World Journal of Diabetes

Online Submissions: http://www.wjgnet.com/1948-9358office
wjd@wjgnet.com
doi:10.4239/wjd.v1.i2.27

World J Diabetes 2010 May 15; 1(2): 27-35
ISSN 1948-9358 (online)

EDITORIAL

Exacerbation of chronic inflammatory diseases by infectious agents: Fact or fiction?

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Author contributions: Wang CM and Kaltenboeck B structured the outline of this article; and Wang CM drafted this manuscript and both authors did the final editing.
Supported in part by NIH grant AI47202, and by grants from the Diabetes Trust Foundation, Diabetes Action Research and Education Foundation Grant #198, and by Graduate-in-Aid and Competitive Research Grant Programs at Auburn University
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Received: November 20, 2009 Revised: March 27, 2010
Accepted: April 3, 2010
Published online: May 15, 2010

Abstract

Chronic inflammatory diseases caused by obesity represent critical public health concerns worldwide. In these diseases such as metabolic syndrome, diabetes and atherosclerosis, adipose tissue acts as an endocrine organ that releases large quantities of inflammatory mediators into circulation. Besides classically recognized effectors on the development of obesity and resultant conditions, infection has attracted attention as an enhancer of chronic inflammatory diseases. Infectious diseases have long been associated with obesity, metabolic syndrome, diabetes and atherosclerosis. However, the infectious hypothesis for chronic inflammatory diseases has been challenged by inconclusive clinical trials. Nevertheless, the large body of evidence accumulated over decades on the association of infectious diseases with obesity, diabetes and cardiovascular disease should not be disregarded. Instead, re-formulation of hypotheses of the mechanisms by which microbes affect obesity-associated diseases may be required with an emphasis on the early events in the progression of such diseases and the multifactorial nature of pathogen-host interactions. This review focuses on pathogens that directly promote obesity and on pathogens that cause chronic infections and thereby enhance metabolic diseases in obese patients. A new perspective on the interaction between infections and obesity-related diseases may improve management of chronic inflammatory diseases that rank high among global threats to human health.

Key words: Chronic inflammatory diseases; Obesity; Diabetes; Adenovirus-36; *Chlamydia pneumoniae*

Peer reviewers: Moshira Abdel Hakim Rateb, MD, Assistant Professor of Human Physiology, Faculty of Medicine (Kasr Al Aini.), Cairo University, Manial El Roda, Cairo, Egypt; Edwin Mariman, PhD, Professor, Department of Human Biology, Maastricht University, 6200 MD Maastricht, The Netherlands

Wang CM, Kaltenboeck B. Exacerbation of chronic inflammatory diseases by infectious agents: Fact or fiction? *World J Diabetes* 2010; 1(2): 27-35 Available from: URL: http://www.wjgnet.com/1948-9358/full/v1/i2/27.htm DOI: http://dx.doi.org/10.4239/wjd.v1.i2.27

INTRODUCTION

The incidence of obesity has dramatically increased during the recent decades worldwide. Currently, two-thirds of adults in the USA are overweight and around 32% are obese with obesity still trending upwards[1,2]. Worldwide, over 1 billion adults are overweight and more than 300 million are clinically obese (body mass index $\geqslant$ 30 kg/m^2)[3]. Alarmingly, obesity has also increased markedly in children[2]. It has only been recognized over

the last 15 years that obesity is an endocrine disease in which particularly white abdominal adipose tissue secretes large amounts of inflammatory mediators[4]. The chronic release of these mediators called adipocytokines in patients with high body mass index results in a combination of clinical symptoms characterized by high blood pressure, resistance to intracellular uptake of glucose such that glucose homeostasis requires increased insulin secretion (insulin resistance) and perturbation of the blood lipid profile (high total cholesterol and low-density lipoprotein). The cluster of these clinical symptoms is termed metabolic syndrome.

Obesity and its associated conditions such as metabolic syndrome, diabetes and atherosclerosis are now considered chronic inflammatory diseases[5]. Inflammation is the key characteristic of obesity and metabolic syndrome and production of pro-inflammatory cytokines such as TNF-α is essential to enhance the development of type 2 diabetes and atherosclerosis. For example, TNF-α induces insulin resistance by stimulating stress hormone production and decreasing tyrosine phosphorylation of insulin-induced insulin receptor substrate 1[6]. Similarly, inflammation is also a key characteristic of the host response to infectious agents[7].

While inflammation is a shared and key characteristic of both chronic inflammatory diseases and infections, infectious diseases have long been associated directly with obesity [i.e. Canine distemper virus (CDV), Rous-associated virus-7 (RAV-7), Borna disease virus (BDV), Scrapie agent and adenoviruses SMAM-1 and 36] as well as the consequences of obesity such as metabolic syndrome, diabetes and atherosclerosis [i.e. *Helicobacter pylori* (*H. pylori*), *Chlamydia pneumoniae* (*C. pneumoniae*), *Porphyromonas gingivalis* (*P. gingivalis*), hepatitis C virus (HCV) and human immunodeficiency virus (HIV)]. Clinical experience clearly shows that infectious diseases worsen glycemic control in diabetic patients[8-10]. Conversely, diabetic patients are also known to be at increased risk for infectious diseases and for higher severity of such diseases[8,11]. Obesity and exposure to infectious agents overlap in large population segments and therefore may mutually influence each other. Thus, profound practical medical benefits may result from a rational comprehensive approach to the management of chronic inflammatory diseases if therapy of either metabolic syndrome or infectious disease would also mitigate the respective other conditions.

This review focuses first on pathogens that directly promote obesity and, as a downstream consequence of obesity, the development of metabolic syndrome and its associated conditions. Subsequently, the review will focus on a second set of pathogens that cause chronic infections and subsequent release of inflammatory mediators and, *via* this mechanism, induce or exacerbate metabolic syndrome. A new perspective on the connection between infections and obesity-related diseases will better the management of these chronic inflammatory diseases that now rank very highly among the global threats to human health.

OBESITY-ENHANCING PATHOGENS

CDV

CDV is a lymphotropic and neurotropic negative-stranded RNA virus belonging to the genus *Morbillivirus*[12,13]. It affects mainly dogs and related mammals by invading the nervous system and replicating in neurons and glial cells of the white cell subgroup resulting in a frequently fatal disease[13]. Even though CDV is not considered a human pathogen, a suggestive association with human disease has been described[14]. CDV is antigenically closely related to human measles virus with both of them belonging to the same family of *Paramyxoviridae* viruses.

CDV was reported as the first obesity-promoting pathogen in 1982 when Lyons *et al*[15] published the landmark article in *Science*, "A virally induced obesity syndrome in mice" that reported that CDV infection induced obesity in Swiss Albino mice. CDV-inoculated mice showed increased body weight as well as an increased number and size of fat cells[15]. Anatomical damage and altered neurochemistry in the hypothalamus was subsequently demonstrated in CDV-infected mice[16-21]. The hypothalamus plays a well-documented role in appetite regulation, energy consumption and neuroendocrine function[18]. CDV-infected mice showed down-regulated leptin receptors in the hypothalamic area of the brain, explaining their inability to generate a proper response to leptin in the brain[18]. With lower number of leptin receptors, hunger may be induced despite high leptin plasma levels that signal satiety. In addition, CDV also down-regulates melanin-concentrating hormone[21], expression levels of neuropeptides and catecholamine[15,22] and production of proinflammatory cytokines[20]. Collectively, these data suggest that persistent CDV infection of the hypothalamus specifically alters satiety-signaling pathways and thereby induces excessive food consumption and eventually obesity.

RAV-7

RAV-7, an avian leukosis virus, was the second microbe reported to induce obesity. RAV-7 (avian leukosis virus subgroup C) is the most common poultry retrovirus associated with neoplastic disease[23]. RAV-7 causes obesity in chickens combined with growth stunting, hypertriglycemia, hypercholesterolemia as well as enlarged fatty liver, anemia and immunosuppression[23]. The lipid content of the diet did not influence the RAV-7-mediated induction of obesity[24]. By 20 d after hatching, infected chickens were smaller than uninfected hatch mates and developed ataxia and obesity over the next 30 d. These chickens also developed mild anemia and lipemia and had high levels of plasma uric acid. RAV-7 infection also induced a marked decrease in the weight of thymus and bursa of Fabricius[23]. The histological appearance of obesity is characterized in the liver by a diffuse panlobular accumulation of fat in microdroplets and by a lymphoblastoid cellular infiltrate in thyroid gland and pancreas. Carter *et al*[24] (1983) hypothesized that RAV-7 infection induces obesity by reducing thyroid hormone levels.

Carter *et al*[25] also investigated the specificity of obesity induction by RAV-7. Avian leucosis viruses of the subgroups A [RAV-1 and MAV-1 (O) causing osteopetrosis], B [MAV-2 (O) and MAV-2 (N) causing nephroblastoma], D (RAV-50) and F (RAV-61 and ring-necked pheasant virus) did not induce obesity[25].

BDV

Borna disease virus is an enveloped, non-segmented, negative-stranded RNA virus of the order *Mononegavirales* with replication and transcription inside the nucleus of the host cells[26-28]. BDV infection is found worldwide and induces fatal disease in numerous animals such as horse, sheep, cat and dog[29,30] and there is also evidence that BDV may affect humans[31,32]. Chalmers *et al*[32] (2005) reported between 0% to 48% BDV seropositivity and 0% to 82% BDV antigen prevalence in humans. Narayan *et al*[33] and Gosztonyi *et al*[34,35] described an obesity syndrome in rats apparently induced by BDV in an age-, genetic background- and virus strain-dependent manner. Infected obese rats showed massive visceral fat deposition with elevated serum glucose levels and hypertriglyceri demia[34]. Several investigators hypothesized that BDV infection induces obesity through inflammatory lesions and viral antigen expression in the brain, particularly in the hypothalamus, similar to CDV infection[36].

Scrapie agent

The causative agent of scrapie is thought to be a prion[37]. Scrapie agent causes a fatal neurodegenerative disease with a long incubation period in sheep and goats[38]. Scrapie agent is not known to infect humans. In the laboratory, many other animals such as hamster, mice, rats, voles, gerbils, mink, cattle and monkeys have been successfully infected with scrapie agent[37]. This disease is classified as transmissible spongiform encephalopathy, similar to human Creutzfeld-Jacob's disease and related TSEs caused by prions[39-40].

Kim *et al*[41] reported that the ME-7 scrapie strain induced obesity and vacuolization in the forebrain of mice but other strains did not. Since adrenalectomy prevented obesity, it was suggested that this scrapie agent induces obesity *via* the hypothalamic-pituitary-adrenal axis[42]. Scrapie agent was also confirmed to cause hyperglycemia, hyperinsulinemia and diabetes by inducing pancreatic lesions and a significant decrease of the glucose transporter GLUT-1 in the brain[43,44].

Adenovirus-SMAM-1

Adenoviruses are non-enveloped DNA viruses with icosahedral symmetry and a diameter of 65-80 nm[45]. Adenoviruses were first isolated in 1953 during establishment of cell lines from pediatric adenoidal tissues obtained by tonsillectomy[46]. Adenoviruses infect a wide range of hosts such as birds, mammals and humans. Approximately 8% of the world-wide reported virus infections were caused by adenoviruses which can cause serious respiratory disease of epidemic proportions reported with a group of military recruits[47]. There are 5 major subgroups of human adenoviruses and each subgroup is also subdivided into several serotypes. The viral genome consists of 5 early transcription units (E1A, E1B, E2, E3, and E4), 2 delayed early units (IX and Iva2) and one major late unit to generate mRNAs (L1-L5)[38]. Adenoviruses produce a variety of serious diseases in people of all ages.

SMAM-1 is a strain of avian adenovirus responsible for a poultry epidemic in India during the 1980s[48] and is serologically related to another poultry adenovirus, chick embryo lethal orphan virus (CELO). SMAM-1-inoculated 3 wk-old chickens showed 53% greater visceral fat 3 wk post inoculation compared to uninfected controls. Paradoxically, the increased adiposity in SMAM-1 infected chickens was accompanied by reduced body weight and lower blood concentrations of cholesterol and triglycerides than in controls[49]. Livers of the SMAM-1 infected chickens were significantly heavier and showed severe congestion, fatty infiltration and presence of intranuclear inclusion bodies under histopathological examination. The infected chickens showed also atrophied bursae, spleen and thymus[49]. Dhurandhar *et al*[50] (1997) reported an association between SMAM-1 seropositivity and human obesity. SMAM-1 antibody-positive humans showed significantly higher BMI and significantly lower blood cholesterol and triglycerides compared to the antibody-negative subjects.

Adenovirus-36

The Adenovirus-36 strain of adenoviruses was first identified in 1978 in Germany from the feces of a 6-year-old girl with diabetes and enteritis[51]. Accumulated evidence from animal models, *in vitro* experiments and human epidemiology strongly suggest a positive association between adenovirus-36 and human obesity. Atkinson et al showed that 11%-30% of Americans are seropositive against adenovirus-36[52]. Dhurandhar *et al*[53] (2000) explored the influence of adenovirus-36 infection on the development of obesity in chickens. Adenovirus-36 challenged chickens showed 100% greater visceral fat and total body weight than the control group inoculated with sterile cell culture medium and these conclusions were confirmed by the subsequent studies[54]. Adenovirus-36 inoculated male marmoset monkeys showed an astonishing 3-fold weight gain compared to uninfected controls[55]. *In vitro* studies showed that adenovirus-36 promotes the proliferation, differentiation and lipid accumulation in 3T3-L1 preadipocytes[38]. Atkinson et al screened the sera of 360 obese (BMI $\geqslant$ 30 kg/m^2) and 142 non obese (BMI $\leqslant$ 30 kg/m^2) subjects in Wisconsin, Florida and New York for adenovirus-36 antibodies. Adenovirus-36 antibodies were 30% and 11% prevalent in obese and non-obese subjects respectively and obese and non obese subjects with adenovirus-36 antibodies had significantly greater BMI than their respective seronegative counterparts[52]. The authors concluded that the influence of adenovirus-36 seropositivity on obesity

was highly significant independent of age, sex and origin of the human subjects[38,52]. *In vitro* studies shed light on the mechanisms of adenovirus-36-inducing obesity. Adenovirus-36 infected human preadipocytes showed increased replication, differentiation, lipid accumulation as well as reduced leptin secretion in fat cells[38,54,56]. This effect is specific for adenovirus-36 and is not observed with nonadipogenic adenovirus (Ad-2). It is likely that adenovirus-36 infection increases the number of fat cells, glucose uptake by adipocytes and promotes lipogenesis[56]. Na *et al*[57] and Atkinson *et al*[58] reported a positive association between human adenovirus-36 and obesity in children. However, two recent epidemiological surveys[59,60] indicated that human adenovirus-36 did not play a direct role in the development of obesity in both Western Europe and the US.

Adenovirus type 5 has been widely used for gene therapy because it is a safe and efficient vector and accommodates large antigen-encoding structures[61]. So *et al*[62] (2005) showed that adenovirus-5 infected mice attained significantly greater body weight and higher adiposity than control group 22-23 wk post inoculation. The same mechanisms as found in adenovirus-36, i.e. increased preadipocyte differentiation, also apply for adenovirus-5 infection[56]. Human adenovirus-37 was first isolated by de Jong *et al*[63]. Adenovirus-37 caused adiposity in chickens and the visceral fat pads were three times heavier in adenovirus-37-inoculated chickens than in controls. Different from adenovirus-36, adenovirus-37 infections did not induce reduced concentrations of serum cholesterol. Among over 50 strains of adenoviruses among five subgroups maintained by ATCC, strains adenovirus-36 and adenovirus-37, adenovirus-5 are adipogenic and adenovirus-2 and adenovirus-31 are not adipogenic. The potential of other human adenoviruses on the development of obesity remains unknown.

PATHOGENS ENHANCING HUMAN CHRONIC INFLAMMATORY DISEASES AND OBESITY

H. pylori

H. pylori is a spiral-shaped gram-negative flagellated bacterium and causes highly prevalent chronic infections worldwide[64]. *H. pylori* is the etiology of diseases such as gastritis and stomach cancer but most *H. pylori* infections are "silent" and produce no clinical symptoms and in particular are asymptomatic in childhood. Worldwide, up to 10% of children and 80% of adults show laboratory evidence of *H. pylori* infection. Aydemir *et al*[65] (2005) provided the first association between chronic *H. pylori* infection and insulin resistance. The homeostasis model assessment of insulin resistance was significantly higher in 36 *H. pylori*-positive subjects than in 27 *H. pylori*-negative ones[65]. Epidemiological evidence also supports the association of *H. pylori* seropositivity with cardiovascular diseases and elevated parameters of metabolic syndrome[66,67].

C. pneumoniae

C. pneumoniae, an intracellular respiratory bacterium, causes acute or chronic bronchitis and pneumonia[68] and is responsible for 10% of the cases of community-acquired pneumonia and approximately 5% of cases of bronchitis and sinusitis in adults[68-70]. Many epidemiological surveys, experimental studies and clinical trials have provided strong evidence for the association between *C. pneumoniae* infection and metabolic syndrome, insulin resistance and cardiovascular disease[70-82]. The current concept of the influence of *C. pneumoniae* on atherosclerosis is that *C. pneumoniae*-infected macrophages traffic to secondary organs including arterial endothelium, induce persistent infection and lead to the local upregulation of proinflammatory molecules (Figure 1A). Subsequently, infected macrophages and smooth muscle cells transform into foam cells and result in plaque destabilization, thrombus formation and myocardial infarction in arterial endothelium[75,85]. Ased on this notion, antibiotic treatment would reduce cardiovascular events by eliminating *C. pneumoniae* persistent infection and preventing re-infection. However, clinical trials with anti–biotic treatment based on this concept failed. This failure to reduce cardiovascular events by antibiotic treatment requires the reformulation of the current mechanistic understanding of the association between *C. pneumoniae* and metabolic syndrome and cardiovascular disease[83].

Wang *et al*[84] examined the influence of *C. pneumoniae* infection on progression of insulin resistance in dependence of host genetic background and dietary fat concentration in an obese mouse model. They concluded that murine *C. pneumoniae* infection enhances insulin resistance and diabetes in a genetically and nutritionally restricted manner *via* circulating inflammatory mediators such as TNF-α[84] and proposed a new mechanism of *C. pneumoniae*-induced exacerbation of insulin resistance developed in this investigation (Figure 1B). By quantifying the levels of *C. pneumoniae* and TNF-α transcripts in different organs, they concluded that the dispersal of a small number of *C. pneumoniae* organisms to secondary tissues was irrelevant to progression of insulin resistance and the early onset of type 2 diabetes. In contrast, the bulk infection of the lung caused an increase in circulating cytokines that drove the long-term exacerbation of insulin resistance (Figure 1B) and accelerated the onset of type 2 diabetes[84]. It was reported that combined pathogen burden[82] and positive serology for both *H. pylori* and *C. pneumoniae*[66] showed the strongest association with insulin resistance. These data suggest that exposure to multiple pathogens may potentiate chronic low-grade inflammation and insulin resistance and that the mechanisms whereby the pathogens affect chronic inflammatory diseases are shared.

P. gingivalis

A national survey with 9 689 subjects from 1988 to 1994 showed that periodontal disease is prevalent in the U.S. adult population[86]. Approximately 35% of the adults

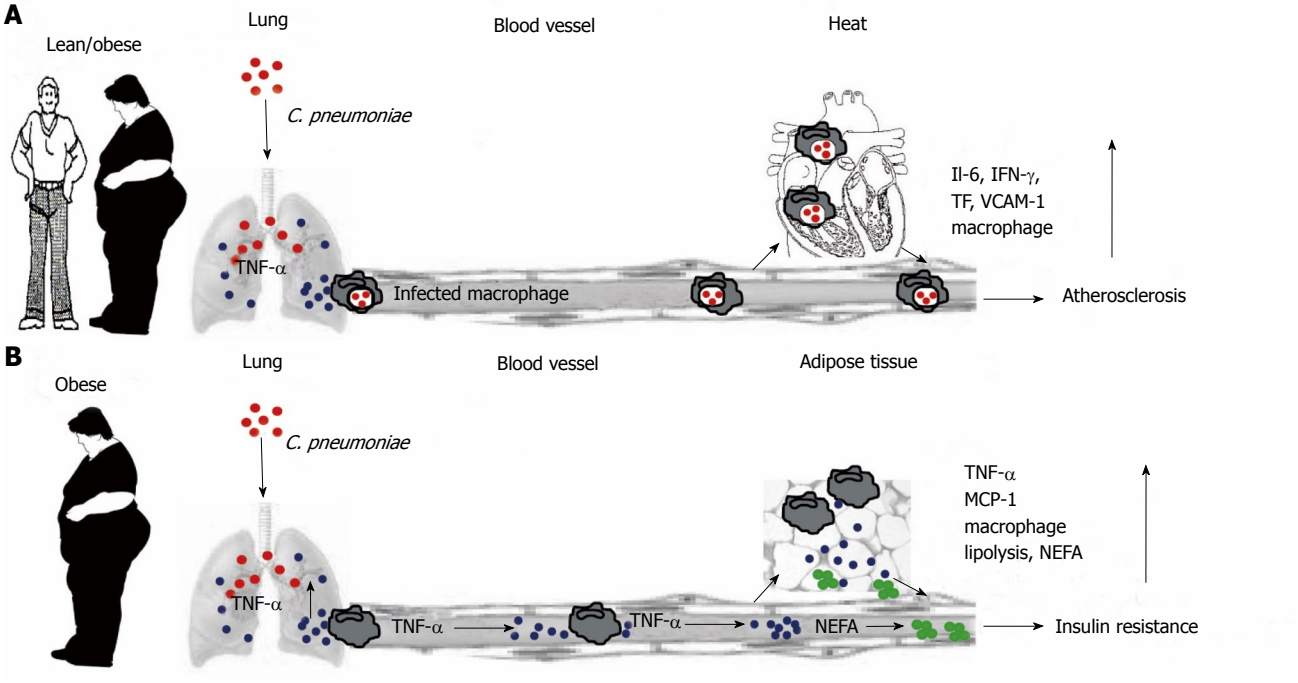

Figure 1 Schematic representation of *C. pneumoniae*-mediated acceleration of inflammatory diseases associated with metabolic syndrome. A: Current concept of the influence of *C. pneumoniae* on atherosclerosis. After respiratory infection, *C. pneumoniae* (red) is endocytosed by alveolar macrophages of infected lean or obese individuals. Infected macrophages re-enter circulation and traffic to secondary organs including arterial endothelium. Disseminated *C. pneumoniae* organisms infect other cell types, leading to up-regulation of pro-inflammatory molecules such as IL-6, IFN-γ, tissue factor and vascular-cell-adhesion molecule 1. These cytokines, in particular IFN-γ, retard chlamydial replication and induce persistent infection. In arterial endothelium, infected macrophages and smooth muscle cells transform into foam cells, affecting atheroma biology and leading to plaque destabilization, thrombus formation or myocardial infarction[85]. B: Concept of *C. pneumoniae*-induced exacerbation of insulin resistance developed by Wang *et al*[84]. *C. pneumoniae* infection results in lung colonization, thereby increasing TNF-α release (blue). Circulating TNF-α induces insulin resistance by inhibiting the function of insulin receptor substrate-1 in peripheral tissues and further exacerbates insulin resistance by promoting lipolysis and increased NEFA (green) production in adipose tissue. TNF-α and NEFA promote further macrophage infiltration and excess production of pro-inflammatory molecules in adipose tissue. In contrast to the atherosclerosis concept, the perpetuation of adipose tissue inflammation is driven by circulating pro-inflammatory cytokines rather than by in situ production stimulated by infected macrophages. Sustained by continuous high-fat nutrition, the inflammatory condition of adipose tissue maintains the vicious cycle of insulin resistance in the absence of *C. pneumoniae* organisms.

in the USA have periodontitis, an inflammation that involves the periodontal ligament and alveolar bone, while about 75% have gingivitis, an inflammation of the gingival tissues surrounding the teeth[8,86]. Periodontal diseases are initiated by gram-negative and anaerobic bacteria such as *P. gingivalis* residing in biofilms on gingival tissues and teeth[87]. Periodontal diseases had been thought of as localized conditions of concern only to dental health professionals. Emerging evidence now suggests that periodontal diseases also exacerbate systemic conditions such as metabolic syndrome and diabetes[88,89]. The oral infection causes elevated circulating IL-1β and TNF-α which lead to hyperlipidemia and development of diabetes[88,90].

HCV

HCV infection is a worldwide problem with approximately 200 million infected individuals[1,2]. Chronic HCV infection may result in liver cirrhosis and hepatocellular carcinoma and is associated with multifaceted disease such as porphyria cutanea tarda, membranoproliferative glomerulonephritis and cryoglobulinemia. While epidemiological studies suggested a linkage between HCV infections and type 2 diabetes[91-95], Shintani *et al*[91] confirmed the direct involvement of HCV infection in the development of insulin resistance in a mouse model using mice with the HCV core gene inserted in their genome. They showed that a high level of TNF-α was the main factor to induce insulin resistance in HCV-transgenic mice and insulin sensitivity was restored by administration of anti-TNF-α antibody.

HIV

Insulin resistance is common in HIV-infected people and the prevalence of hyperglycemia and diabetes is significantly higher in people with HIV infection treated with antiretrovirals as compared with the general population[96]. The prevalence of insulin resistance in HIV subjects is around 35% and up to 47% when they received protease inhibitor therapy, while the incidence of insulin resistance is only around 5% in the general population[97]. Presumably, HIV induces an increased inflammatory state, as evident in elevated levels of adiponectin and free fatty acids in HIV-infected individuals[96].

CONCLUSION

Ranked as one of the three major challenges to human progress along with war and famine, infectious diseases remain among the leading causes of death and disability

Table 1 Pathogens associated with obesity

Pathogen	Effect	Mechanisms	Ref
CDV	Increased body weight in Swiss albino mice	Altered hypothalamic integrity; increased cytokine production, hyperinsulinemia and decreased leptin and neuropeptides	[15-17,21, 22]
RAV-7	Stunting, anemia and increased visceral fat in white leghorn chickens	Decreased thyroxine, hyperlipidemia and hyperinsulinemia	[23,24]
BDV	Obesity with increased visceral fat in Lewis rats	Inflammatory lesions in hypothalamus, increased triglyceride and blood glucose	[35,36]
SMAM-1	Stunting and increased visceral fat in white leghorn chickens	Impaired liver function and lipogenesis and glucagon deficiency	[49,50]
Scrapie agent	Increased body weight and fat accumulation in mice	Altered brain function and reduced GLUT-1	[43,44]
Adenovirus	Increased body weight in chickens, mice, rats and monkeys; seropositive subjects were heavier than seronegative counterparts	Increased replication, differentiation and lipid accumulation of preadipocytes	[51-60]

CDV: Canine distemper virus; RAV-7: Rous-associated virus-7; BDV: Borna disease virus; Ref: Reference.

Table 2 Pathogens associated with increased chronic inflammatory diseases in humans

Pathogen	Effect	Mechanisms	Ref
H. pylori	Affected subjects showed increased insulin resistance	Increased concentrations of plasma glucose and lipids	[64-67]
C. pneumoniae	Increased metabolic syndrome, insulin resistance and cardiovascular disease	Increased production of proinflammatory and circulating cytokines	[68-72]
P. gingivalis	Adults with dental infections demonstrated higher chance of insulin resistance and diabetes	Increased oxidative stress, advanced glycation end-products and altered immune function	[86-90]
HCV	Infected patients showed increased chance to develop insulin resistance and diabetes	Increased production of TNF and IL-6	[92-95]
HIV	HIV patients showed higher insulin resistance (35%) compared to normal subjects (5%)	Impaired glucose tolerance and significant hyperinsulinaemia	[96,97]

H. pylori: *Helicobacter pylori; C. pneumoniae*: *Chlamydia pneumoniae; P. gingivalis*: *Porphyromonas gingivalis;* HCV: Hepatitis C virus; HIV: human immunodeficiency virus; Ref: Reference.

worldwide[98]. More than 25% of annual human deaths are the direct result of infectious diseases[98,99]. Progress in diagnostic methodology now allows the consistent detection of low-number but widely-prevalent pathogens as well as sensitive and precise quantification that captures subtle elevations of inflammatory cytokines which are closely related to metabolism and the immune response. Application of these essential tools in epidemiological, pathological and experimental studies has strongly suggested an infectious influence on obesity, metabolic syndrome, diabetes and cardiovascular diseases.

Following Darwinian adaption in human evolution, thrifty genes have probably evolved to maximize food utilization during periods of mass starvation.This metabolic adaptation combines frugal use of nutrients with vigorous inflammatory responses to pathogens and thus maximizes survival[100,101]. While advantageous under selective pressure of starvation and epidemic infectious diseases, this genetic makeup of large population segments has become a liability in times of food abundance and increased hygiene that eliminates epidemic but not endemic chronic infections. The evolved frugal metabolic characteristics increase obesity under conditions of over-nutrition and intensive inflammatory responses enhance the pathological consequences of obesity under constant stimulation by previously unrecognized ubiquitous but low-level chronic infections.

In summary, the dominant influence on chronic inflammatory diseases is anchored in human genetics and the outcome is driven by food supply and consumption. In this cause-effect network with tightly integrated metabolic and immune response pathways, infections likely play a heretofore underappreciated role in modulating intensity and pathological consequences, thus potentially decisively modulating the cause-effect network in the pathogenesis of chronic inflammatory diseases. Confirmation of the infectious modulation of obesity (Table 1) and chronic inflammatory diseases (Table 2) will facilitate prevention and management of such diseases. Very likely, vaccinations against multiple infectious agents will be the sole effective and realistic approach to ameliorate pathogen-enhanced obesity and related conditions such as diabetes and atherosclerosis.

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