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Adiponectin, Inflammation and Cardiometabolic Risk Factors in Paediatric Obese Patients: Impact of Interventional Studies

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Additional information is available at the end of the chapter

Abstract

Paediatric obesity has significant physic, social and psychological implications. Childhood obesity is usually associated in adulthood with increased risk of type 2 diabetes, metabolic syndrome and cardiovascular diseases. Aggregation of cardiometabolic risk factors is already observed at young ages, with a nonlinear association with enhancement of adiposity. Adiponectin is an adipokine that inhibits inflammation, oxidative stress and metabolic syndrome components, namely dyslipidaemia, high blood pressure and insulin resistance. Obesity has been associated with hypoadiponectinaemia in both adult and paediatric patients, which may contribute to co-morbidities observed in these patients. Interventional studies that aim to tackle obesity reported controversial results. Although the general positive effect on weight loss, inflammatory and cardiometabolic markers has been studied, the impact of these interventional studies on adiponectin remains unclear. Some studies reported that the improvement in adiponectin might only occur in paediatric obese patients with great weight loss or intensive physical exercise; the magnitude of the changes in body composition appears to be of particular importance. A revision about the knowledge on the relation between adiponectin, inflammation and cardiometabolic risk factors in paediatric patients is performed; the impact of interventional studies on adiponectin levels and markers of cardiometabolic risk is also addressed.

Keywords: adiponectin, inflammation, obesity, paediatric age, cardiometabolic risk factors

1. Introduction

The worldwide increase in obesity at paediatric ages has been accompanied by the appearance of diseases that were considered exclusive of adults, namely type 2 diabetes (T2D), dyslipidaemia and hypertension. These pathologies are commonly associated with central obesity, and this association is related with increased cardiometabolic risk [1, 2].

Obesity is closely associated with hypoadiponectinaemia, and low levels of circulating adiponectin are a potential predictor of some obesity-related co-morbidities. Therefore, adiponectin has been studied as a possible link between these conditions. Furthermore, growing evidence supports a relationship between obesity in childhood and low levels of adiponectin, and increased cardiometabolic risk factors in adulthood [3, 4].

2. Adiponectin and its isoforms

Adiponectin is important as a mediator of inflammatory factors and as an anti-atherogenic, anti-dyslipidaemic and insulin sensitiser factor. Adiponectin has particular characteristics, different from most of the other mediators: each one of its three circulating isoforms (high- (HMW), medium- (MMW) and low-molecular weight (LMW)) appears to be linked with different, sometimes opposite, actions in the organism. High-molecular weight (HMW) isoform has been considered a better metabolic marker than total adiponectin [5, 6].

Total and HMW adiponectin concentration were reported to be lower in obese (OB) children and adolescents, when compared to lean controls (CT) [6, 7]. Besides, the relative percentages of the isoforms are, usually, altered: HMW% adiponectin decreases, while low-molecular weight (LMW)% adiponectin increases. In children, HMW adiponectin multimer is usually linked to an improvement in insulin resistance (IR) and lipid profile [6], and it has been negatively associated with cardiometabolic complications [8]. The negative associations of HMW adiponectin with IR and adiposity appear to be present even in pre-pubertal (PP) individuals [9, 10]. Zimmet et al. reported that in PP children, HMW adiponectin was negatively associated with body mass index (BMI) z-score, IR, triglycerides (TG), leptin and soluble intracellular adhesion molecule (sICAM); however, after adjustment for age and sex, only BMI z-score and TG maintained their negative association with HMW adiponectin [11]. These authors did not detect correlations between HMW adiponectin and proinflammatory mediators, such as resistin, interleukin (IL)-8 and IL-18 [11]. This lack of correlation with inflammatory mediators suggests that the levels of adiponectin multimers might be more linked to changes in glucose and lipid metabolisms at young ages.

Figure 1 resumes the reported associations between total, HMW and LMW adiponectin with inflammatory mediators, hormones and other factors [12–31].

Negative association

IL-1β [12]
IL-6 [12]
IL-8 [12]
CRP [13]* [14, 15]
TNF-α [12]
Leptin [16, 17]
Resistin [18]
Vaspin [19]
Uric Ac [6]
FABP [20] ° [21]
Endotoxin [22]
Fetuin-A [23]

Total adiponectin

No significant association

IL-6 [16]
IL-10 [24]
CRP [6, 10, 25]
TNF-α [16, 26]
Leptin [6, 10, 14, 27, 28]
Resistin [6, 10, 16, 29]
Vaspin [30]
Fetuin-A [28] °
Appelin [31]
Ghrelin [14]
RBP-4 [21]
MCP- [12]
IFN-γ [12]
NEFA [26] °
T4 [17]
Cortisol [17]
Homocysteine [14]
Irisin [10]
FGF21 [23]

Negative association

Leptin [11, 28] ° [6]
Uric Ac [6]

HMW adiponectin

No significant association

IL-8 [11] °
IL-18 [11] °
CRP [6]
Resistin [11] ° [6]
Fetuin-A [28]°
MCP-1 [11] °

Positive association

Leptin [5, 6]
Resistin [6]

LMW adiponectin

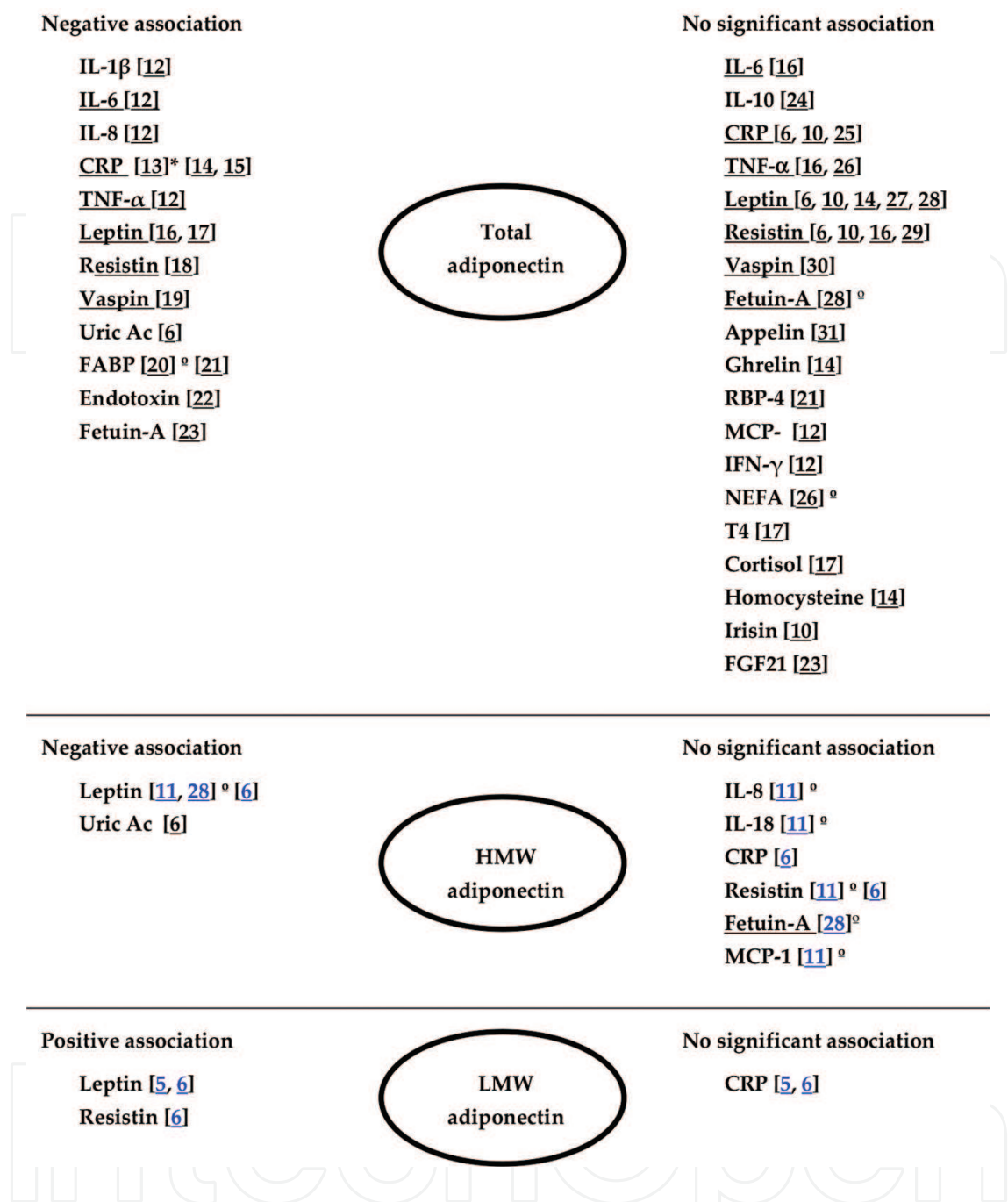**No significant association**

CRP [5, 6]

Figure 1. Studies reporting associations between inflammatory markers and total, high-molecular weight (HMW) and low-molecular weight (LMW) adiponectin. Underlined are the inflammatory factors that appear in both columns (ambiguous results). °, pre-pubertal; *, post-pubertal; Ac, acid; CRP, C-reactive protein; FABP, fat acid-binding protein; FGF, fibroblast growth factor; IL, interleukin; IFN, interferon; MCP, monocyte chemoattractant protein; NEFA, non-esterified fatty acid; RBP, retinol-binding protein; T4, thyroxine; TNF, tumour necrosis factor.

3. Adiponectin and the risk of developing co-morbidities

Some contradiction exists in literature regarding adiponectin levels in young OB patients. Total adiponectin levels are generally accepted to be lower in OB children and adolescents

when compared with CT and overweight (OW) subjects [25, 32]. However, contradictory data have also been reported [12, 33].

Cardiometabolic risk factors, such as dyslipidaemia, hyperglycaemia, hypertension, central obesity and IR, tend to cluster and are associated with increased risk for cardiovascular diseases (CVDs) [1, 2]. These risk factors are already altered in early ages in OB individuals, and changes in adiponectin levels may underlie such risk. Indeed, an association of adiponectin with metabolic risk factors [1, 34] has been reported, leading to the proposal of adiponectin as a marker of cardiometabolic risk [24, 35], and as a potential predictor of obesity-related co-morbidities [36, 37]. An association between adiponectin levels in childhood and the probability of developing co-morbidities in the future has been also raised [21]. In agreement, a study by Morrison et al. showed that lower levels of adiponectin in 16-year-old females were related with the development of cardiometabolic risk features at the age of 23 years [38]. Another study also showed adiponectin as a predictor of cardiometabolic risk, in OW children, even when adjusted for age, gender, Tanner stage, BMI, visceral fat and IR [34].

In T2D OB adolescents, adiponectin levels were found to be lower than in normal individuals, and even lower than in OB individuals without T2D. In this population, IR appeared as a main determinant of adiponectin concentrations, more than BMI itself [2]. There are, however, controversial data about the changes in adiponectin, in OB adolescents with and without T2D [23].

In obesity, it is important to consider body fat distribution, besides weight excess. Indeed, increased abdominal obesity has been associated with lower levels of adiponectin [1, 25, 39, 40] and adiponectin was negatively associated with visceral-to-subcutaneous fat ratio [41]. The association between hypoadiponectinaemia and increased visceral adipose tissue (VAT) seems to appear early in life [33].

Younger age of adiposity rebound (AAR) associates with increased adiposity later in life [42, 43]. Nevertheless, no association was found between AAR and adiponectin in 10-year-old children, whereas an association was found between AAR and leptin [44]. A preferential relationship of AAR with increased subcutaneous adipose tissue, rather than with VAT, might partially explain why no association was found with hypoadiponectinaemia [43].

In adolescents, the increased abdominal obesity and reduced adiponectin levels are accompanied by enhanced TG and decreased levels of high-density lipoprotein cholesterol (HDLc) [1], suggesting that central body fat distribution is also associated with a worse control on lipid metabolism.

The inverse relation of adiponectin with cardiometabolic risk appears to be accepted, especially in pubertal subjects. It is important to highlight that the diagnosis of metabolic syndrome (MS) in young children (under 10 years) should be avoided, as recommended by the International Diabetes Federation, considering the lack of age- and gender-adjusted cut-offs for MS components and the ambiguous causality evidence in such young ages relating MS and increased risk of CVD later in life [45].

4. Adiponectin and cardiometabolic risk factors

4.1. Lipid profile

The effect of adiponectin on lipid metabolism has been widely studied. Adiponectin is known to lower the synthesis of free fatty acids and to stimulate β-oxidation [46]. Furthermore, HMW adiponectin seems to lower the release of apolipoprotein (apo) B and apo E from the liver, decreasing the release of lipoproteins rich in TG (e.g. very-low-density lipoprotein (VLDL)) and increasing HDLc levels [47].

The positive association between adiponectin and an improved lipid profile has been confirmed by several data. The most consensual effects for adiponectin are a positive association with HDLc and a negative correlation with TG [1, 13, 27, 29, 48, 49]. These associations are present even in PP ages [26, 50] (**Table 1**). Through its effect on lipid metabolism, adiponectin might even modulate the influence of genetics. Lower levels of apo B/apo A1 ratios and total cholesterol/HDLc were found for individuals with higher adiponectin levels despite presenting an apo E genotype associated with a worse lipid profile [51]. In adolescent OB girls, adiponectin levels were positively associated with HDLc measured 7 years later, highlighting that adiponectin might modulate lipid metabolism even for a long term. However, no correlation was found between adiponectin and TG or low-density lipoprotein cholesterol (LDLc) [38]. Oppositely, no relation between lipid profile and adiponectin was reported in other paediatric studies [14, 21].

Reference	Country	n (f %)	Age (years)	Cohort	Adiposity	IR	Dyslip
Martos-Moreno et al. [9]	Spain	70 (31.4)	8.92 ± 1.80	OB (61 lean CT)	NS	(-)	
Bansal et al. [50]	UK	138 (35.5) European; 77 South Asian (35.1)	3	Global population	(-)		(-)[#]
Gajewska et al. [7]	Poland	30 (40.0)	7.8 ± 1.3	OB (35 lean CT)	NS		
Gil-Campos et al. [26]	Spain	34 (32.4)	9.4 ± 0.4	OB (20 lean CT)	(-)[*]	(-)	(-)
Medina-Bravo et al. [33]	Mexico	33 (45.4)	9.0 ± 1.6	OB (13 lean CT)	(-)		
Murdolo et al. [11]	Italy	305 (52.8)	5–13	Global population	NS		
Gajewska et al. [71]	Poland	100 (54.0)	8.3 (7.0–9.3)	OB (70 lean CT)	(-)		
Nascimento et al. [72]	Portugal	13 (46.2)	7.9 ± 1.4	OB (10 lean CT)	NS		
Murdolo et al. [28]	Italy	200 (55.5)	5–13	Global population	(-)	NS	(-)[#]

[*], Correlation with total and central adiposity; [#], positive correlation with HDL. CT, control; Dyslip, Dyslipidaemia; f, female; IR, insulin resistance; (-), negative association; NS, not significant; OB, obese; OW, overweight.

Table 1. Studies assessing the relation between total adiponectin levels and cardiometabolic risk factors in pre-pubertal children.

Concerning adiponectin multimers, while LMW adiponectin seems to be linked with a worse lipid profile, through a positive association with TG [5], HMW adiponectin has shown opposite effects [6], even in PP individuals [11].

4.2. Blood vessels and blood pressure (BP)

Adiponectin-positive effects on blood vessels are, apparently, independent of its effect on IR [52]. Adiponectin improves vessel status and reduces atherogenesis by inducing nitrous oxide production by endothelial cells that promotes vasodilatation and reduces platelet adhesion/aggregation. It also reduces vascular smooth muscle cells proliferation [53, 54] and avoids macrophage activation, preventing, therefore, vascular wall remodelling and foam cells formation [55]. Through these effects, adiponectin prevents the development of atherosclerosis while still in early stages. Adiponectin association with vascular changes appears since paediatric ages, as its levels are positively correlated with brachial artery distensibility [52], and inversely correlated with the internal media thickness (IMT) of carotid arteries (cIMT) [56–59]. However, some intervention programmes did not find any correlation between adiponectin improvement and cIMT [13], cIMT variation [60], or retinal vessel diameter [61].

Adiponectin presents anti-oxidant activity reducing the production of reactive oxygen species (ROS) that are deleterious to endothelial cells. Actually, the enhanced production of ROS favours the development of oxidative stress, which is a predictive factor for cardiovascular events (e.g. coronary artery disease) [62, 63]. In OB children, increased markers of oxidative stress have been found together with lower adiponectin levels [64]. The lower anti-oxidant status [65] leads to increased HDL and LDL oxidation in OB children [66]. Increased oxidised LDL (oxLDL) is linked to the formation of foam cells, a key step in atherosclerosis initiation. The anti-oxidant enzyme paraoxonase (PON)1 presents a reduced activity in OB subjects, being adiponectin positively correlated with PON1 arylesterase activity in OB children [66].

Decreased adiponectin levels are negatively associated with other oxidative stress markers, as adipocyte fatty acid-binding protein (A-FABP) and lipocalin-2 [21, 67]. In a 3-year longitudinal study, higher concentrations of A-FABP and lower levels of adiponectin were reported as predictors for the development of CVD risk factors [21]. The improvement of adiponectin levels after an exercise-based intervention programme has been associated with improvements in the oxidant status in paediatric populations [68].

Similar to their opposite biological effects in lipid metabolism, LMW and HMW adiponectin multimers present contrasting activity regarding oxidative stress and vascular changes. An increase in systolic BP (SBP), cIMT and oxidative stress (higher-circulating oxLDL) was positively associated with LMW% adiponectin [6], while HMW adiponectin correlated inversely with a marker of oxidative stress that is increased in OB children—isoprostane [69].

Conflicting results exist in literature regarding the association of adiponectin with BP. Some data reported a negative association between adiponectin and both SBP and diastolic BP (DBP) [13, 16, 36], or with SBP alone [25, 29, 34, 37, 70]. Fewer studies describe the absence of association between adiponectin and BP [14, 27, 49].

Longitudinal studies usually show no association between fluctuations of adiponectin and changes in BP. Choi et al. found in 9-year-old children a positive correlation between baseline adiponectin and BP changes, during a 3-year follow-up study; however, the significances were lost when adjusted for Tanner stage [21]. Another study [38] reported no association between adiponectin concentration in OB 16-year-old girls and the values of BP 7 years later.

4.3. Insulin resistance

IR plays a central role in the pathophysiology of obesity-related co-morbidities such as dyslipidaemia, nonalcoholic fatty liver disease (NAFLD), hypertension and inflammation.

Apart from PP individuals (**Table 1**), the relation between adiponectin, obesity and IR appears to be clear. Total adiponectin levels are negatively correlated with IR, and the increase in adiponectin, following a lifestyle intervention, leadvvvs to a decrease in IR [29, 73]. However, there is still some controversy concerning this association [10].

Hepatic IR is particularly important for the metabolic changes observed in obesity, as it modifies the profile of lipoproteins released by the liver, towards a more atherogenic profile [47, 74]. IR also leads to TG accumulation in hepatocytes, leading to the development of NAFLD. The structural and metabolic changes in hepatocytes induce macrophage activation, increasing the hepatic production of inflammatory mediators and transaminases [74]. Adiponectin is reduced in OB children and adolescents with NAFLD [75–77], and, when adiponectin increases, IR and NAFLD are also improved [75]. Adipose tissue-specific IR also accounts for important metabolic and inflammatory changes in OB individuals, as insulin-resistant adipocytes release more free fatty acids and proinflammatory adipokines [78].

In OB children [6], including PP subjects [12], total adiponectin, and HMW in particular, has a more close relation with IR markers, namely with homeostatic model assessment (HOMA), than with BMI or body fat. On the contrary, a positive association between LMW% adiponectin and HOMA has been reported [6].

The negative association of adiponectin with IR might not be present from birth. Insulin levels increase until 1 year of age, which is accompanied by a reduction in adiponectin; however, those changes are not associated with HOMA [79]. The inverse association between total and HMW adiponectin with IR seems to appear only after 2–6 years of age [11, 14, 26, 80, 81].

The insulin-sensitiser effect of adiponectin is likely to explain, in part, why individuals with two clinical conditions associated with hyperadiponectinaemia, such as Prader-Willi syndrome (PWS) (associated with cognitive impairment) [82] and Laron syndrome (associated with dwarfism) [83], present decreased markers of IR despite severe obesity when compared to BMI-matched CT. HMW% adiponectin is found to be particularly increased in PWS. These two syndromes also have in common a diminished level or activity of the growth hormone (GH). Changes in this hormone might partially explain their paradoxical hyperadiponectinaemia, increased insulin sensitivity and lower percentage of visceral fat.

Adiponectin and leptin are closely related, presenting, however, an inverse association with adiposity and IR. A study by Schiper et al. showed that an increased inflammatory profile increased leptin and leukocyte activation, and IR, in childhood obesity, while lean children presented increased adiponectin, insulin sensitivity and lower leukocyte activation [84]. Adiponectin-to-leptin ratio appears as a relevant marker of IR, with a strong negative association with HOMA and insulin. In fact, it might be a better marker than HOMA to predict IR, as was shown in OB adolescent cohorts [18, 85]. A cross-sectional study in Chinese children proposed leptin as the best predictor of IR, once adiponectin predicted IR only in OB and OW boys and girls, and had no predictive value for lean individuals [32].

The association of adiponectin with IR, adiposity and other CVD markers might be different in paediatric populations, with different/special characteristics. The mechanisms underlying IR in subjects with type 1 diabetes (T1D) are different from those leading to T2D [86, 87]. In adult cohorts of T1D patients, adiponectin is increased, when compared to the general population, and is associated with cardiovascular and all-cause mortality [87]. The exact mechanisms underlying this paradoxal association are still uncertain.

The relation between adiponectin and other metabolic parameters is influenced by the population background. Some ethnic groups, as South Asians (sub-continental India), showed reduced adiponectin levels in infants, despite the normal values of insulin or lipid profile [50]. Lower adiponectin is also present in both adult [88] and adolescent black individuals [38, 89]. Even though presenting lower adiponectin levels, increased prevalence of IR in black adolescents is less clear [38, 89]. It must be highlighted, once again, that the association between adiponectin and other metabolic parameters should always be considered regarding the ethnicity.

4.4. Adiponectin and markers of inflammation

In paediatric ages, as in adults, obesity is a low-grade inflammatory state, usually accompanied by a rise in proinflammatory mediators, and by a decrease in anti-inflammatory molecules, especially adiponectin. In accordance, adiponectin, in paediatrics, is negatively associated with proinflammatory mediators, such as IL-1β, IL-6, IL-8 and tumour necrosis factor (TNF)-α [12]. Different mediators are known to influence adiponectin levels, including other adipokines, hormones (e.g. insulin, insulin-like growth factor 1 (IGF-1), GH), and different types of molecules, produced within the adipose tissue or in other organs and tissues.

Inflammatory status appears to vary according to the degree of obesity, as severely OB children and adolescents, when compared with individuals presenting a moderate type of obesity, present reduced adiponectin and increased C-reactive protein (CRP), leptin, IL-6 and resistin [90]. However, this relation between adiponectin, inflammation and the severity of obesity is still controversial [51].

Adiponectin reduces TNF-α secretion by macrophages [88], and both TNF-α and IL-6 reduce adiponectin mRNA expression, explaining, at least in part, the relations of these cytokines with IR [88, 91]. Actually, TNF-α is known to inhibit insulin signalling [92]. In agreement, Lopez-Alarcon et al. reported that OB and OW adolescents with IR who participated in a

1-month n3 fatty acids supplementation protocol presented an improvement in the inflammatory status (higher-circulating levels of adiponectin and lower TNF-α and leptin), and of IR [93].

In PP individuals, the association between TNF-α and adiponectin might be less obvious, as the studies in this population failed to find any correlation between those adipokines [16, 26]. Another study in OB and OW adolescents, presenting a decrease in TNF-α, IL-10 and IL-8 after weight and body fat loss, following a physical exercise (PE) programme, did not present changes in adiponectin [94].

Leptin is one of the adipokines more closely associated to adiposity, presenting a negative correlation with adiponectin and a positive correlation with BMI. A 3-year longitudinal study showed that children with the highest increase in BMI presented lower adiponectin and increased leptin [3]. Likewise, adiponectin levels were negatively associated with leptin in female adolescents [17]. In OB Romanian children, a worse adipokine profile was observed, when compared to lean CT, with increased IL-6, leptin and resistin, and decreased adiponectin, which correlated, negatively, with leptin; this correlation with leptin disappeared when corrected for waist circumference (WC) and BMI z-score. Actually, WC has been proposed as a good predictor of adiponectin levels, highlighting the influence of adiposity distribution in adipokines [16].

As referred, adiponectin-to-leptin ratio might be a better marker of IR than adiponectin and leptin separated, or even HOMA [18, 85]. Due to the opposite association of adiponectin and leptin with adiposity, this ratio could be also used as an indicator of the anti- or proinflammatory adipokine balance in obesity [95].

The adiponectin multimers are also associated with leptin; the HMW adiponectin is negatively correlated, while LMW and LMW% adiponectin present positive associations [5, 6]. By contrast, other authors did not find any correlation between adiponectin and leptin [10, 14, 96] in OW and OB children, despite the association of both adipokines with IR and adiposity.

CRP is a well-recognised marker of CVD risk in adults. Although it has been associated with the increased inflammation in paediatric obesity patients [48], its association with adiponectin is not so clear in these ages [5, 6, 10, 13, 14, 37, 48, 51]. Nevertheless, there are strong evidence that both are related to obesity and IR [48, 51].

IL-6 is a proinflammatory mediator, usually increased in obesity. In lean individuals, IL-6 controls energy intake but, in OB individuals, a state of resistance to IL-6 appears to develop.

In animal models, resistin was found to associate positively with IR. In human studies, especially in children, the results are not conclusive. No associations between resistin and total adiponectin in children [6, 10, 16, 29], or in PP OB patients [11], as well as with HMW and LMW adiponectin [6], were found.

The anti-inflammatory effect of adiponectin is partially related with IL-10, an anti-inflammatory and anti-atherogenic interleukin, once adiponectin induces the synthesis of

IL-10 by macrophages. Considering that in obesity adiponectin is reduced and an increased infiltration of macrophages occurs in the adipose tissue, hypoadiponectinaemia would lead to diminished IL-10 levels. Despite that, increased circulating IL-10 was reported in OB adults. This increase is probably linked to a state of IL-10 resistance in OB individuals, as observed for IL-6, leptin and insulin. It could be also a response to the obese-related increase in inflammation, as IL-10 is an anti-inflammatory mediator [24, 97]. Conversely, Calcaterra et al. did not find in OB children, the correlation between adiponectin and IL-10 reported in adults [24].

4.5. Interventional studies and adiponectin levels

Longitudinal studies are crucial to obtain causal associations between adiponectin and other factors. **Table 2** presents a summary of interventional studies involving PE and/or nutritional counselling/supplementation programmes and their impact on adiponectinaemia.

Improvements in adiponectin levels may be obtained by energy restriction and PE, and the combination of both approaches appears to have a greater impact, as was observed in OB adolescent boys [18]. According to this study, the magnitude of the weight loss does not seem to be a confounding factor, as the group practicing only exercise had no significant weight loss, but, even so, the adiponectin levels increased. These data raise the hypothesis that variations in adiponectin levels are closely associated with changes in body composition [18]. In fact, even when the weight loss is not significant, changes in plasmatic adiponectin are negatively correlated with the variations in body fat percentage, in children [73]. Similarly, another interventional study for OB adolescents found that increases in adiponectin levels were associated with weight loss, and improvements were kept if the adiposity reduction was sustained [98].

Other factors, such as genetics, PE, inflammation and nutritional habits could influence adiponectin levels. For instance, when considering an intervention programme, involving diet and PE, performed on OB females with eating disorders (nervous bulimia or binge eating) and on BMI-matched controls, both groups benefited from the intervention, as both presented improvements in adiponectin. Nevertheless, changes in adiponectin correlated negatively with changes in HOMA and body fat percentage, only in the CT, and baseline and post-intervention adiponectin levels did not differ between them [99]. The independent role of PE, besides anthropometric improvements, in raising adiponectin levels has also been highlighted [100].

Despite the recognised influence of other factors, studies in children and adolescents have proposed that significant changes in adiponectin require a marked improvement in adiposity [25, 29]. A cut-off value of BMI *z*-score of 0.5 has been proposed as a target for achieving such changes [12, 101, 102].

The need for a considerable adiposity reduction in paediatric ages, even when compared to adults, in order to obtain significant results regarding adiponectin, is partially linked to the age-related decrease in this adipokine levels that occur during this period of life; this decrease is more enhanced during puberty and in boys. In fact, a BMI *z*-score reduction of 0.3 in OB

Intervention programme	Reference	Country	n (f %)	Age (years)	Cohort	Duration	Adiposity	IR	Effect
EP	Shultz et al. [114]	New Zealand	14 (57.1%)	16.1 ± 1.6	OB	16 months			(+) Programme
	Lopes et al. [115]	Brazil	17 (100%)	14.6 ± 1.15	OW (17 OW CT)	12 weeks			NS Programme
ENCP	Lazzer et al. [98]	France	26 (53.8%)	12–16	Severely OB	9 months	(-)		(+) Programme
	Reinehr et al. [116]	Germany	37 (64.9%)	8–12	OB	12 months			(+) Programme (D-BMIzsc > 0.5)
	Elloumi et al. [18]	Tunisia	21 (0%)		OB	2 months[¥]			(+) Programme (> combined energy restriction + exercise)
	Lee et al. [30]	Korea	50 (50.0%)	12.0 ± 0.9	OW + OB	7 days			(+) Programme
	Roth et al. [12]	Germany	62 (54.8%)	11 ± 0.5	OB	12 months	(-)	(-)	(+) Programme (D-BMIzsc>0.5)
	Romeo et al. [94]	Spain	25 (48.0%)	13–16	OW + OB	13 months	NS		NS Programme
	Reinehr et al. [31]	Germany	80 (52.5%)	10.9 ± 0.3	OB	12 months	(-)		(+) Programme
	Carnier et al. [99]	Brazil	83 (66.3%)	15–19	OB*	12 months	(-)	(-)	(+) Programme
	Leao da Silva et al. [95] [22, 41, 59, 60, 75, 117]*	Brazil	84 (59.5%)	15–19	OB	12 months		(-)	(+) Programme
	Siegrist et al. [96]	Germany	402 (59.2%)	13.9 ± 2.3	OW + OB	4–6 weeks			(+) Programme
	Nemet et al. [100]	Israel	21 (47.6%)	10.41 ± 1.96	OB (20 OB CT)	3 months	(-)		(+) Programme
	Racil et al. [118]	Tunisia	34 (100%)	15.9 ± 0.3	OB	12 weeks	(-)		(+) Programme
	Bluher et al. [10]	Germany	65 (46.1%)	12.6 (11.6–13.9)	OW + OB	12 months	NS		NS Programme
	Bocca et al. [104]	Netherlands	75 (72.0%)	4.6 ± 0.8	PP OW + OB	16 weeks	NS	NS	NS Programme
	Inoue et al. [119][106, 120, 121]*	Brazil	45 (62.2%)	16.28 ± 1.34	OB	12 months (AT or AET)	(-)	(-)	(+) Programme (AET)NS (AT)
	Nascimento et al. [15]	Portugal	80 (46.3%)	10.0 ± 2.7	OW + OB (37 OW + OB CT)	8 months	(-)	(-)	(+) Programme
	Seabra et al. [107]	Portugal	58 (0%)	8–12	OB (30 OB CT)	6 months			NS Programme
	Nunes et al. [68]	Brazil	17 (52.9%)	16.18 ± 1.51	OB (8 OB CT)	6 months			(+) Programme[a]

Intervention programme	Reference	Country	n (f %)	Age (years)	Cohort	Duration	Adiposity	IR	Effect
MENCP	Cambuli et al. [73]	Italy	48 (45.8%)	10.7 ± 3.2	OW + OB	12 months	(-) (D-%fat mass)NS (D-weight)		(+) Programme
	Martos-Moreno et al. [9]	Spain	70 (31.4%)	8.92 ± 1.80	OB	18 months	(-) (T, HMW)		(+) Programme
	Gajewska et al. [7]	Poland	30 (40.0%)	7.8 ± 1.3	PP OB	3 months			(+) Programme (T, HMW, HMW% and MMW) (-) Programme (LMW%)
	Vos et al. [25]	Netherlands	40 (55.0%)	13.3 ± 2.0	OB (39 OB CT)	3, 12 and 24 months			NS Programme
	Nascimento et al. [48]	Portugal	60 (48.3%)	11.0 ± 2.4	OB	12 months	(-)		NS Programme
	Gajewska et al. [71]	Poland	100 (54.0%)	8.3 (7.0–9.3)	PP OB	3 months	NS		(+) Programme
	Huang et al. [29]	Mexico	54 (40.7%)	13. 6 ± 1.3	OB	6 months	(-) (WC) NS (BMI and BMI z-sc)	NS	(+) Programme
	Rambhojan et al. [111]	Guadalupe Island, France	55	11–15	OW + OB (28 lean CT)	12 months	NS		(+) Programme
NCP	Pedrosa et al. [14]	Portugal	61 (55.7%)	7–9	OW + OB	12 months		NS	NS
	Saneei et al. [105]	Iran	49 (100%)	11–18	MS	6 weeks	(-)	NS	(+) Programme
	Jensen et al. [122]	Australia	74 (74.3%)	13.3 ± 2.0	OB	12 weeks	(-)	NS	(+) Programme
	Rouhani et al. [123]	Iran	25 (100%)	12–18	OW + OB (25 OW + OB CT)	10 weeks			NS Programme
NSupp	Janczyk et al. [124]	Poland	76 (14.5%)	13 (11.5-15.2)	NAFLD OW + OB	6 months (Ω3 fatty-acids)			(+) Programme
	Machado et al. [125]	Brazil	75 (56.0%)	13.7 ± 2.1	OW	11 weeks (flaxseed)			NS Programme

Intervention programme	Reference	Country	n (f %)	Age (years)	Cohort	Duration	Adiposity	IR	Effect
PI	Clarson et al. [126]	Canada	11 (63.6%)	10–16	IR OB (14 OB CT)	6 months φ			(+) Programme
	Kendall et al. [127]	UK	74 (66.2%)	13.68 ± 2.3	IR OB (77 OB CT)	6 months φ			(+) Programme

*, Different studies from the same group with similar results; +, increase of adiponectin with intervention programme; -, negative association; ¥, exercise and energy restriction, separately or combined; #, 28 with binge eating or bulimia nervous; ᵃ, no increase in intervention group versus reduction control group; φ, 1.5 g of metformin daily.

AET, aerobic and endurance training; AT, aerobic training; BMI, body mass index; CT, control; ENCP, Exercise and Nutritional Counselling Programme; EP, Exercise Programme; f, female; HMW, high-molecular weight adiponectin; IR, insulin resistance; LMW, low-molecular weight adiponectin; MENCP, Motivation to Exercise and Nutritional Counselling Programme; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NCP, Nutritional Counselling Programme; NS, not significant; NSupp, nutritional supplementation; PI, pharmacological intervention; PP, pre-puberty; T, total adiponectin; WC, waist circumference.

Table 2. Interventional studies evaluating the effect on adiponectin levels in overweight (OW) and obese (OB) children and adolescents and the relation between changes in adiponectin and the variation of adiposity and insulin resistance (IR).

children, although already associated with improvements in HOMA and lipid profile, only prevents the age/puberty-associated reduction in adiponectin, observed in the group that did not reach that cut-off [48].

Different strategies have been used in interventional studies; those that appear to achieve changes in body composition, necessary to obtain improvements in adiponectin, are usually short-term/high-intensity programmes that are able to produce in a smaller period of time a greater adiposity reduction [48]. In agreement, adiponectin increased, while BMI reduced, in high-intensity short-term intervention protocols lasting 7 days [30] and 4–6 weeks, in OB children [96].

Strengthening the importance of weight-loss magnitude, Lira et al. found that only the OB adolescents that reduced more than 5% of their fat mass, following PE and dietary intervention, had an increase in adiponectin levels [22]. Nevertheless, the participants in this study were all post-pubertal (Tanner stage 5) and, thus, the improvement in adiponectin might have been facilitated by the absence of the counteracting physiologic reduction. Following a similar intervention, by the same group, decreased IR and increased adiponectin levels were associated with improvements in NAFLD in an OB paediatric population [75].

Regarding the influence of lifestyle interventions on multimeric distribution of adiponectin, a study in PP children found that total and HMW adiponectin were lower in OB children when compared to lean CT. Variation in multimers, in OB children, is probably associated with changes in the multimerisation process that occurs inside the adipocyte, before secretion. In OB individuals, there is a reduction in the percentage of MMW and HMW adiponectin, while LMW% adiponectin increases [7]. Following a lifestyle intervention in OB PP children, a decrease in BMI of 10% was associated with an increase in total adiponectin, along with a decrease in LMW% adiponectin and an increase in the percentage of the other multimers (HMW% and MMW%), despite no association was observed at baseline, between BMI and the multimers or total adiponectin [7]. In a similar way to total adiponectin, changes in multimers concentrations might only be evident if there is a change in body composition, namely a reduction in adiposity, as studies that did not achieve significant reductions also did not have impact on adiponectin multimer levels [103].

Concerning interventional programmes, not only in adolescents but also (and particularly) in children, controversial results are found (**Table 2**). Indeed, some authors report no association with anthropometric changes in PP individuals, as well as no correlation with changes in lipid profile and in IR [104].

Adiponectin did not improve after a lifestyle intervention only with nutritional counselling (without PE programme), despite BMI z-score reduction and lipid profile improvement being achieved [14]. Likewise, in another study involving PE and diet, even though improvements in body fat and BMI were obtained, adiponectin did not increase [94]. Changes in adiponectin levels might be harder to obtain even when compared to other inflammation markers. For example, a decrease in CRP was present following a nutritional intervention programme, despite no significant changes in adiponectin levels and adiposity [105].

The type of PE chosen, namely the training routines and intensity used, will influence the results obtained regarding the body composition and cardiorespiratory fitness and, consequently, adiponectin levels [94, 106, 107]. For instance, although improvements in visceral fat, BMI and dyslipidaemia were obtained by both aerobic training (AT) and aerobic combined with endurance training (AET), these changes were greater with AET, which also presented a significant increase in adiponectin and reduction of IR. It was hypothesised that the greater improvement in dyslipidaemia and IR observed in the AET group was partially caused by the increase found for adiponectin in these individuals, but absent in the AT group [106].

Differences in baseline body composition and physical fitness might also influence the impact of intervention protocols on inflammation mediators, namely on adiponectin. Studies involving non-OB subjects or a mixed population can present different results from those found when only OB individuals are included. Ballet, for instance, is characterised by intense physical activity (PA), associating with an increase in lean mass. Girls practicing ballet have increased adiponectinaemia, when compared to lean CT. Moreover, their adiponectin levels increased during pubertal years (contrarily to CT), despite the trend towards central fat distribution following an increase in BMI z-score in this group [108].

A school-based study in Denmark did not find changes in adiponectin after a 6-week-day camp intervention (involving PA and health classes), although reduction in CRP and leptin and beneficial changes in body composition were achieved [109]. Contrarily, a 12-week exercise intervention study with lean adolescents males found an increase in adiponectin, IL-6 and CRP, although none of these changes were associated with variations in body fat composition [110]. Similar results were found in other studies [111]. It is known that PE, particular high-intensity PE, increases oxidative stress and inflammation markers [112]. As the metabolic profile, the inflammatory balance also differs between lean and OB individuals, with the last presenting a turn towards a more proinflammatory profile. Thus, it is likely that their response to interventional studies also vary, suggesting that comparisons should be done carefully.

A longitudinal study involving only PP lean individuals reported a negative association between adiponectin and the level of PA. Also, the traditional negative association between adiponectin and IR was influenced by the PA levels in this cohort, being stronger for the less-active groups. A mechanism of negative feedback might be present, as children with increased levels of PA would present greater insulin sensitivity (consequence of the PE), making the insulin-sensitiser agent adiponectin less 'necessary'. The opposite effect would occur in the less-active individuals [113]. This postulated negative feedback could also occur in OB individuals participating in interventional programmes, and cause a reduction in adiponectin, following the initial increase, as the intervention continued, due to the increased insulin sensitivity [30]. Actually, in T1D children the increase in IR is accompanied by higher levels of circulating adiponectin [128, 129].

Pharmacological strategies to tackle obesity and obesity-related co-morbidities have been explored. Metformin associates with a small, but consistent, BMI reduction, and increases adiponectin and adiponectin-to-leptin ratio in OB children and adolescents, without notice-

able side effects. Still, the effect of long-term maintenance of metformin on adiponectin levels in children and adolescents is still unknown, particularly in children; thus, its use should be carefully considered [126, 127].

In conclusion, adiponectin association with obesity-related cardiometabolic risk factors, such as IR, dyslipidaemia, atherosclerosis and NAFLD, have been well demonstrated. Interventional studies are good options to tackle obesity and the referred co-morbidities, pharmacological adjuvants being an option to be considered. The variety of interventional approaches, with different study designs, populations and PE protocol makes the impact of these interventions on inflammatory mediators, and particularly on adiponectin, less clear; however, a positive effect is almost consistently found.

5. Conclusions and final remarks

The relation between adiponectin and cardiometabolic risk in children and adolescents is still under research.

Considering the different adiponectin multimers, HMW adiponectin has been associated with a better metabolic control, improving IR, while the LMW multimer presents an opposite effect. The concentrations and the relative percentage of the multimers should be considered as potential markers of CVD risk.

Obesity, and particularly abdominal obesity, is closely associated with lower adiponectin values in paediatric ages. Adiponectin acts as an insulin sensitiser, decreasing as the IR rises. Nevertheless, there might be a negative feedback mechanism, causing a relative decrease in adiponectin as insulin sensitivity improves. Higher adiponectin levels are associated with an improvement in lipid profile, with decreased TG and increased HDLc, being the influence on LDLc more limited. Besides the contribution to a less atherogenic lipid profile, adiponectin further prevents atherosclerosis by a direct positive effect on blood vessels. It reduces the formation of foam cells, macrophage infiltration and activation, and the vascular wall remodelling. Adiponectin is also associated with smaller arterial IMT and increased vessel elasticity, in children. Likewise, increased adiponectin is linked to reduced, healthier, BP.

Combining the specific effects of adiponectin in lipid profile, BP and IR, a decrease in this adipokine will induce clustering of several cardiovascular risk factors in OB children and adolescents that predicts cardiometabolic diseases in the future.

HMW adiponectin seems to be a better predictor of cardiometabolic risk factors than total adiponectin. An increase in total and HMW adiponectin is achieved following interventional programmes, particularly those involving exercise and diet interventions. Changes in body composition, with reduction of total and central body fat, more than changes in body weight, appear to be the key for therapeutic success.

The positive effects of adiponectin on general metabolism are not so clear in PP individuals, particularly the improvement in IR. No significant differences are usually observed between

genders in PP individuals. After puberty, and possibly through a mechanism involving sexual hormones, adiponectin decreases with age in both genders, more markedly in boys [72, 130]. Several studies have reported similar adiponectin levels for both genders, even in OB paediatric populations involving post-pubertal subjects [10, 29, 61, 111, 131].

The controversial data on adiponectin following interventional programmes are, probably, related to different study designs and strategies used, including age, nutritional/body composition characterisation and pubertal stage of the studied subjects, PE or PA practice and type (e.g. aerobic, endurance, strength), group or individual therapy, among others; the population background should also be considered, as genetics plays an important part on adiponectin-circulating levels and, thus, might affect the results. Different populations also have different diets, and nutritional influence on adiponectin levels deserves further studies. Thus, although it is hard to control all variables, a good characterisation of the interventional studies is crucial for future comparisons.

Adiponectin, obesity and IR are so closely associated that it is hard to establish which are causes and which are consequences. The clarification of adiponectin physiological role, the evolution of its normal values throughout life and its relation with other metabolic markers and diseases need well-designed and objective longitudinal studies. These studies should focus on increased follow-up periods, including PP and CT individuals, and evaluate adiponectin isoforms, considering the lack of information on individual multimer levels and function. Further studies would help to better understand the metabolic changes in obesity, and to find new therapeutic targets to obesity itself and obesity-related complications.

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