Old Patients' Cytokines and Appetite

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Contributor: Maryam Pourhassan

There are few data on the longitudinal association of cytokine and appetite among older hospitalized patients. We aimed to investigate the impact of the changes of inflammatory cytokines on appetite in older hospitalized patients. A total of 191 patients (mean age 81.3 ± 6.6 years, 64% women) participated in this prospective longitudinal observational study. Appetite was evaluated using the Edmonton Symptom Assessment System on admission and after seven days. Serum cytokines such as IL-1β, IL-6, IL-8, IL-10, IL-12p70, IL-17, IL-18, IL-23 and IL-33, IFN-α2, IFN-γ, TNF-α and MCP-1 were measured both times. No significant differences in the mean serum levels of all the cytokines could be detected overtime in relation to appetite changes, except for IL-18. Appetite significantly deteriorated overtime in patients with increasing IL-18 levels and improved in those without significant changes in IL-18 levels. In a stepwise regression analysis, changes of IL-18 levels were the major independent predictor for the changes of patients' appetite and explained 4% of the variance, whereas other cytokines and variables, such as age, sex, infection and disease, did not show any impact on appetite changes. We conclude that IL-18 seems to exert a significant impact on appetite in acutely ill older hospitalized patients and should, therefore, be considered as a potential target in the diagnosis, prevention and treatment of malnutrition.

Keywords: appetite ; cytokines ; inflammation ; interleukin-18 ; older persons

1. Introduction

The process of aging is associated with physical, physiological and psychological alteration that may negatively affect appetite and food intake [1]. This condition has been identified as the anorexia of aging and it may potentially lead to the development of malnutrition [2][3][4]. Malnutrition is a frequent complication in older persons. Its etiology in this group is mostly multifactorial and not entirely understood [5]. The pathophysiology of malnutrition may be mediated by low nutritional intake, increased nutritional demands and decreased bioavailability of nutrients [5]. However, low nutritional intake seems to be the key factor in older persons. One of the major risk factors for low nutritional intake is poor appetite with a prevalence of 15% in community-dwelling older persons [6] and 33% in older hospitalized patients [7][8]. Poor appetite and impaired food consumption are often associated with chronic and/or acute illness, which may simultaneously increase energy requirements and accelerate the development of malnutrition in older adults [5][9].

Inflammation and malnutrition tend to occur simultaneously in older adults, which led to the term malnutrition-inflammation-complex syndrome [10][11]. Inflammation exerts an influence on appetite and, thus, lowers food intake [12], which is not yet sufficiently understood. In response to inflammatory conditions, a number of cytokines are synthesized and released. In addition to their biological effects to cope with infection and injury, it has been shown that the accumulation of cytokines potentially diminishes appetite and changes feeding behavior by interacting with the hypothalamus, which is the center for energy homeostasis and appetite [13][14]. Nevertheless, which cytokines have the primary impact on human appetite is unknown.

The association of inflammation expressed by increased levels of cytokines with appetite and food intake has been already confirmed in cross-sectional studies among patients with advanced cancer, renal disease, Alzheimer's disease, depression, infectious diseases and acute disease in general [15][16][17][18]. However, there are relatively few longitudinal studies testing such associations.

To the best of our knowledge, there are no data on the association of cytokine changes with appetite changes among older persons. It is understood that cytokines may lead to poor appetite, but the extent to which the changes of cytokines can alter appetite and food intake and which cytokines play a major role are not known. Although, causality cannot be proven using observational research, simultaneous longitudinal changes and a dose–response relationship would substantiate a probable causality. That is why we conducted this longitudinal study. We investigated the impact of changes of the main inflammatory cytokines on appetite and food-intake in older hospitalized patients, in order to highlight the pathophysiology of the inflammation-associated loss of appetite.

2. Development and Findings

Previous studies have demonstrated significant associations between inflammatory biomarkers such as cytokines and appetite during inflammatory diseases. Indeed, the accumulation of cytokines, which are the key mediators of inflammation, may affect the satiety center in the hypothalamus, resulting in feeding suppression and diminished appetite [13][16][19]. To the extent of our knowledge, this is the first work assessing the effect of cytokine changes on food intake and appetite changes in older hospitalized patients. Our findings demonstrated that alterations of some biomarkers of the systemic inflammatory response such as IL-6 and IL-18 had a potential impact on appetite and food intake, whereas others had not. Our results revealed that the appetite of older hospitalized patients significantly deteriorated overtime in patients with increasing IL-18 levels and improved in those without significant changes in IL-18 levels.

Up to now, the knowledge regarding the effect of inflammation in the development of malnutrition is limited and the data are largely confined to cross-sectional studies and food intake, not appetite. It has been shown that cytokines, especially IL-6, IL-18 and TNFα, are involved in both inflammaging and different chronic conditions such as heart disease, kidney disease and cancer [16][17][20]. To illustrate, in a recent study among 76 older individuals (mean age 71 years), Fatyga et al. [20] demonstrated that inflammation is associated with malnutrition, irrespective of the etiology. In this study, the risk of malnutrition is positively and negatively associated with IL-8 and IL-18 levels, respectively [20].

In the present study, among all cytokines, changes in IL-18 levels overtime were the most evident independent predictor for changes in appetite and explained 4% of the variance compared to other risk factors. In addition, no other significant associations between changes in other cytokines and changes in appetite could be detected in the regression analysis. Of interest, the impact of IL-18 level changes on appetite changes was independent from the CRP level and infections. Our data suggest that changes in IL-18 levels were the main inflammatory mediator of appetite changes. Although there are very few studies on IL-18 as an anorectic inflammatory marker in humans, its regulative role as a potent anorectic cytokine was confirmed in animal studies. As an example, mice with an IL-18 deficiency reduced their food intake and lost weight when subjected to an intraperitoneal or intracerebroventricular injection of IL-18 [21]. In addition, similar animal studies reported significant associations between elevated levels of IL-18 and low food intake, which was consistent with the anorectic property of IL-18 [21][22][23]. Altogether, it appears that IL-18 plays a regulatory role in energy intake and energy homeostasis in diseased subjects. According to the fact that malnutrition and a loss of appetite in older subjects are mostly multifactorial, it is not surprising that IL-18 accounts for only 4% of the variance of appetite.

IL-18, which is an immunoregulatory cytokine, is a member of the IL-1 family and its serum levels are significantly elevated in a state of infection [21][23]. The primary sources of IL-18 are macrophages, dendritic cells and many other cells [24][25]. In addition to it acting in both acquired and innate immunity [26], IL-18 is also involved in chronic inflammation, autoimmune diseases and several cancers [27]. Without proof of causality, the findings of the present study suggest that IL-18 may exert a role in appetite regulation and mediate nutritional alterations during inflammatory conditions in diseased subject.

The measurement of appetite, which is a subjective sensory experience, is challenging [28]. In this study, appetite was evaluated using a single question of the SNAQ and one analogue scale of the ESAS. Although significant correlations between both tools at baseline and at follow-up were observed, none of the cytokine changes showed significant impact on SNAQ-appetite changes in the regression analysis. This discrepancy could be due to the fact that the SNAQ appetite question offers 5 possible answers, whereas the ESAS appetite score can differentiate between 11 different values. This may be the reason why the ESAS appetite assessment appears to be more effective in detecting changes of appetite.

Several limitations of this study should be discussed. Investigating a very heterogeneous group of older hospitalized patients may have influenced our findings, because there have been multiple reasons for a reduction in appetite in this cohort. Therefore, residual, uncontrolled confounding cannot be excluded. Notwithstanding, the relationship of the concurrent alterations of inflammatory biomarkers such as cytokines and appetite cannot prove but may substantiate causality. Future studies are required to reproduce the proposed anorexigenic effect of IL-18 in a population where inflammation may be the main cause of a loss of appetite.

3. Conclusions

We conclude that IL-18 seems to exert a significant impact on appetite in acutely ill older hospitalized patients and should, therefore, be considered as a potential target in the diagnosis, prevention and treatment of malnutrition.

References

1. de Boer, A.; Ter Horst, G.J.; Lorist, M.M. Physiological and psychosocial age-related changes associated with reduced food intake in older persons. Ageing Res. Rev. 2013, 12, 316–328.
2. Landi, F.; Calvani, R.; Tosato, M.; Martone, A.M.; Ortolani, E.; Savera, G.; Sisto, A.; Marzetti, E. Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments. Nutrients 2016, 8, 69.
3. Morley, J.E. Anorexia of aging: Physiologic and pathologic. Am. J. Clin. Nutr. 1997, 66, 760–773.
4. Azzolino, D.; Arosio, B.; Marzetti, E.; Calvani, R.; Cesari, M. Nutritional Status as a Mediator of Fatigue and Its Underlying Mechanisms in Older People. Nutrients 2020, 12, 444.
5. Volkert, D.; Beck, A.M.; Cederholm, T.; Cereda, E.; Cruz-Jentoft, A.; Goisser, S.; De Groot, L.; Großhauser, F.; Kiesswetter, E.; Norman, K.; et al. Management of Malnutrition in Older Patients—Current Approaches, Evidence and Open Questions. J. Clin. Med. 2019, 8, 974.
6. Schilp, J.; Wijnhoven, H.; Deeg, D.J.H.; Visser, M. Early determinants for the development of undernutrition in an older general population: Longitudinal Aging Study Amsterdam. Br. J. Nutr. 2011, 106, 708–717.
7. Pourhassan, M.; Rommersbach, N.; Lueg, G.; Klimek, C.; Schnatmann, M.; Liermann, D.; Janssen, G.; Wirth, R. The Impact of Malnutrition on Acute Muscle Wasting in Frail Older Hospitalized Patients. Nutrients 2020, 12, 1387.
8. Sieske, L.; Janssen, G.; Babel, N.; Westhoff, T.H.; Wirth, R.; Pourhassan, M. Inflammation, Appetite and Food Intake in Older Hospitalized Patients. Nutrients 2019, 11, 1986.
9. Gariballa, S.; Forster, S. Effects of acute-phase response on nutritional status and clinical outcome of hospitalized patients. Nutrients 2006, 22, 750–757.
10. Katona, P.; Katona-Apte, J. The Interaction between Nutrition and Infection. Clin. Infect. Dis. 2008, 46, 1582–1588.
11. Young, P.; Lombi, F.; Finn, B.C.; Forrester, M.; Campolo-Girard, V.; Pomeranz, V.; Iriarte, R.; Bruetman, J.E.; Trimarchi, H. “Malnutrition-inflammation complex syndrome” in chronic hemodialysis. Medicina 2011, 71, 66–72.
12. Plata-Salamán, C.R. Central nervous system mechanisms contributing to the cachexia–anorexia syndrome. Nutrients 2000, 16, 1009–1012.
13. Avila-Carrasco, L.; Pavone, M.A.; González, E.; Aguilera-Baca, Á.; Selgas, R.; Del Peso, G.; Cigarran, S.; López-Cabrera, M.; Aguilera, A. Abnormalities in Glucose Metabolism, Appetite-Related Peptide Release, and Pro-inflammatory Cytokines Play a Central Role in Appetite Disorders in Peritoneal Dialysis. Front. Physiol. 2019, 10, 630.
14. Wong, S.; Pinkney, J. Role of cytokines in regulating feeding behaviour. Curr. Drug Targets 2004, 5, 251–263.
15. Andreasson, A.; Arborelius, L.; Erlanson-Albertsson, C.; Lekander, M. A putative role for cytokines in the impaired appetite in depression. Brain, Behav. Immun. 2007, 21, 147–152.
16. Kalantar-Zadeh, K.; Block, G.; McAllister, C.J.; Humphreys, M.H.; Kopple, J.D. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am. J. Clin. Nutr. 2004, 80, 299–307.
17. Paulsen, Ø.; Laird, B.; Aass, N.; Lea, T.; Fayers, P.; Kaasa, S.; Klepstad, P. The relationship between pro-inflammatory cytokines and pain, appetite and fatigue in patients with advanced cancer. PLoS ONE 2017, 12, e0177620.
18. Mahieux, F.; Couderc, R.; Fénelon, G.; Maachi, M. Relationships between weight loss and circulating cytokines in patients with Alzheimer’s disease. Psychol. Neuropsychiatr. Vieil. 2006, 4, 281–286.
19. Vannini, F.D.; Antunes, A.A.; Caramori, J.C.T.; Martin, L.C.; Barretti, P. Associations between nutritional markers and inflammation in hemodialysis patients. Int. Urol. Nephrol. 2009, 41, 1003–1009.
20. Fatyga, P.; Pac, A.; Fedyk-Łukasik, M.; Grodzicki, T.; Skalska, A. The relationship between malnutrition risk and inflammatory biomarkers in outpatient geriatric population. Eur. Geriatr. Med. 2020, 11, 383–391.
21. Zorrilla, E.P.; Sanchez-Alavez, M.; Sugama, S.; Brennan, M.; Fernandez, R.; Bartfai, T.; Conti, B. Interleukin-18 controls energy homeostasis by suppressing appetite and feed efficiency. Proc. Natl. Acad. Sci. USA 2007, 104, 11097–11102.
22. Zorrilla, E.P.; Conti, B. Interleukin-18 null mutation increases weight and food intake and reduces energy expenditure and lipid substrate utilization in high-fat diet fed mice. Brain Behav. Immun. 2014, 37, 45–53.
23. Francesconi, W.; Sánchez-Alavez, M.; Berton, F.; Alboni, S.; Benatti, C.; Mori, S.; Nguyen, W.; Zorrilla, E.; Moroncini, G.; Tascedda, F.; et al. The Proinflammatory Cytokine Interleukin 18 Regulates Feeding by Acting on the Bed Nucleus of the Stria Terminalis. J. Neurosci. 2016, 36, 5170–5180.
24. Boraschi, D.; Dinarello, C.A. IL-18 in autoimmunity: Review. Eur. Cytokine Netw. 2006, 17, 224–252.

25. Janiak, A.; Leśniowski, B.; Jasińska, A.; Pietruczuk, M.; Małecka-Panas, E. Interleukin 18 as an early marker or prognostic factor in acute pancreatitis. Gastroenterol. Rev. 2015, 10, 203–207.
26. Okamura, H.; Tsutsui, H.; Kashiwamura, S.-I.; Yoshimoto, T.; Nakanishi, K. Interleukin-18: A Novel Cytokine That Augments Both Innate and Acquired Immunity. Adv. Immunol. 1998, 70, 281–312.
27. Usuda, D.; Furumura, Y.; Takeshima, K.; Sangen, R.; Kawai, Y.; Kasamaki, Y.; Iinuma, Y.; Kanda, T. Interleukin-18 as a diagnostic marker of adult-onset Still's disease in older patients: A case report and review of the literature. J. Med. Case Rep. 2018, 12, 1–4.
28. Mattes, R.D.; Hollis, J.; Hayes, D.; Stunkard, A.J. Appetite: Measurement and Manipulation Misgivings. J. Am. Diet. Assoc. 2005, 105, 87–97.