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MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS

42 Votsi Street, Patras 26221, Greece

Tel: +30 2610 279579, Fax: +30 2610 220518

email: iede_pel@yahoo.gr

Publisher

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Editor-in-Chief

Christos Triantos

email: achaiki.iatriki@gmail.com

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CONTENTS

Dear colleagues,

In the current issue, you will find emerging new data on the novel coronavirus SARS-CoV-2 and COVID-19. The editorial by Sirokosta et al. describes the association of diabetes mellitus type 2 with COVID-19, concluding that infection leads to worse outcome in these patients. Moreover, the review by Leonidou et al. provides an overview of the information currently available in the literature and the ongoing guidelines concerning the main treatment options of COVID-19 and briefly reports special considerations for children.

In addition, this issue includes the editorial by Matheakakis et al. which discusses the emerging role of extracellular vesicles derived from mesenchymal stem/stromal cells as appealing candidates for various therapeutic applications including tissue repair and regeneration, treatment of autoimmune disorders and cancer. The editorial by Plachouri et al. focuses on the management of biologics' administration in chronic plaque psoriasis and emphasizes on the fact that further studies are necessary to assess the use of these agents in special patient populations. The last editorial by Papasotiriou et al. addresses the impact of blockade of renin angiotensin system in the acute kidney injury and discusses the related risks and benefits.

Moreover, this issue includes two reviews. The first review, by Konstantopoulou et al. critically appraises the recent findings regarding the role of psychotherapeutic interventions in the management of a wide range of chronic diseases. The review by Iliopoulos et al. presents the current medical literature on the management of obstructive colon cancer and illustrates the guidelines and treatment proposals in palliative and curative settings, as well as the individualized decision algorithm in order to determine the optimal treatment for the patient.

Two original studies are also included in this third issue. The original article by Mantzoukis et al. determines the incidence of mitral annular calcification in patients with chronic end-stage renal disease undergoing hemodialysis and detects any correlations with demographic factors, comorbidities and characteristics of the dialysis process. Another original study is also included in this issue, by Mantzoukis et al., which demonstrates the possible correlation between glycosylated hemoglobin levels and the severity of coronary heart disease as expressed by the SYNTAX score.

Dear colleagues, we are continuing the fight against the virus. Many wishes on behalf of our editorial team.

C. Triantos
Assistant Professor in Internal Medicine
and Gastroenterology Faculty of Medicine,
School of Health Sciences, University of Patras
Editor-in-Chief of the journal "ACHAIKI IATRIKI"

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Extracellular vesicles derived from Mesenchymal Stem/Stromal cells: Emerging therapeutic perspectives

Angelos Matheakakis[1,2], Andria Vryoni[1,2], Charalampos Pontikoglou[1]

Mesenchymal Stem/Stromal Cells (MSCs) are multipotent stem cells capable of differentiating into various mesodermal lineages, including adipose, bone, cartilage, muscle and tendon [1]. They are found in various human tissues such as bone marrow, umbilical cord blood, adipose tissue, lung parenchyma, placenta, peripheral blood and even dental pulp [1]. MSCs constitute one of the principal components of tissue microenvironment, exhibiting a key role in maintaining homeostasis [2].

Because of the ease of isolation, plasticity, homing to injured tissues and their immunosuppressive and immunomodulatory properties, MSCs have emerged as appealing candidates for various therapeutic applications including tissue repair and regeneration, treatment of autoimmune disorders and cancer [3]. There is a large body of evidence to suggest that MSCs exert their therapeutic effects mostly by the release of various agents rather than through cell to cell interactions [4]. Their secretome is rich of growth factors, cytokines, chemokines and extracellular vesicles (EVs) [5]. The latter are small membrane-coated particles secreted by cells containing mRNA, miRNA, DNA, proteins and lipids [4]. EVs have been shown to play a pivotal role in cell-to-cell crosstalk, mediating both local and distant communication [4]. EVs can be classified into three major subtypes based on their size and biogenesis: apoptotic bodies, microvesicles and exosomes [4]. Apoptotic bodies, with a diameter ranging from 50nm to 2 μm, are produced during programmed cell-death, via the plasma membrane blebbing. Microvesicles (MVs) with a size ranging from 150 nm to 1μm are formed through the outward budding of the cell membrane. Finally, exosomes, which are the smallest nanoparticles with a diameter from 40 to 150 nm originate from the invagination of the endosomal membrane to form multi-vesicular-bodies, which then fuse with the cell membrane, thereby resulting to the secretion of exosomes [4]. However, as clearly stated in a recent position paper of the International Society for Extracellular Vesicles, the distinction of the aforementioned EV-subtypes remains challenging [6].

Several methods have been implemented for the isolation of EVs based on their size or protein cargo, including differential centrifugation, filtration, chromatography and immunoaffinity-based technics [5]. Furthermore, various assays have also been proposed for the characterization and quantification of EVs, based either on their physical properties such as dynamic light scattering, flow cytometry, electron microscopy, nanoparticle tracking analysis and tunable resistive pulse-sensing or on their biochemical properties including immunoblotting, immuno-sorbent analysis, ELISA and total protein colorimetric assays [5]. Notably, there is no single optimal EV isolation, characterization or quantification method [5].

The application of MSCs in cell-based therapies reflects their potential to migrate, engraft and interact with other cells, especially in inflamed or damaged tis-

[1]Hemopoiesis Research Laboratory, School of Medicine, University of Crete, Heraklion, Greece
[2]These authors contributed equally to this work

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sues [7]. However, despite the well documented efficacy of MSC therapy in both preclinical and clinical studies, this therapeutic modality has raised concerns regarding potential infusion toxicities, undesired differentiation, genetic instability of the ex vivo expanded cells and tumor formation risk [8]. On the other hand, a rapidly growing body of evidence has clearly demonstrated that MSC-derived EVs retain the biological activity and therapeutic potential of MSCs and can therefore be considered as an alternative cell-free therapeutic approach [8]. Interestingly, EVs may be more attractive that their cellular counterparts due to their favorable safety profile. In fact, they are less immunogenic than MSCs, they are non-replicative and their use bypasses the transfer of cells harboring potentially mutated or damaged DNA. In addition, due to their small size MSC-derived EVs can readily circulate in contrast to MSC which are larger and are often trapped in lung capillary beds, an issue that eventually hampers their systemic administration [5].

In order to achieve an enhanced therapeutic effect, EVs can be modified and loaded with molecules of interest. To this end, parental MSCs can be manipulated in order to produce EVs carrying specific cargoes. Alternatively, naive EVs can be processed and loaded exogenously [4]. In this way, RNA molecules or proteins with therapeutic potential can be packed in EVs and delivered to specific recipient cells thereby providing a targeted treatment approach [4].

The clinical benefits of MSC-EVs as regards to tissue repair, immune modulation and microenvironment crosstalk have been investigated in various disease settings. Thus far, encouraging results have been reported in several animal models and human studies [7].

Within the context of cardiovascular regeneration, MSC-EVs' administration has been shown to mitigate ischemia-reperfusion injury via the modulation of Akt and MAPK8 pathways in mice [9]. Furthermore, through the up-regulation of myocardial LC3B, an autophagy related protein, MSC-EVs reduced infarct size and improved heart function in myocardial ischemia rat models [10]. Additionally, in vivo angiogenesis and blood reperfusion was enhanced by MSC-EVs in a murine limb ischemia experimental setting [11].

Several studies have demonstrated the potential efficacy of MSCs-EVs in the treatment of acute respiratory distress syndrome (ARDS), as reviewed by Shah et al [12]. To this end, administration of MSC-derived EVs enhanced anti-inflammatory cytokine production, decreased apoptosis and reduced inflammatory cells influx in murine models. In addition, MSC-derived EVs exhibited regenerative features as they restored endothelial cells' tight junctions, thereby reducing protein permeability and pulmonary edema [12]. An anti-inflammatory pattern was also demonstrated in a hypoxia-induced pulmonary hypertension model by using umbilical cord MSC- EVs [13]. Furthermore, in an animal model of lower respiratory viral infection, the intratracheal administration of MSC-EVs had beneficial effects, as evidenced by the inhibition of influenza virus shedding and replication as well by the reduction of inflammatory lung lesions [14]. Recently, the therapeutic role of MSCs has been addressed in COVID-19 patients. Results are promising, as suggested by the clinical improvement being attributed to MSC anti-inflammatory effect [15]. In an attempt to overcome the aforementioned limitations of cellular therapy, a clinical study using MSC derived exosomes in patients with SARS-CoV2 infection has been designed (identification No. NCT04276987).

The regenerative potential of MSC-EVs has also been demonstrated in acute kidney injury animal models. In that experimental setting MSC-EVs were effective in improving renal function, decreasing fibrosis and lymphocyte infiltration as well as accelerating the proliferation of tubular cells [4]. Human trials have shown promising results as well. In a phase II/III clinical trial, the administration of MSC-EVs in patients with chronic kidney disease led to improvement of eGFR and decreased albuminuria [16]. This beneficial effect is probably attributed to the modulation of chronic inflammation, as the levels of anti-inflammatory cytokines TGF-β and IL-10 were increased while those of the pro-inflammatory cytokine TNF-α were decreased in patients treated with MSV-EVs [16].

The therapeutic efficacy of MSC-EVs has also been investigated in liver disorders. More precisely, in murine models of acute hepatic failure and liver fibrosis MSC-EVs were able to regulate inflammatory cytokine pathways, reduce liver injury and increase survival [17].

Moreover, in a mouse model of type 1 diabetes, MSC-EVs suppressed Th1 and Th17 response due to their immunomodulatory potential [18]. Based on these findings, a clinical trial evaluating the use of MSC-EVs in patients with type 1 diabetes mellitus has been undertaken (identification No. NCT02138331). The results of this trial are eagerly awaited.

Finally, as exosomes have been shown to bypass the blood-brain barrier, their role in central nervous

system disorders is drawing much attention and this is supported by encouraging preclinical and clinical data. For example, MSC-EVs loaded with miR-124 promoted post-stroke neurovascular recovery in murine models [19]. Based on this, a phase I/II clinical trial is aiming to assess allogenic miR-124 bearing exosomes' regenerative effect after acute ischemic stroke (identification No. NCT03384433).

However, despite the aforementioned studies reporting encouraging results regarding the therapeutic potential of MSC-EVs, there are still important obstacles to overcome so as to optimize their clinical use. To this end, standard validated protocols for the isolation, large scale preparation, characterization and storage of EVs have to be established, along with clearly defined quality control (QC) criteria for cellular therapeutics [7]. This is expected to diminish the heterogeneity of EV batches, which currently results in unpredictable therapeutic efficacy, as documented in some clinical trials. Finally, despite the fact that the few existing preclinical studies have not reported toxicities or harmful effects of MSC-EVs, clinical trials are absolutely required so as to establish a safety profile and determine the optimal dosage before cell-free therapies find their way to the clinics.

In conclusion, due to their size, ability to transport genetic material and potential to mediate immunosuppressive and other MSC paracrine-acting effects, MSC-EVs represent a promising treatment modality in various areas of medicine including inflammatory disorders, regenerative medicine and cancer. Additional research is warranted though, in order to extend existing knowledge on MSC-EVs and pave their way for clinical applications.

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Corresponding author:

Charalampos Pontikoglou
Hemopoiesis Research Laboratory, School of Medicine, University of Crete, Heraklion, Greece
Tel.: +30 2810 394637, Fax: +30 2810 394632,
E-mail: c.pontikoglou@med.uoc.gr

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Biologics in psoriasis: Challenges and management

Kerasia-Maria Plachouri, Sophia Georgiou

Psoriasis is a chronic inflammatory disease, with a complex therapeutic management [1]. Biologics are modern agents that target key molecules in the pathogenetic pathways of psoriasis, with impressive therapeutic results [2]. However, due to their partially immunosuppressive profile, several problems may occur in cases of concomitant conditions, such as infections, past malignancy or pregnancy. This article focuses on the management of biologics' administration in these challenging occasions frequently encountered in standard clinical practice.

BIOLOGICS AND HEPATITIS

Screening for Hepatitis B and C before the initiation of anti-TNF (Tumor Necrosis Factor) therapy is mandatory, with assessment of the following parameters: For hepatitis B, detection of HBsAg, anti-Hbc and anti-HBs, and in case of positive HbsAg or anti-HBc, HBV-DNA measurement (Hepatitis B Virus), while for hepatitis C, detection of anti-HCV (Hepatitis C Virus), and if positive, HCV-RNA measurement [3-4]. These recommendations are based on the fact that TNF-a is known to play an important role in the elimination of HBV from liver cells, therefore a therapy with anti-TNF-a agents could have a modulating effect in the course of HBV-infection with potential reactivation of the infection [3] (Table 1).

HBV vaccination is recommended for the non-infected or not immune patients before treatment initiation [3]. No biologic treatment is allowed in patients with acute HBV [4]. Patients with chronic HBV hepatitis and inactive carriers (HbsAg +, anti-HBc +, HBV-DNA< 2000 IU/ml, normal transferase levels), can receive anti-TNF treatment, as long as antiviral prophylaxis with agents such as entecavir or tenofovir is administered 2-4 weeks before treatment initiation and for a time period of up to 6-12 months after treatment end [3,5]. Occult carriers (HBsAg -, anti-Hbc +, anti-Hbs -, HBV-DNA < 200 IU/mL or undetectable) should be either very closely monitored or prescribed antiviral treatment [5]. Biologic therapy is allowed in patients with a history of HBV infection, however only under careful monitoring [4].

Anti-TNF therapy is relatively safer in patients with chronic HCV compared to patients with chronic HBV [3]. However, even in this case, regular patient follow-up (liver function parameters and HCV-RNA viral load every 3-6 months) is suggested by some dermatologic societies [3-4]. An important aspect that should be taken into consideration when it comes to HCV-positive patients, is the role of the new direct-acting antiviral (DAA) IFN-free therapies, that can result in extremely satisfactory outcomes, with almost complete and long-lasting clearance of HCV-RNA in patients' serum [6]. When it comes to possible interactions of biologics and DAAs, data is extremely limited [6]. However, data on the metabolic and elimination profile of the latter rather advocate against clinically significant pharmacokinetic interactions between these two drug categories [6].

As far as IL-12/23- (Ustekinumab) is concerned, antiviral prophylaxis is suggested for patients with HBsAg +/anti-HBc + before treatment initiation, during treatment, and up to 6 months after therapy discontinuation, always under careful monitoring [3,7]. When it comes to the management of HBsAg -/ anti-HBs-/ anti-HBc + positive patients, they should either undergo very careful monitoring or receive antiviral prophylaxis [5]. This

Department of Dermatology, University of Patras, Greece

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Table 1. *Pathogenetic potential of biologic agents with regard to HBV-reactivation*

Agent	Pathogenetic potential of biologic agents with regard to HBV-reactivation in psoriatic patients	Mechanism of Action
TNF-a-inhibitors	Strong	TNF-a plays an important role in the elimination of HBV from liver cells
IL-12/23-inhibitors	Strong	IL-12 plays a crucial role in modulating an immune response against intracellular pathogens
IL-17-inhibitors	Not sufficient experimental and clinical data in psoriatic patients available, reactivation cannot be ruled out	Th17-involvement in the pathogenesis of viral hepatitis. HBV patients show increased number of intrahepatic IL-17 and circulating IL-17-producing blood mononuclear cells

is based on the fact that IL-12 is known to play a crucial role in modulating an immune response against intracellular pathogens, and therefore it can be assumed that reactivation of HBV could be expected under IL-12/23-inhibitors [3] (Table 1). Clinical data on secukinumab in psoriatic patients with an HBV infection are rather scarce [4] (Table 1). Both HBsAg-positive and HBsAg-negative/HBcAb-positive psoriasis patients as well as HBsAg-negative/HBcAb-positive patients with a positive viral load at baseline are under the risk of virus reactivation while on immunosuppressive treatment, therefore regular monitoring of viral load and antiviral prophylaxis is suggested [5]. Overall, no sufficient data are available concerning HCV and ustekinumab or secukinumab in psoriatic patients, for safe assumptions to be made [3].

BIOLOGICS AND TUBERCULOSIS

Another infectious complication that physicians often have to face when dealing with biologics is tuberculosis. Tuberculosis screening (tuberculin skin test (TST) or interferon gamma release assay (IGRA) and a chest X-ray) before treatment initiation is strongly recommended for such patients [4]. In case of unclear findings, prophylaxis with isoniazid for a period of 9 months is necessary, with initiation of the anti-TNF agent at least 1 month after isoniazid initiation [4].

Given that a small risk of disease activation is also present in patients under ustekinumab, the aforementioned measures concerning tuberculosis screening and prophylaxis apply in this case [8]. When it comes to secukinumab, although no data of latent tuberculosis reactivation have been published so far, screening as well as appropriate prophylaxis –if necessary- are to be recommended [9].

BIOLOGICS AND MALIGNANCY

Malignancy in patients under a biologic treatment is another common therapeutic challenge. According to the British Guidelines for Dermatology concerning the use of biologics in psoriatic patients, a history of malignancy is not considered to be an absolute contraindication [10]. The administration of anti-TNF therapy is, however, advisable to occur after consulting the treating oncologist, and especially if the malignancy was diagnosed and treated < 5 years prior to therapy initiation [10]. Some societies tend to favorize ustekinumab or secukinumab over TNF-inhibitors in patients with a history of malignancy [4], while others do not differentiate between these two categories, especially if the diagnosis and treatment of a past solid malignancy took place >5 years prior to the planned biologic treatment [11].

When it comes to the use of ustekinumab or secukinumab in patients with a history of malignancy, published data are too limited to allow for safe assumptions [12]. Preliminary data seem to indicate that the incidence of recurring malignancy for both agents is comparable to that of the general population [13-14]; however clinical studies in larger patient cohorts as well as meta-analyses of long-term real-life data are necessary to adequately estimate the malignancy-associated safety of these agents [15].

BIOLOGICS AND HIV

A therapeutic dilemma that physicians commonly have to face is the administration of biologics in HIV-infected (Human Immunodeficiency Virus) patients. The administration of biologics in HIV-infected patients poses several challenges, since these patients are already under virus-mediated immunosuppression [4].

Furthermore, HIV-positive patients tend to be excluded from clinical trials, and for this reason, the management of TNF-inhibitors in this group is mostly based on case reports and case series [4]. Most of the data derived from these cases involve the use of etanercept and infliximab, which –at least in psoriatic patients-resulted in good therapeutic outcomes without alterations of the CD4 count or viral load and without additional opportunistic infections [4,8]. Cases of successful use of adalimumab without additional complications are also published in the literature, but are substantially fewer compared to those assessing etanercept or infliximab treatment [8]. Reports on certolizumab pegol and HIV-infected patients are not available at this point. It is important to point out that the administration of biologic agents should always take place under the supervision of HIV specialists to avoid disease-related complications [8].

Preliminary data on ustekinumab demonstrate a satisfactory safety profile as well as good therapeutic outcomes in psoriatic patients [16]. Interestingly, it has been proven that in several cases, CD4 count and viral load not only remained stable, but also showed improvement [16]. Generally, fewer cases of infectious complications are documented under ustekinumab compared to anti-TNF agents, however among the possible explanations is the fact that the latter are available over a longer period of time than IL-12/23-inhibitors [16].

No sufficient data on secukinumab or any other IL-17-inhibitor, are available at this point.

BIOLOGICS AND PREGNANCY

Pregnant patients are another population group, where the use of biologics should be carefully managed. When it comes to the safety profile of anti-TNF agents in pregnancy, no clear indication of embryotoxicity or teratogenicity under adalimumab, infliximab, etanercept and certolizumab pegol compared to the general population has been documented so far [16]. All aforementioned anti-TNF agents are classified by the Food and Drug Administration (FDA) as pregnancy class B medications [17].

In order to avoid neonatal infection due to active placental transfer of these agents during pregnancy, that can then be detected in infants up to the 6th month of life, it is advisable to discontinue therapy with infliximab or adalimumab in the 20th pregnancy week, otherwise infants should not receive any kind of live-attenuated vaccination up to the 6th month after delivery [4,17-18]. Due to differences in the transport rate of etanercept and certolizumab pegol, the former can be continued up to the 32nd week while the latter throughout pregnancy [4,17-18]. However, given that studies describing pregnancy-associated drug-specific harm tendencies have also been published -even though their findings often lack statistical significance-, each case should be individually assessed, taking into consideration the risk and benefit ratio for the affected patient [19]. These harm tendencies refer mostly to major congenital malformations, such as vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities, as well as unfavorable pregnancy outcomes, including preterm delivery, low birth weight, spontaneous/elective abortion and adverse maternal measures [19].

Clinical data concerning the use of IL-12/23-inhibitors in pregnancy are rather scarce; although some publications with limited patient numbers report uncomplicated pregnancy outcomes under ustekinumab (FDA pregnancy class B), reports on spontaneous abortions during such treatments are also published in the literature [20]. Studies on IL-17 agents are also limited. Preliminary information derived from a global safety database and concerning 292 secukinumab-exposed pregnancies, describes no increased abortion rates under secukinumab (FDA pregnancy class B) compared to the general population, however no safe suggestions can be made on the ground of insufficient data [21].

Overall, despite the undoubtable benefits that accompany the administration of biologics in serious chronic diseases like chronic plaque psoriasis, that until recently were proven refractory to the conventional immunosuppressive treatments, physicians still have to face challenges and dilemmas concerning their use, particularly when confronted with special conditions, such as pre-existing chronic infections or unprecedented events in the form of a pregnancy. The conduction of clinical trials in larger patient cohorts, as well as findings derived from isolated case series or case reports, are necessary in order to enrich existing knowledge on how to adequately manage these potentially complex situations.

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Corresponding author:

Kerasia-Maria Plachouri
University General Hospital of Patras, Rio 265 04
Tel.: +30 694 66 39 340,
E-mail: kerasia.plachouri@hotmail.com

Renin angiotensin system blockade and acute kidney injury: Risks and benefits

Marios Papasotiriou[1], Vasileios Zavvos[2], Evangelos Papachristou[1]

Renin-angiotensin system (RAS) blockade with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) is recommended as a first-line therapy for the reduction of proteinuria, slowing progression of chronic kidney disease (CKD), and reducing cardiovascular risk, with clear benefits proven through a series of large, well-designed clinical trials [1]. In CKD, RAS blockade is recommended even in the absence of hypertension, because its reno- and cardioprotective effects are, at least in part, independent of blood pressure (BP) reduction. In general, the effects of ACEi or ARBs on hypertension and proteinuria are dose-dependent, while their use should be continued beyond CKD stage 4 [estimated glomerular filtration rate (eGFR): 15-29 ml/min/1.73 m^2] [2, 3]. Nevertheless, during intercurrent illness, patients with CKD are vulnerable to drug side effects, particularly hyperkalemia and acute kidney injury (AKI) [4]. For this reason, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that in patients with eGFR below 60 ml/min/1.73 m^2 (CKD stages G3a to G5) who have serious intercurrent illness, potentially nephrotoxic and renally excreted drugs should be temporarily discontinued (including ACEi/ARBs, aldosterone inhibitors, direct renin inhibitors, diuretics, nonsteroidal antinflammatory drugs, metformin, lithium, and digoxin) [5].

ACEi and ARBs cause vasodilation of the efferent glomerular arteriole, further reducing intraglomerular pressure already compromised by their BP-lowering effect. Therefore, in patients with renal parenchymal disease, ACEi and ARBs can cause mild or even severe reduction in GFR. When serum creatinine increases more than 30% above the baseline value, 5-7 days after the initiation of ACEi or ARBs, certain co-morbidities should be suspected (bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, diffuse intrarenal small-vessel disease or generalized volume depletion) and the drugs should be discontinued. In an observational Canadian database study that included more than 63,000 patients who were prescribed a RAS blocker, use of RAS blockers increased the risk of AKI independent of common confounding variables. After adjustment for confounders though, the risk fell away and became non-significant for moderate and severe AKI. However, in patients who had RAS blockers prescribed without an evidence-based indication, the risk of AKI remained greater [6]. Another important aspect is ACEi and ARBs induced hyperkalemia, due to reduced potassium excretion [7]. Hyperkalemia within the first year of ACEi/ARB therapy is relatively uncommon among people with eGFR >60 mL/min/1.73 m^2, but rates are much higher with lower eGFR [8]. According to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, when serum potassium levels are between 5.1 and 5.5 meq/l, measures must be taken to lower K^+ concentration when initiating RAS blockers [9]. This threshold is even lower according to the National Institute for Health and Care Excellence (NICE) and American Heart Association (ACCF/AHA) guidelines which recommend against initiating RAS blockers unless serum K^+ concentration is less than 5

[1]Department of Nephrology and Kidney Transplantation, University Hospital of Patras, Patras, Greece
[2]Center for Diagnosis, Treatment & Research on Kidney Diseases, Hygeia Hospital, Athens, Greece

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meq/l [8-10]. Moreover, hyperkalemia (serum K^+ >5.5 meq/l) following the initiation of ACEi or ARBs will lead to discontinuation or down-titration of the drug. Combined administration of ACEi and ARBs is not indicated for the treatment of hypertension as it is associated with an increased risk of hyperkalemia, hypotension, and impaired renal function compared to either class of RAS blocking agent alone especially in diabetic patients, while it offers no benefit regarding mortality or end stage renal disease [11-13]. In addition, dual RAS blockade is associated with an increased risk of AKI especially in patients with diabetes compared to monotherapy. However, it is important to note that in the prospective, randomized VA NEPHRON-D study, AKI in the setting of RAS blockade monotherapy was associated with lower rates of recovery of kidney function, higher mortality, and higher risk of kidney progression compared to dual therapy. This finding probably emphasizes the hemodynamic nature of AKI in the latter group as opposed to more severe underlying disease burden in the former group of patients [14].

Although initiation of RAS blockade can lead to an acute decrease in GFR, recent studies suggest that this does not reflect true tubular injury [15]. From a pathophysiological standpoint, RAS blockade promotes greater vasodilation of efferent arterioles over afferent arterioles which in turn leads to reduced intraglomerular pressure, subsequent decreased glomerular filtration, and impaired capacity for autoregulation of GFR [16]. Impaired autoregulation makes the kidney prone to GFR decline following minor physiologic and hemodynamic insults such as BP reduction or volume depletion. However, the accompanying improvement in tubular blood flow and oxygenation reduces progression of tubulointerstitial fibrosis and thus progression of CKD. Clinical evidence to support this notion were shown in a subgroup analysis of the SPRINT trial where participants who were randomized to the intensive BP lowering arm had reductions in GFR due to lower achieved BP, but at the same time did not have elevated levels of tubular-injury biomarkers compared to those in the standard arm [15]. Therefore, it is essential that all physicians, from primary care providers to tertiary centers, must be able to distinguish true AKI with intrinsic tubular injury from just a clinically insignificant hemodynamic eGFR decline attributed to RAS blockade with no true kidney damage so as to avoid interrupting treatment in the latter case [17].

Recurrent AKI is a common event after hospitalization complicated by AKI. In a retrospective cohort study with more than 38,000 hospitalized patients with AKI, analyses showed that older age, lower eGFR, proteinuria and anemia are associated with recurrent AKI. Comorbidities including heart failure, acute coronary syndrome, diabetes, and chronic liver disease, are also predictors of a recurrent AKI episode. Those who had more acute illness during the initial hospitalization were more likely to have recurrent AKI, but greater AKI severity was not independently associated with increased risk for recurrent AKI. Most importantly, this study showed in multivariate analysis that recurrent AKI was associated with an increased rate of death (HR, 1.66; 95% CI, 1.57-1.77) [18]. In a closer look though, conditions that are predictors of recurrent AKI like diabetes and coronary disease, are also first-class indications for RAS blocker therapy.

How to best medically manage patients who survive hospitalized AKI is unclear, as the use of RAS blockers in this setting may increase the risk of recurrent AKI. To address this question, Hsu et al. included more than 10,000 patients who experienced AKI and survived in a cohort study in Northern California. In this study though, patients with heart failure or prior use of ACEi or ARBs during the preceding 5 years were excluded. Forty-seven percent of the study population had a documented eGFR < 60 ml/min/1.73 m^2 or documented proteinuria before hospitalization. With a median follow-up of 3 years, 1,853 (18%) patients were administered ACEis/ARBs and 2,124 (21%) patients experienced recurrent AKI. Crude rate of recurrent AKI was 6.1 (95% CI, 5.9 to 6.4) per 100 person-years off ACEis/ARBs and 5.7 (95% CI, 4.9 to 6.5) per 100 person-years on ACEis/ARBs. Overall, the adjusted (for baseline and potential time-dependent confounders) analysis of these patients concluded that exposure to ACEi/ARB use was not associated with higher incidence of recurrent AKI (adjusted odds ratio, 0.71; 95% CI, 0.45 to 1.12) [19]. Another study from Brar et al. addressed the question of RAS blockade re-initiation after AKI and its potential risks. In this retrospective cohort study that included 46,253 adults, the authors evaluated whether the use of ACEis or ARBs after hospital discharge is associated with better outcomes in patients with AKI. Within 6 months since hospital discharge, 22,193 (48.0%) of the participants were prescribed an ACEi or ARB and their use was associated with lower mortality after 2 years (adjusted hazard ratio, 0.85; 95% CI, 0.81-0.89) while no association was found between ACEi or

ARB use and progression to end stage renal disease (ESRD). This finding was true both for patients with a new onset and resumption of treatment. Nevertheless, this came at the cost of a higher risk of hospitalization for a renal cause (adjusted hazard ratio, 1.28; 95% CI, 1.12-1.46) [20].

Overall, on the basis of large observational studies, there is evidence that RAS blockade even after an event of AKI is indeed associated with favorable outcomes in terms of slowing future loss of kidney function and reducing risk of cardiovascular disease events and all-cause death despite a higher risk of (re-)hospitalization. Are patients from all age groups and degrees of frailty candidates for initiation or re-initiation of RAS blockage after an AKI event and, more importantly, when exactly such a therapy should be reconsidered? It seems from the study of Hsu et al. that patients even in the >60 years age group benefit from RAS blockade which should be initiated no prior to 3 months after an AKI episode [19]. Thus, available evidence suggests that the risk-benefit profile supports the use of ACEi or ARBs in these patient groups and health care providers should be less hesitant to prescribe. Nevertheless, this should be applied only to patients with evidence-based indications for RAS blockade therapy, starting at low doses and carefully up-titrating with close monitoring of kidney function.

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Corresponding author:

Marios Papasotiriou
Department of Nephrology and Renal Transplantation,
University Hospital of Patras, Patras, Greece
Tel.: +30 2613 603986, Fax: +30 2610 994424,
E-mail: mpapasotiriou@yahoo.com

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Diabetes mellitus type 2 and COVID-19 pandemic

Ioulia Sirokosta

"Man may be the captain of his fate, but he is also the victim of his blood sugar"

Wilfred G. Oakley

From antiquity to the present day, infections have been among the most devastating challenges that humans have to cope with. Millions of people have died from epidemics caused by deadly viruses. Today the human race is being severely tested by the COVID-19 pandemic. Since the beginning of the 21st century, this is the third time that a beta coronavirus threatens the human population with a fatal pandemic [1]. Early during the epidemic, it was found that older and frail individuals with chronic diseases are more likely to exhibit more severe symptoms and worse outcome [2]. A medical history of Diabetes Mellitus (DM) was confirmed as a condition with a worse outcome when these individuals are affected by COVID-19 infection [2]. Nowadays, DM prevalence is fairly high in many parts of the world and in view of the COVID-19 pandemic, it is essential to assess the risks implicated on comorbid medical conditions. Almost 500 million people have DM globally and in the future this number is expected to rise dramatically [3]. Although individuals with diabetes have the same possibility as everyone else to get infected by the virus [4], it seems that they manifest a more severe disease; a number of them get hospitalized and often are treated in intensive care units with a high mortality rate [2]. In one of the largest retrospective, multicenter cohort studies from China, 44.672 individuals were found to be affected by the COVID-19 infection and the overall case fatality ratio (CFR) was 2.3%, while for diabetics this rate was 7.3% [5]. Recently, the high fatality in diabetics was also corroborated by the CORONADO study [6]. A multicenter study from 53 hospitals in France, included 1.317 adult diabetic (89% had type 2 and 3% had type 1) inpatients, admitted between 10 - 31 March 2020, with a laboratory confirmation of COVID-19 [6]. The study showed that one in ten patients died in the first week of hospitalization, while 20% of patients were severely affected and required mechanical ventilation as compared to 5% of non-diabetics [6].

The main question that needs to be answered is whether DM per se, increases infection susceptibility, worse outcome or fatality that can be correlated with bad glucose control. Micro and macro vascular complications, age or obesity often coexist with diabetes, mainly DM type II [7]. Moreover, DM can affect the immune system's ability to fight infection due to alterations in cytokine profile and changes in immune-responses including T-cell and macrophage activation [8]. Lower respiratory tract infections including tuberculosis, are more prevalent in individuals with DM [9]; one third of diabetics treated for infection are diagnosed with pneumonia and, have a high risk for being diagnosed with pneumococcal pneumonia with an increased hospitalization rate. DM individuals also have an increased risk for influenza, often with a severe clinical course and

Division of Infectious Diseases, Department of Internal Medicine, University Hospital of Patras, Patras, Greece

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more frequent complications [10]. Diabetes is associated with structural changes in patients' lungs including increased vascular permeability and alveolar damage [11].

In the current pandemic of SARS CoV-2, these observations are re-confirmed [2,4,5]. Bad glycaemic control does not seem to be a key factor for worse outcome in a French study [6]. However, this evidence remains controversial as it is well documented in other studies that hyperglycemia affects innate immunity and impairs macrophages and neutrophils function [7,8,12]. In support of this, studies pertaining to influenza virus infections suggest that high blood glucose levels enhance viral replication [10]. It has been postulated that glycosylated end products, like glycosylated transmembrane protease/serine subfamily member 2(TMPRSS2), may facilitate SARS-CoV-2 entry into the host cell [13]. Hyperglycemia and insulin resistance are characterized as chronic low-level inflammatory conditions that may lead to enhanced levels of inflammation following SARS-CoV-2 infection [7,11]. Hyperglycemia is generally associated with a significant reduction in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) [11]. Hyperglycemia is directly implicated in cardiovascular and renal diabetes complications [12]. In the CORONADO study, the complication rate affecting the eyes, kidneys and nerves was 47%; on the other hand, macro vascular complications affecting arteries, heart problems, stroke or leg ulcers, was 41% [6]. When one group of complications as outlined above are observed, the mortality rate increases by two-fold during the first week of hospitalization [6]. DM complications, such as kidney failure and cardiovascular disease, have been shown to increase the severity of COVID-19 disease and the risk of death [2,6,12]. Obesity is often present in most cases of DM, especially in adults with insulin resistance [14]. The connection between abdominal obesity, insulin resistance and inflammation are well documented; abnormal secretion of adipokines, pro-inflammatory cytokines (TNF-a, IL-1β, IL-6, IL-8, IL-12 and interferons) and acute phase reactants are increased in the serum, causing a reduced immune response [8,14,15].

According to these findings, obese individuals with DM are more susceptible to an inflammatory cytokine storm eventually leading to acute respiratory distress syndrome (ARDS), shock and rapid deterioration of their health status. In parallel, obese individuals experience a restrictive respiratory function, due to thickness and may more readily require mechanical ventilation [14,15].

Age is an independent risk factor of worse outcome in all individuals affected by COVID-19 [2,4,5,6]. Persons older than seventy-five years old with DM have a 14-times higher risk to die when infected with COVID-19 than those with an age of less than 55 years old [6].

Management of DM patients infected with SARS-CoV-2is quite challenging. Viral infection may cause a sharp fluctuation of blood glucose levels in DM patients, increasing stress hormones which may adversely affect recovery [7,9]. Based on a study carried out in Wuhan, hypoglycemia (<3.9 mmol/L) accounts to approximately 10% of hospitalized patients, leading to platelet activation and thrombosis [12]. On the other hand, SARS-CoV-2 virus can also directly cause β-cell damage due to abundant ACE2 cellular expression which facilitates the entry of the virus into these cells eventually leading to cell death [7]. Higher D-dimer levels have been reported in COVID-19 patients with DM, leading to rapid progression, adverse prognosis and outcomes [7]. COVID-19 infection is associated with hypokalemia, hyperglycemia and hypertension because of high aldosterone levels [16]. The International Diabetes Federation puts great emphasis in optimal glucose levels monitoring especially during the pandemic period. Specialists suggest insulin treatment during the prolonged hospitalization periods in these patients [17]. Continuous monitoring of blood glucose levels and ketone levels are required to prevent hyperglycemia, hypoglycemia ketoacidosis and non-ketotic hyper osmotic coma. Although, previous studies have reported better outcome in DM patients receiving metformin when affected by lower respiratory tract infections [14], these individuals should discontinue treatment in case of fever, because of lactate acidosis risk [17]. The sodium glucose co transporter 2 (SGLT-2) has been implicated in the pathogenes is of euglycaemic ketoacidosis and there is a risk of dehydration (fever, vomiting) [17]. Pioglitazone and long-acting glucagon-like peptide-1 (GLP-1) receptor agonists (like liraglutide) are not recommended during acute infection, as they have been associated with angiotensin-converting enzyme 2 (ACE2) up regulation in animal studies [12,13,17]. The beneficial or adverse effect of ACE inhibitors/ARBs treatment remains unclear. The American Heart Association suggests continuous treatment in case of patients with COVID-19 infection [7]. Although no treatment has been approved for SARS-CoV-2, hydroxychloroquine may be beneficial to diabetics, as studies have reported that hydroxychloroquine block virus-cell fusion and improves glycaemic control.

CONCLUSIONS

COVID-19 infection leads to worse outcome in DM patients. Therefore, it is imperative that people with diabetes take all the necessary precautions (e.g. vaccines) and achieve good glycaemic control, as judged by measuring HbA1c, in the midst of the ongoing pandemic. Special attention should be paid to individuals with DM older than 70 years, obese with heart and kidney complications. Personal hygiene, social distancing, diabetic diet with low calories, daily exercise, adequacy of medicine and supplements are strongly suggested. Also, ensuring confidentiality and sufficient access to personal doctor during a pandemic are required. Lastly, it is fundamental to mention that good glycaemic control is also crucial for patient's good prognosis during their hospitalization.

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Corresponding author:

Ioulia Sirokosta
Division of Infectious Diseases,
Department of Internal Medicine, University Hospital of Patras, Patras, Greece
Tel.: +30 261999744, Fax: +30 2610999740
E-mail: juliasirokosta@yahoo.com

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Current Treatment of Coronavirus Disease 2019 (COVID-19)

Lydia Leonidou[1,2], Maria Lagadinou[1,3], Despoina Gkentzi[4], Markos Marangos[1,2]

Abstract

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). The disease was first identified in December 2019 in Wuhan, China and since then, hundreds of scientific teams and biotech companies have been developing and testing an array of drugs approved for other indications, as well as multiple investigational agents to treat the disease. So far, no specific antiviral medicine is available either to treat or prevent the aggravation of COVID-19. Herein, we provide an overview of the current research findings and guidelines concerning the main treatments of COVID-19, with a brief reference to the management of the infection in children.

Key words: *COVID-19; SARS-CoV-2; treatment guidelines*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the causative agent of COVID-19 (coronavirus disease-2019), originated from Wuhan, China during late December of 2019 and led to the greatest global health crisis since the 1918 Spanish flu pandemic. It rapidly spread outside of China to the rest of the world, consequently, the World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020 [1] that is currently shows no significant plateauing.

Coronaviruses are enveloped positive-stranded RNA viruses. SARS-CoV-2 is a beta coronavirus of the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses), but of a different clade. The SARS-CoV-2 enters the host cells through the S spike protein by binding to ACE2, aided by the type 2 transmembrane serine protease (TMPRSS2). Viral entry into the lung cells, myocytes and endothelial cells of the vascular system results in inflammatory changes mainly mediated by pro-inflammatory cytokines including IL-6, IL-10, tumor necrosis factor α and granulocyte colony stimulating factor (GCSF) [2]. These changes contribute to lung injury pathogenesis, hypoxia-related myocyte injury, body immune response, intestinal and cardiopulmonary changes. The spectrum of coronavirus disease-2019 can range from asymptomatic infection to severe pneumonia with ARDS and death. Although COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac, dermatologic, hematological, hepatic, neurological, renal and other complications.

So far, no specific antiviral medicine has been available either to treat or prevent the aggravation of COVID-19. Current management consists of supportive care (invasive and noninvasive oxygen support) and treatment with off-label or compassionate-use therapies including antiretrovirals, anti-inflammatory and

[1]Department of Internal Medicine
[2]Division of Infectious Diseases
[3]Emergency Department
[4]Department of Pediatrics
University Hospital of Patras, Greece

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antiparasitic agents and convalescent plasma. [2, 3] The scientific community is actively exploring treatments that would potentially be effective against COVID-19.

The scope of the present review is to look for and update all the information currently available concerning the main treatments of COVID-19, including a brief report on the management of pediatric COVID19. We will review potential antiviral drugs and immune-based therapies (human blood-derived products and immunomodulatory therapies) under evaluation for the treatment of COVID-19 in addition with adjunctive therapies frequently used in patients with COVID-19 to treat the infection (Table 1).

SEARCH STRATEGY

A search of international publications was undertaken using PubMed and Google Scholar databases and the following search terms: coronavirus; 2019-nCoV; SARS-CoV-2; treatment; guidelines and COVID-19. Further relevant articles were identified from the citations referenced in the reviewed articles. The main selection of treatments in this review is based on the COVID-19 treatment guidelines of National Institutes of Health (NIH). Active clinical trials were identified using the disease search term 'coronavirus infection' on ClinicalTrials.gov

A. ANTIVIRAL TREATMENT

Remdesivir

It is an experimental anti-viral medicine which as an adenosine analogue prodrug putatively disrupts viral RNA transcription and is considered a broad-spectrum antiviral agent [4, 5]. Initially developed to treat Ebola (where it was not effective), it showed potential effectiveness in treating SARS and Middle East respiratory syndrome (MERS) also caused by coronaviruses in animal studies in a rhesus macaque model of SARS-CoV-2 infection; remdesivir-treated animals had lower viral levels in the lungs and less lung damage compared to the control animals [6].

The recommendations for remdesivir are largely based on data from the Adaptive COVID-19 Treatment Trial [7]. This is a multinational, randomized, placebo-controlled trial which included 1,063 hospitalized patients with COVID-19 and evidence of lower respiratory tract infection who received IV remdesivir or placebo for 10 days. Patients who received remdesivir had a shorter time to clinical recovery than those who received placebo (median recovery time was 11 days vs. 15 days respectively, $p<0.0001$) but a non-significant reduction in overall mortality was detected (7.1% versus 11.9%). Greater benefit was reported for those requiring oxygen and no benefit for patients with mild or moderate COVID-19. This trial contributed to the FDA's decision to authorize the emergency use of remdesivir as a COVID-19 treatment on May 1, 2020 [7,8].

In June and July 2020, remdesivir was conditionally approved in several other countries/regions worldwide, including the European Union [9]. The drug is indicated for the treatment of COVID-19 in adults and adolescents (aged ≥ 12 years and with a body weight ≥ 40 kg) with pneumonia requiring supplemental oxygen. For patients who require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), there is uncertainty regarding whether starting remdesivir confers clinical benefit, according to the current guidelines of National Institute of Health [10].

Remdesivir is administered intravenously and is available as a solution and/or lyophilized powder for infusion over 30–120 min. Data from a multinational,

Table 1. *Agents under evaluation for the treatment of COVID-19*

Antiviral Drugs	Immune Based Treatment	Adjuctive Therapy
• Remdesevir • Chloroquine and Hydroxychloroquine +_ Azithromycin • HIV Protease Inhibitors -Lopinavir/Ritonavir -Darunavir/Ritonavir • Ivermectin • Favipavir	• Corticosteroids • Interferons • Anti-GM-CSF • IL-6 inhibitors • IL-1 inhibitors • Convalescent plasma and neutralizing antibodies • SARS-CoV-2-Specific Monoclonal Antibodies	• Thrombolytic treatment • Vitamins -VIt D -Vit C • Zinc

open-label trial of hospitalized patients with severe COVID-19 showed that remdesivir treatment for 5 or 10 days had similar clinical benefit [11]. The optimal duration of therapy for patients who do not improve after 5 days of receiving remdesivir is unclear [10].

Remdesivir should not be used in patients with an estimated glomerular filtration rate (eGFR) of < 30 mL/min and can cause side effects like gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and an increase in prothrombin time (without a change in the international normalized ratio)

Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; co administration of these drugs is not recommended [12].

A double-blinded RCT in China (n = 237) revealed no superiority of remdesivir over placebo in time to clinical recovery, 28-day mortality or viral clearance [13]. Even though remdesivir was proposed as a promising option for treating COVID-19 based on data from compassionate use, its safety and effect in humans requires high-quality evidence from well-designed strong clinical trials for further clarification.

Chloroquine and Hydroxychloroquine with or without Azithromycin

Chloroquine (CQ) and hydroxychloroquine (HCQ) are antimalarial agents with immunomodulatory properties that exhibit antiviral activity in vitro against SARS-CoV-2 [14,15]. The in-vitro activities of CQ and HCQ have been shown to have an inhibitory effect on SARS-CoV-2 mRNA production, with HCQ showing greater efficacy than CQ [16]. However, in vitro activity cannot necessarily be interpreted as clinical activity against COVID-19; in vitro activity of CQ/HCQ against many other viruses, such as Ebola virus has been reported previously, but their clinical efficacy did not reach that seen in vitro. Literature on azithromycin alone as a treatment option for COVID-19 is scarce, and it is not clear whether macrolides can be used alone or should be used in combination with HCQ. Masashi et al. support that macrolides alone, or in combination with other drugs, are effective against SARS-CoV-2 [17].

In a non-randomized trial in France on 36 patients with COVID-19, HCQ was administered alone or in combination with azithromycin and reduced SARS-CoV-2 viral burden, although the clinical significance was unclear [18]. Based on these limited data combined with early series from China which revealed shortened disease course among patients diagnosed with COVID-19 when treated with CQ [19] and under the intense pressure to prescribe a medication to COVID-19 patients, on March 28, 2020 the FDA issued an emergency use authorization of hydroxychloroquine for the treatment of COVID-19 [20].

In contrast, several recent subsequent studies have not shown a benefit with HCQ but rather a trend towards potential harm, as CQ and HCQ have a narrow therapeutic index and can cause QT interval prolongation, arrhythmia, bone marrow suppression, seizure, retinopathy, and myopathy [21]. High-dose CQ (600 mg twice daily for 10 days) has been associated with more severe toxicities than lower-dose CQ (450 mg twice daily for 1 day, followed by 450 mg once daily for 4 days) [22].

On 5 June 2020, the large randomized RECOVERY study announced that HCQ will no longer be used to treat COVID-19 given that more than 1100 deaths were reported questioning the safety of the drug. On 4 July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's HCQ arm and the United States National Institutes of Health terminated its trial of HCQ in hospitalized patients, as preliminary data from the trials did not show any benefit [23, 24, 25]. In another open-label trial of hospitalized patients who required no or only low-flow oxygen supplementation (≤4 L/min), HCQ (with or without azithromycin) did not improve clinical status at 15-day follow-up compared with standard of care [26]. Given the lack of evidence and the potential of toxicity, the use of HCQ or CQ to treat COVID-19 in hospitalized patient is no longer recommended in current guidelines but only in the context of a clinical trial [10].

HIV Protease Inhibitors (lopinavir/ritonavir-darunavir/ritonavir)

Lopinavir and ritonavir (LPV/RTV) are both antiviral protease inhibitors typically used in HIV (lopinavir is the actual antiviral agent, with ritonavir boosting lopinavir levels). Lopinavir was found to inhibit the in vitro replication of MERS-CoV and SARS-CoV [27] but the plasma drug concentrations achieved using typical doses of lopinavir/ritonavir seem to be far below the levels that may be needed to inhibit SARS-CoV-2 replication [28]. The Chinese Clinical Trial (Registered Number, ChiCTR2000029308) failed to report benefits with LPV/RTV treatment alone (400/100 mg administered orally twice daily for 14 days) compared to standard care and reported gastrointestinal adverse effects (nausea, vomit-

ing, and diarrhea) induced by LPV/RTV [29].

On March 2020, at the RECOVERY trial, a total of 1596 patients were randomized to lopinavir-ritonavir and compared with 3376 patients randomized to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality and there was also no evidence of beneficial effects on the risk of progression to mechanical ventilation. As a result, on July 2020 WHO discontinued the Solidarity trial's lopinavir/ritonavir arm [25].

Lopinavir/ritonavir acts synergistically with ribavirin. It is suggested that adding ribavirin increases lopinavir's potency by about 400%. Ribavirin in combination with interferon-α 2b was shown to be active against MERS-CoV in a rhesus macaque model [10]. Additionally, the regimen of LPV/RTV plus ribavirin was shown to be effective against SARS-CoV in patients and tissue culture. In a clinical trial, triple combination of interferon beta-1b, LPV/RTV, and ribavirin for the treatment of patients admitted to hospital with COVID-19 was safe and superior to LPV/RTV alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 but as participants in both arms received LPV/RTV, it is impossible to determine whether LPV/RTV contributed to the observed treatment effects [30].

Darunavir /ritonavir (DRV/c), another promising protease inhibitor against SARS-CoV-2 in vitro, typically used in HIV infection, is under investigation. Five days of DRV/c did not increase the proportion of negative conversion vs standard of care alone, although it was well tolerated according to a recent study [31].

At this point there are no data from clinical trials that support the use of HIV protease inhibitors to treat COVID-19 in clinical practice

Ivermectin

In the late 1970s, ivermectin was developed as a new class of drug to treat parasitic infections and has been previously studied as a therapeutic option for viral infections with in vitro data showing some activity against viruses like Dengue, Influenza and Zika virus [32]. In a recent study, Wagstaff et al. demonstrated that ivermectin was a potent in-vitro inhibitor of SARS-CoV-2, showing a 99.8% reduction in viral RNA after 48 hours [33].

Ivermectin was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support according to the ICON (Ivermectin in COvid Nineteen) [34] study but overall, the available clinical data on the use of ivermectin to treat COVID-19 are limited.

Favipiravir

Favipiravir is an antiviral agent which inhibits RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its anti-influenza and anti-Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses [35, 36].

Favipiravir was first used against SARS-CoV-2 in Wuhan at the very epicenter of the pandemic. Then, as the pandemic spread to Europe, this drug received approval for emergency use in Italy [37], and currently has been in use in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan. Approval has also recently been granted in Saudi Arabia, Turkey, Bangladesh, and most recently Egypt

On May 30, 2020, the Russian Health Ministry approved a generic version of favipiravir, named avifavir, as it was found to be highly effective in a randomized, open-label trial that included hospitalized patients who were on room air or receiving supplemental oxygen through mask or nasal cannula; favipiravir enabled SARS-CoV-2 viral clearance in 62.5% of patients within 4 days, and was safe and well-tolerated [38]. In a non-randomized Chinese study in patients with non-severe disease, the use of favipiravir was associated with faster rates of viral clearance (median time to clearance 4 versus 11 days, p=0.003) and more frequent radiographic improvement (in 91 versus 62 percent by day 14, p= 0,004) compared with lopinavir-ritonavir [39] The results should be interpreted with caution as the co-administration of other drugs in both trials could affect the results. In June 2020, favipiravir received The Controller General of India (DCGI) approval in India for mild and moderate COVID-19 infections [40].

Favipiravir, has a similar mechanism of action to remdesivir but is orally administered, has less strong supportive data to back its use, but is nevertheless emerging as an agent that is worth considering in mild to moderate cases. An expanded phase 2 clinical trial in the US, evaluating the safety and efficacy of the antiviral tablets for the control of coronavirus 2019 (COVID-19) outbreaks in long-term care facilities is ongoing [41].

B. IMMUNE-BASED THERAPY

Corticosteroids

Infection with COVID-19 causes exuberant lung

inflammation leading to respiratory failure, ARDS, and death. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. Different studies have found corticosteroid effects ranging from harmful to beneficial [10].

Observational studies of other respiratory infections (e.g., SARS, MERS, influenza) [42] and randomized controlled studies of ARDS suggested an increased risk of multiorgan dysfunction, no mortality benefit, and possibly an increased risk of death with the use of corticosteroids [43]. The World Health Organization (WHO) on 13th March 2020 recommended against the routine use of systemic corticosteroids in the clinical management of severe viral pneumonia, if COVID-19 is suspected [42].

In contrast, a preliminary report of the RECOVERY trial in June 2020 suggested that dexamethasone reduced mortality in COVID-19 patients, but the benefit was restricted to patients with severe and critical COVID-19 [44]. The use of corticosteroids has been evaluated in patients with ARDS by several randomized, controlled trials (RCTs). A meta-analysis of 7 RCTs concerning the use of corticosteroids in 851 patients demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI, 0.59–0.95) and the duration of mechanical ventilation (mean difference, -4.93 days; 95% CI, -7.81 to -2.06 days) [45].

On the basis of this report, the COVID-19 Treatment Guidelines NIH panel recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated [10]. The Surviving Sepsis Campaign COVID-19 subcommittee (a joint initiative of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine) recommends against the routine use of systemic corticosteroids in mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS) [46]. However, these experts generally support a weak recommendation to use low-dose, short-duration systemic corticosteroids in the sickest patients with COVID-19 and ARDS. On 2 September, the WHO recommended treatment with systemic steroids for patients with severe and critical symptoms, but continued to advise against their use for other patients [47]. Whether the use of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) for the treatment of COVID-19 provides the same benefit as dexamethasone is unclear [10].

Interferon (IFN)

Interferon induces several antiviral processes by triggering viral RNA degradation, RNA transcription changes, protein synthesis inhibition and apoptosis [48]. Literature reviews point out that interferons have been in use for many years against emerging viruses when no other treatment options have been available. Interferons have been used for both SARS-CoV and MERS-CoV in the past and have shown positive results both in vitro and in vivo [49].

SARS-CoV and MERS-CoV are able to influence interferon signaling pathways by interfering with proteins involved in interferon expression. The excessive in vitro sensitivity of SARS-CoV2 to interferons is probably explained by the fact that SARS-CoV-2 might have lost these anti-interferon actions [50]. An open-label, uncontrolled retrospective study on SARS showed that treatments including Alfacon-1(IFN-α) and corticosteroids were associated with accelerated lung recovery and shorter duration of intubation time compared with corticosteroids as monotherapy. Moreover, a randomized, four-arm open-label, retrospective study on SARS in Guangzhou, China, demonstrated that IFN plus high-dose steroid therapy achieved respiratory improvement, faster resolution of pulmonary infiltrates and less need for mechanical ventilation [48].

Moreover, as interferon treatment is more effective at earlier stages, IFN can be used prophylactically against SARS-CoV2 and this is further supported by the in vitro efficacy of interferon pre-treatment against the virus. Shen et al. reported that interferon-2α can effectively reduce the infection rate of SARS-CoV-2, which further supports the above statement [50].

The recommended guidelines for the treatment of SARS-CoV-2 in China include administering 5M units of interferonα via an inhaler in combination with oral ribavirin twice a day. The advantage of inhalation therapy is that it acts directly on the respiratory tract [49].

Anti-granulocyte-macrophage colony stimulating factor antibodies (anti- GM-CSF)

Granulocyte-macrophage colony stimulating factor (GM-CSF) is believed to be a key cytokine mediator of the pro-inflammatory state in patients with SARS-

CoV-2 infection. In later stages of COVID-19, illness severity appears to be driven by the inappropriate release of several cytokines, such as IL-6 and GM-CSF. These mediators are involved in inflammatory lung injury, predisposing patients to respiratory failure and eventually ARDS. Therefore, inhibition of GM-CSF signaling may be a reasonable treatment in this stage of the disease [51].

Although there has been no clinical data on its use in patients with COVID-19, mechanistically, blocking the GM-CSF pathway is expected to reduce the severity of cytokine-induced inflammation. Based on this, a randomized control trial was planned to assess the efficacy and safety of lenzilumab, a humanized recombinant monoclonal antibody against GM-CSF. Lenzilumab has undergone phase I and II studies where it was assessed as a treatment of the cytokine release syndrome which is believed to be associated with COVID-19 infection [52]. Lenzilumab has received FDA approval for compassionate use in COVID-19 patients (FDA), while a phase 3 study is ongoing [51].

Gimsilumab has been tested in a phase I study of healthy volunteers. It has also been proved that by binding to GM-CSF receptor it will block the signaling pathway that leads to cytokine release syndrome (CRS), which is also believed to characterize the pro-inflammatory stage of COVID-19 [54]. A clinical trial has also been approved for gimsilumab for the treatment of COVID-19 and is now enrolling patients in the US [53].

Another prospective interventional single-center cohort study tested the efficacy and safety of mavrilimumab in patients with severe COVID-19 pneumonia and evidence of hyper-inflammation in Italy. Thirteen non-mechanically ventilated patients with severe COVID-19 pneumonia and hyper-inflammation were treated with a single intravenous dose of mavrilimumab 6 mg/kg upon admission to the hospital. Twenty-six non-mechanically ventilated patients with severe COVID-19 pneumonia and hyper-inflammation and with similar baseline characteristics were evaluated as a control-group. Over the course of the 28-day follow-up period, mavrilimumab treated patients experienced earlier and improved clinical outcomes than control patients. Death occurred in 0% (n = 0/13) of mavrilimumab-treated patients by day 28 compared to 27% (n = 7/26) of control patients [53].

IL-1 inhibitors

Another option in tackling the cytokine storm which characterizes COVID-19 infection is targeting interleukin -1 (IL-1), by inhibiting IL-1 binding to the IL-1 type I receptor.

Canakinumab, is a monoclonal antibody against IL-1-beta, which has been approved by the Italian Drug Agency (AIFA) for COVID-19 pneumonia. It is used for the treatment of Familial Mediterranean fever and atherosclerotic diseases for its anti-inflammatory properties. A clinical phase 2 trial of Canakinumab is ongoing in patients with COVID-19 pneumonia [53].

Anakinra is another option in targeting IL-1 receptor, which is used for rheumatoid arthritis. Anakinra is a biopharmaceutical drug with a wide therapeutic range and high safety. Anakinra is tested with tocilizumab in a phase 2 clinical trial (COVID-19 Clinical Trials, 2020). It is also being tested in COVID-19 patients combined with emapalumab (Phase 2/3 multicenter randomized clinical trial [52]. The SARS CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells. After entering to type II alveolar epithelial cells of the lungs, SARS CoV-2 triggers life-threatening cytokine release syndrome in its host, which can result in excessive levels of pro-inflammatory cytokines production including IL-6, TNF-a and IL-1b. A group of American researchers suggested that continuous intravenous anakinra infusions might have significant survival benefits possibly by reversing the cytokine storm in patients with COVID-19 [54].

IL-6 inhibitors

IL-6 has been considered the main culprit of the "cytokine storm" found in COVID-19 infection [55]. In critically ill patients with COVID-19, IL-6 levels were almost 10-fold higher. For that reason, blocking IL-6 by using monoclonal antibodies has gained space as a significant potential therapeutic option.

Tocilizumab is a recombinant humanized IL-6 receptor antagonist [56]. A recent single-group, multicentre study showed that within a few days of administration of tocilizumab, temperature curve was normalized and oxygen intake was lowered in 75% of patients with severe or critical SARS-CoV-2 infection [49]. This suggests that tocilizumab may be a new therapeutic strategy. In China, tocilizumab has been used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels. An initial dose of 4–8 mg/kg is infused over more than 60 minutes. If initial dose is not effective, a second dose can be administered after 12 hours but no more than 2 doses should be given [56].

Sarilumab is another human monoclonal antibody that inhibits the IL-6 pathway by binding and blocking the IL-6 receptor. Common toxicities include neutropenia, thrombocytopenia, infusion reaction and infection. Global clinical trials of sarilumab in COVID-19 treatment have been initiated to evaluate clinical outcomes such as fever, the need for supplemental oxygen, mortality, mechanical ventilation, ICU stay and hospitalization [49]. A clinical trial involving sarilumab for the treatment of severe COVID-19 is ongoing, where the efficacy and safety of sarilumab 200 mg and 400 mg doses administered intravenously over 1 hour are being compared with standard of care. Because measurement of IL-6 levels is not readily available in most institutions, C-reactive protein (CRP) levels may be used as surrogate markers of the increased pro-inflammatory state. IL-6 inhibitors rapidly decrease CRP levels after administration; therefore, CRP levels may be used to monitor the response to therapy [57].

Siltuximab, which is approved in the USA to treat patients with multi-centric Castleman disease, is the third potential IL-6- targeted therapy for COVID-19 trials. Recently, an Italian clinical team reported that among 21 COVID-19 patients with ARDS who received siltuximab (70 0–120 0 mg, median 90 0 mg), the serum CRP level was reduced in 16 patients. Moreover, 33% of patients exhibited clinical improvement, 43% remained stable and 24% deteriorated [58] The efficacy and safety of siltuximab in the treatment of COVID-19 patients need to be further studied [49].

NIH COVID-19 Treatment Guidelines Panel recommends against the use of IL-6 inhibitors in the treatment of COVID-19, except in a clinical trial [10].

Convalescent plasma and neutralizing antibodies

The US FDA has approved the emergency investigational use of convalescent plasma (CP) for the treatment of critically ill patients with COVID-19. CP is collected from COVID-19 recovered individuals who are eligible for blood donation and their symptoms have resolved at least 14 days before donation. They should also have negative PCR for SARS-CoV-2 and high SARS-CoV-2 neutralizing antibody titers [52]. It seems that CP acts through viral neutralization, cellular cytotoxicity induced by antibody, activation of complement system, and phagocytosis but the exact mechanism of action has remained elusive. Although, almost all studies on CP (in severe patients) reported its effectiveness, only one study supported that there was no significant difference in time to clinical improvement compared to control group [55].

A preliminary report of a series of five patients with severe COVID-19 pneumonia complicated by ARDS showed that the administration of CP containing neutralizing antibody (SARS-CoV-2 IgG titers greater than 1:1000 by enzyme linked immunosorbent assay and neutralizing antibody titer >40) led to clinical improvement. There was a normalization of body temperature in four patients within 3 days, the sequential organ failure assessment score decreased, and viral load declined to negativity by day 12. ARDS resolved within 12 days in four patients. These preliminary findings seem promising for the future [56].

Available data suggest that serious adverse reactions following the administration of COVID-19 CP are infrequent and consistent with the risks associated with plasma infusions for other indications.

SARS-CoV-2-Specific Monoclonal Antibodies

Monoclonal antibodies (mAbs) used in the treatment or prevention of infectious diseases are engineered versions of antibodies naturally produced by the immune system in response to invading viruses or other pathogens. SARS-CoV-2-specific mAbs are designed to directly target the virus and may act as neutralizing antibodies (nAbs). Most SARS-CoV -2-specific mAbs being investigated target epitopes on the spike protein (S protein) of the virus and block the receptor-binding domain (RBD) of the S protein from interacting with human angiotensin-converting enzyme 2 (ACE2), thereby preventing the virus from entering cells thus inhibiting viral replication [59].

REGN-COV2 is a combination of two monoclonal antibodies (REGN10933 and REGN10987) and was designed specifically to block infectivity of SARS-CoV-2 COVID-19. Antibodies produced by mice, which have been genetically modified to have a human immune system, as well as antibodies identified from humans who have recovered from COVID-19 were used in a clinical trial of 275 patients with laboratory-confirmed COVID-19 treated in the outpatient setting. Enrolled patients were randomized 1:1:1 to receive a single IV infusion of 8 g of REGN-COV2 (high dose), 2.4 g of REGN-COV2 (low dose), or placebo. Regeneron Pharmaceuticals (the manufacturer of REGN-COV2) stated that data analysis showed that the drug reduced viral load and time to alleviation of symptoms and there was a positive trend in reduction of medical visits; the greatest treatment benefit appeared to be in patients who had

not mounted their own effective immune response (no measurable antiviral antibodies) [60]. On 2 October 2020, it was announced that US President Donald Trump had received "a single 8 gram dose of REGN-COV2" after testing positive for SARS-CoV-2.The drug was provided by the company in response to a "compassionate use" (temporary authorization for use) request from the president's physicians [61].

In addition to this trial in non-hospitalized patients, REGN-COV2 is currently being studied in a Phase 2/3 clinical trial for the treatment of COVID-19 in hospitalized patients, the Phase 3 open-label RECOVERY trial of hospitalized patients in the UK and a Phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals. Recruitment in all 4 trials is ongoing.

LY-CoV555 is another Neutralizing IgG1 mAb whose preclinical studies demonstrated protective effects against SARS-CoV-2 infection and viral replication in an animal model [62]. A randomized, double-blind, placebo-controlled phase 2 study is evaluating efficacy and safety of LY-CoV555 used alone or in conjunction with a second mAb (LYCoV016 [LY3832479]) for early treatment of COVID-19 in adults who are outpatients with mild to moderate disease is ongoing and an interim analysis of the study suggested [63].

SARS-CoV-2-specific mAbs are not commercially available. Although results of many controlled clinical trials are needed to provide information on the safety and efficacy of mAbs that specifically target SARS-CoV-2, it has been suggested that such mAbs may offer some advantages over other immunotherapies used for the treatment of COVID-19 (e.g., COVID-19 convalescent plasma, IGIV) in terms of specificity and safety.

C. ADJUNCTIVE THERAPY

Antithrombotic therapy

COVID-19 may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. Hematologic and coagulation parameters have been associated with worse clinical outcomes in hospitalized patients with COVID-19 [64].

The incidence of Venus Thromboembolism (VTE) in COVID-19 patients is not well established. Reports have ranged between 8% in all COVID-19 patients to 69% in ICU patients screened with lower extremity ultrasound [65].

Several studies have examined the prophylactic use of anticoagulants, mainly in the form of low molecular-weight heparin (LMWH) and unfractionated heparin (UFH), to reduce the risk of VTE in COVID-19 patients [66].

No difference in overall mortality has been observed when thromboprophylaxis with either enoxaparin or UFH (29.7% in treatment group vs 30.3% in no-treatment group, p=0.91). However, significant mortality reduction has been observed when treatment was given to patients with D-dimer levels increased by more than six-fold compared to the upper normal limit (32.8% vs 52.4%, p=0.017) and patients with a sepsis-induced coagulopathy (SIC) score of 4 or greater (40.0% vs 64.2%, p=0.029). Significant reduction in hospital mortality has also been observed in mechanically ventilated patients given anticoagulants (29.1% vs 62.7%, p<0.001) [59]. In a French prospective multicenter cohort of 150 ICU patients, 16.7% had pulmonary embolism despite prophylactic anticoagulation [66].

According to the NIH guidelines, hospitalized adults with COVID-19, should receive VTE prophylaxis, and the standard of care like any other hospitalized adults. Routine post-discharge VTE prophylaxis is not recommended for patients with COVID-19. However, the benefits of post-discharge prophylaxis for certain high-risk patients without COVID-19 led to the Food and Drug Administration approval of two regimens: rivaroxaban 10 mg daily for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days [10].

Vitamins

Vitamin D has important functions beyond those of calcium and bone homeostasis, which include modulation of the innate and adaptive immune responses. Vitamin D has immunomodulatory effects that could potentially decrease the severity of COVID-19 infection; vitamin D supplements may also increase T regulatory cell activity [10].

Two randomized, double-blind, placebo-controlled clinical trials (VIOLET, VITdAL-ICU) in critically ill patients with vitamin D deficiency (but not with COVID-19) showed that high-dose vitamin D did not reduce hospital stay or mortality rate compared with placebo. Patients in both studies received a single enteral dose of 540,000 international units (IU; units) of vitamin D3 [67, 68].

There are many ongoing trials administering vitamin D alone or in combination with other agents to participants with and without vitamin D deficiency to evaluate the use of vitamin D for the prevention or treatment of COVID-19 [69].

There is some evidence suggesting that similarly to vitamin D, vitamin C might help manage the immunopathologic responses contributing to the pathogenesis of severe respiratory viral infections [70]. A recent meta-analysis compared the effect of vitamin C versus non-vitamin C infusion in patients with sepsis. Data from 10 studies (4 randomized controlled trials [RCTs] and 6 retrospective studies) involving 1671 patients indicated that the use of vitamin C did not reduce the risk of 28-day, intensive care unit or in-hospital mortality and only two RCTs suggested that vitamin C treatment showed reduced 28-day mortality. Several trials of oral and IV vitamin C supplementation in people with COVID-19 are also ongoing [71].

Zinc

The importance of the trace element zinc for the development and function of the immune system has been proven in numerous studies as well as the impressive intersection of known zinc deficiency and the predisposition for a severe COVID-19 infection. Zinc supplementation might already prevent viral entry and also suppresses its replication, while it supports the anti-viral response of the host cells [72].

A retrospective, observational study compared zinc supplementation to no zinc supplementation in 932 hospitalized patients with COVID-19 who received hydroxychloroquine and azithromycin from March 2 to April 5, 2020. Zinc was given as a zinc sulfate 220-mg capsule (50 mg of elemental zinc) twice daily for 5 days. The addition of zinc did not affect the length of hospitalization, duration of ventilation, or ICU duration but in univariate analyses, zinc sulfate increased the frequency of patients being discharged, and decreased the need for ventilation, admission to the ICU, and mortality or transfer to hospice for patients who were never admitted to the ICU [73]. The optimal dose of zinc for the treatment of COVID-19 is not established. Reversible hematologic defects (i.e., anemia, leukopenia) and neurologic manifestations (i.e., myelopathy, paresthesia,) have been reported with long-term zinc supplementation. The data so far are insufficient to guide clinical practice.

Treatment options for children with COVID-19

Due to the lack of evidence from trials in children, all cases should be discussed at an individual basis and decisions to treat with antivirals usually occur within the context of a relevant clinical trial.

As expected, antiviral therapy for COVID-19 should be reserved for children with severe SARS-CoV-2 infection. Remdesivir has not been evaluated in clinical trials that include children with COVID-19. A phase 2/3 open-label trial (CARAVAN) of remdesivir started in June 2020 to assess safety, tolerability, pharmacokinetics, and efficacy in children from birth to age 18 years [74]. The use of HCQ or CQ for the treatment of COVID-19 in children is currently not recommended due to concerns about its efficacy and could only be considered as part of a clinical trial. HCQ should be avoided in children with underlying QTc abnormalities and those who require other medications that could interact. The pediatric glucocorticoid arm of the RECOVERY trial is ongoing.

Low-dose glucocorticoids may be beneficial in children with COVID-19 when given up to 10 days and include: dexamethasone 0.15 mg/kg orally, intravenously (IV), or nasogastrically (NG) once daily (maximum dose 6 mg); prednisolone 1 mg/kg orally or NG once daily (maximum dose 40 mg); or methylprednisolone 0.8 mg/kg IV once daily (maximum dose 32 mg).

At present, immune modulators such as IL-6 inhibitors, interferon-beta 1b, CP from recovered COVID-19 patients are not recommended due to lack of efficacy data in children

CONCLUSION

Although the fact that an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in clinical trials and can be accessed through Emergency Use Authorization, or compassionate use mechanisms, the optimal approach to treatment of COVID-19 is uncertain. Literature data suggest a clinical benefit with remdesivir and a mortality benefit with dexamethasone, but no other therapies have clearly proven effective. SARS-CoV-2-Specific Monoclonal Antibodies offer some advantages over other immunotherapies and seem to help prevent and treat early infections of COVID-19 but more data are needed. As far as the other medication agents discussed in the review are concerned, outcomes from case reports and case series cannot be generalized for a larger population and their use is recommended only in clinical trials.

This review does not include, nitazoxanide, angiotensin II receptor blockers, famotidine, colchicine and other medications that have been suggested for SARS-CoV-2 that are awaiting evidence, or any oral-route traditional Chinese medications with insufficient evidence of qual-

ity, safety and efficacy.

In conclusion, management of COVID-19 disease remains largely supportive with particular emphasis on prevention and management of complications. It is important to caution readers that new data emerges daily regarding treatment options for COVID-19. Further well-designed RCTs in COVID-19 therapies are warranted before final conclusions on efficacy could be made..

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Corresponding author:

Lydia Leonidou,
Internist and Infectious Diseases Specialist,
University General Hospital of Patras,
E-mail: lydleon@yahoo.gr

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Evidence-based psychotherapeutic interventions in patients suffering from chronic physical diseases

Georgia Konstantopoulou[1], Katerina Karaivazoglou[2]

Abstract

Chronic diseases prevalence is continuously rising and they constitute a major cause of poor health, disability and mortality in developed countries. Chronic disease patients experience persistent symptoms which impair their health-related quality of life and are vulnerable to increased levels of psychological distress which further impede their overall functioning and put an extra burden on caregivers and healthcare systems resources. The key role of psychological parameters for patients' prognosis and overall well-being has led research and clinical practice to focus not only to symptom management but also to psychosocial interventions addressing the needs of chronic patients. There are several studies assessing the effects of specific psychotherapeutic interventions on patients' psychological functioning and on disease severity indices and progression. In this context, the aim of the current narrative review is to present and critically appraise recent findings regarding the role of psychotherapy in the management of a wide range of chronic diseases including cancer, gastrointestinal disorders, cardiovascular disorders, multiple sclerosis, autoimmune disorders and chronic pain. This evidence-based information may provide physicians with useful knowledge regarding the optimal and holistic management of their patients' physical and psychosocial needs.

Key words: *Chronic disease; psychotherapy; psychosocial functioning; health-related quality of life*

INTRODUCTION

According to the Centers for Disease Control and Prevention, chronic diseases are defined as medical conditions that last more than three months, with periods of latency, but with a prolonged clinical course that show gradual changes over time, are usually multifactorial and require continuous management for a period of years or decades [1]. Some of the most prevalent chronic physical diseases include cardiovascular and respiratory diseases, cancer, diabetes, neurological and gastrointestinal diseases, autoimmune disorders and skin conditions [2,3]. A great percentage of the adult population worldwide suffer from chronic physical illness and have to cope with several challenges in everyday living [4]. In Greece, one in two people over the age of 15 report at least one chronic illness, while five in ten women (53.9%) and four in ten men (44.2%) state that they have a one-year disease. Moreover, compared to 2009, Greek chronic patients have increased by 24.2% [5]. Chronic diseases constitute the main cause of poor health, disability and death in developed countries hence representing a major burden for healthcare systems. In addition, chronic disease patients commonly report high levels of psychological distress, disturbed

[1]Special Office for Health Consulting Services, University of Patras, Greece
[2]Department of Psychiatry, University Hospital of Patras, Rion, Greece

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quality of life, interpersonal difficulties and have to face high financial costs which compromise their living conditions [6,7].

According to the biopsychosocial model, health is not just the absence of disease or disability but a state of complete physical, mental and social well-being (WHO). In this context, the concept of health is not only attributed to medicine, but also to other factors such as the environment, the economy, work and more. Genetic, environmental factors (lifestyle, home, work, working environment, environmental pollution), life factors (diet, smoking, exercise, addictive behavior, behavior), health and system-related factors, and health education factors affect people's health but also the social representation of the health-disease dipole [8]. Taking into account these theoretical formulations, it has become increasingly evident that chronic disease management calls for a holistic approach incorporating biological, psychological and social parameters. In this respect, there has been a growing interest in designing and implementing targeted psychotherapeutic interventions for chronic sufferers aiming at alleviating their symptoms, lowering their psychosocial burden and improving their quality of life and everyday functioning.

The aim of the current narrative review is to present and critically appraise recent findings regarding the role of psychotherapy in the management of a wide range of chronic diseases including cancer, gastrointestinal disorders, cardiovascular disorders, multiple sclerosis, autoimmune disorders and chronic pain.

MATERIALS AND METHODS

We performed an extensive search of the PubMed database until December 2019 using all possible combinations of the following categories of terms: chronic disease or cancer or gastrointestinal disorders or cardiovascular disorders or multiple sclerosis or autoimmune disorders or chronic pain and psychotherapy or psychotherapeutic interventions or psychosocial interventions. Results are presented by disease category.

CANCER

30-35% of cancer patients suffer from a psychiatric disorder, mainly depression and anxiety, while an additional 20% report psychosocial distress and existential worries which do not meet formal diagnostic criteria, however add significantly to patients' turmoil [9]. There are numerous studies assessing the effects of psychotherapeutic interventions in cancer patients and cancer survivors. According to several meta-analyses, cognitive behavioral therapy, existential therapy, problem-solving therapy, interpersonal therapy and hypnosis have proven effective in alleviating symptom-related discomfort, reducing depressive and anxiety symptoms and improving cancer patients' quality of life [10,11]. Furthermore, there have been several therapeutic protocols targeting specific cancer-related symptoms such as pain and fatigue which have shown efficacy. An earlier review [12] emphasizes that the quality of therapeutic alliance and group cohesion appear as factors which mediate the benefits of psychotherapy for cancer patients.

In the case of patients with advanced cancer, psychosocial interventions can be classified in 6 categories: cognitive behavioral therapy based; meaning enhancing; dignity, life review, and narrative; other counselling; education only; and music, writing, and others [13]. In general, cognitive behavioral therapy has demonstrated the strongest efficacy evidence in addressing cancer patients' psychosocial needs and reducing anxiety and depression levels [14]. Mindfulness-based interventions have also shown promising results in reducing cancer-related psychological distress although further studies are needed to determine whether these benefits persist after the cessation of the intervention [15-18].

CHRONIC GASTROINTESTINAL DISEASES

Gastrointestinal diseases have been associated with increased psychosocial burden and patients' care integrates multidisciplinary approaches including standard psychiatric evaluation and psychopharmacological and psychotherapeutic interventions when indicated [19]. Irritable bowel syndrome (IBS) is a prototype of psychosomatic disorders characterized by unusual visceral hypersensitivity and increased psychological co-morbidity [20]. Several psychological interventions have been implemented in IBS management and research data suggest that cognitive behavioral therapy, interpersonal therapy and psychodynamic therapy may provide benefits for IBS patients, although there is no convincing evidence that treatment effects are sustained after treatment completion [21,22]. In addition, cognitive behavioral therapy seems to have a greater effect in alleviating IBS symptoms compared to reducing psychosocial distress [23].

Inflammatory bowel diseases (IBD) constitute severe medical conditions which are characterized by chronic intestinal inflammation and have a major impact on patients' psychosocial functioning and quality of life.

Anxiety and depressive symptoms commonly affect IBD patients and are associated with poorer prognosis, increased hospitalization rates and lower treatment adherence [24,25]. There seems to be a bidirectional relationship between patients' mental health and disease activity, given that psychological distress may either trigger IBD symptoms or be the aftermath of patients' debilitating symptoms. Cognitive behavioral therapy, mindfulness therapy and gut directed hypnotherapy have been associated with reduced healthcare utilization and better psychosocial functioning especially in adolescent populations, while relaxation techniques have proven effective in reducing patients' pain and psychological distress [26]. In addition, psychotherapeutic interventions have shown quite promising results in fatigue management [27]. In contrast, there is no adequate evidence that psychotherapy improves GI symptoms and decreases disease activity indices [24,28]. All these findings need further corroboration given that existing data are limited and relevant studies are characterized by small sample sizes and high levels of bias [29]. In this context, the British Society of Gastroenterology consensus guidelines encourage IBD patients with psychological co-morbidity to seek psychological therapy including cognitive behavioral therapy, hypnotherapy or mindfulness mediation as part of a holistic strategy of disease management. Experts on psychogastroenterology agree that patients with clinical levels of depressive and anxious symptomatology would benefit from psychotherapeutic treatment and further research is needed to clarify which parameters mediate psychotherapy's beneficial effects [30].

CARDIOVASCULAR DISEASES

Anxiety and depression are highly prevalent in patients with cardiovascular conditions including acute coronary syndrome and congestive heart failure [31] and have been associated with poor prognosis and lower survival rates [32]. Several psychological interventions have been implemented in the management of cardiovascular diseases which aim at lifestyle modification and a decrease in patients' psychological distress. These interventions include psychoeducational and self-management approaches, cognitive behavioral therapy and mindfulness therapy and have shown efficacy in establishing a healthier lifestyle and improving patients' quality of life [33].

According to a recent meta-analysis, cognitive behavioral therapy alleviates depressive symptomatology and improves quality of life in heart failure patients and these benefits largely remain at 3 months follow-up. However, no significant benefits were observed in hospital admission and mortality rates [34]. In a similar way, the latest Cochrane review on the topic revealed that psychological therapies did not significantly affect total mortality in coronary heart disease patients but reduced cardiac mortality by 21% and improved psychological functioning. Nevertheless, most studies included in this review suffered from reporting bias hence their evidence was of low quality. In addition, there were no data regarding which patient- and intervention-specific characteristics were associated with better outcomes suggesting that further large-scale studies are needed to focus on the impact of specific psychotherapeutic interventions on certain sub-populations of heart disease patients [35].

OTHER CHRONIC DISEASES

Apart from cancer, gastrointestinal and cardiovascular disorders, there is a wide constellation of other chronic diseases which impair patients' everyday functioning and are commonly accompanied by high levels of psychological distress thus calling for appropriate and effective interventions to alleviate patients' suffering. Findings regarding the whole spectrum of chronic diseases would not be possible to be included in a single review and for this reason we chose to selectively provide brief references of research evidence on the effects of psychotherapy in multiple sclerosis patients, other autoimmune disease patients and patients suffering from chronic pain. The psychological correlates and relevant psychosocial interventions have been extensively studied in these patient populations.

Multiple sclerosis (MS) is an autoimmune disorder affecting the nervous system which puts great strains on patients' and families' emotional resources and may severely impede personal independence and quality of life. MS patients are prone to depression and have to cope with high levels of stress which in turn may lead to disease relapse and impaired prognosis [36]. Psychosocial therapies are commonly used as an adjunct to the medical management of multiple sclerosis [37] and in clinical practice neurologists encourage their patients to engage in stress-reducing activities. Several psychological therapies including cognitive behavioral therapy, acceptance and commitment therapy and motivational interviewing counseling have been compared to usual care in MS patients and have been associated with sig-

nificant reduction in depressive symptomatology but were not effective in anxiety management [38]. Another recent meta-analysis concluded that psychosocial interventions reduce depressive symptoms, anxiety and fatigue levels and improve mental and overall quality of life but have no significant effect on physical quality of life [37]. Cognitive behavioral therapy has also been extensively used in MS-related fatigue and has shown moderate positive effects, however, these effects were not maintained after treatment completion [39]. Comorbid anxiety symptoms have also been addressed by mindfulness-based interventions which promote self-awareness and emotional regulation. These techniques have shown quite promising results in reducing psychological distress, pain and fatigue and promoting quality of life in MS patients [36]. By promoting metacognitive abilities, mindfulness training may facilitate positive coping and problem-solving thus empowering patients to manage disease-related challenges in everyday living.

There is a complex interplay between neuropsychological factors and immunological disturbances underlying the pathogenesis of autoimmune disorders. Depression is a highly prevalent co-morbid condition in patients suffering from systematic lupus erythematosus (SLE) or rheumatoid arthritis (RA), while stress-induced pathophysiological alterations seem to trigger autoimmunity responses leading to symptom exacerbation [40,41]. A comprehensive systematic review on the effect of psychosocial intervention in RA patients revealed small to moderate beneficial effects of several types of psychological treatments including cognitive behavioral therapy, supportive counselling, psychotherapy, self-regulatory techniques, mindfulness-based cognitive therapy and disclosure therapy in global functioning, pain, fatigue, psychological functioning, coping, self-efficacy and physical activity. Improvements in coping and physical activity and remission of depression were maintained at 8-14 months post-intervention. Moreover, longer therapy duration and the inclusion of follow-up sessions were associated with greater efficacy [42]. Similarly, psychological interventions provided as adjuncts to traditional medical management of SLE lead to significant improvements in psychological status and quality of life and to pain and fatigue relief [43].

Chronic pain is a debilitating symptom severely impairing patients' productivity, social relationships and quality of life. Pain-relieving medications demonstrate limited efficacy in chronic persistent pain and may be associated with severe adverse effects including the risk of addiction [44]. In this respect, pain management through psychological interventions might be better tolerated by chronic pain patients. There are several randomized controlled studies assessing the effect of mindfulness-based interventions on chronic pain reporting positive outcomes, however most of them suffer from low methodological quality and their findings need to be further corroborated [45]. Cognitive behavioral therapy is another type of psychotherapeutic intervention which has been shown to reverse functional disability and pain symptoms, increase self-efficacy, reduce catastrophizing cognitions and improve psychological functioning in chronic pain patients [46]. Furthermore, there are limited yet interesting neuroimaging data suggesting that psychotherapeutic interventions promote alterations in pain-associated neural circuits [47,48].

In conclusion, chronic disease patients have to cope with major limitations in their living conditions and are prone to enduring feelings of sadness, loss, anger, despair and anxiety which compromise their psychological functioning and quality of life. Proper management should address both their physical and psychosocial needs by incorporating educational, counseling and psychotherapeutic approaches adjunctively to traditional biomedical treatments. In the case of comorbid psychopathology, mostly depression and anxiety disorders, psychological interventions appear as effective alternatives to psychotropic medication due to the limitation imposed by the chronic disease status on pharmacological therapies. Cognitive behavioral therapy and mindfulness-based interventions have shown the strongest efficacy evidence in reducing psychological distress, relieving pain, coping with fatigue and functional impairment and improving quality of life in a variety of medical conditions. However, there is still a need for large-scale randomized controlled studies of high methodological quality to further investigate the role of psychotherapy in chronic disease and identify which patient- and intervention-related parameters are associated with the optimal outcome.

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Corresponding author:

Georgia Konstantopoulou,
psychologist, Special Office for Health Consulting Services, University of Patras, Greece
E-mail: geokonstantop@gmail.com

Obstructive colorectal cancer: Current treatment strategy

Evangelos Iliopoulos, George Skroubis

Abstract

Despite the availability of colorectal cancer screening, approximately 10% of patients present with obstruction as first symptom of the disease. The aim of this review is to present the current medical literature for the management of obstructive colon cancer. For obstructive right colon cancer the treatment of choice is right colectomy with primary anastomosis. For patients with acute or subacute obstructive left cancer, treatment options include Hartmann's procedure with temporary colostomy or endoscopic metallic stent placement as a bridge to the surgery or one-stage surgical resection with primary anastomosis or diverting stoma. This review illustrates guidelines and treatment proposals in palliative and curative settings, as well as individualized decision algorithm in order to determine the optimal treatment for the patient.

Key words: *Colorectal cancer; obstruction; diagnosis; treatment*

BACKGROUND

Colorectal cancer represents the 3rd most commonly diagnosed malignancy that accounts for 1.4 million new cases per year. The incidence varies by geographic region, and in particular, is higher in Europe than in North America followed by Oceania, Latin America and Africa [1,2].

Complications of large bowel diseases account for 47% of emergencies of the gastrointestinal tract, while colorectal cancer presents as emergency in around 30% of reports, ranging from 7 to 40%. Large bowel obstruction represents almost 80% of the emergencies related to colorectal cancer, while 20% concerns perforation cases. The most common location of obstruction is the sigmoid colon with 75% of the tumors located distal to the splenic flexure [3-5].

Department of Surgery, University of Patras, University Hospital of Patras, Greece

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DIAGNOSIS

Obstruction of the large bowel can present acutely with abdominal bloating, colic-like abdominal pain and vomiting that is less frequent than in small bowel obstruction, or subacutely with changes in bowel habits and recurrent abdominal pain especially at the left lower quadrant. Absence of flatus or feces passage and abdominal distention form the most common symptoms and physical signs [6].

Abdominal examination reveals tenderness, abdominal distention and increased or absent bowel sounds. A rectal cancer may be palpable, by digital examination, as an intrinsic lesion.

Electrolyte imbalance (elevated urea nitrogen and metabolic alkalosis) may appear in laboratory tests, as a consequence of vomiting and dehydration [7,8].

Consequently, the clinical suspicion of bowel obstruction should be investigated by abdominal x-ray or abdominal US. Abdominal computed tomography scan (CT) achieves diagnostic confirmation, with higher sensitivity and specificity than abdominal ultrasound

and abdominal plain x-ray and represents the imaging test of choice in current clinical practice. Furthermore, it has the absolute advantage to provide the clinician with an optimal grade of information, regarding the staging of neoplastic disease and to identify synchronous neoplasms. A water-soluble contrast enema is an alternative, in order to identify the site and cause of obstruction in cases where a CT scan is not available [9].

The role of colonoscopy is limited; especially in the emergency setting. The purpose of direct visualization is to differentiate between the various etiologies of obstruction, while endoscopic biopsies may be considered if placement of endoscopic stent and delay of surgical resection is the treatment strategy of choice [5, 10, 11].

In patients with an incomplete colonoscopy due to an obstructing colorectal cancer, the presence of a synchronous colonic tumor must be excluded. Many population – based studies show that about 4% of these patients have synchronous colorectal tumors. Of these synchronous tumors, 35-45% is located in a different colonic segment than the index tumor and they are significantly smaller. The European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) recommend performing a CT colonography after an incomplete colonoscopy, due to its high accuracy for both colorectal cancer and large polyps. In conclusion, CT colonography may lead to a change in the surgical plan based on the presence of a synchronous tumor (in 1.4% of cases), while it provides information regarding the length and quality of the colon and the ability to better localize the tumor preoperatively [12].

Regarding preoperative staging of colorectal cancer presenting as an emergency, there are no specific data. Abdominal CT scan should be suggested, while evidence to support the indication for routine CT of the thorax is weak. In conclusion the need for staging CT should never delay the decision for surgical treatment [13].

MANAGEMENT OF OBSTRUCTION OF THE LEFT COLON (FROM DISTAL TRANSVERSE COLON TO UPPER RECTUM)

Hartmann's procedure remains one of the most common procedures in emergency surgery of the left colon and is still the preferred option in patients with high surgical risk. It should be preferred over simple colostomy, since the latter appears to be associated with longer overall hospital stay and need for multiple operations without a reduction in perioperative morbidity. On the other hand, creating a stoma provides colonic decompression with minimal surgical trauma, allows intensive resuscitation and a better staging prior to definitive treatment. Loop colostomy should be reserved only for unresectable tumors, whenever the placement of self expandable metallic stents (SEMS) is not feasible, and for severely ill patients who are not fit to receive general anesthesia or be submitted to major surgical procedures [14].

The historical concept that in order to avoid anastomotic leak, a completely clear colon is necessary, has been questioned. In recent years there has been an increasing trend toward a one-stage resection for left-sided bowel obstruction, but no randomized control trials have been conducted comparing Hartmann's procedure to resection with primary anastomosis. Grade A or B evidence are not available and the choice depends on the individual surgeon's preference. Many retrospective series present rates of anastomotic dehiscence ranging from 2.2 to 12%, compared to 2 – 8% rate after elective surgery [14-17].

The main advantage of primary resection and anastomosis is the avoidance of a second major operation, which is associated with overall higher morbidity rates. Furthermore, due to possibly necessary adjuvant treatment and disease progression, a great proportion of stomas created during Hartmann's procedure for colorectal cancer are not reversed [18].

All these must be counterbalanced by the potentially catastrophic results from an anastomotic leak in a severely ill patient. A tension-free anastomosis with good blood supply remains the gold-standard in order to prevent anastomotic dehiscence. The surgeon's subspecialty and experience seem to be important factors in surgical decision. Concerning the role of a diverting stoma, there is no evidence supporting that a defunctioning stoma can reduce the incidence of anastomotic leakage, though it seems to only reduce the clinical severity of an occurred anastomotic leak [19, 20].

Subtotal colectomy is not preferred to segmental colectomy in the absence of caecal serosal tears or perforation, evidence of bowel ischemia or synchronous right colon cancer, since it does not reduce morbidity or mortality and may be associated with higher rates of postoperative diarrhea [10,21,22].

Endoscopic stent placement was introduced initially for the palliative treatment of obstructive rectal or rectosigmoid cancer. The development of self expandable metallic stents (SEMS), that can be introduced through

the scope, allowed to extend their use not only with palliative intent to avoid a stoma, but also in order to transform an emergency surgical operation into an elective procedure; concomitantly reducing morbidity, mortality, and stoma rate. In facilities with endoscopic capability, SEMS should be preferred for the palliative treatment of obstructing left colon cancers since they are associated with similar mortality and morbidity rates and shorter hospital stay.

For resectable tumors, according to the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE), the recommended interval between SEMS placement and concomitant curative operation should not be more than 5-10 days [23]. Although a longer interval would allow for a more thorough preoperative assessment of the patient and even an improvement on nutritional status, this delay could increase the risk of stent-related complications. These, according to the literature, include perforation, bleeding, pain, re-obstruction etc, with perforation being the most serious, in a reported rate of 7.7% according to a recent study [24]. Although there is a concern about oncologic drawbacks with SEMS placement, a recent meta-analysis did not show any significant differences on recurrence rate25.

An increased risk of perforation in patients receiving bevacizumab was outlined by a recent meta-analysis that included 4086 patients from 86 studies. For this reason, the latest guidelines of the European Society of Gastrointestinal Endoscopy (ESGE), do not recommend the use of SEMS in patients who are under treatment with antiangiogenic agents. As a bridge to an elective surgery, SEMS seem to offer a better short-term outcome than emergency surgery, but long-term outcomes appear comparable; further studies are necessary. All the randomized control trials have shown that the use of SEMS has reduced the rate of stomas and as they allow a progressive resolution of the obstruction, they may lead to an increased possibility of an elective surgical procedure. Moreover, the odds of laparoscopic resection are increased with the use of SEMS, the so-called endo-laparoscopic approach [23,26-28].

EXTRAPERITONEAL RECTAL CANCER

Rectal cancer that is complicated by obstruction represents a locally advanced disease and has particular features that influence its management. If curative resection is intended, neoadjuvant chemoradiotherapy followed by elective surgery should be undertaken. Therefore, a stoma should be fashioned in order to decompress the bowel, and then should be followed by the appropriate oncologic treatment. The use of SEMS is not indicated for obstructive low rectal cancer cases, as it is complicated with tenesmus and chronic pain, worsening patients' quality of life. The migration of the stent or rectal perforation as a consequence of tumor necrosis and shrinkage due to chemoradiation may compromise the final oncologic results [29].

The type and location of an emergency created stoma should correspond to the type and location of the future diverting or definitive stoma. A decompressing right-sided loop transverse colostomy may be preferred to a decompressing sigmoid colostomy because it may be left in place after the planned surgical resection, it has low risk of damaging the marginal arcade, and it is fashioned easier due to the mobility of the transverse colon. A loop ileostomy could be used alternatively as a temporary decompressing stoma, only in the case of incomplete colonic obstruction with an inadequate ileocaecal valve – otherwise, colonic distension will not be resolved. A competent ileocaecal valve mandates the need for a decompressing colostomy. When an abdominoperineal resection is planned, an end sigmoid colostomy should be the decompressing stoma of choice [30-32].

MANAGEMENT OF OBSTRUCTION OF THE RIGHT COLON

The medical literature regarding the treatment of obstructive right colon cancer is less extensive compared to that of obstructive left colon cancer and this is probably related to variable anatomical reasons. The hepatic flexure is easier to mobilize compared to the splenic flexure. The surgeon is allowed to perform a primary ileocolic anastomosis without additional maneuvers, due to the mobility of the small bowel. The blood supply of an ileocolic anastomosis is always better compared to colocolic or colorectal anastomosis, whose blood supply depends on the patency of the marginal arcade [33].

Right colectomy with primary ileocolic anastomosis for obstructing right-sided colon cancer represents the option of choice, despite the fact that patients are usually older with more comorbidities and usually more advanced coloregional disease than those with left colon cancer. If intraoperatively a primary anastomosis is considered unsafe, a terminal ileostomy with colonic fistula represents a good alternative. The rate of anastomotic leakage for emergency right colectomy is acceptable, when compared to elective cases and to left colon resections with anastomosis [34].

A side-to-side, by-pass anastomosis, between terminal ileum and transverse colon may be performed, as a palliative surgical treatment, in cases of unresectable right-sided colon cancer. It is preferable to loop ileostomy that can be fashioned alternatively. Nowadays, decompressive cecostomy has been abandoned, and should be reserved only for fragile patients via percutaneous technique. Finally, the use of SEMS is not recommended for obstructive right colon cancer, as a bridge to elective surgery, and could be an option only for high risk patients [35, 36, 37].

CONCLUSION

As a conclusion, although there is an almost universal clinical consensus concerning the management of obstructive right and transverse colon cancers, the treatment strategy of obstructive left colon cancer includes many alternatives. The practice of self expandable metallic stents introduction for colonic decompression, although not something quite new in the medical armamentarium, is a useful tool as a bridge for surgery or as palliative treatment for inoperable cases or for patients with distant colon metastases. Until now, there are only a few randomized studies, comparing alternatives, with conflicting results. Based on the advantages and disadvantages of different alternatives and personal experience, clinicians should construct a decisional algorithm for the management of obstructing colon cancer.

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Corresponding author:

George Skroubis,
Associate Professor of Surgery,
Department of Surgery, University of Patras,
University Hospital of Patras, Greece
Tel.: +30 2610999460,
E-mail: skroubis@med.upatras.gr

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Mitral annular calcification in hemodialysis patients

Stavros Mantzoukis[1], Nikolaos Tsigaridas[1], Elisavet Kokkolou[2], Marina Gerasimou[3]

Abstract

Background: Mitral annular calcification (MAC) is a chronic, degenerative condition more frequently encountered in haemodialysis patients. The aim of the current study was to determine the incidence of MAC in patients with chronic end-stage renal disease undergoing hemodialysis and to detect any correlations with demographic factors, comorbidities and characteristics of the dialysis process.

Methods: We estimated the prevalence and severity of MAC (through echocardiography) in dialysis patients referred to the Hemodialysis Unit of the General Hospital of Ioannina and evaluated its association with laboratory parameters and time since dialysis initiation (TSDI). The mean values of six-monthly measurements of serum calcium, phosphorus and calcium-phosphorus product levels were recorded and used for statistical analysis. TSDI and history of diabetes, hypertension and dyslipidemia were documented. All data were analyzed with the Stata software.

Results: Mitral annular calcification was observed in 26 patients (56.5%) and in terms of severity, most of them had mild calcification. No statistically significant correlation was observed between the severity of calcification of mitral annulus and calcium, phosphate levels and their product. However, a statistically significant correlation was observed between TSDI and the degree of mitral annulus calcification ($p<0.01$).

Conclusion: The severity of calcification was significantly related to TSDI. More research is needed on the reasons for this correlation. Possibly the accumulated action of cardiovascular risk factors and hemodynamic effects of the dialysis process are related to the observed changes in the mitral annulus. The effect of the electrolyte composition of dialysis solutions should also be investigated.

Key words: *Mitral annular calcification; hemodialysis; chronic kidney disease*

INTRODUCTION

Mitral annular calcification (MAC) is a chronic degeneration of the fibrous skeleton of the mitral valve. It is often an accidental finding during an echocardiographic examination [1]. Its incidence ranges between 8-15% and is higher in people with multiple cardiovascular risk factors as well as in people with chronic kidney disease. Its pathophysiology is not fully understood. Advanced age, atherosclerosis and its risk factors, female sex as well as disorders of calcium and phosphorus metabolism appear to be involved in its pathophysiology [1]. These electrolyte disturbances are often seen in chronic kidney disease and therefore, mitral annular calcification is more common in patients with chronic end-stage renal disease undergoing dialysis [2-4]. The purpose of this study was to estimate the incidence of MAC in patients with chronic end-stage renal disease undergoing hemodialysis and detect any correlations with demographic factors, comorbidities and characteristics of the dialysis process.

MATERIALS AND METHODS

All patients attending a chronic dialysis program

[1]Department of Cardiology
[2]Department of Nephrology
[3]Department of Microbiology
General Hospital of Ioannina "G. Hatzikosta"

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at the Hemodialysis Unit of the General Hospital of Ioannina were eligible to enter the study. For all participants, age, body mass index, history of hypertension, diabetes mellitus and dyslipidemia were recorded, as well as a set of laboratory parameters based on the laboratory values of the last six months. Specifically, the average value of calcium and phosphorus in the last six months was recorded, as well as the average value of the calcium - phosphorus product in the last six months. Time since dialysis initiation (TSDI) was also recorded. Finally, all patients underwent echocardiography and the presence and severity of mitral annular calcification were assessed. Philips EPIQ 7 ECHO machine ECHO images were reviewed by two experienced and certificated in TTE by the European Association of Cardiovascular Imaging (EACVI) cardiologists. More specifically, from a parasternal short axis view at the level of the mitral annulus (PSAX-MV), the degree of mitral annular calcification was assessed as follows: Grade I (mild) - focal noncontiguous calcification limited to <180° total annular circumference with no extra-annular calcification. Grade II (moderate) - dense continuous calcification limited to <270° total annular circumference. Posterior and/or anterior leaflet calcification may be present. Grade III (severe) - dense continuous calcification extending past the commissures into anterior annulus or complete circumferential MAC (≥270° calcification arc). Posterior and/or anterior leaflet calcification may be present. Papillary muscle or ventricular myocardial calcification may be present [1,5]. No other echocardiographic parameters were recorded. There were no exclusion criteria. Patients with calcific aortic stenosis were also enrolled in the study. There was no patient with irradiation history. Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Statistical analysis was performed using the Stata software both for the use of descriptive statistics and for regression analysis.

RESULTS

In total, the characteristics of 48 patients of the Hemodialysis Unit of the General Hospital of Ioannina G. Hatzikosta were recorded. However, echocardiographic study and determination of the severity of MAC was only performed in 46 patients because the other 2 patients had poor acoustic window and were excluded from the study. The mean age of participants was 71.3 years and 69.57% of the patients were men (36 patients). The average duration of inclusion in a dialysis program was 26.76 months. In terms of comorbidities, diabetes was present in 33.84% of patients (16 patients), hypertension in 65.22% (30 patients) and dyslipidemia in 32.61% (15 patients) as demonstrated in Table 1. The average value of calcium, phosphorus and their product during the study semester was 8.97, 5.1 and 46.96, respectively. Mitral annular calcification was observed in 26 patients (56.5%) and most of them had mild calcification as indicated in Table 2. No statistically significant correlation was observed between the severity of calcification of mitral annulus and calcium and phosphate levels and their product. However, a statistically significant correlation was observed between time since dialysis initiation and the degree of MAC ($p<0.01$).

Table 1. *Patients baseline clinical characteristics.*

Age in years ± SD	71.3 ± 11.4
Hemodialysis duration (months ± SD)	101.32 ± 38.7
Midweek pre-dialysis serum creatinine (mg/dl ± SD)	7.5 ± 2.05
Comorbidities	***N (%)***
Hypertension	30 (65.2)
Dyslipidemia	15 (32.6)
Diabetes	16 (33.8)
Cause of ESRD	***N (%)***
Glomerulonephritis	9 (18.8)
Diabetes	8 (16.7)
Polycystic kidney disease	3 (6.3)
Hypertension	5 (10.4)
Unknown	21 (43.8)
Other	2 (4.2)

ESRD: End Stage Renal Disease

Table 2. *Degree of MAC severity among study patients.*

Degree of MAC severity	Number of patients	Percentage of patients (%)
Grade I	17	36.96
Grade II	5	10.87
Grade III	4	8.70

DISCUSSION

Mitral annular calcification is associated with the presence of cardiovascular risk factors and an increased risk of cardiovascular disease and death of cardiovascular etiology [1,6-9]. However, chronic kidney disease itself is associated with high cardiovascular risk [10]. This study did not study the association between mitral annular calcification and cardiovascular mortality because this would require much more time (months or years) in order to reliably record morbidity and mortality, which exceeds the time period of our study. However, patients with end-stage renal disease should be considered high cardiovascular risk patients and measures should be taken to aggressively regulate cardiovascular risk factors in order to reduce the incidence of cardiovascular events in these patients.

In patients with chronic end-stage renal disease, there are studies showing association between calcium - phosphorus product and MAC [11,12]. However, no such correlation was observed in the present study. Severe MAC is known to be associated with several conduction disturbances or arrhythmias. In the population of our study, atrial fibrillation was observed only in 5 patients from whom 3 have MAC (2 mild and one severe). This number was too small to detect any correlations.

In addition, the coexistence of mitral annular calcification and atherosclerotic events (coronary heart disease, peripheral arterial disease) led to the development of the theory that these two entities share common risk factors and common pathophysiology [1,8,13-15], although, this has not yet been clearly demonstrated. Several studies have shown an association between patients' age and the presence of mitral annular calcification [16,17], but no similar association was seen in the present study. No association was found with classic cardiovascular risk factors such as high blood pressure, diabetes and dyslipidemia in contrast to previous studies. This could perhaps be attributed to the short average TSDI (26.76 months) as opposed to previous studies which have shown an association with classic risk factors where the observation period was longer [18]. However, the correlation found with TSDI may be related to the cumulative effect of various classic cardiovascular risk factors as the period increases. Similar findings in terms of TSDI have been described in previous studies [12,16,19].

Future studies should examine possible correlations between MAC and mean serum albumin concentration (as malnutrition index), as well as drug treatment (such as calcitriol, calcium-based phosphate binders). These factors may be able to explain the increased incidence of MAC in patients undergoing hemodialysis.

CONCLUSIONS

Mitral annular calcification is more common in hemodialysis patients. In fact, it is related to the time from patient's enrollment to a chronic dialysis program. More research is needed on the reasons for this correlation. Probably, the accumulated action of cardiovascular risk factors and the hemodynamic effects of the dialysis process are related to the observed changes in the mitral annulus. The effect of the electrolyte composition of dialysis solutions on the occurrence and progression of mitral calcification should also be investigated, but in order to draw safe conclusions, future studies should be carried out during a longer time-period. Moreover, given that past studies have correlated MAC with inflammatory activity, correlations between MAC and inflammation indexes such as C- reactive protein should be examined in future studies. In conclusion, patients with chronic end-stage renal disease undergoing dialysis and especially patients with mitral annulus calcification should be treated with aggressive regulation of cardiovascular risk factors in order to improve their overall cardiovascular profile.

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Corresponding author:

Marina Gerasimou
MD, MSc Department of Microbiology,
General Hospital of Ioannina "G. Hatzikosta",
1 Makrigianni Str, Ioannina 45500, Greece
Tel.: +2651366434, E-mail: marinagerasimou@gmail.com

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Correlation between glycosylated hemoglobin and syntax score

Stavros Mantzoukis[1], Marina Gerasimou[2]

Abstract

Background: Glycosylated hemoglobin is used in both diabetes diagnosis and glycemic control assessment. The aim of this study was to demonstrate the possible correlation between glycosylated hemoglobin levels and the severity of coronary heart disease as expressed by the SYNTAX score.

Methods: All patients who were admitted to the Cardiology Clinic of the General Hospital of Ioannina from 16/11/2018 to 14/1/2019 due to either stable angina or acute coronary syndromes and were subjected to coronary angiography which demonstrated coronary artery disease were enrolled. A total of 93 patients were included in the study. In all participants, glycosylated hemoglobin was measured and SYNTAX score was calculated after the coronary angiography.

Results: Higher SYNTAX score was observed in patients with elevated levels of glycosylated hemoglobin. Glycosylated hemoglobin level did not emerge as an independent prognostic factor for the severity degree of coronary artery disease when the SYNTAX score was used as a severity index. However, the history of diabetes mellitus was found to be an independent prognostic factor for angiographic severe coronary disease.

Conclusion: The history of diabetes mellitus and its long-term effects on coronary arteries appear to be the most important independent risk factor for severe coronary heart disease. Glycosylated hemoglobin levels could be an important prognostic marker for the severity of coronary heart disease even in subjects with glycosylated hemoglobin within normal limits. However, this should be confirmed by larger clinical studies.

Key words: *Glycosylated hemoglobin; coronary heart disease; diabetes mellitus; coronary angiography; SYNTAX score*

INTRODUCTION

Diabetes mellitus (DM) is one of the major risk factors for cardiovascular disease. Western lifestyle is associated with increased incidence of type 2 DM and increased cardiovascular morbidity and mortality. Glycosylated hemoglobin (HbA1c) is used both in the diagnosis of DM and in the assessment of glycemic control for a period of 2-3 months prior to sampling. Higher levels of HbA1c in diabetic patients appear to be associated with an elevated risk for cardiovascular events [1]. The purpose of the present study was to demonstrate the possible association between HbA1c levels and the angiographic severity of coronary heart disease both in patients with a history of DM and patients without a history of DM. The severity of coronary heart disease was quantitatively expressed by the value of SYNTAX SCORE.

METHODS

All patients who were admitted to the Cardiology Clinic of Ioannina General Hospital from 16/11/2018 to 14/01/2019 either due to acute coronary syndrome or stable coronary artery disease and underwent coronary angiography were eligible to enter the study. More specifically, participants had been admitted due to unstable angina, myocardial infraction with ST elevation (STEMI), myocardial infraction without ST elevation (NSTEMI) or

[1]Department of Cardiology
[2]Department of Microbiology
General Hospital of Ioannina "G. Hatzikosta""

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stable angina. Written informed consent was obtained from each patient included in the study and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. In all of these patients, serum HbA1c (normal values: 4.3-6.1%) levels were measured one day after the coronary angiography. SYNTAX score was calculated based on coronary angiography findings in all patients. The calculation of the SYNTAX score takes into account the localization and the individual characteristics of the lesions. Stenosis is defined as a reduction in the diameter of the lumen by more than 50% compared to the diameter of the proximal healthy segment for vessels > 1.5 mm in diameter. The degree of stenosis is not included in the calculation formula except in cases of total occlusion. It is considered whether the right or left coronary artery is the dominant vessel and in which part of the coronary artery the lesion is located. For chronic obstructions, the score calculation algorithm takes into account whether obstruction dates >3 months, whether there is blind occlusion or bridging, the first segment beyond the total occlusion that is visualized by antegrade or retrograde contrast and whether there are smaller arterial branches before occlusion, and what size are they. Other features of lesions considered to be unfavorable and rated higher are: ostial lesions, bifurcation or trifurcation lesions, severe tortuosity, large length of the lesion (> 20mm), severe calcification, the presence of thrombosis as well as diffuse coronary artery disease [2]. At the same time, the existence of other risk factors that increase cardiovascular risk and may be a confounding factor in the study was recorded. More specifically, we recorded whether there was a history of arterial hypertension or a diagnosis of hypertension during hospitalization, a history of dyslipidemia or a diagnosis of dyslipidemia during hospitalization, a history of smoking in the past five years, a history of DM or a diagnosis of DM during hospitalization and a family history of coronary artery disease. In total there were 98 recordings from patients admitted to the cardiology clinic during the aforementioned period due to acute coronary syndrome or stable angina and in whom coronary angiography revealed coronary artery disease. However, the statistical analysis only included 93 individuals as 5 records were excluded for the following reasons:

- Three patients because the first blood sample was not analyzed due to technical issues, and no second sample was taken as the patients had already been discharged.
- Two patients enrolled twice during the study as they were twice admitted due to acute coronary syndrome during the study period. At these admissions,

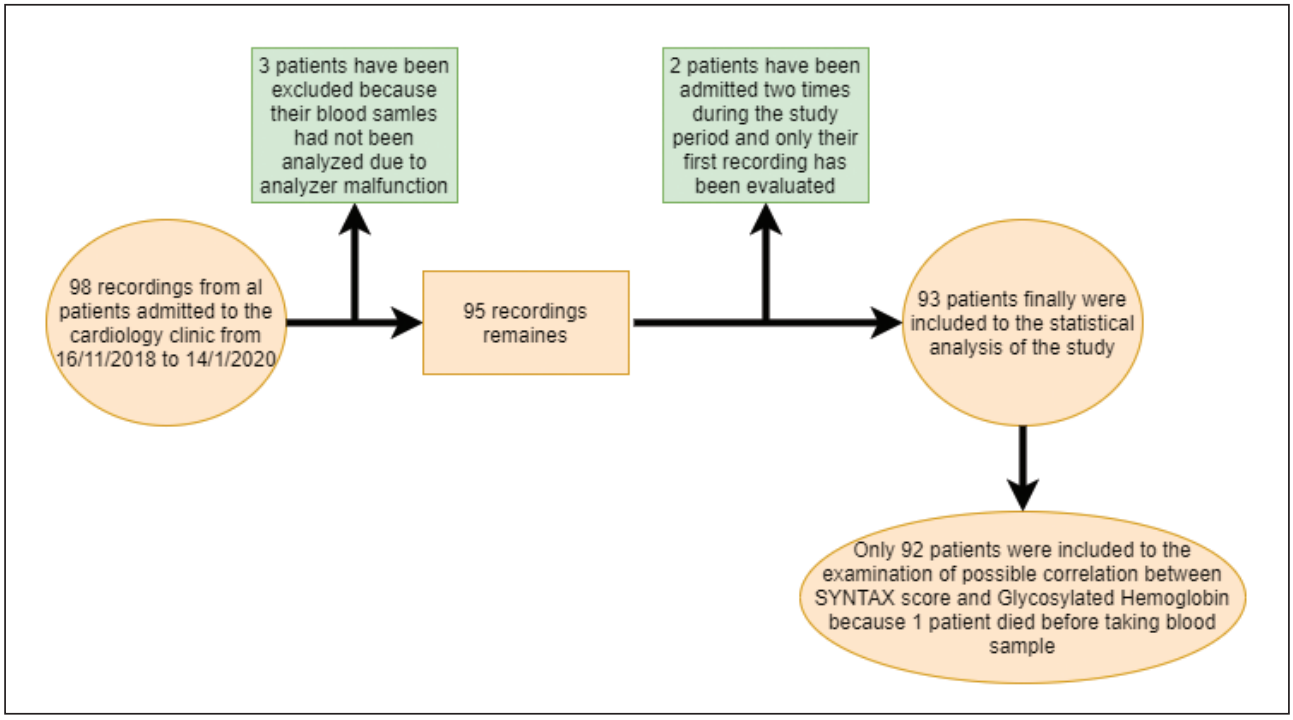

Figure 1. Flow chart with registered and 'dropout' patients of the study.

Table 1. *Inclusion – exclusion criteria of the study.*

Inclusion Criteria	Exclusion Criteria
All patients admitted to the Cardiologic Clinic of General hospital of Ioannina from 16/11/2018 to 14/1/2019, regardless of age, sex, ethnicity.	Patients with anemia, hemoglobinopathy or history of recent blood transfusions (events that may affect HbA1c measurement).
	Patients with known coronary heart disease but with the same as in the past findings during the coronary angiography (It is worth noting that all patients of the study had more severe angiographic findings than in the past).

these patients had a fixed glycosylated hemoglobin value and a similar angiographic image. Therefore, only their first admission was recorded.

- It is noteworthy that one patient died before taking a sample for HbA1c measurement. This patient's data were used in the sample description but were not used in the correlation analysis (Figure 1).
- None of the participants had anemia, hemoglobinopathy or a history of recent blood transfusions (events that may affect HbA1c measurement). In addition, all patients with a history of coronary heart disease who underwent coronary angiography at that time had more angiographically severe coronary heart disease.
- Inclusion and exclusion criteria of the study are described in Table 1.

Descriptive measurements were described using frequencies and percentages for categorical variables while mean values and standard deviations were used for continuous variables. For the correlations between the categorical data, the x2 test was used, and in cases of non-fulfillment of the conditions, the Fisher's exact test. The Mann Whitney test was used to detect differences between the two groups in continuous parameters, while the Pearson test was used to detect correlations between continuous variables [3-5]. Based on the results of the univariate analyses, a logistic regression model was created with the SYNTAX score as the dependent variable. Statistical analysis was performed with the SPSS v22 software and statistical significance was set at 0.05 in all cases.

RESULTS

Descriptive data

A total of 93 patients were included in the study with a mean age of 68.83 years (40 to 88 years) for whom a set of demographic characteristics was recorded. Specifically, 79 patients were men and 14 women, 30 were smokers, 17 had a family history of coronary heart disease, 71 had hypertension, 53 had dyslipidemia, 34 had DM and 31 had known coronary artery disease. Glycosylated hemoglobin levels ranged from 4.3 to 11.1 with a mean of 6.358. By categorizing these values, it appears that 39 (42.4%) exceeded the normal threshold. The cause for admission to the cardiology clinic was 33% NSTEMI, 18% STEMI, 13% unstable angina and 29% stable angina. The mean value of the SYNTAX score was 14.81 (0-45). The SYNTAX score can also be assigned to categories depending on the values recorded. Table 2 shows that most patients had low rates (77.4%) while only 7 had a "very high" SYNTAX score.

First degree correlations

The Pearson correlation table shows that there was a statistically significant positive correlation of SYNTAX score with glycosylated hemoglobin levels, meaning that higher SYNTAX score values were expected for higher glycosylated values (p = 0.002) (Table 3). Differences were also found for the SYNTAX score depending on whether glycosylated hemoglobin level was normal or abnormal. Patients with abnormal glycosylated level had higher SYNTAX score than patients with normal glycosylated (p = 0.002) (Table 4). Differences were also found for the SYNTAX score depending on the presence of DM history. SYNTAX score values were significantly higher for patients with history of DM compared with patients without history of DM (p = 0.009) (Table 5).

Table 2. *Distribution of patients according to the SYNTAX score category.*

	Category of SYNTAX SCORE				
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Low	72	77.4	77.4	77.4
	High	14	15.1	15.1	92.5
	Very high	7	7.5	7.5	100.0
	Total	93	100.0	100.0	

Table 3. *Correlation between glycosylated hemoglobin (HbA1c) and SYNTAX SCORE.*

Correlations			
		SYNTAX SCORE	HbA1c
SYNTAX SCORE	Pearson Correlation	1	0.320*
	Sig. (2-tailed)		0.002
	N	93	92

*Correlation is significant at the 0.01 level (2-tailed)

Table 4. *Correlation between glycosylated hemoglobin (normal or abnormal value) and SYNTAX SCORE*

Report		
Category of HbA1C		SYNTAX SCORE
Normal	Mean	11.78
	Std. Deviation	8.616
	Median	9.00
	Range	32
	N	53
Abnormal	Mean	18.77
	Std. Deviation	11.601
	Median	15.00
	Range	41
	N	39

Test Statistics[a]	
	SYNTAX SCORE
Mann-Whitney U	640.000
Wilcoxon W	2071.000
Z	-3.112
Asymp. Sig. (2-tailed)	0.002

[a]Grouping Variable: HbA1C Category

Regression analysis

Logistic regression analysis was performed to determine the independent predictors. The approach of categorizing the SYNTAX score at the threshold value of 22 was adopted as this value is a critical point for the choice of coronary artery bypass grafting or not. The analysis showed that the model including DM history and left main disease can improve the prediction of whether the patient will have a SYNTAX score greater than or below 22 by approximately 7.6% while correctly predicting 1/3 of the patients who had a moderate to very high SYNTAX score (i.e. above 22). Model fit was good with p = 0.480. The analysis showed that patients with left main coronary artery disease were about 17 times more likely to have SYNTAX score greater than 22, compared to patients without left main coronary artery disease (p = 0.001). The 95% confidence interval for this estimation was approximately 3.4 to 87 times. This large discrepancy was due to the fact that only 10 patients had left main coronary artery disease. At the same time, patients with DM were about 5.5 times more likely to have SYNTAX score greater than 22, compared to patients without DM (p = 0.023). The 95% confidence interval for this estimation was approximately 1.2 to 24 times. This large discrepancy could be attributed to the relatively small number of patients with DM that did not allow to reduce uncertainty. (Table 6, Figure 2 and 3)

DISCUSSION

The study involved 93 people, the majority of whom were men and presenting multiple cardiovascular risk factors at the same time. HbA1c level was selected as an indicator of patients' chronic glycemic status, as it takes into account both post-operative hyperglycemia episodes that are positively related to diabetes complications and mainly cardiovascular complications [6]. Regarding the distribution of clinical manifestations of coronary heart disease, the results of this study coincide with data from international literature. In particular, coronary heart disease occurs either in the form of stable angina or in the form of acute coronary syndromes. Acute coronary syndromes according to the guidelines of the European Cardiology Society appear in decreasing frequency as NSTEMI, STEMI and less as unstable angina (as is the present study) [7].

The present study showed a correlation between glycosylated hemoglobin levels and SYNTAX score values. The SYNTAX score is an angiographic score to describe the severity or complexity of a coronary artery disease. SYNTAX stands for "SYNergy between PCI with TAXUS and Cardiac Surgery". The SYNTAX Score I is calculated using a computer program that asks sequential and interactive questions. The algorithm consists of 12 main questions, which in turn can be divided into 2 groups: the first 3 determine the dominance, the total number of vascular segments and the number of segments involved per lesion. The last 9 questions refer to the adverse lesion characteristics (e.g. calcification, degree of occlusion and length of the lesion) and are repeated

Table 5. *Correlation between history of diabetes mellitus (DM) and SYNTAX score*

SYNTAX SCORE * History of DM					
SYNTAX SCORE					
HISTORY OF DM	Mean	Std. Deviation	Median	Range	N
No	12.59	9.292	10.00	41	59
Yes	18.66	11.425	16.50	41	34
Total	14.81	10.483	13.00	45	93

Test Statistics[a]	
	SYNTAX SCORE
Mann-Whitney U	676.000
Wilcoxon W	2446.000
Z	-2.611
Asymp. Sig. (2-tailed)	0.009

[a]Grouping Variable: History of DM

for each lesion. The SYNTAX-Score I takes neither the patient characteristics nor the treatment strategy into account, but only the coronary anatomy. The SYNTAX Score II takes account age, gender, left ventricular ejection fraction, creatinine clearance, chronic obstructive pulmonary disease and peripheral artery disease. In our study, elevated SYNTAX score values are observed in subjects with elevated glycosylated hemoglobin. The above results are consistent with data from international literature showing that glycosylated hemoglobin levels constitute a risk factor for cardiovascular disease and are associated with more severe coronary heart disease as defined on the basis of the SYNTAX score [8]. The above applies not only to people with abnormal glycosylated hemoglobin but also to individuals with normal glycosylated hemoglobin levels. Even in these cases, individuals with a higher glycosylated hemoglobin value show an increased SYNTAX score. It therefore appears that the role of early intervention in glycemic control (even in patients with normal glycosylated hemoglobin levels) should be explored to reduce cardiovascular risk. It appears that in subjects with chronic hyperglycemia and glycosylated hemoglobin values at higher normal levels, there is a greater likelihood of angiographic severe coronary artery disease possibly through the same mechanisms acting in individuals with diabetes such as endothelial dysfunction and oxidative stress [8].

The role of HbA1c as an independent risk factor was not corroborated when the SYNTAX score was used as a coronary artery disease severity index. It appears that

Table 6. *Correlation between history of diabetes mellitus or left main coronary artery disease and SYNTAX score*

Classification Table[a]					
			Predicted		
			SYNTAX score category		Percentage Correct
	Observed		Low	High or Very high	
Step 1	SYNTAX score category	Low	68	3	95.8
		High or Very high	14	7	33.3
	Overall Percentage				81.5

[a]The cut value is 0.500

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1[a]	HbA1C	-0.110	0.271	0.166	1	0.684	0.895	0.526	1.524
	History of DM	1.718	0.754	5.189	1	0.023	5.572	1.271	24.426
	Left main coronary artery disease	2.852	0.827	11.890	1	0.001	17.314	3.424	87.560
	Constant	-1.693	1.606	1.111	1	0.292	0.184		

[a]Variable(s) entered on step 1: HbA1C, History of DM, Left main coronary artery disease.

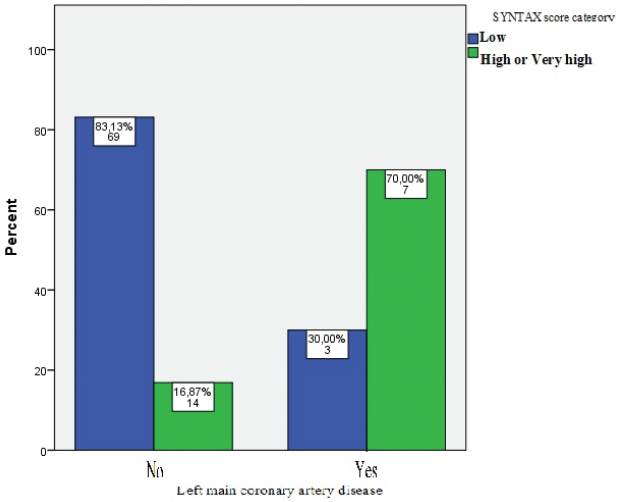

Figure 2. Correlation between left main coronary artery disease and SYNTAX score

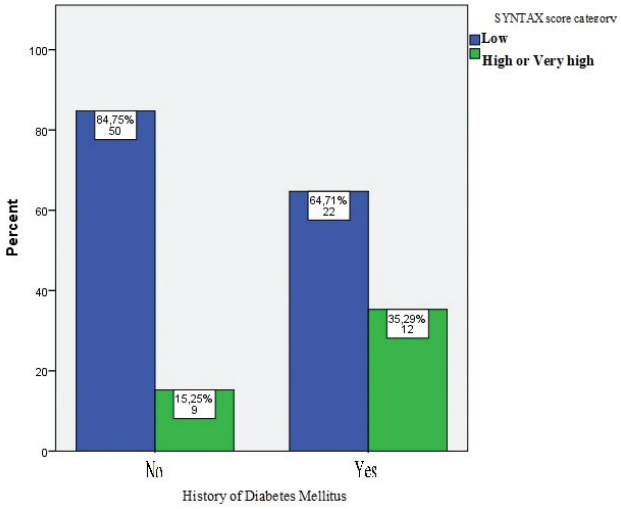

Figure 3. Correlation between history of diabetes mellitus and SYNTAX score

other cardiovascular risk factors interact with DM in the development of coronary heart disease. This is not consistent with studies suggesting that the value of HbA1c is an independent factor that determines angiographic severity of coronary disease even in non-diabetics regardless of the type of clinical manifestation for which they underwent coronary examination [6,8-13]. It is worth noting that there are limited studies that show that HbA1c is not an independent cardiovascular risk factor in non-diabetic patients [14] or that patients with severe angiographic lesions usually have higher HbA1c values but without being an independent risk factor [15].

In the present study, the history of DM and left main coronary artery disease appeared to be independent risk factors for the severity of coronary heart disease as expressed by the SYNTAX score. This finding could explain the absence of a statistically significant association between HbA1c and angiographic severe coronary artery disease as many patients with known diabetes mellitus (which is an independent risk factor as mentioned above) counteract the pathophysiological effects (oxidative stress - inflammation - atherosclerotic lesions) of diabetes which usually existed many years before glycemic control was achieved via dietary supplementation and medication. It should also be remembered that HbA1c levels reflect the patient's glycemic status during the last trimester and not over a longer period of time.

This study has two main limitations. The first is that a single measurement of HbA1c was used and therefore no reliable conclusions can be drawn on the effect of HbA1c on coronary vessels over time. This is perhaps one of the reasons that HbA1c was not statistically proven to be an independent prognostic factor for severe coronary heart disease in the present study. Another limitation of the study is the failure of coronary angiography to provide accurate information on the composition of atherosclerotic plaques and thus the possibility of a minor angiographic lesion leading to a clinically significant event in the future. To avoid this limitation, intravascular ultrasound could be used in future studies in addition to coronary angiography, in order to provide important information on the arterial wall and atherosclerotic plaque formation.

In conclusion, subjects with higher HbA1c values had more severe coronary heart disease as expressed by the SYNTAX score. Glycosylated hemoglobin levels reflecting patients' chronic glycemic status appeared to be a useful tool in the future to distinguish high-risk patients who may benefit from earlier intervention to reduce the risk of cardiovascular events. However, it remains unclear at this time whether therapeutic agents should be administered to individuals with normal HbA1c levels. Larger studies should be carried out on this topic and certainly an extensive interdisciplinary discussion should be conducted regarding the role glycosylated hemoglobin as a prognostic marker for coronary heart disease and as an indicator of early intervention even in non-diabetic patients. Studies are also needed to investigate the possible association of glycosylated hemoglobin levels, especially in non-diabetic patients, with clinical outcome, morbidity and mortality. Existing data in diabetic patients have already demonstrated the association of HbA1c with clinical outcome and morbidity [16-17]. It should also be remembered that people with

coronary artery disease that cause stenosis >50% may never develop acute coronary syndrome while people with <50% lesions can develop acute coronary syndrome that can even lead to death. After all, coronary angiography only depicts the lumen of the vessel and does not provide information on the arterial wall and the status of atherosclerotic plaques (stable or unstable plaque). Therefore, in addition to the association of glycosylated hemoglobin levels with angiographic severity, it is also necessary to investigate its association with the clinical outcome.

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Corresponding author:

Stavros Mantzoukis
MD, MSc. Department of Cardiology,
General Hospital of Ioannina "G. Hatzikosta",
1 Makrigianni Str, Ioannina 45500, Greece
E-mail: stavrosmantzoukis@gmail.com

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