Al-Zahiri J, Nair A, Akter M, Hamud A, Elmakawey N, Aziz HA, Watts T. An Exploration of the Use of Statin Therapy in Pediatric Metabolic Syndrome. J Pediatrics & Pediatr Med. 2021; 5(2): 1-5

Journal of Pediatrics and Pediatric Medicine

Journal of Pediatrics and Pediatric Medicine

Review of Literature

Open Access

# An Exploration of the Use of Statin Therapy in Pediatric Metabolic Syndrome

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**Article Info**

**Article Notes**
Received: March 01, 2022
Accepted: May 10, 2022

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**Keywords**
Pediatric metabolic syndrome
Statin
Obesity
Insulin resistance
Pediatrics

## Abstract

The increasing prevalence of childhood obesity is a global public health concern with metabolic syndrome (MetS) at its forefront. Due to the rising levels of pediatric obesity within the past few years, 18.4% of children were classified as obese and 5.2% as severely obese in the United States in 2016. It is imperative to investigate pharmacological options for the treatment of pediatric MetS. Conservative management, namely the incorporation of dietary intervention and physical activity, has been the only adopted treatment approach for pediatric MetS while pharmacological and surgical (bariatrics) methods have only been reserved for high-risk severe cases. The use of HMG-CoA reductase inhibitors known as statins for the treatment of pediatric MetS has been fairly controversial. Statin therapy would be primarily used in pediatric metabolic syndrome as a means to reduce LDL levels to further prevent adverse cardiometabolic events. Nonetheless, the predominant concern for the use of statin therapy in children was that of adverse effects. This article will delve into the use of statin therapy in the pediatric population and how this relates to the prevention of cardiometabolic adverse events in pediatric metabolic syndrome.

## Introduction

In recent years, pediatric obesity has established itself as a global public health burden. From 1980 to 2013, the prevalence of childhood obesity increased by 47.1%[1]. Due to the dire sequelae, it exhibits later in adulthood, WHO Health Assembly has religiously endorsed the Comprehensive Implementation Plan on Maternal, Infant, and Young Child Nutrition comprising of six nutritional targets to tackle obesity in children on a global scale[2].

The reason why pediatric obesity is a worrisome issue is because of its propensity to serve as an independent cardiovascular risk factor leading to increased morbidity and mortality in adulthood[3]. Other risk factors include hypertension, dyslipidemia, hyperglycemia, low high-density lipoprotein (HDL), hyperuricemia, along with prothrombotic and proinflammatory states.

The combination of obesity and other metabolic derangements has been coined under the term metabolic syndrome (MetS). MetS was first described as a concept by Reaven in 1988. He noticed the presence of several risk factors mentioned above in conjunction with insulin resistance leading to higher CVD mortality[4]. Henceforth, MetS

has been continually redefined by multiple organizations with varying cut-offs for different parameters creating important differences. The Joint Task Force's attempt to create a consensus for MetS in the adult population ended with the proposition that it should include 3 out of 5 of the following criteria[4]:

1. Increased waist circumference after adjusting to population and country-specific definitions
2. Systolic BP > 130 mmHg or a Diastolic BP > 85 mmHg
3. Fasting plasma glucose > 100 mg/dL
4. Triglyceride levels > 150 mg/dL
5. HDL levels less than 50 mg/dL in females and 40 mg/dL in males

In 2001, the National Cholesterol Education Program (NCEP) described MetS as having 3 out of 5 of the risk factors[5].

More recently, the addition of hyperuricemia, sleep disturbances, and non-alcoholic fatty liver disease (NAFLD) was taken into consideration due to recent studies presenting them as early signs of cardiovascular abnormalities not only in adults but in the pediatric population too[6]. NAFLD has been a particular area of interest because its prevalence has shown a parallel increase along with obesity. It is now the most common hepatic disorder of childhood with its overall prevalence being around 40% in all obese children[7]. It appears two times more often in boys than girls and patients of Caucasian and Hispanic descent seem to be more at risk compared to their other counterparts. NAFLD has been labeled as the hepatic version of MetS because the disease progression is driven by insulin resistance[8]. A recent investigation also reported that around 60% of MetS-diagnosed children had NAFLD with a positive biopsy[9]. Despite the current advancements regarding NAFLD and its association with MetS, the clinical consequence is still undefined[10].

Keeping track with novel insights into metabolic syndrome, high fructose intake is directly related to high serum urate levels which has been implicated in the development of hypertension, atherosclerosis, heart failure, chronic kidney disease, and type 2 Diabetes Mellitus (T2DM)[11]. Though uric acid is not a parameter in the diagnostic criteria of MetS, it plays a key role in the understanding of the pathophysiology of the disease[12].

Sleep disturbances and metabolic derangements have a more conflicted association in the pediatrics versus the adult population. Some studies, however, have shown that short-term sleep restriction resulted in increased hunger hence dietary intake in preschool children[13,14]. Additionally, Wang et al [14], portrayed that both acute and chronic sleep restriction are related to an increased risk of obesity in preschool-aged children along with impaired lipid profile. The intricate details of the pathophysiology are still unknown at this moment in time[15]. Obstructive Sleep Apnea (OSA), a condition characterized by repetitive pharyngeal narrowing and closure, is associated with MetS in both adults and children. A study mentioned that 59% of OSA-positive children also had MetS. Similarly, all individual components of MetS corresponded to OSA[15].

The rapid increase in the prevalence and severity of obesity displayed that MetS has a propensity to be present in both adolescents and children. More than 40 definitions have been suggested so far but no general guidelines or consensus is available to diagnose, screen, or treat MetS in this specific age group[4]. Due to the variance in definition, the prevalence of MetS in children has been hard to deduce. To put the difficulty into perspective, one of the earliest articles about MetS in adolescents, by Goodman et al, alluded that there was a two-fold increase in the prevalence using the WHO criteria versus NCEP during a study done by the Princeton University[16]. Different publications have observed numbers ranging from 0.2% to 38.9% [6] which showed the Hispanic population were more likely to be diagnosed with MetS compared to the Caucasian or African-American population[7].

## Stratifying Risks and Treatments

With regards to pediatric obesity, lifestyle modifications such as healthy diets and increased physical activity have been the primary form of prevention. Additional modifications that could help combat this health burden include reduced screening time, proper sleep hygiene, and the involvement of families and communities to enhance the efficacy in terms of prevention[17].

Despite the recent progress regarding the understanding of MetS, weight loss has been the keystone in the management of the pediatric population. The incorporation of dietary intervention, physical exercise, and behavioral therapy contribute to weight loss. Although pharmacological and surgical (bariatrics) methods are available, they are reserved for extreme cases[23]. Bariatric surgery remains the most efficient method of treatment for obesity and its related complications such as MetS for all ages[23]. Although these interventions produce positive outcomes, the knowledge regarding the efficacy long-term in children and adolescents is still limited[24].

When it comes to pharmacologic therapies, the recommendations vary depending on the component of MetS present. In children with T2DM, dyslipidemia, and hypertension, appropriate medications should be started[18]. However, with attention to obesity, it is only indicated if all other methods have failed and the severity index is detrimental to the patient's health. Currently, Orlistat, an intestinal lipase inhibitor, was approved in 2003 by the

FDA for the treatment of obesity in adolescents 12 years and older[17]. Due to its notoriety in causing gastrointestinal symptoms and impeding fat-soluble vitamin absorption, caution should be practiced during usage[19]. Additionally, although not FDA approved, metformin has been used off the record for the treatment of obesity. It acts by enhancing the sensitivity of tissue to insulin[20] and may also play a role in the suppression of appetite[21]. Although there is no clear evidence of its efficacy long-term, acutely, metformin in conjunction with lifestyle modifications resulted in a significant reduction of BMI and weight[22]. Metformin is also known to reduce levels of both triglycerides and total cholesterol[20]. These benefits are not in the absence of the potency for adverse effects. Gastrointestinal symptoms are most commonly reported and resolve with dose reduction and lactic acidosis is the most dangerous of adverse effects but has not been reported in children[20].

To dive into the focus of our article, the HMG-CoA reductase inhibitors, also known as statins, follow a relatively resolute relationship with dyslipidemia[25]. Despite being one of the most prescribed medications to reduce cardiac-related morbidity and mortality in adults, its use in the pediatric sector is fairly controversial[26]. Currently, FDA has approved the use of the following statins for children in the management of Familial Hypercholesterolemia such as Atorvastatin, Simvastatin, Pravastatin, and Lovastatin[27].

In 2017, AACE/ACE recommended the following guidelines for the prevention of CVD and treatment of dyslipidemia in children and adolescents:

- Initiation of pharmacotherapy in children older than 10 years after the failure of aggressive lifestyle modification provided it satisfies the following criteria:

1. LDL-C levels > 190 mg/dL
2. LDL-C levels > 160 mg/dL in addition to two or more CVD risk factors despite lifestyle intervention
3. Family history of early ASCVD (< 55y)
4. History of obesity + other elements of metabolic syndrome[28]

The use of the statin class of medications has changed drastically over the past decade. The majority of cases in pediatrics received statin therapy specifically for inherited dyslipidemia disorders and pediatric type 2 diabetes mellitus. A study conducted by Wagner et al[29] in 2016 reviewed the updated guidelines set forth by the National Cholesterol Education Program (NCEP) which emulated quite similarly to the adult guidelines for initiation of statin therapy. Understandably, the concerns for the use of statin therapy in children were that of adverse effects predominantly. Wagner et al explored the risk of statin therapy by comparing multiple clinical trials and found no additional risk when compared to placebos. Although the clinical trials were short, a decrease of 20% - 50% reduction in low-density lipoprotein (LDL) was found; however, there was concern regarding the long-term effects of statins in the pediatric population.

In light of this concern, a study was carried out by Luirink et al in 2019[30] that conducted a 20-year follow-up of children diagnosed with Familial Hypercholesterolemia and who had taken statin medications. The intervention was deduced as beneficial as the study reported a 32% decline in LDL from baseline and lower cumulative incidence of adverse cardiovascular events when compared to the children's parents. It is also imperative to note that in this study, 4 of the 146 patients had discontinued statin therapy due to side effects. Fortunately, no episodes of rhabdomyolysis, hepatotoxicity or other serious adverse events were reported. This can be viewed as a promising indication for widening the use of statin therapy as a first-line medication for other related conditions. In place of this finding, Vuorio et al conducted a study in 2017[31] on the use of statins in children diagnosed with Familial Hypercholesterolemia and reported similar findings. Although labeled as low-risk evidence due to a lack of long-term follow-up, no significant difference was found with regards to adverse events when comparing patients who had received statins or placebo. Combining both studies by Luirink and Vuorio would suggest that statins do not have a significant side effect profile in children.

When comparing the management guidelines and protocols for both adult and pediatric metabolic syndrome, there is an almost identical nature in the progression of interventions. While examining the management components of adult metabolic syndrome[32,] the main emphasis lies on increasing physical activity and diet initially as echoed by the American Academy of Pediatrics guidelines[33, 34]. With regards to the pharmacological interventions currently mediated by the American Academy of Pediatrics (AAP), although pharmacological agents such as Metformin can be used as a treatment for insulin resistance and to lower BMI, there is insufficient data currently to substantiate the use of this treatment modality. Pediatric metabolic syndrome management largely takes into account a combination of dietary and physical activity modification to target obesity, hypertension, dyslipidemia, and diabetes mellitus. This combination has successfully been replicated in other studies to reduce the risk of developing dyslipidemia and hypertension[34]. Therefore, this can call into question where statin medications can play a role in preventing the further progression and increased risk of cardiometabolic adverse events into adulthood.

It is important to explore the possible answers to two particular questions in this scenario: What is the

benefit versus the risk in adding statin therapy as a potential pharmacological modality in pediatric metabolic syndrome and specifically, how would adding statins improve short-term and long-term clinical outcomes in patients with pediatric metabolic syndrome? The primary use of statin therapy in pediatric metabolic syndrome would be to reduce LDL levels to prevent further adverse cardiometabolic events[35]. Within the spectrum of pediatric metabolic syndrome, statin therapy would be particularly useful in treating certain components of this condition including increased very-low-density lipoprotein (VLDL) and decreased levels of high-density lipoprotein (HDL) due to the lack of response from mechanisms that respond to increased insulin secretions that lead to lipogenesis[36]. However, due to the lack of clear recommendations and guidelines[37], the management of pediatric metabolic syndrome alongside the adaptation of the treatment model from the guidelines join together to tackle adult metabolic syndrome. It would be difficult to ascertain a correct treatment protocol as this would require multiple longitudinal follow-up studies looking at the effectiveness of each pharmacological agent used to combat each manifestation of metabolic syndrome.

When considering incorporating statin therapy for pediatric metabolic syndrome, it would first be imperative to establish detailed diagnostic criteria specific to the pediatric population followed by implementation of conservative and pharmacological interventions, sequentially. In 2016, it was revealed that 18.4% of children were classified as obese and 5.2% had severe obesity in the United States[38] and this trend is expected to rise in the coming years. Factors such as socioeconomic status, level of education, and nationwide screening programs play a distinctive role in determining the epidemic of obesity. When conservative interventions such as dietary modifications in combination with increased physical activity do not alleviate the issue at hand, it is important to consider additional pharmacological interventions. Statin therapy in similar conditions, such as Familial Hypercholesterolemia, has proven effective without a significant side effect profile and therefore it can be recommended to be started in children to prevent further cardiometabolic adverse events.

## Conclusion

Metabolic syndrome has been used to describe the combination of obesity and the clustering of other cardiovascular risk factors such as dyslipidemia, hypertension, and insulin resistance. Lifestyle modifications, such as increased physical activity, healthy diets, and weight loss, have been the mainstay of management, with surgical methods (bariatrics) reserved for only severe cases of pediatric MetS. When discussing the pediatric population, pharmacological management of metabolic syndrome (MetS) with the use of statin therapy, an HMG-CoA reductase inhibitor, is controversial. This controversy is mainly due to concerns about the potential adverse effects statins may have on the pediatric demographic. However, this article has shown that statins do not have a significant side effect profile in children in the long term. Statin therapy has been effective and did not exhibit a significant side effect profile for the treatment of similar conditions such as pediatric familial hypercholesterolemia. For these reasons, the use of statin therapy in children with MetS can be recommended for the prevention of further cardiometabolic adverse events. Therefore, when conservative measures are not sufficient to alleviate the burden of potential cardiometabolic events in children with MetS it is recommended to consider the addition of HMG-CoA reductase inhibitors.

## Acknowledgements

1. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

2. The authors declare that there is no conflict of interest.

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