

Reasons why COVID-19 survivors should follow dietary World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations: from hyper-inflammation to cardiac dysfunctions

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Abstract. – The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) advise cancer survivors to follow their lifestyle recommendations for cancer prevention. Recent research indicates that a proper diet could exert beneficial metabolic and immune effects in humans through the involvement of several, not yet properly known, metabolic pathways. Here, we argue that following WCRF/AICR recommendations could be a strategy to prevent cardiovascular outcomes [fulminant myocarditis, heart failure, venous thromboembolism (VTE)] and acute respiratory distress syndrome (ARDS) in patients during follow-up post COVID-19 infection. We discuss the metabolic effects of a WCRF/AICR based diet, highlighting on the involved cardio-metabolic pathways related on NLRP3 inflammasome-cytokines axis aimed to improve prognosis of COVID-19, especially in patients with cancer.

Key Words:

COVID-19, Nutrition, Cancer, Cardio-oncology, Diet.

Introduction

Incidence and mortality of pandemic coronavirus disease 2019 (COVID-19) is constantly growing¹. SARS-CoV-2, an enveloped and non-seg-

mented RNA based virus, is the etiological agent of coronavirus disease 2019 (COVID-19)². The main causes of death are actually well known and involve a broad spectrum of cardiovascular diseases (mainly VTE, fulminant myocarditis, myocardial infarction) and ARDS³. Clinical characteristics of patients with COVID-19 clearly identified a cytokine storm, secondary to the interaction of SARS-CoV-2 with human cells expressing angiotensin converting enzyme-2 (ACE2), an integral (type I) membrane zinc metalloproteinase widely expressed in heart, lungs, esophagus, kidneys, bladder and small intestine^{4,5}.

To date, over 114.6 million total cases are ascertained, with over 2,544.22 of deaths¹. After 1 year of clinical experience, several strategies aimed to improve outcomes and survival in patients with COVID-19 are available⁶. Several drugs are being used in clinical trials to reduce COVID-19 mortality, including cytokine-blocking agents (monoclonal antibodies against Interleukin-1 or Interleukin-6), remdesivir, hydroxychloroquine, azithromycin⁷⁻⁹. RNA or DNA-based vaccines and inactivated viral-based vaccines are currently administered to peoples in a worldwide distribution campaign, currently underway¹⁰.

Unfortunately, SARS-CoV-2 is well able to mutate with great frequency¹¹, aimed to replicate more effectively and resist to the immune system

of the host organism. In a historical moment full of uncertainties and socio-economic difficulties, a proper lifestyle should be a *conditio sine qua non* to reduce the relative risk of cardiometabolic diseases and mortality^{12,13}. Especially patients with established cardiovascular diseases (CDV) and cancer should follow a proper diet and an anti-inflammatory lifestyle aimed to reduce risk of high cholesterol, hyperglycemia, obesity and diabetes¹⁴. Moreover, it is well established that COVID-19 survivors experienced sarcopenia¹⁵, characterized by reduced muscle mass and muscle strength. Patients with sarcopenia have poor immune response and metabolic stress when facing acute infection, surgeries and others¹⁶. Considered the overall lifestyle of peoples during COVID-19 pandemic, especially for COVID-19 survivors, follow a proper diet is of crucial importance in order to reduce the risk of cardiometabolic diseases and mortality. Here we highlight on the metabolic effects of a proper anti-inflammatory diet based on the principles of WCRF/AICR recommendations. A diet following the WCRF-AICR recommendations¹⁷ is able to change the cardiometabolic profile through several pathways, including the NLRP3 inflammasome-and myddosome called MyD88^{18,19}, being upstream of cytokine storm causing multi-organ failure in COVID-19 as well as myocarditis, venous thromboembolism (VTE), hypertension and acute respiratory distress syndrome (ARDS)²⁰.

World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Recommendations: Principles and Metabolic Effects

It was recently estimated that about 30-50% of the world's cancer cases may be preventable through a proper lifestyle and diet¹⁷. The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) published Diet, Nutrition, Physical Activity, and Cancer: A Global Perspective, the WCRF/AICR Third Expert Report in 2018²¹. This report summarized the global research on diet, nutrition, physical activity, and cancer and updated the 10 evidence-based Cancer Prevention Recommendations on modifiable lifestyle behaviors able to reduce the incidence and mortality of cancer²². The WCRF-AICR recommendations are the backbone of a proper lifestyle based on physical activity and a proper anti-inflammatory diet. Briefly, Table I summarized the principles of WCRF-AICR recommendations. Several studies²¹⁻²³ showed that

WCRF/AICR are associated with reduced cancer risk and improved outcomes after a diagnosis of cancer²³. Other reports concluded that WCRF/AICR 2018 recommendations could reduce significantly the global burden of cancer. The most recent version of the recommendations focalized on the “limit consumption of fast food and other processed food high in fat, starches or sugar” and “limit consumption of sugar sweetened drinks”, highlighting on the dangerous effects of high glycemic index foods²⁴.

Outcomes in Patients Following Dietary World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Recommendations: Clinical Evidence

A diet following the WCRF/AICR recommendations can significantly reduce the incidence and recurrence of the most known cardiovascular risk factor called Metabolic Syndrome⁴³, associated to significant systemic anti-inflammatory effects. Metabolic syndrome is a multifactorial disease characterized by the aggregation of 3 or more metabolic disorders⁴³. In accordance to the updated harmonized “International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute” criteria, Metabolic Syndrome involves the increased distribution of visceral adiposity, dyslipidemia with lower HDL levels and higher triglycerides, glucose intolerance and/or reduced insulin sensitivity and abnormal blood pressure^{44,45}. Numerous studies⁴⁴⁻⁴⁷ suggest that metabolic syndrome predisposes to different chronic disease, including type 2 diabetes (T2D), obesity, cardiovascular diseases, osteoarthritis, neurodegenerative diseases like Alzheimer syndrome, as well as cancer of the breast, prostate, pancreas, colorectal and liver^{46,47}. The beneficial effects of a diet based on the WCRF/AICR recommendations may be related to monounsaturated fatty acids, omega-3 fatty acids like ALA and polyphenols chemically associated to the fibers in whole grains, fruits, vegetables and olives^{48,49}. Several studies⁴⁸⁻⁵⁰ has shown the impact of changes in diet in the reversion on Metabolic syndrome. Esposito et al⁵⁰ demonstrated in non-cancer patients affected by metabolic syndrome how 2 years of Mediterranean diet can reduce the hs-CRP and IL-6, IL-7, IL-18, improve the endothelial function, and decrease the metabolic syndrome components. Recent studies^{51,52} suggested that a diet rich in whole grains, vegetables and legumes improved

Table I. Association of circ_001680 expression with clinicopathologic characteristics of glioma.

Recommendations	Specifications	Involved overall metabolic effects	Ref.
Be at a healthy weight	Ensure that body weight during childhood and adolescence projects toward the lower end of the healthy adult BMI range. Keep your weight as low as you can within the healthy range throughout life. Avoid weight gain (measured as body weight or waist circumference) throughout adulthood.	Low waist circumference is associated to high levels of adiponectin and low levels of IL-1 β , leptin, IL-6 and hs-CRP. Patients with low BMI and waist circumference have reduced phosphorylation of muscle AMPK, but increased phosphorylation of mTOR.	25-27
Be physically active	Be at least moderately physically active and follow or exceed national guidelines. Limit sedentary habits.	Patients physically active have low levels of circulating chemokines, cytokines and growth factors associated to CDV, TVE, atherosclerosis, heart failure and cancer. Patients physically active have reduced hs-CRP, HOMA-IR and leptin levels through LKB1-AMPK-mTOR related pathways (reduced levels of NLRP3 are also demonstrated)	28,29
Eat a diet rich in whole grains, vegetables, fruit, and beans	Consume a diet that provides at least 30 g/d of fiber (based on the AOAC methods) from food sources. Include in most meals foods containing whole grains, nonstarchy vegetables, fruit, and pulses (legumes) such as beans and lentils. Eat a diet high in all types of plant foods including at least 5 portions or servings (at least 400 g or 15 oz in total) of a variety of nonstarchy vegetables and fruit every day. If you eat starchy roots and tubers as staple foods, eat nonstarchy vegetables, fruit, and pulses regularly, too, if possible.	Patients consuming high doses of fibers have an anti-inflammatory microbiota profile. High dietary fiber intake is and all-cause mortality. High-fiber effects rely on epithelial GPR43 and immune cell GPR109a. High whole grains intake is associated to low levels of fasting glucose, glycated-Hb and OxLDL. Whole grain intake has also been inversely associated with other less common causes of death including deaths from infection and respiratory diseases. High legumes and vegetables are associated to improved immune functions and low levels of NLRP3 inflammasome-IL-1-IL-6 pathways.	30-32
Limit consumption of “fast foods” and other processed foods high in fat, starches, or sugars	Limit consumption of processed foods high in fat, starches, or sugars – including fast foods (readily available convenience foods that tend to be energy dense and are often consumed frequently and in large portions); many pre-prepared dishes, snacks, bakery foods, and desserts; and confections (candy).	Processed foods high in fat, starches, or sugars activated pro-inflammatory pathways associated to high risk of CDV, VTE, heart failure, cancer and metabolic syndrome. Processed foods high in fat, starches, or sugars increased AGE-RAGE axis, which increases the activation of NLRP3-MyD88-NF-kB related pathways High glycemic index foods are associated to reduced immune functions (low levels of circulating CD8+ and CD4+ cells)	33-35

Continued

and reversed metabolic syndrome by reducing systemic inflammation due to reduced intake of refined carbohydrates, cholesterol and increased intakes of n-3 fatty acids (especially ALA), dietary fibers (30g/day, from vegetables, fruit and whole grains) with a specific attention to brown rice. Other studies⁵³⁻⁵⁵ showed significant reductions in fasting glucose, hs-CRP, homocysteine, LDL cholesterol, triglycerides, insulin, HOMA score and plasma calprotectin, a new marker of

visceral obesity and a putative marker of atherosclerosis and heart failure⁵³⁻⁵⁵. Calprotectin is a protein activated by human granulocyte and macrophages in the inflammatory state and its function is based principally on the activation of the toll like receptors 4 (TLR4), and advanced glycation end products (AGEs) receptors, which are important proteins involved in the activation of the NF-kB *via* an upstream signaling cascade composed of tyrosine kinases and several onco-

Table 1 (Continued). Association of circ_001680 expression with clinicopathologic characteristics of glioma.

Recommendations	Specifications	Involved overall metabolic effects	Ref.
Limit consumption of red and processed meat	If you eat red meat, limit consumption to no more than ~3 portions per wk. Three portions is equivalent to ~350-500 g (12-18 oz) cooked weight of red meat. The term “red meat” refers to beef, veal, pork, lamb, mutton, horse, and goat. Consume very little, if any, processed meat, which refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavor or improve preservation.	High consumption of red and processed meat increased the intake of saturated fatty acid and pro-inflammatory molecules associated to high levels of NLRP3 inflammasome, circulating IL-1, IL-6, IL-8 and hs-CRP and TNF- α . Trans fats are associated with all-cause mortality, total CHD, and CHD mortality, probably because of higher levels of intake of industrial trans fats than ruminant trans fats. Overall red and processed meat intake was positively associated with serum leptin levels in men and women. In women, higher red and processed meat consumption was significantly associated with higher CRP and lower adiponectin levels.	36-38
Limit consumption of sugar-sweetened drinks	Drink mostly water and unsweetened drinks. Sugar-sweetened drinks are defined as liquids that are sweetened by adding free sugars, such as sucrose, high fructose corn syrup, and sugars naturally present in honey, syrups, fruit juices, and fruit juice concentrates. This includes, among others, sodas, sports drinks, energy drinks, sweetened waters, cordials, barley water, and coffee- and tea-based beverages with sugars or syrups added. This does not include version of these drinks which are “sugar free” or sweetened only with artificial sweeteners.	Consumption of sugar-sweetened drinks is associated to higher adiposity, CRP, leptin, and MCP-1, but lower SFRP-5. High fructose intake is associated to activation of NLRP3-inflammasome increasing the production of chemokines associated to cancer, overall mortality and CDV.	39,40
Limit alcohol consumption	Consuming alcoholic drinks is a cause of several cancers. For cancer prevention, it's best not to drink alcohol There is no threshold for the level of consumption below which there is no increase in the risk of at least some cancers.	Alcohol intake affects the production, site of action and metabolism of cytokines, which are regulatory peptides of the immune and inflammatory response of lymphocytes, monocytes/macrophages and a variety of other cell types.	41,42

Dietary WCRF/AICR recommendations: principles and putative metabolic effects/pathways involved.

genes PI3-K, PKC and p38 MAPK⁵⁶. Recently, plasma calprotectin has been associated to metabolic syndrome, type 2 diabetes and atherosclerosis, those emerging as new marker of obesity-associated chronic low-grade inflammation⁵⁶. Instead, high sensitivity C-reactive protein has become in the last years an important marker of systemic inflammation, CVD and type 2 diabetes⁵⁷. Notably, these biomarkers are strictly associated to the secondary hemophagocytic lymphohistiocytosis (sHLH)⁵⁸. SARS-CoV-2 infection, as other viral-related diseases, leads to sHLH, a multi organ hyperinflammatory condition driven by cytokines^{59,60}. sHLH induces hyper-activation of cytotoxic T lymphocytes, macrophages and

natural killer cells, leading to multiorgan failure (including myocarditis and coronary artery aneurysm) and consequently to death⁵⁸. Although pathogenesis of sHLH is not well understood, in patients with sHLH monoallelic mutations or polymorphisms they have been detected in genes involved in cytokine production and signaling, such as NLRP3, other inflammasome proteins and toll-like receptors⁶¹. Interestingly, a diet rich in whole grains, vegetables and legumes are associated to an anti-inflammatory profile of circulating cytokines and low levels of CVD biomarkers^{62,63} (including IL-1, IL-6, IL-8, CXCR4, NLRP3 inflammasome, hs-CRP and growth factors) involved in pathogenesis of sHLH; there-

fore, following an appropriate nutrition should be of key importance in patients with COVID-19, especially in those particularly vulnerable like cancer long survivors who have undergone pharmacological therapies and/or radiotherapy and/or hormone therapy that are associated to an high risk of heart failure, arrhythmia, venous thromboembolism and myocarditis^{64,65}. Several studies^{66,67} demonstrated that a diet rich in whole grains, especially in brown or red rice, millet, quinoa, amaranth, buckwheat, durum wheat semolina pasta and low in red meat, high in vegetables and high in fibers (30 g/day) are associated with less incidence and recurrence of cancer and cardiovascular complications⁶⁶. Interestingly, an anti-inflammatory diet with low-glycemic index increased quality of life of cancer patients reducing also fatigue and neuropathy⁶⁷.

Moreover, an essential recommendation of WCRF/AICR is based on the daily physical activity; especially cancer survivors with moderate-to-vigorous physical activity were found to be associated with lower levels of fatigue and neuropathy and increased overall survival⁶⁸.

Moreover, a longitudinal study showed that colorectal cancer patients following a 'Western' diet characterized by high consumption of potatoes, red and processed meat, poultry and cakes had lower chances to improve in physical functioning 1-year post-treatment compared with patients following a diet rich in fruit and vegetables⁶⁹. Recently, it was demonstrated that a diet based on WCRF/AICR recommendation reduced fatigue in cancer survivors many years after cancer diagnosis, improving cardiovascular risk factors and overall survival⁷⁰. Another recent observational study⁷⁰ concluded that WCRF/AICR recommendations are associated to a reduced risk of overall cancer incidence. Moreover, a diet based on low glycemic index foods reduced several cardio-metabolic biomarkers, including IL-1, IL-6, IL-8, CXCR4, NLRP3 inflammasome, hs-CRP and growth factors associated to secondary hemophagocytic lymphohistiocytosis, myocarditis, VTE and arrhythmia^{71,72}.

Putative Effects of Dietary World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Recommendations in Patients with COVID-19 at High Risk of Developing Cardiovascular Dysfunctions

A proper anti-inflammatory nutrition is able to modulate metabolic pathways. Firstly, dietary

recommendations following WCRF/AICR recommendations activates p-AMPK, thus reducing mTOR-related pathways⁷³. The anti-inflammatory mechanisms of a diet in line with WCRF/AICR recommendations are linked to high levels of SCFAs that are physiologically active bio-products mainly composed of acetate, propionate and butyrate, able to regulate host metabolism, immune system and cell proliferation⁷⁴. A diet rich in whole grains increases *Bacteroides spp.*, *Bifidobacterium spp.* and *Prevotella spp.*, but also *Streptococcus spp.*, *Firmicutes*, *Clostridium spp.* able to produce high levels of SCFAs that are absorbed into the blood stream and transported to peripheral tissues where they are able to regulate the immune system and host metabolism and reduce inflammation⁷⁴. A diet rich in legumes, whole grains and vegetables increased the SCFAs that, in turn, inhibit the NLRP3-cytokine axis⁷⁵. Notably, SCFAs reduces chemokines, cytokines and growth factors associated to high risk of overall mortality, CDV, atherosclerosis, VTE, arrhythmia and cancer incidence⁷⁶. Interestingly, it has also been shown that SCFAs may enhance the synthesis and growth of dendritic cells and a TH-2 pathway of immune cells both in lung tissue and intestine; a TH2 immune activation increases antiviral and antibacterial functions.

Furthermore, a diet rich in legumes and whole grains have a beneficial effect on lung injuries and to reduce chronic respiratory disease mortality. A healthy diet following WCRF/AICR recommendations, rich in protein and based to high consumption of vegetables, whole grains, plant oils and fish would be recommended, along with physical exercises in three categories of subjects, such as asymptomatic patients, patients with mild symptoms or in quarantine and COVID-19 survivors. Especially patients with cancer, characterized by a high vulnerability and multiple cardio-metabolic risk factors, should benefit from a WCRF/AICR diet in order to reduce systemic and cardiac inflammation, improve alveolar-capillary functions and reduce the hypercoagulability state⁷⁷. A diet based on the WCRF/AICR recommendations improves the immune system through several mechanisms; in fact, patients treated for 6 months with an anti-inflammatory diet improved functions of neutrophil and macrophages against bacteria and virus⁷⁸; these effects were mediated by high intake of fibers (> 30 g/die) and SCFA production by enterobacteria in small intestine. Another interesting study⁷⁹ demonstrated that

anti-inflammatory diet rich in whole grains, legumes and vegetables improves the antibody production from plasma-cells after virus and bacteria infections. These effects could be mediated by the downregulation of T-reg cells due to low leptin and insulin levels, hypoglycemia and increased levels of adiponectin⁸⁰. Conventionally, T-reg cells expression is linked to eicosapentanoic mediators and NLRP3 inflammasome⁸¹. Another effect of a WCRF/AICR diet is based on the reduction of death after severe viral or bacterial infection⁸². Interestingly, diet increases cardio-pulmonary fitness in these patients through the reduction of hs-CRP, IL-6, IL-1 and leukotrienes⁸³. Retrospective trials evidenced that patients with low BMI and visceral fat affected by SARS-CoV-2 infection have a better prognosis compared to overweight or obese ones⁸⁴. Diabetes mellitus type 2 or 1 is an established negative prognostic factor for viral diseases, including COVID-19. Currently available data indicate that metabolic syndrome, obesity, previous cardiovascular diseases, diabetes mellitus or hyperglycemia are prognostic risk factors in patients with COVID-19⁸⁴. Patients with cancer and cardiovascular diseases are particularly vulnerable and classifiable as high-risk patients. As a community, we should pay close attention to these patients especially to those recently treated with cardiotoxic anticancer therapies or radiotherapy associated to heart failure, myocarditis and VTE⁸⁵. A close cardiovascular and hematological screening should be promoted in high-risk patients stimulating theme to follow WCRF/AICR recommendations based on healthy and physically active lifestyle.

Another clinical aspect not properly discussed among clinicians is the sarcopenia associated to COVID-19⁸⁶. Most patients with COVID-19 have moderate-to-severe sarcopenia, with negative repercussions on glucose, immune and cardiovascular metabolism⁸⁷. Sarcopenia is well associated with a higher overall mortality risk compared to the general population⁸⁷. Based on this data, COVID-19 survivors, especially cardio-oncology patients, should be followed up with personalized routes of daily physical activity associated with nutrition based on the principles of WCRF/AICR, especially with a controlled daily protein intake associated to meals with low glycemic index and low insulin load. Furthermore, corticosteroid therapy is an important therapeutic component in patients with COVID-19; however, it is associated to a high risk of sarcopenia and hyperglycemia⁸⁸,

therefore, a low glycemic index and low insulinemic load diet could be of key importance in these patients, providing an appropriate intake of micronutrients useful to the maintenance of glucose homeostasis.

Although WCRF/AICR recommendations discourage the use of multivitamin supplements for cancer prevention, a note on the usefulness of supplementation with oral nutraceuticals in COVID-19 patients is needed⁸⁹. Interestingly, Cereda et al⁹⁰ suggest the Vitamin D supplementation in COVID-19 patients could reduce the risk of incubation and overall mortality. Other evidence is available on ascorbic acid, boswellic acid and resveratrol supplementations in this cohort of patients. Ascorbic acid is still known to increase immune functions in randomized clinical trials through a TH2-induced stimulation with increased antibody production after viral or bacterial infection⁷⁹. Boswellic acid, a natural inhibitor of leukotrienes, is an anti-inflammatory nutraceutical agent conventionally used to improve lung functions in patients with asthma and to reduce pain in patients with rheumatoid arthritis and ulcerative colitis^{91,92}. Resveratrol is a natural flavonoid with pleiotropic properties which start from antioxidant to immuno-stimulating and cardioprotective effects and its oral administration in randomized clinical trial reduced cardiovascular events in high risk patients without and with cancer^{93,94}.

Conclusions

Patients with COVID-19, especially those at high risk of vulnerability, could benefit from a proper anti-inflammatory diet at low glycemic index and insulin load. It is well known that WCRF/AICR based diet improve the cardio-respiratory fitness and reduced systemic inflammation in randomized trials through the involvement of several pathways mediated by NLRP3 Inflammasome and AMPK-mediated cytokines. Notably, COVID-19 survivors experienced sarcopenia, a well-known cardio-metabolic risk factor, so it is urgent to follow a proper protein-controlled diet aimed to prevent and control muscle loss. Based on these considerations, institutions should provide and explain to the population the principles of the WCRF/AICR diet based on the daily intake of anti-inflammatory foods rich in whole grains and legumes, even every day, in order to

reduce cardiometabolic risk factors like hyperglycemia, chemokines and systemic biomarkers of inflammation consequently reducing myocarditis, VTE, heart failure and multiorgan failure associated to SARS-CoV-2 infection.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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