Mini Review
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Obesity, COVID-19 and vitamin D: is there an association worth examining?

Abstract

Many COVID-19 deaths among those enumerated in the context of the 2020 corona virus pandemic appear to be associated more often than not with obesity. At the same time, obesity has been linked to a deficiency in vitamin D, a factor that appears to hold some promise for advancing our ability to intervene in reducing COVID-19 severity. This mini-review reports on what the key literature is reporting in this regard, and offers some comments for clinicians and researchers. Drawn from PUBMED, data show that a positive impact on both obesity rates and COVID-19 morbidity and mortality rates may be attained by efforts to promote vitamin D sufficiency in vulnerable groups.

Keywords: coronavirus, COVID-19, infection, immune system, obesity, vitamin D

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Ray Marks
Department of Health and Behavior Studies, Columbia University, USA

Correspondence: Ray Marks, Department of Health and Behavior Studies, Teachers College, Columbia University, Box 114, 525W, 120th Street, New York, NY 10027, United States, Email rm26@columbia.edu

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Background

The current 2020 Coronavirus [COVID-19} pandemic appears to be highly implacable to any immediate solution and/or primary prevention strategy, although some benefit is attributed to physical distancing laws and an emphasis on personal protection and sanitation. At the same time, epidemiologists and others note that most COVID-19 deaths occur among older persons, especially those who are obese, or have comorbid health problems associated with obesity, such as diabetes, and heart disease,[1] though obesity ranks higher than cardiovascular disease and diabetes among older victims.[1] Obese adults with diabetes and cardiovascular disease are also likely to be sicker and require ventilation at higher rates than those with a healthy weight.[1] As well as the challenges of treating obese cases, including imaging and turning patients, which may retard their recovery process[1] prior research into factors influencing obesity, an epidemic in its own right in many countries, shows vitamin D as one possible factor that influences obesity rates.[2] Moreover, as discussed by Carter et al.,[3] there is a possible link between diminished immune function and individuals with obesity that may foster a state of greater viral pathogenicity in this population. A further challenge to those with obesity during the current pandemic may involve an associated vitamin D deficiency/insufficiency. In addition, to the possible role played by deficient vitamin D in mediating obesity, plus COVID-19 infections, other data show that low population mortality rates from COVID-19 tend to occur in countries south of latitude 35 degrees North, where there is more consistent sunlight, a precursor to vitamin D.[4]

Luzi et al.,[5] report that within the basal hormone milieu, a defective response of both innate and adaptive immune system functions and sedentariness are major determinants in determining the severity of influenza viral infections in obese patients. According to this group, being overweight not only increases the risk of infection and complications for the individual obese person, but a large prevalence of obese individuals within the population might increase the chance of appearance of more virulent viral strains, while prolonging virus shedding throughout the total population and eventually, possibly increasing overall mortality rates in the context of an influenza pandemic. Not discussed is the possibility that the prolonged recovery and debility of the COVID-19 patient may foster more weight gain than anticipated if physical activity is severely curtailed, and energy dense foods continue to be eaten or promoted for building energy and strength in the infected individual case. In another report, Savastano et al.,[6] discusses the fact that persons who are obese, may also be expected to have a low level of possible sun exposure due to their sedentary lifestyle and less possible desire to carry out outdoor physical activities. As a result, the vitamin D sequestration in adipose tissue, and volumetric dilution of ingested or cutaneously synthesized vitamin D3 in the large fat mass of obese patients, might produce a lower than desirable vitamin D serum status, which has adverse implications for the immune system and others such as inflammatory processes, and cognitive processes. Alternately, the expression of both vitamin D3 receptors and enzymes responsible for vitamin D3 metabolism in adipocytes has implied a role for low vitamin D status per se in the realm of obesity development.

According to a recent report, vitamin D not only influences COVID-19 morbidity, but also mortality rates, as well as obesity. Other data show vitamin D may reduce infection rates, while boosting immune system functioning,[4] however, obesity has the opposite effect it seems, even if vitamin D levels are not considered as indicated by Dixit et al.,[7] who reported emerging evidence suggesting that the state of chronic caloric excess seen during obesity is associated or driven by changes in metabolic factors that can also impact immune function and lifespan. As argued by Rhodes et al.,[4] in consideration what is known about obesity, vitamin D, and the COVID-19 pandemic, it may be relevant to consider the interrelationship of these facts in efforts directed towards minimizing excess COVID-19 risk, and the severity thereof.

Aims

This brief aimed to both examine and supplement the above facts in an effort to provide more clarity and detailed facts about this issue than that outlined above for the readers' consideration. Sought were articles chosen from the PUBMED data base to represent the state of the art in this regard. The mini review specifically aimed to cover four overlapping themes: Obesity and Vitamin D; Obesity and Infection; Obesity and Immunity, Vitamin D and Infection.

Evidence for a hypothesized link as per Figure 1 was specifically sought.

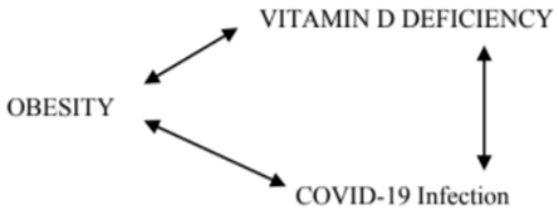

Figure 1 Possible interplay between obesity, vitamin D, and COVID-19 risk.

Results

General observations

The key topics researched in PUBMED from January 1980-May 10, 2020 yielded varying degrees of interest or opportunity in the realm of the present discourse as outlined below in Table 1. Most recent articles were reviews, rather than actual research studies.

Table 1 Summary of relative numbers of publications listed in PUBMED between Jan 1980-May 2020 and keywords applied during search

Key term applied	Numbers of citations listed
Obesity	308859
Obesity+Infection	13438
Obesity+Immune system	8712
Obesity+Vitamin D	3464
Obesity+Vitamin D deficiency	1541
COVID-19	7273
Obesity+COVID-19	87
COVID-19+Obesity prevention	19
Vitamin D	67866
Vitamin D and Covid-19	18

Specific observations

Obesity and vitamin D

In the context of obesity and vitamin D, an essential vitamin, Vranić et al.,[8] notes that obesity, defined as an excess amount of body fat, and one that represents a significant health problem worldwide, is also one where low vitamin D cannot yet be excluded as a causative factor. Thus, targeting lifestyle through a healthy diet and exercising outdoors might prove to be an important first line treatment option by those who wish to affect both obesity and vitamin D deficiency simultaneously and impactfully. However, supplementation remains a treatment option, rather than a routine form of intervention for those who are obese, both in general, as well as among individuals who may still have a residual vitamin D deficiency after weight loss. Alloubani et al.,[9] who sought to assess the prevalence of a vitamin D among adults in Saudi Arabia, revealed lifestyle and nutritional habits appear to be important in producing a deficient state of vitamin D, often found in adults with chronic health conditions, such as diabetes. As discussed by Savastano et al.,[6] both low vitamin D status and obesity have concomitantly reached epidemic levels worldwide, and this may be occurring simultaneously or in parallel if for example obese individuals adopt a more sedentary lifestyle with less outdoor activity, and/or persons suffering from obesity may have more of a problem absorbing vitamin D through sunlight exposure. The clothing commonly worn in some countries can also act as a specific barrier to sunlight exposure. This is important because research suggests the expression of both vitamin D3 receptors and enzymes responsible for vitamin D3 metabolism in adipocytes, if deficient, may have a role to play in the development of obesity. Perreira Santos et al.,[2] who evaluated the association between obesity and vitamin D deficiency found that the prevalence of a vitamin D deficiency was 35% higher in obese subjects compared to a control group and 24% higher than controls in the overweight group. These results were taken to indicate that the prevalence of vitamin D deficiency is likely to be more elevated in obese or overweight subjects. According to Pourshahidi[10] vitamin D deficiency and sub-optimal status are increasingly associated with unfavourable metabolic phenotypes, including insulin resistance, type 2 diabetes and cardiovascular conditions, also commonly linked with overweight and obesity. Several plausible explanations provided included the hypothesis that heavier individuals may partake in less outdoor activity, may also cover-up and wear more clothing than leaner individuals, thus decreasing sun exposure and limiting endogenous production of cholecalciferol, an important vitamin D compound, in the skin. Walsh et al.,[11] noted a consistent vitamin D deficiency to prevail among adults classified as obese. Hussein et al.,[12] too, found high levels of obesity were inversely related to the presence of low serum vitamin D levels.

Obesity and the immune system

In terms of a possible link between obesity and the immune system, Maurizi et al.,[13] who outlined the fact that obesity is a condition likely associated with several dysmetabolic conditions or worsening of cardiovascular and other chronic disturbances, also reported that obesity is associated with the onset of low-grade systemic inflammation, thus highlighting the importance of the interplay between adipocytes and the immune system cells. Contributing to this, Anderson et al.,[14] further suggest obesity is associated with metabolic disturbances that cause tissue stress and dysfunction, and that obese individuals are at a greater risk for chronic disease, low-grade inflammation states, immunity and pathogen defense alterations, plus poor coordination of innate and adaptive immune responses. These changes are further associated with an overall negative impact on chronic disease progression, immunity from infection, and vaccine efficacy. De Heredia et al.,[15] who share the aforementioned views state that obesity, as found in other states of malnutrition, is known to impair immune functioning, while altering leucocyte counts as well as cell-mediated immune responses. In addition, evidence has arisen that an altered immune function contributes to the pathogenesis of obesity. Milner & Beck[16] also noted strong evidence indicating that excess adiposity negatively impacts immune function and host defense mechanisms in obese individuals. Moreover, they substantiated that obesity, characterized by a state of low-grade, chronic inflammation, is also associated with disturbed levels of irculating nutrients and metabolic hormones. Unsurprisingly, while not widely publicized,

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obesity was found to be an independent risk factor for increased morbidity and mortality following infection with the 2009 pandemic influenza A (H1N1) virus. In sum, there is a positive feedback loop between local inflammation in adipose tissue and altered immune response in obesity that appears to have the potential to contribute to the development of related metabolic complications, and possible heightened risk of acquiring COVID-19 and associated viral infections compared to lean controls.

Obesity and infection

As discussed by Dobner & Kaser[17] nutritional status is a well-known risk factor for metabolic and endocrine disorders. In addition, more recent studies suggest that dietary intake also affects immune function and hence infection risk. In reviewing the effect of body weight on infection rates at different periods of life, data from industrialized countries suggest that infection rates are increased in obese children and adolescents, and in obese adults infections of the skin and respiratory tract are common. As well, surgical-site infections have consistently been reported to be more common in obese adults than in normal-weight adults. In terms of viral infection and obesity, Sohrab et al.,[18] confirm the association of pathogenic viruses with obesity in both human and animals. At the same time, adenoviruses play a significant role in the induction of obesity by affecting various pathways highly negatively. Due to impaired immunity, obese individuals who are more prone to infectious agents are also more susceptible to complications of infection. Accordingly, the prevention of obesity associated infections by an effective vaccination will undoubtedly be helpful in the context of reducing highly adverse obesity related outcomes, especially the global impact of COVID-19 that currently prevails.

In explicating the interplay between obesity and infection, and its possible reciprocal relationship, Hainer et al.,[19] argue that this relationship may reflect the greater susceptibility of obese individuals to infection due to impaired immunity. In such cases, the infection is not related to obesity as a causal factor but represents a complication of obesity. In contrast, several infections have been suggested as potential causal factors in the context of human obesity. For example, the adenovirus 36 (Adv36), is said to activate lipogenic and proinflammatory pathways in adipose tissue, and improves insulin sensitivity, lipid profile and hepatic steatosis. The E4orf1 gene of Adv36 exerts insulin senzitizing effects, but is devoid of its pro-inflammatory modalities. Consequently, the development of a vaccine to prevent Adv36-induced obesity or the use of E4orf1 as a ligand for novel antidiabetic drugs could open new horizons in the prophylaxis and treatment of obesity and diabetes. As discussed by the authors, more experimental and clinical studies are needed to elucidate the mutual relations between infection and obesity, and to identify additional infectious agents causing human obesity, as well as the conditions that predispose obese individuals to specific infections, such as COVID-19. Huttunen & Syrjänen[20] affirm that the interactions between obesity and infectious agents has recently received increasing recognition, wherein data show an association between obesity and poor outcomes in the context of the H1N1 influenza pandemic, plus other infections, such as skin infections. As such, even though more research is needed, the consequences of obesity appear to have substantial relevance in the context of the current global pandemic, because as outlined by Falagas & Kompoti[21] obesity can impact the immune response through a variety of immune mediators, and which can foster heightened susceptibility to various forms of infection.

Vitamin D and infection

As the world struggles to control the COVID-19 outbreak, Jakovac[22] have raised the question of the possible use of vitamin D as an intervention in the context of averting COVID-19 morbidity and mortality. Martineaus et al.,[23] who assessed the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, found the vitamin to reduce the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses, but not in those receiving one or more bolus doses. Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L than in those with baseline 25-hydroxyvitamin D levels ≥25nmol/L. Even though 12 vitamin D did not influence the proportion of participants experiencing at least one serious adverse event, it was concluded that vitamin D supplementation is safe and protects against acute respiratory tract infection overall. Patients deemed highly vitamin D deficient and those not receiving bolus doses experienced the most benefit. Indeed, Karar et al.,[24] have drawn attention to the possible association between severe vitamin D deficiency and mortality pertaining to COVID-19.[24]

Discussion

Obesity, an intractable problem of pandemic proportion that is increasing globally is associated with enormous human and social costs. At the same time, high rates of obesity, known to reduce protection against infectious agents[16] are found among COVID-19 sufferers, and especially among those with metabolic syndrome, linked to obesity. Indeed, as outlined by Carter et al.,[3] as the biomedical community races to disentangle the unknowns associated with COVID-19 - the link between diminished obesity and suboptimal immune function and infection proclivity raises important questions about the possibility for greater viral pathogenicity in this population. COVID-19 disease severity may also increase relative to body mass index.[17] One plausible mechanism proposed to explain this finding is that increased adiposity may undermine the pulmonary microenvironment wherein the virus that appears to interact with the host in this environment sets up a maladaptive cycle of local inflammation, immune responses, and secondary injury.[3] Another related issue is that obesity may involve a vitamin D deficiency/insufficiency,[3,4] thus lowering the ability of the obese individual to mitigate the risk of viral infections as successfully as lean individuals. A vitamin D deficiency may also produce or foster states of obesity, diabetes, and cardiovascular disease in its own right.[25] Unsurprisingly, people who suffer from low vitamin D, as well as those who are obese, appear to be at higher risk for COVID-19.[10] Consequently, to stem the tide of suffering as a result of COVID-19, and specifically among the at risk obese population, it can be argued that until a vaccine or some form of therapy is forthcoming, and beyond, a role for obesity prevention,[27] weight loss, plus vitamin D supplementation as needed, should not be overlooked. Other data show that due to the impact of obesity on prolonging viral shedding, quarantine in obese subjects should likely be longer than is recommended for normal weight individuals. As per Grant et al.,[26] and given the world is clearly in the midst of both an obesity epidemic, plus an unprecedented viral pandemic, we thus urge researchers and clinicians to immediately consider ways other than vaccination and isolation to either prevent or mitigate the impact of obesity, as well as COVID-19 and its ability to spread rapidly. As well, we urge all public health workers and policy makers to do all they can through

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sound public health measures and media messages to focus on efforts to reduce obesity as well as the risk of COVID-19 infections, often associated with obesity. In this regard, and in addition to public health measures, this may involve educating the public concerning the roles of vitamin D in reducing the risk of respiratory tract infections, and in increasing infection resistance, as well as favorably impacting those who are obese, who are at heightened risk for COVID-19. In the meantime, it appears reasonable to conclude: that in addition to weight loss strategies, where needed, vitamin D supplementation or exposure may provide a safe means of favorably influencing obesity and COVID-19 infection rates. Moreover, efforts to support optimal immune function via weight reduction in the obese may similarly prove helpful. The projected benefits of this approach are possibly that obese adults who attain a healthy or desirable weight may have less risk of acquiring COVID-19 infections, and may recover more readily, require less intense hospitalization, and be able to be more active and partake in outdooractivity within recommended safety limits more readily than not.[27,28] For specific nutrients that contain D, health educators and dieticians and other public health officials can possibly extend this information to social media health sites and blogs used by adults, while ensuring what adults are already exposed to in this regard is grounded in science and provides for potentially effective safe affordable remedies and practices, especially during the winter months.[29]

Conclusion

Current data reveal that obesity interferes with protection against infectious agents,[16] as well as recovery rates in the case of COVID-19 hospitalization, while raising the risk for infectious agents. More research is need though to examine this potentially modifiable COVID- 19 determinant. As well, obesity may be linked to a vitamin D deficiency, and as outlined by Silberstein et al.,[30] Retrospective comparative study of vitamin D levels in previously obtained blood samples between COVID-19 survivors and confirmed fatalities may be taken to support further exploration in this realm to examine the dual role of vitamin D supplementation among at obese risk adults as far as infection rates and level of obesity are evidenced. Given the immense costs of obesity, as well as COVID-19 in their independent rights, and as discussed per Busceni et al.,[31] we advocate immediate attention to researching the specific relationship between these two existing public health epidemics. Attention to the possible mediating role of vitamin D is also strongly indicated. Consideration of these current facts and acting on them is we believe highly critical to potentially averting a worldwide catastrophy within available health systems, whose resources are already compromised as the world's population has become older and more obese and vulnerable to infections. According to Nieman,[32] while COVID-19 is considered a possible 'plague', its unrelenting presence does indeed cause us to carefully consider all possible primary prevention countermeasures we can muster, given the burgeoning prevalence of obesity and its impact on infection risk[33] and COVID-19 disease severity and recovery rates.[34,35]

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Conflicts of interest

Author declare that there is no conflict of interest.

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