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Infectious Concept of Obesity: Review Article

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Abstract Obesity is currently experiencing an epidemic as declared by the World Health Organization. Obesity has multiple etiologies, one of them an infection. Many microbes are linked to obesity both in animals and human, but conclusive evidence for its role in human is lacking. At least, six pathogens are reported to cause obesity in animals. Canine distemper virus was discovered as the first virus reported to cause obesity in mice, followed by Rous-associated virus-7, which has been shown to cause obesity and hyperlipidemia in chickens. The obesity-promoting effect of Borna disease virus was demonstrated in rats. Scrapie agent was reported to increase the risk of obesity in mice and hamsters. The last two reports were of SMAM-1 and Ad-36, a human adenovirus that caused obesity in animals. An association with human obesity is the unique feature of SMAM-1 and Ad-36. Human studies are less convincing; but two adenoviruses, Ad-36 and SMAM-1, did show adipogenic properties. It is clear that in response to certain infections, adipose tissue expands similar to the expansion of cells of the immune system. In vitro studies with 3T3-L1 cells stated the activation of the enzymatic pathway that leads to fatty tissue accumulation; also higher levels of antibodies against such viruses in obese subjects were detected in vivo studies. Also, recent studies showed that C. pneumoniae and H. pylori are also associated with human obesity. This review discusses the related published data as well as the characteristics of pathogens that may be implicated in obesity.

Keywords: *obesity, infection, virus*

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1. Introduction

There are more than one billion overweight people (BMI ≥25) in the world; approximately 350 million of them are obese (BMI ≥30.0). [1] The WHO recommends measurement of the BMI as a universal criterion of overweight (>= 25) and obesity (>=30). [2] Obesity is a major risk factor for the development of chronic diseases and mortality. [3] Prospective studies have shown that the abdominal fat accumulation is an independent risk factor for type 2 diabetes mellitus and cardiovascular diseases, such as cerebrovascular disease, ischemic heart disease, and hypertension. [4] Obesity is considered as one of the most common risk factors for Nonalcoholic Fatty Liver Disease (NAFLD); with an estimated 69%–100% of the obese patients have NAFLD in one review. 18.5% of the morbidly obese patients compared to only 2.7% of normal weight patients had histologic in autopsy studies. High prevalence of morbidly obese patients who underwent metabolic surgery had evidence of nonalcoholic steatohepatitis on biopsy examination. [5] It has been estimated that 2.5 million deaths are attributed to overweight/obesity worldwide. [1] The prevalence of obesity in the United States is high, with an estimated 30% of adults and 17% of children are overweight/obese. [6] In Saudia Arabia (KSA), the prevalence of obesity is 49.15% and 29.94% in women and men, respectively, while the prevalence of being overweight but not obese was 31.55% in women and 41.91% in men. Obese and overweight women and men were significantly more likely to be older. [7] Obesity is a multifactorial, complex disease that involves the interaction of genetic, metabolic, behavioral, social and cultural factors. [8] Over the past 20 years, 8 pathogens have been reported to cause obesity in animal models. The relative contributions of these pathogens to human obesity are not yet clear. This relatively novel concept may be potentially important if future studies showed to be relevant to humans. An adequate understanding of such pathogens is needed for better management of obesity [9].

2. Antibiotic and Obesity

The relationship between antibiotic exposure and obesity and its related complications has been recently a growing area of research. Recent study evaluated the impact of prescribed antibiotic during the infancy and the impact on early childhood obesity. [10] They found that antibiotic resulted in a significant relative risk increase of 11% and that broader spectrum and earlier exposure were significantly correlated with later obesity development. Other studies showed that it only increased the risk of being overweight in boys only [11,12].

No existing data regarding this relation between the antibiotic exposure later than 2 years of age and obesity. Recently a correlation between antibiotic exposure in adulthood and obesity related complication (diabetes) has

been published. [13] In a case-control design, the antibiotic exposure of 2 courses or more resulted in a dose dependent higher risk for type 2 diabetes and the risk were more pronounced with quinolones. Recently metanalysis of eight studies confirmed the excess risk of infancy antibiotic exposure and childhood asthma development.

This above discussed relationship largely related to the gut microbiota profile changes as well as to the low antibiotic dose used in the food. [14] Lastly, antibiotics when used wisely and when indicated could be a lifesaving measures, but unnecessary prescription not only will result in more resistance but rather to increase obesity and its related complications.

3. Chlamydia pneumoniae

A research team at the Institute of Biomedicine, University of Oulu, Finland found that exposure to Chlamydia (C) pneumoniae, the most common pathogen causing human pneumonia, correlates strongly with overweight especially in women. The presence of C. pneumoniae IgG antibodies, alone and with elevated CRP, correlated firmly and independently with elevated BMI for women and men. Women, but not men, also showed correlations between C. pneumoniae exposure and high waist and hip circumference [15].

4. Helicobacter Pylori

Eradication of Helicobacter pylori (H. pylori) is accompanied by many metabolic and hormonal changes that have been demonstrated in numerous studies. Weight gain following H. pylori eradication is a well-described phenomenon whose mechanism is poorly understood. It has been speculated that H. pylori eradication, an increase in gastric ghrelin secretion leads to increased plasma ghrelin levels, resulting in obesity. One study measured BMI, plasma ghrelin and gastric ghrelin, expression before and after H. pylori eradication and found that plasma ghrelin levels decrease following eradication therapy and were inversely correlated with body weigh expression increased following eradication but did not correlate with BMI. This suggests that plasma ghrelin concentration more strongly influences body weight change than increases in gastric ghrelin, and that increased expression of preproghrelin mRNA in the stomach does not directly influence the total plasma ghrelin level. Obestatin and ghrelin are derived from a common precursor preproghrelin, but obestatin exhibits opposite effects of ghrelin. Obestatin antagonizes growth hormone secretion and decrease food intake. The ghrelin/obestatin balance may be a key factor determining weight gain following H. pylori eradication [16].

5. Gut microbiota

The gut microbiota is microorganisms that live in the digestive tracts and the diversity of species found in populations. It performs many functions in the human, including, digestion of energy substrates, and repressing the growth of harmful microorganisms. The gut microbiota may play a role in the development of obesity via nutrient acquisition and energy regulation. The bacterial flora of obese mice contains fewer Bacteroides and more Firmicutes than lean groups. Gut microbiota can increase body weight and free fatty acids, and induce insulin resistance. Therefore, the interaction among microorganisms in the gut has a significant role in host energy homeostasis [17].

Human study showed that the phyla Bacteroidetes and Firmicutes dominated, but to a variable degree. [18] Recent human studies evaluated the role of diet on the gut bacteria at baseline and at 52 weeks and compared them to lean controls. [19] At baseline obese participants had fewer Bacteroidetes and more Firmicutes than lean controls and with diet the Bacteroidetes increased and Firmicutes decreased in obese irrespective of the diet. Those changes associated with an increased energy harvest and as the lean subject overfed, this was associated with a greater fractional decrease in stool energy losses [20].

The gut microbes changes after obese patients undergo bariatric (metabolic) surgery has been a hot area for research recently. The gut microbes profile of 30 obese patients who underwent Roux-en-Y gastric bypass (RYGB) surgery were assessed and compared to 13 lean control individuals. [21] They found that *Bacteroides*/*Prevotella* group and the *E. coli* increased in the surgical group at 3 months and was inversely related to the fat mass. Those changes correlated with favorable hormonal and inflammatory changes.

6. Human Adenovirus

6.1. Adenovirus 36 (Ad-36)

Ad-36 is transmitted through the respiratory, fecal-oral and sexual pathways, as well as through contaminated personal objects. Ad-36 has a great affinity with fatty tissue as its DNA is found directly related to body fat. Dhurandhar and Cols., [22] performed virus inoculation in animals, revealed obesity development in 60%-70% of the cases and found that total body fat growth and visceral fat increase, with a decrease in serum lipid levels. Atkinson and Dhurandhar, [23] did two experiments, first one was monkeys were inoculated through their blood streams; 18 months later, 15% of weight gain and 25% of the serum lipid levels drop were observed, thus confirming the findings of the animal studies. The second study, monkeys were inoculated through nasal mucosa; after seven months, all subjects presented an increase in fat tissue with an increase of visceral fat in 66% of the cases. In humans, available data show that the prevalence of positive Ad-36 antibodies among obese people is larger than in regular people (30% versus 11%). In vitro studies revealed that 3T3-L1 cell seems to accelerate the preadipocyte - adipocyte differentiation rate. [9] When viral gene E4orf1 was inserted into 3T3-L1 cells, C/EBP-β, PPARγ-2 and glycerol-3-phosphate dehydrogenase was stimulated when compared to 3T3-L1 controls, suggesting that the E4orf1 gene is responsible for adipocyte differentiation stimulation. It was reported that, the suppression of leptine mRNA expression in 3T3-1 cells in 50% of the cases after 3-5 days of infection, as well as an up-regulation of the enzymatic genes involved in lipogenesis, as acetyl-CoA carboxylase-1 and fatty acid synthase, when compared to

a non-infected control group, thus confirming the adipogenic role of Ad-36. [24] It is hypothesized that Ad-36 proteins decrease both TNF-α and leptin levels, thereby contributing to upregulation of preadipocyte differentiation by their relative absence [9].

6.2. Adenovirus-37 (Ad-37)

Whigham and Cols, [25] found a 111% increase in visceral fat and a 262% increase in total body fat over a period of 3-5 weeks after Ad-37 infection in chickens. Caloric intake did not vary with a between the Ad-37 infected group and the control group. Cholesterol levels increased and triglyceride levels diminished in contrast with infection by Ad-36 [25].

6.3. Adenovirus-5 (Ad-5)

So and Cols, [26] demonstrating a 300% increase in total body fat, without an increase in caloric intake after inoculated mice peritoneum with adenovirus Ad-5. They speculate that viral inflammation would be the stimulating the production of PPAR-β; which could cause an increase in adipocyte differentiation inducing obesity.

6.4. Adenoviruses-31 and 2 (Ad-31 and Ad-2)

In vitro studies, revealed that Ad-2 and Ad-31 exposed cells, showed hypertriglyceridemia [25].

7. SMAM-1

Inoculation chicken peritoneum with the virus leads to an increase in visceral fat that could not be justified by any dietary uptake. It was noticed that birds that were not inoculated with the virus, but were kept in the same environment with the infected ones did contract the infection through their respiratory tracts but developed obesity. [27] A paradoxical decrease in serum lipid levels was observed. Also, infected animals presented with enlarged livers and hepatic steatosis. [28] Testing blood samples from 52 Indian obese patients for SMAM-1 antibodies. Ten patients proved to be positive, but they had statistically significant larger BMI as well as lower cholesterol and triglyceride values. It remains unknown whether SMAM-1 antibodies develop as a result of viral infection or against genetically similar adenoviruses [29].

8. Canine Distemper Vírus

Lyons and Cols. in 1982, [30] published the first report of animal viral Canine distemper virus (CDV) induced obesity in rats. CDV is transmitted mainly through respiratory secretions. Obesity was found in up to 26% of survivors of the acute, neurologic stage of the disease, and in 16% of cases of the virus inoculated in the peritoneum. CDV seems to cause obesity through the central nervous system (CNS) infection with hypothalamic damage. Circulating catecholamine levels decreased, especially noradrenalin; a down regulation of hypothalamus leptine receptors, MCH mRNA receptors also found and pancreatic hyperplasia. Adipogenesis is manifest as an increase in the number and size of the adipocytes. These changes may be due to an imbalance in hypothalamic function. Up to date, there is no evidence of relation between CDV infection and human obesity. Morbilliviruses such as CDV and measles virus (MV) potentially use the same cell surface receptor. CDV and others animal morbilliviruses have not yet been definitively implicated in any human disease. [28] However, some studies have implicated CDV in the pathogenesis of Paget's disease. Selby et al, 2006 [31] provide the first conclusive proof that CDV can infect and replicate in human osteoclast precursors, raising possible zoonotic implications for CDV. A direct link was unequivocally established between CDV and multiple sclerosis and CDV infection of humans is probably not widespread under natural conditions [32].

9. Rous-associated Virus Type 7

Avian leucosis viruses (AVL) are retroviruses that may induce neoplastic growth, such as B-cell lymphomas and chronic degenerative diseases, such as anemia and immunosuppresion. Rous-associated virus 7 (RAV-7) is an AVL that causes an obesity syndrome in chickens. [33] RAV-7is a leukocyte aviary virus can lead to obesity in chickens, and is frequently associated with low thyroid hormone levels, growth impairment, dislipidemia and hepatic fatty infiltration, with thyroid and pancreas lymphocyte infiltration. This feature only be observed when the infection takes place during the embrionary stages of life, didn't occur during adulthood. Infection can reach humans from infected chicken and egg products. Human serum analysis has shown positivity to RAV-7 specifically, however, there is no evidence of human infection in obesity [34].

10. Borna Disease Vírus

This is one of Bornaviridae viral family. Transmission occurs through contact with saliva, nasal and eye secretions from infected animals. Horses, sheep and other animals such as cats, dogs and mice can carry this virus. Mice inoculation infection can lead to obesity, behavioral changes and neurologic symptoms. [35] Pancreatic hyperplasia, hypertriglyceridemia and high glucose levels can also be found. In humans, there is no evidence of its relation with obesity. [36] A link between BDV and human neuropsychiatric disorders has been suggested after seroepidemiological studies revealed a higher BDV seroprevalence among patients with major affective disorders, schizophrenia and obsessive compulsive disorders compared to healthy controls. It has been speculated that the limbic system may be a target for BDV. [37] The spectrum of BDV pathogenicity in humans has not yet been defined and further molecular, seroepidemiological and clinical studies are required to associate BDV with human obesity.

11. Prion

Scrapie or spongiform encephalopathy is a neurologic degenerative disease caused by prion. It is found among sheep, with a long incubation period. During the pre-clinical stage, there is an increase in the caloric dietary

intake and weight gain; however, during the clinical course of the illness there is a progressive weight loss. It is transmitted through direct inoculation, mice, hamsters and monkeys. Weight gain starts around the ninth week after inoculation, with its peak after 17 weeks with observed a decrease in insulin sensitivity on these animals. Adrenalectomies on these subjects had a preventive role in the metabolic disturbances, but no effect on the neurologic deterioration. This protective effect of the adrenalectomy is based on three findings: 1) scrapie induced obesity is more severe when the prion is directly inoculated into the hypothalamus; 2) adrenal glands' weight was larger on infected animals (due to enlarged cortex); 3) prion specimens found in the adrenal glands of infected mice were of low virulence, suggesting that obesity in these subjects may not be related to adrenal infection. There is no evidence of scrapie in humans, but other spongiform encephalopathies such as Creutzfeldt-Jakob have been related [28].

12. Inflammatory State in Obesity

Preadipocytes act like macrophages and have a phagocytic and microbicidal activity. Adipocytes secrete many cytokines. Macrophage colony-stimulating factor (MCSF) is also secreted by adipocytes and its overexpression in vivo induces significant adipose tissue hyperplasia. It is unknown if the obesity-promoting pathogens stimulate MCSF production that leads to the growth of adipose tissue. [38] It was found that obesity is characterized by macrophage accumulation in white adipose tissue, which can explain the development of adipose tissue inflammation. Macrophages in adipose tissue are likely to contribute to the production of inflammatory mediators either alone or in concert with adipocytes. [39] Many studies revealed association of obesity with cytokines and inflammatory markers. Elevated levels of interleukin-6 and C-reactive proteins are found in obese individuals. Some investigators showed that inflammatory markers can predict weight gain in middle-aged adults. It was discovered that TNF-α is overexpressed in the adipose tissues of rodent models of obesity. Also, TNF-α is overproduced in the adipose as well as muscle tissues of obese humans. [39] Leptin, enhances proliferation and activation of human circulating T-cells and stimulates cytokine production. The prospective studies show an association of obesity with the presence of a chronic, mild state of inflammation. It is not clear that the noted inflammation was in response to certain infections [38].

13. Discussion

The treatment for obesity has been one of the greatest challenges in modern medicine. It implies great lifestyle changes and sometimes cultural ones. Genetic studies led to the identification of several adipogenic genes, however; clinical results have been unsatisfactory. These may be some reasons why we are now searching for new etiologic possibilities and perhaps, even new therapeutic options. The role of infections on the onset and development of obesity has been questioned. Many studies, successes in identifying and proving these relations. At least eight viruses that lead to weight gain are known. Human studies are less, but started to generate well founded research lines, studying not only the infectious agent, but also the entire pathologic process involved. One can observe that most adipogenic infections seem to induce obesity through a CNS lesion, except for Ad-36; its DNA being identified directly within the fatty issue, causing an increase in both adipocyte size and number. Pasarica, [36] suggested that, Ad-36 induced CNS disturbances could also contribute to obesity. Low cortisol and noradrenalin levels have been found in patients with positive Ad-36 antibodies. The mechanism of inducing obesity specifically in humans, was evaluated by Vangipuram, [40] concluded that glycerol-3-phosphate dehydrogenase, an adipocyte differentiation marker, was increased in 3T3-L1 and human cells infected with Ad-36 with suppression of leptine mRNA expression. Another observation was that acetyl-coenzyme-A-carboxylase and fatty acid synthase were both increased in infected mice. Whigham and Cols, [25] evaluated adenoviruses Ad-2, Ad-31, Ad-36 and Ad-37 and confirmed that all agents apart from the first, stimulate adipocyte differentiation. Knowledge on obesity is constantly expanding; we still need to understand it completely.

Dart et al., 2002, [41] screened 43 newly identified cases of coronary heart disease (CHD) and 127 matched controls without CHD, for the presence of serum IgG and IgM against C. pneumoniae, C. trachomatis and C. psittaci. The prevalence of seropositivity for C. pneumoniae was not significantly different in subjects with or without CHD found that the C. pneumoniae antibody positive group had significantly greater body mass index (BMI) and smaller low-density lipoprotein (LDL) particle size. Antibody prevalence was significantly greater for subjects with insulin levels above the median and for those with LDL particle size below the median. However, after multivariate analysis, only BMI continued to be associated with seropositivity. There is no direct relation between H. pylori and obesity, however, eradication of H. pylori is accompanied by many metabolic and hormonal changes that may be implicated in weight gain but the mechanism is poorly understood. [23] Gut microbiota has a significant role in host energy homeostasis and can increase body weight [17].

More human studies are needed to clarify possible, pathologic factors and explore the correlation between infection and obesity. A causative role of infectious pathogens in human obesity is difficult to establish because of the insidious onset of human obesity, which makes it is difficult to retrospectively link it to a particular episode of infection beside the ethical considerations, as humans cannot be experimentally infected with these pathogens also; linking the infection to long term weight gain is often impossible.

14. Conclusion

Many pathogens have been implicated in the pathogenesis of obesity in animal models, of which at least 4 are human pathogens. These data raise the possibility of infection as a contributing factor for obesity in some humans. The relative contributions of these pathogens to human obesity are not yet clear. Exposure to C. pneumoniae correlates strongly with overweight

especially in women. Weight gain following H. pylori eradication is a well-described phenomenon whose mechanism is poorly understood. The gut microbiota may play a role in the development of obesity via nutrient acquisition and energy regulation. Two adenoviruses, Ad-36 and SMAM-1, did show adipogenic properties in human. Recent study found that prescribed antibiotic during the infancy and early childhood resulted in a significant relative risk increase of later overweight and/or obesity development. Established the infectious origin of obesity could have a role in prevention and treatment. The prevention of obesity of infectious origin could be achieved by vaccination; whereas antimicrobial agents may be used to prevent or treat some cases of obesity depending on the adipogenic mechanism of individual pathogens. Extensive epidemiological surveys and longitudinal section studies are needed to define the role of these pathogens.

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