-related severity during infection[82].





**Figure 1 Coronavirus disease 2019 physiological process in healthy and obese people.** COVID-19: Coronavirus disease-2019; IL: Interleukin; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TNF- $\alpha$ : Tumor necrosis factor-alpha.

Thus, patients with diabetes are usually affected by a low-grade chronic inflammation, which facilitates cytokine storms, contributing to the serious results of COVID-19 and possible death. Still, one of the main risk factors in diabetic patients with severe condition is obesity[83].



## OBESITY AND COVID-19

Considering that obese individuals also have a pre-defined pro-inflammatory medium, it is possible that COVID-19 may further exacerbate the inflammation, exposing them to higher levels of circulating inflammatory molecules compared to non-obese individuals[84]. In addition, it has been proven that the lung function is affected in several ways, in connection with the mechanical and inflammatory aspects, making obese people more likely to suffer from respiratory problems, symptoms and progression to respiratory failure[85].

In the current pandemic, there are higher rates of obesity and severe obesity in patients with COVID-19[86]. In the United States, among patients with COVID-19 under 60 years of age, those with 30 to 35 kg/m<sup>2</sup> body mass index (BMI) and those with BMI above 35 kg/m<sup>2</sup> were 1.8 and 3.6 times more likely to be admitted to the ICU, respectively, compared to those with adequate BMI[87]. In the United Kingdom, 38% of patients with COVID-19 admitted to the ICU were obese[88]. In China, where the first cases of COVID-19 occurred, investigations have shown that obesity increases approximately three times the risk of severe manifestation of the disease, with a consequent longer hospital stay[89].

The causal relationship between obesity and diabetes was suggested in 1965 in a longitudinal study carried out by the National Institute of Health in Arizona, where the risk of developing diabetes was 40-fold in obese women compared to those who remained slim[90]. From the first epidemiological reports, obesity and diabetes were identified as risk comorbidities for the development of more severe clinical forms of SARS-CoV-2 infection, since the cytokine storm can be amplified, leading to multisystemic failure and death[91,92].

Although the connection between these comorbidities is still not fully understood, in an obese and diabetic condition, the adipose tissue is impaired and may be directly or indirectly involved in interactions with SARS-CoV-2 at different levels, since the virus can change the fate of the adipocytes in adipose tissue or adipocyte-like cells in the lungs, which can positively regulate the genes associated with lipid metabolism in lung epithelial cells and the genes involved in leptin regulation[93,94].

Increased release of non-steroidal fatty acids is seen in both obesity and DM2 and both are associated with insulin resistance[95]. Insulin promotes glucose uptake and the increase of adipocytes, causing activation and recruitment of resident macrophages in adipose tissue and resulting in the release of pro-inflammatory cytokines and chemokines such as IL-1, IL-6, IL-8, monocyte-1 chemoattractive protein, and CRP[96,97]. The serum levels of IL-6 and TNF- $\alpha$ , therefore, are independent and significant predictors of the severity of the disease and deaths of COVID-19 patients[97]. These factors can increase the probability of developing endothelial dysfunction and platelet aggregation, causing the formation of occlusive thrombus in the heart and lungs in patients with COVID-19[98].

A tentative explanation for this relationship may be the fact that the expression of ACE-2, the functional receptor for SARS-CoV, is positively regulated in patients with obesity and diabetes[94], in addition to the deregulation of lipid synthesis and clearance, which can initiate or worsen lung inflammation and injury[93]. The presence of ACE-2 may allow SARS-CoV-2 to promote the adipocytes, which makes adipose tissue an important viral reservoir[94]. Consequently, adipose tissue can also be infected by SARS-CoV-2 and allow dissemination to other organs[99].

Cytokine production is a key element of the inflammatory and immunological response to viral infection, since after the host is released, the virus is first recognized by the innate immune system through molecular pattern recognition receptors, such as the receptors of C-type lectin and the NOD receptor of the toll-like receptor and exposure to the virus causes the expression of inflammatory factors in several ways, in particular the maturation of dendritic cells and the synthesis of interferons which role is to limit the spread of the virus and to accelerate phagocytosis of viral antigens[100].

In individuals with obesity and diabetes, the low-grade chronic inflammatory state can worsen the inflammatory response to SARS-CoV-2[101-103] infection. The prevalence of viral infection and its clinical consequences are more evident in the elderly and in individuals with obesity and diabetes, since this group exhibits weak immune activity and increased oxidative stress due to the decline in endogenous antioxidants[104].

Obesity and DM have been considered critical risk factors for different infections, post-infection complications and mortality from serious infections. Both have deleterious effects on the host's immunity, mainly increasing the risk of infectious susceptibility and disease severity[105].

Studies have shown obesity and type 2 diabetes as comorbidities in the development of SARS into COVID-19, in addition to being associated with severe forms of COVID-19 in all ethnic groups[105,106]. In a study carried out in the United States with 5700 hospitalized patients with severe forms of COVID-19, the authors observed that many of them presented with obesity (41%) or type 2 diabetes (33%). A retrospective study of 1158 hospitalized patients in Kuwait revealed that patients with morbid obesity and type 2 diabetes were much more likely to be admitted to the ICU, showing an OR of 5.18 and 9.38, respectively[106].

The WHO has been publishing a series of documents and guidelines to facilitate the understanding of the population with diabetes and obesity, and to direct them to self-care in times of quarantine and social isolation[107]. The recommendations continue to be related to health care in general: Healthy eating, practice physical activity, monitor and control glycemic rates and indexes, take medications correctly and reduce the risk of contagion[107].

When it comes to diseases that are largely related directly to modifiable factors, such as obesity and type 2 diabetes, it is important for the population to assume self-care. In this connection, recommendations and access to information on the part of patients, as well as the guidance of health professionals involved in the treatment of those patients is essential. It is necessary that patients become protagonists during treatment, have autonomy and enhance disease control.

## CONCLUSION

The large increase in cases of COVID-19 infection worldwide in people with obesity and DM stands out as a factor of concern for public health. These comorbidities accelerate the inflammatory process and post-infection complications, such as increased production of cytokines, which when associated with the consequences of SARS-CoV-2 infection produce harmful effects, which can lead to death.

SARS-CoV-2 infection can increase the risk of sepsis in people with obesity and DM, especially for sedentary or insufficiently active people, as they have low respiratory and neuromuscular capacity. This risk is further exacerbated by the increase in circulating inflammatory molecules in individuals with obesity, and the diabetogenic effect that drugs for the treatment of SARS-CoV-2 can produce.

Therefore, it is recommended to patients with these comorbidities self-care such as the practice of regular physical activity, balanced diet and, in the case of individuals with DM, glycemic control. Social isolation to avoid contamination, maintenance of a healthy lifestyle, are still the best forms of prevention, as long it is not possible to immunize everyone against SARS-CoV-2. Among post-COVID patients, rehabilitation with follow-up for lifestyle changes is essential to improve quality of life and to avoid hospital readmissions.

## REFERENCES

- 1 **Apovian CM.** Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care* 2016; **22**: s176-s185 [PMID: 27356115]
- 2 **Vedrova IN, Sapelkina IM.** [The effect of various doses of vitamin A on the rat epidermis]. *Vestn Dermatol Venerol* 1968; **42**: 35-38 [PMID: 5741209 DOI: 10.1159/000480525]
- 3 **Bradbury EM.** Conformations and flexibilities of histones and high mobility group (HMG) proteins in chromatin structure and function. *Ciba Found Symp* 1983; **93**: 246-270 [PMID: 6220876 DOI: 10.1002/dmrr.3042]
- 4 **Centers for Disease Control and Prevention.** National diabetes statistics report, 2020. [cited 4 May 2021]. Available from: <https://www.cdc.gov/diabetes/data/statistics-report/index.html>
- 5 **Nazir MA, AlGhamdi L, AlKadi M, AlBejan N, AlRashoudi L, AlHussan M.** The burden of Diabetes, Its Oral Complications and Their Prevention and Management. *Open Access Maced J Med Sci* 2018; **6**: 1545-1553 [PMID: 30159091 DOI: 10.3889/oamjms.2018.294]
- 6 **Takahara T, Saeki M, Nosaka S, Shimoyamada K, Suemitsu I, Nakajima Y, Yoshikawa T, Ishikawa T.** [The use of high concentration ferric ammonium citrate (FAC) solution as a negative bowel contrast agent: application in MR cholangiography]. *Nihon Igaku Hoshasen Gakkai Zasshi* 1995; **55**: 697-699 [PMID: 7478957]
- 7 **Ruigrok TJ, Cella F, Voogd J.** Connections of the lateral reticular nucleus to the lateral vestibular nucleus in the rat. An anterograde tracing study with Phaseolus vulgaris leucoagglutinin. *Eur J Neurosci* 1995; **7**: 1410-1413 [PMID: 7582116 DOI: 10.4239/wjd.v11.i10.400]
- 8 **Favilli S, Iacopetti L, Fradella GA, Righi D, Nuzzaci G.** Observations on changes in intermittent claudication after the administration of creatine phosphate. *Pharmatherapeutica* 1982; **3**: 221-226

- [PMID: 7146037 DOI: 10.34172/hpp.2020.18]
- 9 **The International Diabetes Federation.** Type 2 Diabetes. IDF 2020. [cited 4 May 2021]. Available from: <https://www.idf.org/aboutdiabetes/type-2-diabetes.html>
  - 10 **World Health Organization.** WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. [cited 4 May 2021]. Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-openingremarks-at-the-media-briefing-on-covid-19---11-march-2020>
  - 11 **Chatterjee S, Khunti K, Davies MJ.** Type 2 diabetes. *Lancet* 2017; **389**: 2239-2251 [PMID: 28190580 DOI: 10.1016/S0140-6736(17)30058-2]
  - 12 **Azziz R, Deal CL, Potter HD, Gargosky SE, Rosenfeld RG.** Regulation of extragonadal insulin-like growth factor-binding protein-3 by testosterone in oophorectomized women. *J Clin Endocrinol Metab* 1994; **79**: 1747-1751 [PMID: 7527410 DOI: 10.3389/fendo.2020.582870]
  - 13 **Armanini MP, McMahon SB, Sutherland J, Shelton DL, Phillips HS.** Truncated and catalytic isoforms of trkB are co-expressed in neurons of rat and mouse CNS. *Eur J Neurosci* 1995; **7**: 1403-1409 [PMID: 7582115 DOI: 10.4239/wjd.v11.i10.468]
  - 14 **Bonomo L.** [Antibiotic resistance: a serious danger too ignored]. *Recenti Prog Med* 1995; **86**: 47 [PMID: 7754170 DOI: 10.4239/wjd.v11.i12.644]
  - 15 **World Health Organization.** Global strategy on diet, physical activity and health: childhood overweight and obesity. [cited 4 May 2021]. Available from: [https://www.who.int/dietphysicalactivity/strategy/eb11344/strategy\\_english\\_web.pdf](https://www.who.int/dietphysicalactivity/strategy/eb11344/strategy_english_web.pdf)
  - 16 **Hill PJ.** Reversals in reading: are they abnormal? *Am J Optom Physiol Opt* 1980; **57**: 162-165 [PMID: 7386577 DOI: 10.1371/journal.pmed.1003198]
  - 17 **Malone JL, Hansen BC.** Does obesity cause type 2 diabetes mellitus (T2DM)? *Pediatr Diabetes* 2019; **20**: 5-9 [PMID: 30311716 DOI: 10.1111/pedi.12787]
  - 18 **Kunishima S, Mizuno R, Fujishiro N, Ohno R.** [A case of chronic neutrophilic leukemia with abnormal karyotype]. *Rinsho Byori* 1989; **37**: 943-947 [PMID: 2585758 DOI: 10.1210/jc.2008-1585]
  - 19 **Harrington MG, McGeorge AP, Ballantyne JP, Beastall G.** A prospective survey for insulinomas in a neurology department. *Lancet* 1983; **1**: 1094-1095 [PMID: 6133118 DOI: 10.1007/s11325-017-1599-x]
  - 20 **Chooi YC, Ding C, Magkos F.** The epidemiology of obesity. *Metabolism* 2019; **92**: 6-10 [PMID: 30253139 DOI: 10.1016/j.metabol.2018.09.005]
  - 21 **Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL.** Trends in Obesity Among Adults in the United States, 2005 to 2014. *JAMA* 2016; **315**: 2284-2291 [PMID: 27272580 DOI: 10.1001/jama.2016.6458]
  - 22 **Centers for Disease Control and Prevention.** Adult Obesity Prevalence Maps. [cited 4 May 2021]. Available from: <https://www.cdc.gov/obesity/data/prevalence-maps.html>
  - 23 **World Health Organization.** Obesity and overweight. [cited 4 May 2021]. Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
  - 24 **Patton GC, Coffey C, Carlin JB, Sawyer SM, Williams J, Olsson CA, Wake M.** Overweight and obesity between adolescence and young adulthood: a 10-year prospective cohort study. *J Adolesc Health* 2011; **48**: 275-280 [PMID: 21338899 DOI: 10.1016/j.jadohealth.2010.06.019]
  - 25 **Alberti A, Ruiz Reyes MA, De Jesus JA, Rossoni C, Grigollo L, Da Silva BB, Fin G, Baretta E, Comim CM, Nodari RJ Jr.** Identification of obesity in children and teenagers. *Minerva Pediatr* 2021 [PMID: 33438850 DOI: 10.23736/S0026-4946.20.05731-X]
  - 26 **Johnson AR, Milner JJ, Makowski L.** The inflammation highway: metabolism accelerates inflammatory traffic in obesity. *Immunol Rev* 2012; **249**: 218-238 [PMID: 22889225 DOI: 10.1111/j.1600-065X.2012.01151.x]
  - 27 **Barazzoni R, Gortan Cappellari G, Ragni M, Nisoli E.** Insulin resistance in obesity: an overview of fundamental alterations. *Eat Weight Disord* 2018; **23**: 149-157 [PMID: 29397563 DOI: 10.1007/s40519-018-0481-6]
  - 28 **Osborn R, Boland T, DeLuchi S, Beirne OR.** Osteomyelitis of the mandible in a patient with malignant osteopetrosis. *J Oral Med* 1985; **40**: 76-80 [PMID: 3858467 DOI: 10.1016/j.bbi.2013.06.007]
  - 29 **Badimon L, Cubedo J.** Adipose tissue depots and inflammation: effects on plasticity and resident mesenchymal stem cell function. *Cardiovasc Res* 2017; **113**: 1064-1073 [PMID: 28498891 DOI: 10.1093/cvr/cvx096]
  - 30 **Michailidou Z.** Fundamental roles for hypoxia signalling in adipose tissue metabolism and inflammation in obesity. *Curr Opin Physiol* 2019; **12**: 39-43 [DOI: 10.1016/j.cophys.2019.09.005]
  - 31 **Trayhurn P.** Hypoxia and adipose tissue function and dysfunction in obesity. *Physiol Rev* 2013; **93**: 1-21 [PMID: 23303904 DOI: 10.1152/physrev.00017.2012]
  - 32 **Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S.** Adipokines: molecular links between obesity and atherosclerosis. *Am J Physiol Heart Circ Physiol* 2005; **288**: H2031-H2041 [PMID: 15653761 DOI: 10.1152/ajpheart.01058.2004]
  - 33 **Galic S, Oakhill JS, Steinberg GR.** Adipose tissue as an endocrine organ. *Mol Cell Endocrinol* 2010; **316**: 129-139 [PMID: 19723556 DOI: 10.1016/j.mce.2009.08.018]
  - 34 **Maury E, Brichard SM.** Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Mol Cell Endocrinol* 2010; **314**: 1-16 [PMID: 19682539 DOI: 10.1016/j.mce.2009.07.031]

- 35 **Bollinger T**, Gies S, Naujoks J, Feldhoff L, Bollinger A, Solbach W, Rupp J. HIF-1 $\alpha$ - and hypoxia-dependent immune responses in human CD4<sup>+</sup>CD25<sup>high</sup> T cells and T helper 17 cells. *J Leukoc Biol* 2014; **96**: 305-312 [PMID: 24664971 DOI: 10.1189/jlb.3A0813-426RR]
- 36 **Westendorf AM**, Skibbe K, Adamczyk A, Buer J, Geffers R, Hansen W, Pastille E, Jendrosseck V. Hypoxia Enhances Immunosuppression by Inhibiting CD4<sup>+</sup> Effector T Cell Function and Promoting Treg Activity. *Cell Physiol Biochem* 2017; **41**: 1271-1284 [PMID: 28278498 DOI: 10.1159/000464429]
- 37 **Finer N**, Garnett SP, Bruun JM. COVID-19 and obesity. *Clin Obes* 2020; **10**: e12365 [PMID: 32342637 DOI: 10.1111/cob.12365]
- 38 **Patel PS**, Buras ED, Balasubramanyam A. The role of the immune system in obesity and insulin resistance. *J Obes* 2013; **2013**: 616193 [PMID: 23577240 DOI: 10.1155/2013/616193]
- 39 **Castoldi A**, Naffah de Souza C, Câmara NO, Moraes-Vieira PM. The Macrophage Switch in Obesity Development. *Front Immunol* 2015; **6**: 637 [PMID: 26779183 DOI: 10.3389/fimmu.2015.00637]
- 40 **Apovian CM**, Bigornia S, Mott M, Meyers MR, Ulloor J, Gagua M, McDonnell M, Hess D, Joseph L, Gokce N. Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1654-1659 [PMID: 18566296 DOI: 10.1161/ATVBAHA.108.170316]
- 41 **Lopategi A**, López-Vicario C, Alcaraz-Quiles J, García-Alonso V, Rius B, Titos E, Clària J. Role of bioactive lipid mediators in obese adipose tissue inflammation and endocrine dysfunction. *Mol Cell Endocrinol* 2016; **419**: 44-59 [PMID: 26433072 DOI: 10.1016/j.mce.2015.09.033]
- 42 **Iyer A**, Fairlie DP, Prins JB, Hammock BD, Brown L. Inflammatory lipid mediators in adipocyte function and obesity. *Nat Rev Endocrinol* 2010; **6**: 71-82 [PMID: 20098448 DOI: 10.1038/nrendo.2009.264]
- 43 **Unamuno X**, Gómez-Ambrosi J, Rodríguez A, Becerril S, Frühbeck G, Catalán V. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Invest* 2018; **48**: 1-26 [PMID: 29995306 DOI: 10.1111/eci.12997]
- 44 **de Mello AH**, Schraiber RB, Goldim MPS, Mathias K, Mendes C, Corrêa MEAB, Gomes ML, Silveira PCL, Schuck PF, Petronilho F, Rezin GT. Omega-3 polyunsaturated fatty acids have beneficial effects on visceral fat in diet-induced obesity model. *Biochem Cell Biol* 2019; **97**: 693-701 [PMID: 31774300 DOI: 10.1139/bcb-2018-0361]
- 45 **Cancello R**, Clément K. Is obesity an inflammatory illness? *BJOG* 2006; **113**: 1141-1147 [PMID: 16903845 DOI: 10.1111/j.1471-0528.2006.01004.x]
- 46 **de Mello AH**, Uberti MF, de Farias BX, de Souza NAR, Rezin GT. n-3 PUFA and obesity: from peripheral tissues to the central nervous system. *Br J Nutr* 2018; **119**: 1312-1323 [PMID: 29580307 DOI: 10.1017/S0007114518000429]
- 47 **Moore KJ**, Tabas I. Macrophages in the pathogenesis of atherosclerosis. *Cell* 2011; **145**: 341-355 [PMID: 21529710 DOI: 10.1016/j.cell.2011.04.005]
- 48 **Ouchi N**, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011; **11**: 85-97 [PMID: 21252989 DOI: 10.1038/nri2921]
- 49 **Petronilho F**, Giustina AD, Nascimento DZ, Zarbato GF, Vieira AA, Florentino D, Danielski LG, Goldim MP, Rezin GT, Barichello T. Obesity Exacerbates Sepsis-Induced Oxidative Damage in Organs. *Inflammation* 2016; **39**: 2062-2071 [PMID: 27645696 DOI: 10.1007/s10753-016-0444-x]
- 50 **Cai D**. Neuroinflammation and neurodegeneration in overnutrition-induced diseases. *Trends Endocrinol Metab* 2013; **24**: 40-47 [PMID: 23265946 DOI: 10.1016/j.tem.2012.11.003]
- 51 **Shefer G**, Marcus Y, Stern N. Is obesity a brain disease? *Neurosci Biobehav Rev* 2013; **37**: 2489-2503 [PMID: 23911925 DOI: 10.1016/j.neubiorev.2013.07.015]
- 52 **Mazon JN**, de Mello AH, Ferreira GK, Rezin GT. The impact of obesity on neurodegenerative diseases. *Life Sci* 2017; **182**: 22-28 [PMID: 28583368 DOI: 10.1016/j.lfs.2017.06.002]
- 53 **de Bona Schraiber R**, de Mello AH, Garcez ML, de Bem Silveira G, Zacaron RP, de Souza Goldim MP, Budni J, Silveira PCL, Petronilho F, Ferreira GK, Rezin GT. Diet-induced obesity causes hypothalamic neurochemistry alterations in Swiss mice. *Metab Brain Dis* 2019; **34**: 565-573 [PMID: 30635861 DOI: 10.1007/s11011-018-0337-9]
- 54 **Ebrahimi M**, Heidari-Bakavoli AR, Shoeibi S, Mirhafez SR, Moohebaty M, Esmaily H, Ghazavi H, Saberi Karimian M, Parizadeh SM, Mohammadi M, Mohaddes Ardabili H, Ferns GA, Ghayour-Mobarhan M. Association of Serum hs-CRP Levels With the Presence of Obesity, Diabetes Mellitus, and Other Cardiovascular Risk Factors. *J Clin Lab Anal* 2016; **30**: 672-676 [PMID: 26857805 DOI: 10.1002/jcla.21920]
- 55 **American Diabetes Association**. . (2) Classification and diagnosis of diabetes. *Diabetes Care* 2015; **38** Suppl: S8-S16 [PMID: 25537714 DOI: 10.2337/dc15-S005]
- 56 **Saeedi P**, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9<sup>th</sup> edition. *Diabetes Res Clin Pract* 2019; **157**: 107843 [PMID: 31518657 DOI: 10.1016/j.diabres.2019.107843]
- 57 **Flor LS**, Campos MR. The prevalence of diabetes mellitus and its associated factors in the Brazilian adult population: evidence from a population-based survey. *Rev Bras Epidemiol* 2017; **20**: 16-29 [PMID: 28513791 DOI: 10.1590/1980-5497201700010002]
- 58 **Iser BP**, Malta DC, Duncan BB, de Moura L, Vigo A, Schmidt MI. Prevalence, correlates, and



- description of self-reported diabetes in brazilian capitals - results from a telephone survey. *PLoS One* 2014; **9**: e108044 [PMID: 25255096 DOI: 10.1371/journal.pone.0108044]
- 59 **Malta DC**, Duncan BB, Schmidt MI, Machado IE, Silva AGD, Bernal RTI, Pereira CA, Damacena GN, Stopa SR, Rosenfeld LG, Szwarcwald CL. Prevalence of diabetes mellitus as determined by glycated hemoglobin in the Brazilian adult population, National Health Survey. *Rev Bras Epidemiol* 2019; **22**Suppl 02: E190006.SUPL. 2 [PMID: 31596377 DOI: 10.1590/1980-549720190006.supl.2]
  - 60 **GBD 2015 Mortality and Causes of Death Collaborators**. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1459-1544 [PMID: 27733281 DOI: 10.1016/S0140-6736(16)31012-1]
  - 61 **Rao S**, Lau A, So HC. Exploring Diseases/Traits and Blood Proteins Causally Related to Expression of ACE2, the Putative Receptor of SARS-CoV-2: A Mendelian Randomization Analysis Highlights Tentative Relevance of Diabetes-Related Traits. *Diabetes Care* 2020; **43**: 1416-1426 [PMID: 32430459 DOI: 10.2337/dc20-0643]
  - 62 **Zhou Y**, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). *Diabetes Metab Res Rev* 2021; **37**: e3377 [PMID: 32588943 DOI: 10.1002/dmrr.3377]
  - 63 **Guo W**, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020; e3319 [PMID: 32233013 DOI: 10.1002/dmrr.3319]
  - 64 **Yan Y**, Yang Y, Wang F, Ren H, Zhang S, Shi X, Yu X, Dong K. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. *BMJ Open Diabetes Res Care* 2020; **8** [PMID: 32345579 DOI: 10.1136/bmjdr-2020-001343]
  - 65 **Petrosillo N**, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect* 2020; **26**: 729-734 [PMID: 32234451 DOI: 10.1016/j.cmi.2020.03.026]
  - 66 **Fung M**, Otani I, Pham M, Babik J. Zoonotic coronavirus epidemics: Severe acute respiratory syndrome, Middle East respiratory syndrome, and coronavirus disease 2019. *Ann Allergy Asthma Immunol* 2021; **126**: 321-337 [PMID: 33310180 DOI: 10.1016/j.anaai.2020.11.021]
  - 67 **Mariano G**, Farthing RJ, Lale-Farjat SLM, Bergeron JRC. Structural Characterization of SARS-CoV-2: Where We Are, and Where We Need to Be. *Front Mol Biosci* 2020; **7**: 605236 [PMID: 33392262 DOI: 10.3389/fmolb.2020.605236]
  - 68 **World Health Organization**. Coronavirus disease (COVID-19) pandemic. Dashboard in 5 January 2021. [cited 4 May 2021]. Available from: <https://covid19.who.int/>
  - 69 **Iser BPM**, Sliva I, Raymundo VT, Poleto MB, Schuelter-Trevisol F, Bobinski F. Suspected COVID-19 case definition: a narrative review of the most frequent signs and symptoms among confirmed cases. *Epidemiol Serv Saude* 2020; **29**: e2020233 [PMID: 32609142 DOI: 10.5123/S1679-49742020000300018]
  - 70 **Yuki K**, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol* 2020; **215**: 108427 [PMID: 32325252 DOI: 10.1016/j.clim.2020.108427]
  - 71 **World Health Organization**. Emergencies. Diseases. Coronavirus disease 2019 (COVID-2019) pandemic. [cited 4 May 2021]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
  - 72 **Song Z**, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C. From SARS to MERS, Thrusting Coronaviruses into the Spotlight. *Viruses* 2019; **11** [PMID: 30646565 DOI: 10.3390/v11010059]
  - 73 **Grasselli G**, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; **323**: 1574-1581 [PMID: 32250385 DOI: 10.1001/jama.2020.5394]
  - 74 **Schuelter-Trevisol F**, Raimundo LJ, Soccas HD, Antunes AF, Mohr RLD, Marcon CEM, Trevisol DJ. Assessment of patients with Covid-19 hospitalized in southern Santa Catarina. *Rev Soc Bras Med Trop* 2020; **53**: e20200579 [PMID: 33263690 DOI: 10.1590/0037-8682-0579-2020]
  - 75 **Marazuela M**, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. *Rev Endocr Metab Disord* 2020; **21**: 495-507 [PMID: 32643004 DOI: 10.1007/s11154-020-09569-2]
  - 76 **Booth CM**, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, Walmsley SL, Mazzulli T, Avendano M, Derkach P, Ephtimios IE, Kitai I, Mederski BD, Shadowitz SB, Gold WL, Hawryluck LA, Rea E, Chenkin JS, Cescon DW, Poutanen SM, Detsky AS. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003; **289**: 2801-2809 [PMID: 12734147 DOI: 10.1001/jama.289.21.JOC30885]
  - 77 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]
  - 78 **Wu C**, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk



- Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; **180**: 934-943 [PMID: 32167524 DOI: 10.1001/jamainternmed.2020.0994]
- 79 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
  - 80 **Lim S**, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol* 2021; **17**: 11-30 [PMID: 33188364 DOI: 10.1038/s41574-020-00435-4]
  - 81 **Hussain A**, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. *Diabetes Res Clin Pract* 2020; **162**: 108142 [PMID: 32278764 DOI: 10.1016/j.diabres.2020.108142]
  - 82 **Bhandari S**, Rankawat G, Singh A, Gupta V, Kakkar S. Impact of glycemic control in diabetes mellitus on management of COVID-19 infection. *Int J Diabetes Dev Ctries* 2020; **1**-6 [PMID: 32905072 DOI: 10.1007/s13410-020-00868-7]
  - 83 **Bhaskar S**, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, Rajagopal S, Pai AR, Kuttu S. Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. *Front Immunol* 2020; **11**: 1648 [PMID: 32754159 DOI: 10.3389/fimmu.2020.01648]
  - 84 **Mraz M**, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade inflammation. *J Endocrinol* 2014; **222**: R113-R127 [PMID: 25006217 DOI: 10.1530/JOE-14-0283]
  - 85 **Dixon AE**, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med* 2018; **12**: 755-767 [PMID: 30056777 DOI: 10.1080/17476348.2018.1506331]
  - 86 **Al-Sabah S**, Al-Haddad M, Al-Youha S, Jamal M, Almazeedi S. COVID-19: Impact of obesity and diabetes on disease severity. *Clin Obes* 2020; **10**: 1-6 [PMID: 33079448 DOI: 10.1111/cob.12414]
  - 87 **Lighter J**, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. *Clin Infect Dis* 2020; **71**: 896-897 [PMID: 32271368 DOI: 10.1093/cid/ciaa415]
  - 88 **Thomson RJ**, Hunter J, Dutton J, Schneider J, Khosravi M, Casement A, Dhadwal K, Martin D. Clinical characteristics and outcomes of critically ill patients with COVID-19 admitted to an intensive care unit in London: A prospective observational cohort study. *PLoS One* 2020; **15**: e0243710 [PMID: 33320904 DOI: 10.1371/journal.pone.0243710]
  - 89 **Gao F**, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Chen YP, Targher G, Byrne CD, George J, Zheng MH. Obesity Is a Risk Factor for Greater COVID-19 Severity. *Diabetes Care* 2020; **43**: e72-e74 [PMID: 32409499 DOI: 10.2337/dc20-0682]
  - 90 **Colditz GA**, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990; **132**: 501-513 [PMID: 2389754 DOI: 10.1093/oxfordjournals.aje.a115686]
  - 91 **Fernández García L**, Puentes Gutiérrez AB, García Bascones M. [Relationship between obesity, diabetes and ICU admission in COVID-19 patients]. *Med Clin (Barc)* 2020; **155**: 314-315 [PMID: 32651070 DOI: 10.1016/j.medcli.2020.06.009]
  - 92 **Smati S**, Tramunt B, Wargny M, Caussy C, Gaborit B, Vatie C, Vergès B, Ancelle D, Amadou C, Bachir LA, Bourron O, Coffin-Boutreux C, Barraud S, Dorange A, Fremy B, Gautier JF, Germain N, Larger E, Laugier-Robiolle S, Meyer L, Monier A, Moura I, Potier L, Sabbah N, Seret-Bégué D, Winiszewski P, Pichelin M, Saulnier PJ, Hadjadj S, Cariou B, Gourdy P; CORONADO investigators. Relationship between obesity and severe COVID-19 outcomes in patients with type 2 diabetes: Results from the CORONADO study. *Diabetes Obes Metab* 2021; **23**: 391-403 [PMID: 33051976 DOI: 10.1111/dom.14228]
  - 93 **Drucker DJ**. Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications. *Endocr Rev* 2020; **41** [PMID: 32294179 DOI: 10.1210/edrev/bnaa011]
  - 94 **Kruglikov IL**, Scherer PE. The Role of Adipocytes and Adipocyte-Like Cells in the Severity of COVID-19 Infections. *Obesity (Silver Spring)* 2020; **28**: 1187-1190 [PMID: 32339391 DOI: 10.1002/oby.22856]
  - 95 **Guilherme A**, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat Rev Mol Cell Biol* 2008; **9**: 367-377 [PMID: 18401346 DOI: 10.1038/nrm2391]
  - 96 **Gonzalez LL**, Garrie K, Turner MD. Type 2 diabetes - An autoinflammatory disease driven by metabolic stress. *Biochim Biophys Acta Mol Basis Dis* 2018; **1864**: 3805-3823 [PMID: 30251697 DOI: 10.1016/j.bbadis.2018.08.034]
  - 97 **Reddy P**, Lent-Schochet D, Ramakrishnan N, McLaughlin M, Jialal I. Metabolic syndrome is an inflammatory disorder: A conspiracy between adipose tissue and phagocytes. *Clin Chim Acta* 2019; **496**: 35-44 [PMID: 31229566 DOI: 10.1016/j.cca.2019.06.019]
  - 98 **Del Valle DM**, Kim-Schulze S, Hsin-Hui H, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz T, Madduri D, Stock A, Marron T, Xie H, Patel MK, van Oekelen O, Rahman A, Kovatch P, Aberg J, Schadt E, Jagannath S, Mazumdar M, Charney A, Firpo-Betancourt A, Mendu DR, Jhang J, Reich D, Sigel K, Cordon-Cardo C, Feldmann M, Parekh S, Merad M, Gnjatic S. An inflammatory cytokine signature helps predict COVID-19 severity and death. *medRxiv* 2020 [PMID: 32511562 DOI: 10.1101/2020.05.28.20115758]

- 99 **Bourgeois C**, Gorwood J, Barrail-Tran A, Lagathu C, Capeau J, Desjardins D, Le Grand R, Damouche A, Béréziat V, Lambotte O. Specific Biological Features of Adipose Tissue, and Their Impact on HIV Persistence. *Front Microbiol* 2019; **10**: 2837 [PMID: [31921023](#) DOI: [10.3389/fmicb.2019.02837](#)]
- 100 **Yi Y**, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *Int J Biol Sci* 2020; **16**: 1753-1766 [PMID: [3226295](#) DOI: [10.7150/ijbs.45134](#)]
- 101 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: [32109013](#) DOI: [10.1056/NEJMoa2002032](#)]
- 102 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: [32171076](#) DOI: [10.1016/S0140-6736\(20\)30566-3](#)]
- 103 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: [32192578](#) DOI: [10.1016/S0140-6736\(20\)30628-0](#)]
- 104 **Cardinali DP**, Hardeland R. Inflammaging, Metabolic Syndrome and Melatonin: A Call for Treatment Studies. *Neuroendocrinology* 2017; **104**: 382-397 [PMID: [27165273](#) DOI: [10.1159/000446543](#)]
- 105 **Frydrych LM**, Bian G, O'Lone DE, Ward PA, Delano MJ. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. *J Leukoc Biol* 2018; **104**: 525-534 [PMID: [30066958](#) DOI: [10.1002/JLB.5VMR0118-021RR](#)]
- 106 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: [32320003](#) DOI: [10.1001/jama.2020.6775](#)]
- 107 **World Health Organization**. Physical inactivity a leading cause of disease and disability, warns WHO. 2020. COVID-19: vulnerable and high risk groups. 2020. [cited 4 May 2021]. Available from: <https://www.who.int/westernpacific/emergencies/covid-19/information/high-risk-groups>



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

