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Orlistat for obesity management with high levels of TNFα in children

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ABSTRACT

Childhood obesity has increased significantly over the past four decades. Obesity is the leading cause of preventable death in the world. An excess of body fat or adiposity characterizes it. TNFα expression in adipose tissue increases during the development of obesity. With the magnitude of the risk caused by obesity, efforts must be carried out to overcome obesity. Orlistat is a drug approved for obesity treatment in adolescents and children by the FDA. The data collection method was collected from articles related to orlistat in obesity management with high levels of TNFα in children. The inclusion criteria were from original articles, case-control studies, and review papers on childhood obesity, TNFα, and orlistat. Orlistat is effective in obesity management with high levels of TNFα in children. Obesity is associated with low-level inflammatory processes in WAT. The increase in adipose tissue mass simultaneously activates inflammatory processes in WAT, located in the liver and immune cells. WAT is the source of several pro-inflammatory cytokines, mainly TNFα. The use of orlistat has been recognized as an effective way to lose weight in childhood obesity. Along with weight loss, a decrease in adipocytes reduces TNF α levels in children.

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INTRODUCTION

Obesity is the leading cause of preventable death in the world. Obesity and overweight are now as the fifth global risk factors of mortality (Pandita *et al.*, 2016). It is well known that obesity induces all major metabolic disorders, especially diabetes, cardiovascular disease, hypertension, and liver disease (Cao, 2014). Obesity rates are rising in adults and children (Gazioglu *et al.*, 2015). Overweight children tend to keep in overweight condition when adults (Liang *et al.*, 2014). Obesity is characterized by an excess of body fat or adiposity. Obesity is determined by body mass index (BMI) (Güngör, 2014). It is associated with increased metabolism due to greater adipose tissue (Cote *et al.*, 2013; Cunningham *et al.*, 2014).

Childhood obesity has increased significantly over the past four decades (Hossain *et al.*, 2019). World Health Organization (WHO) experts estimate that there are 43 million overweight

children under the age of five and more than 60% of the global disease burden will result from obesity-related disorders in 2020. Childhood obesity is associated with several short and long-term health hazards (Kelishadi & Azizi-Soleiman, 2014). The consequences of obesity include an increased risk of metabolic syndrome, cardiovascular disease, type 2 diabetes and associated retinal and kidney complications, non-alcoholic fatty liver disease, obstructive sleep apnea, polycystic ovary syndrome, infertility, asthma, orthopedic complications, psychiatric diseases, and an increased possibility of cancer. This disorder can begin as early as childhood and increase the likelihood of morbidity and early mortality (Kelsey *et al.,* 2014; Ohashi *et al.,* 2014; Pulgarón, 2013; Rajjo *et al.,* 2017).

Fatty tissue releases many bioactive molecules, called adipokines, which affect whole-body homeostasis (Ohashi *et al.,* 2014). Obesity causes an increase in the expression of pro-inflammatory adipokine and a reduced expression of anti-inflammatory adipokin by producing the development of chronically low-level inflammatory states (Nakamura *et al.,* 2014). Adipokin consists of a large number of proinflammatory mediators, including monocyte chemoattractant protein-1 (MCP)-1, interleukin (IL)-6, and especially tumor necrosis factor alpha (TNF α) that promotes disease progression (Ohashi *et al.,* 2014). TNFα expression in adipose tissue increases during the development of obesity (Tateya *et al.,* 2013). Many studies imply obesity caused by chronic inflammation (Rodríguez-Hernández *et al.,* 2013). Since obesity tends to continue into adulthood, prevention and intervention strategies should be started at the earliest possible age (Gurnani *et al.,* 2015).

With the magnitude of the risk caused by obesity, the efforts need to be carried out to overcome obesity by lowering the body mass index (BMI) which is expected to reduce adipose and minimize inflammation that can cause various diseases. One of the efforts that can be done is through medicamentosa orlistat therapy. One study showed that orlistat therapy was shown to have a significant BMI for 6 months (Salem & Rezaeian, 2012). Orlistat is a drug approved for the treatment of obesity in adolescents and children by the Food and Drug Administration (FDA) (Dolinsky *et al.,* 2013). Orlistat is a reversible pancreatic lipase inhibitor that limits the absorption of dietary cholesterol by about 30% (Marques, 2015).

This study aims to obtain the orlistat information for obesity management with high levels of TNFα in children.

RESEARCH METHOD

This literature review was conducted to gain as much information as possible about orlistat for obesity management with high levels of TNFα in children. This is a type of review article that aims to obtain information regarding the effectiveness of a drug in overcoming pathological circumstances whose effectiveness is also characterized by a decrease in a biomarker. The data source used a secondary source (Lenis *et al.,* 2020). Data analysis technique selects literature based on title, year, and indexed articles, then reviews articles that match the subject matter. the articles from those journals are compared to find the differences and similarities.

RESULTS AND DISCUSSIONS

Obesity

The term obesity refers to the excess fat (Kumar & Kelly, 2017). Obesity is characterized by excess body fat or adiposity (Güngör, 2014). Obesity is the result of a chronic calorie imbalance with more calories consumed than are expended daily. Most obese adults are obese as teenagers and most obese adolescents are overweight and/or obese as children. In fact, the origins of obesity are traced to early childhood development. Children who experienced an early adiposity rebound (before the age of 5) by experiencing an increase in average body mass index (BMI) from age three years to adolescence (Pulgarón, 2013).

Obesity is most often determined by a BMI measured by dividing body weight in kilograms by height in meters squared (kg/m2). BMI has a high correlation with adiposity and also correlates well with overweight at the population level (Güngör, 2014). BMI is the most commonly used measure of adiposity, but it has limitations. People with well-developed muscles but little fat will have a high BMI anyway (Llewellyn *et al.,* 2016).

Overweight and obesity in children are clinically assessed by BMI calculations. BMI values can be plotted on age and gender-specific growth graphs. Overweight is defined as the BMI of the 85th to 95th percentile (Center for Desease Control and Prevention (CDC)) or the 85th to 97th percentile (WHO). Obesity is a condition where the BMI at the 95th percentile (CDC) or greater than or equal to the 97th percentile (WHO) (Gurnani *et al.,* 2015).

Prevalence

The prevalence of childhood obesity has increased in recent decades in the world (Rivera *et al.*, 2014). The WHO has reported that obesity has grown at an alarming rate, accounting for about 35% of the population (Lee *et al.,* 2013). Most overweight or obese children and adolescents live in developing countries, where the rate of increase is 30% higher than developed countries. Without intervention, obese infants and young children are likely to continue to be obese during childhood, adolescence, and adulthood (Hossain *et al.,* 2019).

Globally, the number of obese children and adolescents (ages 5–19) increased from 11 million in 1975 to 124 million in 2016, a 10 times increase. The number of overweight or obese babies and young children (aged 0–5 years) was 41 million in 2016. If this trend keeps continue, the number of overweight or obese infants and young children (ages 0–5) will rise to 70 million by 2025 globally (Hossain *et al.,* 2019).

Etiology of Obesity

Genetics is one of the biggest factors studied as a cause of obesity. Genetic factors derive from parental genes, often causing children to become overweight (Xu & Xue, 2016). Some studies have found that a BMI of 25–40% is inheritable. Genetic factors account for less than 5% of childhood cases of obesity. Genetics can play a role in the development of obesity, but it is not the main cause of the dramatic increase in childhood obesity (Sahoo *et al.,* 2015). From a genetic point of view, obesity can be classified as a syndrome or monogenic or polygenic. Syndromeic obesity beside obesity is also distinguished by mental retardation, dysmorphic features, and organ-specific developmental abnormalities. Monogenic obesity is obesity associated with a single gene mutation that is capable of causing weight gain. Obesity due to a single gene mutation is usually severe and characterized by early onset. General obesity is usually determined by some gene polymorphism and such a genetic makeup that can affect energy storage (Aldhoon Hainerová & Lebl, 2013).

Endocrine disorders, such as hypothyroidism, Cushing's syndrome, growth hormone deficiency, and pseudohypoparathyroidism can appear with weight gain and slow growth. Of these, only Cushing's syndrome usually appears with severe obesity. After all, all disorders can lead to more central patterns of weight deposition. The cause of endocrine obesity was found to be less than 1% in children and adolescents with obesity. Hipothyroidism becomes the most common cause of endocrine-related weight gain. Levels of leptin as a hormone produced by adipocytes that work at the hypothalamic level aims to regulate weight and induce satiety, increase in obesity (Gurnani *et al.,* 2015).

The basal metabolic rate has been studied as a possible cause of obesity. The basal metabolic rate is responsible for 60% of the total energy expenditure in sedentary adults. It has been hypothesized that obese people have a lower basal metabolic rate (Sahoo *et al.,* 2015).

Dietary factors have been extensively studied for their possible contribution to increased obesity rates. Dietary factors studied include the consumption of fast food, sugary drinks, snacks, and portion sizes (Sahoo *et al.,* 2015). Behavioral factors include the consumption of foods and

drinking with high-calorie sugars sugary drinks of low nutritional value, which are available to children (Xu & Xue, 2016).

Lack of physical activity also contributes to obesity. Children spend a lot of time using technologies, such as mobile phones, televisions, computers or video games. On average, children aged 8 years and 18 years spend 7.5 hours per day using such gadgets and do not participate in physical activity and actively play (Campbell, 2016; Xu & Xue, 2016).

Complications of Obesity

An evidence suggests that there are many of the obesity comorbidities (Reilly & Saltiel, 2017). Childhood obesity has direct consequences to health including hyperlipidemia, hypertension, and abnormal glucose tolerance. It also increases the risk of orthopedic, neurological, pulmonary, gastroenterological, endocrine, and hepatic disorders. Other consequences are psychosocial, including discrimination, negative self-image, social exclusion, and depression. From a third to half of obese children become obese when adults. A possible mechanism underlying this situation is that maturation early in life leads to increased adiposity in adulthood. Obesity is a risk factor for non-communicable diseases in adults, such as hypertension, type 2 diabetes, cardiovascular disease, gallbladder disease, osteoarthritis, endocrine disorders, some types of cancer, and sleep apnea. Thus, an increase in the prevalence of overweight and childhood obesity is likely to be followed by an increase in the incidence of chronic diseases, with associated disability and death (Rivera *et al.*, 2014; Xu & Xue, 2016).

TNFα

TNFα is a powerful pro-inflammatory cytokine that plays an important role in the immune system during inflammation, cell proliferation, differentiation, and apoptosis. TNFα is a cytokine that exhibits significant cytotoxic activity after stimulation of the immune system (Zelová & Hošek, 2013). TNFα is a pleiotropic cytokine with an important function in homeostasis and pathogenesis of the disease (Kalliolias & Ivashkiv, 2016).

TNFα is a powerful pro-inflammatory cytokine, mainly secreted from myeloid cells through activation of mitogen-activated protein kinase (MAPK) signaling pathways and nuclear factor kappa-light-chain-enhancer of activated B cells, nuclear factor-kappaB (NF-κ B) that produce other inflammatory cytokines, such as IL-1 and IL-6 (Makki *et al.*, 2013). TNFα is mostly produced by monocytes/macrophages and is involved in many inflammatory diseases. TNFα is found in adipose tissue in models of diabetes and obesity, providing preliminary evidence for a link between inflammation and obesity (Nakamura *et al.*, 2014)

Obesity and TNFα

Obesity results in the accumulation of visceral fat causing chronic low-grade inflammation, which contributes to the initiation and development of metabolic disorders (Ohashi *et al.*, 2014). Obesity is associated with a low-level inflammatory process in white adipose tissue (WAT). This is the source of several pro-inflammatory cytokines, mainly TNFα (Stępień *et al.*, 2014). WAT is the result of chronic activation of the immune system and it can contribute to the development of insulin resistance, impaired glucose tolerance or diabetes. The increase in adipose tissue mass simultaneously activates the inflammatory process in WAT, in the liver, and immune cells (Seo *et al.*, 2015). Inflammation is a sequence of events engineered to maintain tissue and organ homeostasis (Ellulu *et al.*, 2017). The activation of this mechanism increases glucocorticoid levels, which can induce the development and differentiation of preadipocytes with a further increase in WAT which ultimately leads to an increase in the secretion of proinflammatory cytokines, one of which is TNFα. Results from several previous studies have shown that WAT in obesity is infiltrated by macrophages, which can locally produce inflammatory cytokines. Macrophage infiltration of adipose tissue increases in line with the proportion of BMI and body fat mass (Stępień *et al.*, 2014).

Orlistat

Orlistat is an inhibitor of pancreatic lipase is used to treat obesity (Kose *et al.,* 2015). Orlistat inhibits gastrointestinal lipase by preventing the hydrolysis of ingested dietary fats into free fatty acids and glycerol (Chapman, 2021; Dolinsky *et al.,* 2013; Hossain *et al.,* 2019; Othman *et al.,* 2021). Orlistat has very mild side effects on the gastrointestinal system, especially diarrhea, dyspepsia, and flatulence. Orlistat is recognized as one of the anti-obesity drugs approved by the FDA for long-term use. Considering its easy availability, cost-effectiveness, and significant effects in weight loss, orlistat has become the standard drug and it is the most widely used obesity drug in the wider population with obesity (Othman *et al.,* 2021)

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It has been reported that using orlistat contributes to significant weight loss. The effect of orlistat was measured using the value of excretion of fecal fat within 24 hours as a representative pharmacodynamic parameter. When a balanced low-calorie diet is followed by the application of appropriate doses of orlistat treatment, orlitstat treatment can partially inhibit fat absorption similar to 30% fat intake equivalent to about 200 extra calories. In long-term studies, the effect of orlistat is able to prevent weight gain (Qi, 2018).

In similar studies, it was shown that orlistat therapy in pre-puberty children with <12 years showed a weight loss of about 4.0 kg over a 3-month period (Wright & Wales, 2016). This weight loss was associated with a decrease in TNF-α levels in the orlistat group compared to the placebo group (Viner *et al.,* 2020)

In addition, orlistat has been approved by the FDA for the treatment of childhood obesity and adolescents aged 12 to 16 years. However, the effectiveness of orlistat in childhood obesity is controversial. There is one study that considers orslitate as an invalid anti-obesity drug for children, while in other studies consider orlistat effective for treating childhood obesity (Qi, 2018).

CONCLUSION

An excess of body fat or adiposity characterizes obesity. Obesity results in the accumulation of visceral fat, which causes chronic low-grade inflammation. The pro-inflammatory cytokine of TNFα triggers inflammation in obese conditions. With the implementation of the orlistat use, efforts in losing weight obesity can be carried out. Orlistat proved its effectiveness in significant weight loss. This weight loss is in line with the decrease in adipocytes and has the effect of reducing TNFα levels. The limitation of this research is that it only examines the published research literature.

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