Relationship between Common Dietary Polyphenols and Obesity-Induced Inflammation

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Abstract The incidence of obesity and its related metabolic disorders has escalated dramatically in the past decades worldwide. Defined as abnormal or excessive fat accumulation caused by an imbalance between energy intake and expenditure, obesity is presently the major health challenge in developed countries and the causative factor of numerous diseases such as heart problems, hypertension, hyperlipidemia and type 2 diabetes. Presence of high level of cytokines and acute phase proteins associated with inflammation in obese individuals relates obesity to chronic low-grade inflammation. Obesity-induced inflammation has an impact on insulin resistance and cardiac health. Polyphenols including catechins, tocopherols, resveratrol, curcumin and anthocyanins have been shown to reduce adipose tissue inflammation. It has been broadly accepted that adipocyte dysfunction plays a major role in development of obesity and obesity related complications. This state is characterised by hypersecretion of pro-atherogenic, pro-inflammatory and pro-diabetic adipokines as well as decreased secretion of adiponectin. The dietary polyphenols described in this review have potential as nutritional strategies for the prevention of obesity and associated inflammation as well as increase in insulin sensitivity in diabetic people.

Keywords Obesity, Obesity-Induced inflammation, Adipose tissue dysfunction, Dietary intervention, Polyphenols

1. Introduction

The incidence of obesity and its related metabolic disorders has escalated dramatically in the past decades worldwide reaching epidemic proportions and becoming a key public health issue with a massive burden to the health-care system [1, 2]. It is not that just the high-income countries are affected with this condition, obesity is a worrying escalation in developing countries as well [1, 2]. In 2008 the World Health Organisation estimated that globally 1.5 billion > 20 years old adults were overweight and 200 million men and nearly 300 million women were obese. Overall, more than one in ten of the world's adult population is obese. Statistically, obesity is the fifth leading risk for human mortality around the globe resulting in 2.8 million adult deaths each year [3]. Furthermore, 44% of diabetes increase, 23% of the ischemic heart disease increase and 7-41% increase of certain cancer is related to the overweight and obesity epidemic [3].

More alarming is that childhood obesity is on upsurge also and it has increased dramatically since 1990 [4]. Globally, in 2010, 43 million children were estimated to be overweight and obese with 92 million at risk of being overweight [4]. In 2012, around 44 million (6.7%) of the world's children aged less than five years were overweight or obese [5]. Overweight children are likely to become obese adults and are more likely than non-overweight children to develop diabetes and cardiovascular diseases (CVDs) at a younger age, which can lead to premature death and disability [5]. Childhood obesity is one of the most serious public health challenges of the 21st century and it is expected to increase to about 60 million obese children, in 2020 [4].

Obesity is a complex disease controlled by many factors such as genetic, environmental and behavioural [6]. Amongst the environmental factors, the continuing intake of high fats (HF) in the diet is strongly linked with the development of obesity which further can lead to insulin resistance and development of type 2 diabetes [7]. It is linked to an increase in certain type of cancers as well as pulmonary diseases [1].

1.1. Inflammation, Obesity and Associated Diseases

It has been accepted for over a decade that obesity is connected with chronic low-grade inflammation [1, 8]. The basis for this view is that the circulatory levels of several cytokines and acute phase proteins associated with inflammation are increased in obesity. While many of them are secreted by adipocytes it is believed that increased adipose tissue mass is either directly or indirectly associated with increased production of inflammation-related factors [9]. Various cell types contribute to chronic low grade inflammation, which has been suggested to increase adipose tissue mass in metabolic disorders [10]. One of the first

cytokines to be found elevated in obese mice tissue and the one which links obesity and inflammation was tumour necrosis factor-α (TNF-α) [11]. After that many studies looked at this phenomenon and found that many other cytokines such as interleukin (IL)-6, IL-1β and chemokine (C-C motif) ligand 2 (CCL2) are increased in adipose tissues in obese animals and humans [12, 13]. Furthermore, it has been shown that not only the adipose tissue but other tissues such as liver, pancreas, brain and probably muscle, also experience increased level of these cytokines and possible insulin resistance in the obese state [14-17]. In other words, the state of inflammation in adipose tissue in obesity plays to an important role in increased production and secretion of inflammation related factors and insulin sensitivity.

Increased adipose tissue has been associated with abnormal lipid and glucose metabolism, hypertension, and inflammation as risk factors of cardiovascular disease, type 2 diabetes, the metabolic syndrome and various cancers. Obesity-induced inflammation and the activation of the innate immune system are closely involved in the pathogenesis of type 2 diabetes and further development of CVDs [18]. There is proven link between obesity related insulin resistance and increased production of tumour necrosis factor-α (TNF-α) and interleukin (IL-6) by the adipose tissue through the nuclear factor-kappa B (NF-kB) and c-jun terminal NH2-kinase (JNK) tissue specific signalling pathway [19]. Many obesity induced pathophysiologies are linked to plasminogen activator inhibitor-1 (PAI-1). Besides its role in fibrinolytic system in blood, recently it has been considered as one of the biomarkers in prediction of obesity associated diseases [20]. Elevated PAI-1 mRNA level have been found in adipose tissues from obese ob/ob/mice and also in human obesity with higher expression levels in visceral compared to subcutaneous adipose tissue depots [21, 22].

1.2. Therapeutic Options for Obesity

Several therapeutic options approved by the FDA have been used as a short-term treatment of obesity. Noradrenergic activators such as phentermine, diethylpropion, phendimetrazine and benzphetamine cause appetite suppression and are used for less than 12 weeks in the management of obesity [23]. The most widely prescribed obesity drug between 2008-2011 was phentermine however, similar to others with a noradrenergic method of action, it can cause unpleasant side-effects such as dizziness, headache, anxiety, elevated heart rate and gastro-intestinal issues [23]. Phentermine may also be used with topiramate as a combination therapy. Topiramate is usually used as an anti-epileptic drug, but in a non-standard dose, it has shown effectiveness for weight loss. Topiramate may not be used by pregnant women due to an increased risk of oral clefts in the offspring, and side effects of this particular combination therapy include insomnia, dizziness, elevated heart rate and cognitive changes [23].

Approved by the FDA in 2012, the selective serotonin 2C receptor agonist Lorcaserin also causes appetite suppression, but has similar unpleasant side effects such as dizziness, headaches, nausea and hypoglycaemia in type 2 diabetics [23]. Another obesity drug is Orlistat. It is a reversible inhibitor of lipases; enzymes responsible for hydrolysing dietary fat in the form of triglycerides into absorbable molecules such as free fatty acid and monoglycerides. It can cause excretion of up to 30% if dietary fat but, because of its mechanism of action, it can result in unpleasant gastrointestinal side-effects if patients do not reduce their fat intake [23].

In addition to this several other anti-obesity drugs are undergoing clinical development at the moment but because of possibly hazardous side-effects and presents of high cost there is demand for more natural and safe anti-obesity drug [24].

There is strong evidence supporting the therapeutic use of polyphenols such as stilbenes, flavonoids and curcuminoids which show potential in prevention and/or treatment of obesity and its diabetic complications [6, 25, 26]. They are widely accepted in health promotion due to their antioxidant, anti-inflammatory, anti-carcinogenic, anti-obesity, anti-diabetic and anti-aging properties [2, 6, 27, 28]. The actions of their affect are believe to be through suppression of adipocyte differentiation and proliferation, inhibition of fat absorption from gut, inhibition of lipogenesis, stimulation of β-oxidation as well as inhibition of production of pro-inflammatory adipokines and stimulation of adiponectin secretion [27, 28].

Understanding the mechanisms leading from obesity to inflammation may have important implications for the design of novel therapies to reduce the morbidity and mortality of obesity and its associated complications. Many commonly used food compounds, such as antioxidant polyphenols, vitamins, long-chain unsaturated fatty acids, and carotenoids, have been reported to have anti-inflammatory and/or antioxidant effect resulting in reduction in weight and increase in insulin sensitivity [29]. This review discusses some of the commonly used polyphenols and their anti-inflammatory and anti-obese properties.

1.3. Characteristics of Obesity-Induced Inflammation

Many studies have revealed that the inflammatory state induced by metabolic surplus is in many ways different to the classic inflammation which is characterised with redness, swelling, heat and pain [1]. Although classical inflammation helps in fighting foreign invaders, obesity-induced inflammation is different in several points. The obesity-induced inflammation is metabolic in nature caused by the surplus of nutrients and that the cells which stimulate the inflammatory response are metabolic cells - adipocytes [1]. Secondly, the metabolic signals start inflammatory intracellular signalling pathways such as the kinases c-jun N-terminal kinase (JNK), inhibitor of κ kinase (IKK), or protein kinase R (PKR) that facilitate a modest, low-level

induction of inflammatory cytokines, TNF-α, CCL2, or Il-1β [30, 31].

Another characteristic of obesity-induced inflammation is greater infiltration of immune cells into the adipose tissue [1]. Studies have revealed that obese mice have increased macrophage population compared with lean mice [32, 33]. More specifically the increased macrophage population would be one of proinflammatory M1 type, which has a damaging effect on insulin sensitivity [34]. Besides, the obesity-induced inflammation is characterised by its continuity, where the inflammatory pathways continue to reinforce each other, from metabolic cell signalling to immune cell responses, and it remains unresolved [1]. In conclusion, obesity-induced inflammation is linked with a reduced metabolic rate which is in contrast to the classic inflammation where we see a quite opposite-increase in metabolic rate [1].

The obesity-induced inflammation found in animal studies has been observed in humans as well. Numerous studies found induced inflammatory cytokine, increased kinase activity and macrophage infiltration in the adipose tissue of obese humans [35-37]. Furthermore, supported by strong evidence it was demonstrated that normal metabolism and proper insulin signalling are affected by activation of the inflammatory pathways and that can further result in development of insulin resistance in adipocytes [1].

One of the fundamental goals in preventing and/or combating obesity would be to ameliorate the adipocytes dysfunction which is very much present in this disorder. Targeting the inflammatory component of obesity to improve insulin sensitivity and reduce body weight is a new approach. A few promising pieces of evidence have emerged recently. Stanley et al. have shown that treatment of obese type-2 diabetic patients with etanercept, a TNF-α antagonist, resulted in decreased blood glucose and increased adiponectin levels [38]. Another study used recombinant IL-1 receptor antagonist and observed improved glycaemia and increased insulin secretion from β cell [39].

The use of anti-inflammatory nutrients, as part of an everyday diet, is a novel and promising therapeutic method in the battle with obesity and metabolic disorders [1]. Since adipose tissue inflammation is linked with the development of insulin resistance and several chronic diseases, improving adipose tissue inflammation through dietary interventions could be a useful strategy for improving the overall metabolic profile [40].

2. Dietary Intervention to Reduce Adipose Tissue Inflammation and Insulin Resistance

It has been widely accepted that dietary composition and not just reduction in energy intake can influence metabolic and endocrine function and overall energy balance [40, 41]. A diet rich in fruit and vegetables, recommended by many health professionals, would provide significant amounts of bioactive components, enhancing their beneficial effects mostly due to their anti-inflammatory properties [42]. Evidence shows that dietary bioactive compounds in the form of supplementation provide comparable benefits. Esfahan et al. conducted a literature review of 18 human trials with 1362 participants and found that fruit and vegetable concentrates significantly increase serum levels of antioxidant pro-vitamins and vitamins such as β-carotene and vitamins C & E as well as folate [43].

Reduction of adipose tissue inflammation by dietary bioactive molecules could be achieved through different mechanisms either through suppression of pro-inflammatory adipokines production or stimulation of anti-inflammatory adipokines production such as adiponectin. Despite some controversy regarding adiponectin expression under different conditions, it is accepted that adiponectin is a powerful anti-inflammatory adipokine showing decreased serum level with increasing body fat. Adiponectin level is also recorded to be lower in type-2 diabetes individuals and CVD patients [44]. It has been demonstrated that chronic consumption of grape phenols resulted in reduction of obesity and related metabolic pathways as well as increased production of adiponectin [45].

2.1. Polyphenols and Adipose Tissue Inflammation

Naturally present in plants, polyphenols are compounds with a wide range of biological features such as anti-oxidant, anti-inflammatory, anti-thrombotic, anti-cancer, anti-obesity and anti-aging properties which enables them to display strong protective actions of many pathological conditions especially those caused by oxidative stress and/or chronic inflammation such as CVD and metabolic disorders [46-48]. Furthermore, the ability of polyphenols to suppress the growth of the adipose tissue through their antiangiogenic activity and by modulation of adipose metabolism make them very good therapeutic modulators of obesity [49].

The range and diversity of polyphenol distribution in plants have led to various forms of classification of these naturally occurring compounds. They have been categorised by their source of origin, biological function, and chemical structure. The majority of polyphenols in plants exist as glycosides with different sugar units and acylated sugar at different positions of the polyphenol skeletons. Based on the number of phenol rings present and the number and type of the structural binding element polyphenols are grouped into following classes: simple phenolic acids (fruit vegetables and grains like bran or hull); stilbenes (resveratrol); curcuminoids (turmeric); chalcones (fruit like apples); lignans (flaxseeds); flavonoids (anthocyanins from red pulp fruits); isoflavones (beans); and flavonoids (catechins). Amongst these catechins, resveratrol, curcumin, and anthocyanin rich flavonoids express very potent antioxidative and anti-inflammatory properties [27]. It has been proposed that their beneficial effect may occur through several mechanisms such as suppression of fat absorption, uptake of glucose by skeletal muscles, inhibition of

angiogenesis in adipose tissue, inhibition of differentiation of pre-adipocytes to adipocytes, stimulation of apoptosis of mature adipocytes, and reduction of chronic inflammation associated with obesity through the regulation of adipokines production [27, 50, 51]. In addition to this, it has been found that resveratrol and curcumin alter gene expression of adipocyte specific genes and genes involved in energy metabolism and lipid accumulation respectively [49].

2.2. Catechins and Tocopherols

Well studied polyphenols present in green tea and cocoa (chocolate), catechins, and vitamin E tocopherols proved to have beneficial effect on human's health such as antioxidant and anti-inflammatory activities, anti-obesity, anti-thrombotic, cardiovascular disease and cancer prevention [27, 51-54]. Several epidemiological and clinical studies have revealed that routine intake of green tea extract is associated with low body fat and lower BMI [55, 56]. Its anti-obesity effects are displayed through suppression of adipocyte differentiation and proliferation, inhibition of fat absorption from the gut and suppression of catechol-o-methyl transferase (COMT) [27]. Catechins intake decreases the risk of type 2 diabetes by increased glucose uptake into the skeletal muscles through up-regulating glucose transporter 4 (Glut 4) and by reducing translocation of Glut 4 and insulin levels in adipose tissues [57, 58]. In a cell model, gamma-tocopherol treatment increases the glucose uptake by skeletal muscles under induced oxidative stress as well [59].

2.3. Resveratrol (RSV)

A non-flavonoid polyphenol, called resveratrol, is found in grapes, red wine, peanuts and some berries such as blueberries and cranberries. RSV is recognized antioxidant and powerful anti-inflammatory molecule as well [60]. RSV has been found to be effective in inhibiting the development of several disease including CVD, diabetes, cancer, and obesity [61-63]. Several studies have revealed that RSV treatment considerably reduces adipose tissue and total body fat in high fat fed and genetically obese mice [64, 65]. Another study examining long-term consumption of RSV in rodents showed reduction in plasma triglycerides, free fatty acids, cholesterol and liver triglyceride possibly through 5'-AMP-activated protein kinase mechanisms [66].

Its anti-inflammatory effects, which result in reduction in adipose tissue inflammation, are likely achieved through suppression of NF-κB and extracellular signal-regulated kinase (ERK) activation [67]. *In vivo* studies demonstrate ability of RSV to attenuate high-fat diet-induced production of TNFα and IL-6 and their upstream signalling molecules [68]. Furthermore, human an animal studies have revealed increase in adiponectin levels and the suppression of lipid accumulation with diet rich with RSV [69, 70].

Based on this evidence RSV seems to be a promising dietary bioactive molecule that can be easily encompassed into the diet to regulate adipose tissue inflammation and obesity-associated metabolic disorders.

2.4. Curcumin

The most studied of all curcuminoids is curcumin found in the plant turmeric and is usually used as a spice and colorant [27]. Due to its antioxidant, anti-inflammatory, anticancer, anti-angiogenesis, chemo-preventive and chemotherapeutic properties it is used in Asian medicine since the second millennium BC along with its wide use in research [71]. Some of the first reports dating back as much as 50-80 years ago revealed benefits of curcumin to health and its effect on liver cholesterol, weight loss as well as blood triglyceride and free fatty acids level [72]. In recent days studies have shown that curcumin indeed has significant impact on body weight, lipid metabolism, adiposity and improves obesity associated inflammation [73-75]. This is achieved through curcumin's capability to regulates several important molecules such as transcription factors, growth factors, inflammatory cytokines, protein kinases, some enzymes and several signalling pathways [76, 77]. It has been shown that two weeks of supplementation of rodent diets with 2 and 10g/kg of curcumin, decreases adipose tissue, reduced liver fatty acid synthesis and increases rats liver acetyl CoA oxidase activity [78]. Supplementation with 500mg/kg of curcumin to high fat hamsters decreases the level of free fatty acids, total cholesterol, triglycerides, leptin and the insulin resistance index [79]. Furthermore, consumption of large amount of dietary curcumin by insulin resistant obese mice resulted in significant improvement of type 2 diabetes and inflammation in the liver [80].

Curcumin's anti-inflammatory properties have been reported in genetic obese (ob/ob mice) and diet-induced obesity models. Reduced macrophage infiltration into adipose tissue, increased adiponectin production, and decreased hepatic NF-κB activation [80]. Suppression of NF-κB resulted in suppression of TNF-α, IL-1β and IL-6 gene expression in differentiated adipocytes [67].

The anti-inflammatory and anti-obesity properties of curcumin discussed above suggest its potential use in control of adipose tissue growth and inflammation.

2.5. Anthocyanins

Belonging to a family of polyphenols anthocyanins are responsible for red, purple and blue colour in plants [81]. There are 600 naturally occurring anthocyanins up to date and while they all vary slightly in the structure of their molecule they all play an important role as dietary antioxidants in the prevention of oxidative damage [82]. They also have several other biological activities, such as being an anticonvulsant, anti-carcinogenic, anti-atherosclerotic and anti-inflammatory agent, and playing a role in lowering the risk of coronary heart disease [81, 83].

Recent studies have reported that anthocyanins exhibit an anti-obesity effect as well and they display potency to regulate adipocyte function and adipokines expression.

Tsuda et al. showed that anthocyanins in purple corn color made from purple corn prevent weight gain in the high-fat-diet-induced obese mice [84]. Similar results have been found in the experiment conducted by Kwon et al. where stable body weight was achieved in rats on high-fat diet (HFD) supplemented with anthocyanin from black soybeans [81]. Furthermore, serum triglycerides and cholesterol levels were significantly lower and HDL-cholesterol levels were higher in the rats fed on HFD plus black soybean anthocyanins compared with pure HFD rats [81]. This could indicate anthocyanins' possible positive effect on lipid profile.

Human adipocytes response to anthocyanins was observed by the microarray assay revealing up-regulation of adiponectin level, and down-regulation of plasminogen activator inhibitor-1 (PAI-1) and IL-6 levels [84]. Since high expression of PAI-1 and IL-6 in adipose tissue and low expression of adiponectin is connected with obesity and type-2 diabetes, regulation of their expression is an important therapeutic target for treating obesity and its relevant disorders [3].

Furthermore, Jayaprakasam et al. investigated the effect of anthocyanins on attenuation of insulin resistance in high-fat-fed C575L/6 mice. The mice were supplemented with the mixture of pure anthocyanins, cyaniding 3-O-galactoside, pelargonidin 3-O-galactoside, and delphinidin 3-O-galactoside, isolated from Cornelian cherry [85]. They found that the glucose tolerance in animals improved after 6 weeks of treatment with anthocyanins. The improvement could be seen either because the anthocyanins increased insulin sensitivity and/or increased insulin secretion [85]. In additions to these findings anthocyanins-fed mice had decreased body weight gain as well as decreased plasma cholesterol level which is in corroboration with results from two previous mentioned studies [81, 84].

Anthocyanins are broadly distributed in the human diet, and consumed in significant amount form plants on a daily basis. They have great potential for their health-promoting effect and can be used as a functional food factor. Anthocyanins have a unique therapeutic advantage due to their involvement in the regulation of the adipocyte function and may be an important factor for preventing obesity and obesity related disorders [84].

3. Conclusions

Obesity is a complex and multifactorial condition of chronic inflammation and oxidative stress. Although there are many diet and exercise programs for weight loss available, results are disappointing. Use of antiobesity drugs, and in extreme cases bariatric surgery, do not provide sufficient support for their efficacy. The incompetence of most of these programs is evidenced by the increase in obesity incidence and in weight regain. Novel treatments for obesity and its related diseases might be possible by targeting the production and/or action of specific adipokines, particularly those linked to inflammation. The dietary polyphenols described in this review have potential nutritional strategies for the prevention of obesity and associated inflammation as well as the increase in insulin sensitivity in diabetic people. There is still need for more *in vivo* research on human obese subjects to further investigate the anti-obesity and anti-inflammatory effects of polyphenol and their possible use as a novel therapeutic models in the battle with this disease.

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