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Invited Review-pharmacology across disciplines

An update on the assessment and management of metabolic syndrome, a growing medical emergency in paediatric populations

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ABSTRACT

In the last decades the increasing rate of obesity in children and adolescents worldwide has led to the onset in paediatric age of metabolic syndrome, a disease commonly associated to adulthood.

Central obesity, dyslipidaemia, hyperglycaemia, and hypertension are typical features of metabolic syndrome that seem to hesitate often in type 2 diabetes, cardiovascular disease, non-alcoholic fatty liver disease, and many other clinical conditions. Thus preventing and curing metabolic syndrome in paediatric patients is becoming an urgent need for public health.

While diagnostic criteria and therapy of metabolic syndrome in adults are very well defined, there is no consensus on the definition of metabolic syndrome in children and adolescents as well as on healing approaches.

The aim of this review is to describe the recent advances on the pathogenesis and clinical outcomes of paediatric metabolic syndrome. We then detail the therapeutic strategies (*i.e.* dietary regimens, physical exercise, nutraceuticals, and medications) employed to manage the disease. Finally, we analyse the safety profile of the drugs used in children and adolescents by performing a retrospective review of paediatric adverse reactions reported in the FDA's Adverse Event Reporting System database.

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1. Introduction

Metabolic syndrome is generally defined as a cluster of cardiovascular risk factors such as central obesity, hyperglycaemia, dyslipidaemia and hypertension historically related to adulthood [1,2]. Currently, metabolic syndrome affects c.a. 20–25% of the world's adult population, not only in developed countries but also in developing countries [3] (http://www.idf.org/metabolic-syndrome). Cardiovascular disease (CVD) and type 2 diabetes (T2DM) are known to be the two major adverse health outcomes of metabolic syndrome. Patients with metabolic syndrome have increased chance of having or dying for a stroke or heart attack compared with people not affected by the syndrome. Moreover, they have an increased risk of developing T2DM [4]. In the last decades, metabolic syndrome has been associated with many other clinical conditions such as hepatic steatosis and non-alcoholic fatty liver disease (NAFLD), hyperandrogenism and polycystic ovary syndrome (PCOS), hypogonadism, chronic low grade inflammation, oxidative stress, obstructive sleep apnoea, vascular dementia and Alzheimer's disease [5]. Even an association of metabolic syndrome or its components with cancer development (such as pancreatic and colon-rectal cancer) and cancer-related mortality has been recently described [6]. Thus, patients with metabolic syndrome need higher medical care utilization compared to subjects with no metabolic syndrome, determining a significant increase (about 20% per additional risk factor) of health care expenditure [7]. All these aspects make metabolic syndrome one of the major current public health and clinical challenges worldwide.

In recent years, with growing rates of obesity in children and adolescents, metabolic syndrome is appearing also in paediatric population with increasing frequency. Such cluster of conditions is rising great concern and attention since several longitudinal cohort studies have shown as individual components of the syndrome track from childhood to adulthood and as specific components are predictive of development of adverse health outcomes such as left ventricular hypertrophy and increased intimal-medial thickness in childhood. Moreover metabolic syndrome also predicts the presence of adverse outcomes in adulthood such as type 2 diabetes and increased cardiovascular risk. Nevertheless, many aspects of metabolic syndrome in children and adolescents are not currently well characterised. Outstanding points are the lack of consensus regarding diagnostic criteria for paediatric population, the clinical utility of metabolic syndrome in childhood especially its persistence over time to adulthood and its predictive value for short and long-term health outcomes.

This paper offers an overview of the current proposed definitions and epidemiology of metabolic syndrome in paediatric age as well as pathogenesis and clinical presentation in children and adolescents with an emphasis on data published in the last decade. We also provide a picture on the state-of-the-art of the common approaches and drug-based interventions with a clinical and pharmacological perspective.

2. Definition of metabolic syndrome in paediatrics

To date no universally accepted definition of metabolic syndrome in paediatric population exists. Since the first publication on metabolic syndrome in adolescents in 2003 [8], more than 40 definitions of metabolic syndrome have been released [9]. In general, they are an adaptation of the adult definitions and share some common features including an obesity estimate (typically body mass index (BMI) or waist circumference), blood pressure measures, blood lipid measures (typically triglycerides, low-density lipoprotein (LDL) or high-density lipoprotein (HDL) cholesterol) and a diabetes related risk factor (fasting glucose, glucose tolerance or insulin). The most commonly used definitions proposed by some researchers are summarised in Table 1.

In 2007, the International Diabetes Federation (IDF) released its definition of metabolic syndrome in childhood and adolescence (Table 2). One particular feature of the IDF definition is the division