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The effect of diet or exercise on ectopic adiposity in children and adolescents with obesity: a systematic review and meta-analysis.

Introduction

Overweight and obesity remain one of the most prevalent chronic health conditions in children and adolescents.[1, 2] The worldwide prevalence of overweight and obesity is increasing rapidly, with the fastest rise in low and middle-income countries.[1]

The increasing prevalence of childhood obesity is associated with the raise of metabolic and cardiovascular comorbidities including hypertension, dyslipidemia and type 2 diabetes mellitus.[1, 3] Since disease progression into adulthood is plausible, this current situation constitutes a challenge for future demands on health services.[3-7]

However, children and adolescents with a “metabolically healthy obesity” (MHO) phenotype exist. These individuals are currently not diagnosed with any common metabolic complication such as dyslipidemia, insulin resistance or arterial hypertension.[8-10] Comparable to adults, there are numerous reasons why some children and adolescents with obesity do not develop any metabolic complications.[11] One of the possible contributing factors is a difference in fat distribution. Individuals with MHO have a better ability to absorb free fatty acids in adipocytes and store less ectopic fat than individuals with unhealthy metabolic obesity.[12] Ectopic adiposity is defined as excess of fat in places not classically associated with adipose tissue storageand and may contribute to inflammation and insulin resistance.[13-16] Furthermore, ectopic fat deposition is associated with an increased risk of cardiovascular disease and insulin resistance.[17-19]

Consequently, in addition to body weight and whole-body fat mass, a stronger focus on ectopic adiposity is necessary in the follow-up of children and adolescents with overweight or obesity. In adults, ectopic adiposity has been described in the abdomen, skeletal muscles, liver, heart and kidneys and such ectopic fat accumulation may lead to metabolic and cardiovascular diseases.[20, 21]

Fat deposits in the liver of children and adolescents can lead to paediatric Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) [22-24] Since a liver biopsy is still the gold standard for the diagnosis of NAFLD, the prevalence of NAFLD amongst children is relatively unknown due to its invasive character. Estimations, however, suggest that worldwide, 38% to 90% of all children with obesity develop NAFLD.[22, 25-27] Consequently, early diagnosis and treatment of paediatric NAFLD should be mandatory to prevent the development of NASH.[23, 24] It is equally important to obtain knowledge of the effect size of a liver steatosis treatment.

Diet or exercise have a significant effect on the decrease of ectopic adiposity in adults with overweight and obesity and simultaneously improve the cardio metabolic profile.[28-30] Although research in this area is still scarce concerning children or adolescents with overweight or obesity, previous investigation supports a decrease in visceral adiposity in children and adolescents.[31] Moreover, guidelines highlight the importance of weight loss and lifestyle modification in children and adolescents with overweight or NAFLD.[32-35]

The aim of this systematic review and meta-analysis is to summarize the evidence for the use of a non-invasive weight loss intervention (diet and/or exercise) in children and adolescents with overweight or obesity and its effect on ectopic adiposity located in and around skeletal muscles, liver, heart, pancreas and kidneys.

Methods

This systematic review and meta-analysis is designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement.[36] The protocol of this review has been registered in PROSPERO under the number CRD42014015381.

Search Strategies

The PubMed, PEDro and Cochrane databases were used to run an electronic search specified to each anatomical fat deposition area.

Key words were based on the PICO acronym and were combined with BOOLEAN operators “OR” and “AND”. The search strategy is shown in Table 1. When applicable, limits were set on “clinical trials” and “children”.

Study Selection and Quality Assessment

The three databases were systematically searched using a priori defined in- and exclusion criteria. To obtain consistent results, only clinical trials in which the outcome measurement was ectopic fat were included. Studies in which echography evalulated hepatic adiposity were excluded because no quantifiable data were reported. Since histological abnormalities in liver biopsies are not always paired with elevated liver enzymes in children with NAFLD [37, 38], studies in which liver enzymes were used as an indication of liver adiposity were excluded. Papers describing children or adolescents (mean age<19y) with obesity-related complications such as impaired glucose tolerance, NAFLD or impaired liver function were included. Overweight and obesity were identified in agreement with established international paediatric cut-off criteria and curves.[39, 40] This meta-analysis focuses on lifestyle interventions aiming to reduce body weight including the achievement of a negative energy balance by implementing a hypocaloric diet, exercise, the combination of diet and exercise or healthy lifestyle advice. Studies or study arms in which medication or nutritional supplements were a part of the treatment, were excluded. The Cochrane risk of bias tool was used by two independent investigators to assess the study quality.[41]

Screening and Data Extraction

Titles, abstracts and full-text articles were screened by two independent investigators. Studies fulfilling the criteria mentioned above were included. Figure 1 illustrates the flow diagram of the systematic reviewing process. A standardized data extraction form was used to compile Tables 2 and 3. Whenever methods or data were not clearly reported, the corresponding authors were contacted.

Statistical Analysis

The extracted data was entered into the CMA-2 software (Comprehensive Meta-Analysis 2nd version, Biostat, Englewood, USA). A random-effects model was used to pool the individual study results and to examine the overall weighted effect size of a lifestyle intervention on ectopic adiposity. Effect sizes (changes in ectopic adiposity) were calculated as standardized mean differences. It is likely that the analysis, based on small study groups, results in an overestimation of the effect size. Therefore, a correction was made with a factor g, expressed as Hedges' g.[42] A negative or positive value for Hedges' g indicates a decrease or increase in ectopic adiposity, respectively. The value of the effect size is defined as 0.2=small, 0.5=moderate and 0.8=large.[41]

The 95% confidence intervals [95%CI] were calculated for the individual studies and the overall weighted estimate. Using a correlation coefficient of 0.7 between pre- and post-intervention values and a random-effects model, a balanced and conservative approach is maintained which allows true variations in the effect size and heterogeneity across included studies.[43] The Cochran's Q statistic and its corresponding p-value were calculated for heterogeneity testing, and the I^2 statistic was assessed to express the degree of heterogeneity across studies. To facilitate the clinician's interpretation of the overall effect of lifestyle intervention on hepatic adiposity, the value of Hedges' g was re-expressed to Intra Hepatic Lipids (IHL) and described as proton density fat fraction (%). Baseline % IHL standard deviations of the intervention and control groups from the Lee et al. study[44] were pooled and multiplied by the pooled standardized mean difference. Two additional subgroup analyses were performed based on commonly accepted confounding variables such as study design (Randomized controlled trials versus non-randomized controlled trials) and the ethnicity of subjects. Finally, an additional sensitivity analysis was done in which one study was excluded.

P-values less than 0.05 were considered significant (2-tailed).

Results

Study Selection

The initial search resulted in 18 hits in the search strategy of muscular adiposity (Intra MyoCellular Lipids-IMCL) (search strategy a), 99 hits in the search strategy of hepatic adiposity (search strategy b) and nine hits in the search strategy of pancreatic adiposity (search strategy c). The search strategy of ectopic adiposity of the heart and kidneys (search strategy d and e) yielded three hits each.

After removing duplicates and eliminating papers based on the eligibility criteria, 14 studies remained available for full-text analysis. Due to insufficient data reporting, one article was excluded.[45] After completion of the full-text screening, nine articles on the effect of lifestyle interventions on hepatic fat (320 patients) and three articles on IMCL (55 patients) remained for the meta-analysis. No articles were found on lifestyle interventions and the deposition of ectopic fat in/around the heart, kidneys or pancreas.

Risk of bias

Four clinical trials and six randomized controlled clinical trials were included in this meta-analysis. The results of the risk of bias assessment are shown in Table 4. Since the aspect of blinding was often inadequately explained and the results were repeatedly not transparently presented, a risk of bias was plausible. Only two papers report the adherence to the exercise program or dietary regime.[46, 47]

Population characteristics

According to classification criteria of overweight and obesity in children and adolescents [39, 40], all articles addressed a lifestyle intervention in children or adolescents with obesity. Teenagers (Tanner stage between 4 and 5) without cardiometabolic comorbidities were examined in most studies. In three studies, (part of the) subjects were diagnosed with NAFLD or NASH.[47-49] Most studies described the exact number of ethnic groups to the total population.

Intervention Characteristics

In the included studies, supervised physical activity or the advice to increase physical activity was a part of the lifestyle intervention. Study duration ranged between 3 and 12 months, and the weekly used exercise volume ranged between 90 and 180 minutes.

Anthropometric Data

A statistically significant reduction in BMI or BMI z-score was described in almost all studies. In only two studies conducted by Lee et al., the aerobic training [44, 50] and a strength training [44] did not result in statistically significant BMI decreases. BMI changes were not reported in one study.[51] Changes in whole-body fat mass and fat-free mass were reported in the majority of studies. Only in one study, whole-body fat mass did not change.[52] These anthropometric parameters were not reported in three studies.[46, 47, 51]

Adiposity of the liver

Hepatic adiposity was evaluated in nine studies including 320 subjects (table 2). A forest plot of this analysis is shown in figure 2. A lifestyle intervention led to a decrease in hepatic adiposity (-0.54 Hedges' g [95% CI: -0.69 to -0.38] with $p<0.0001$). By re-expressing the observed overall weighted effect size based on the population variability of Lee et al's research.[44] , it was confirmed that diet and/or exercise interventions resulted in an absolute IHL reduction of 2% in children and adolescents with obesity. No between-study heterogeneity was observed (Cochran's Q = 10.19, df(Q) = 12, p=0.6; I^2 = 0%).

a) Subgroup analysis study design

A first subgroup analysis based on study design (non-randomized versus randomized clinical trials) showed a higher, non-significant overall weighted effect size (p=0.71) (-0.55 Hedges' g (CI) versus -0.48 Hedges' g)

b) Subgroup analysis modality of the intervention

In a second subgroup analysis, groups were compared by intervention modality. Exercise training seemed to lead to the greatest reductions in hepatic adiposity (-0.64 [95% CI: -1.00 to -0.27]) compared to the combination of diet and exercise (-0.54 [95% CI: -0.74 to -0.34]) or diet-only (-0.47 [95% CI: -1.00 to 0.05]). Though, the differences in effect size between groups were not significant (p=0.86). There was no heterogeneity between the exercise-only studies or other study groups (with Cochran's Q = 1.79, df (Q) = 4, p=0.38; I^2 =5.48%) and heterogeneity in the studies applying diet and exercise was negligible (Cochran's Q = 4.23, df (Q) = 4, p=0.76; I^2 = 0%).

Heterogeneity was moderate (albeit not statistically significant) in diet-only studies (Cochran's Q = 3.65, df (Q) = 2, p=0.16; I^2 = 45.3%). Hasson et al's study [51] was the only study in which dietary advice was not described, changes in BMI or total whole-body fat mass were not reported and strength training was applied. Hereby it was uncertain that subjects obtained a negative energy balance. Moreover, since no decrease in hepatic adiposity was observed, it was considered to be an outlier. In a sensitivity analysis, Hasson et al. were therefore excluded. This analysis suggested that a hypocaloric diet has a greater effect on reducing hepatic adiposity (-0.76 [95% CI: -1.27 to -0.25]) compared to exercise-only (-0.64 [95% CI: -1.01 to -0.27]) or to the combination of diet and exercise (-0.55 [95% CI: -0.81 to -0.30]). However, the differences between intervention groups were not statistically significant (p = 0.77) (Figure 3).

Intramyocellular lipids (IMCL)

The effect of an intervention on IMCL was measured in three studies including 55 subjects (Table 3). The overall weighted mean effect size of diet or exercise on IMCL, expressed as Hedges' g was -0.03 [95% CI: -0.52 to 0.47].

Further analysis showed moderate, non significant heterogeneity across studies (Cochran's Q = 4.99, df(Q) = 3, p=0.17; I^2 = 39.9%).

Discussion

Although the link between overweight or obesity and metabolic diseases in childhood obesity could be provoked by body fat distribution and ectopic adiposity[15], research on ectopic adiposity patterns in children and adolescents is scarce.

This meta-analysis concerns only data of hepatic adiposity (nine studies, including 392 subjects) and intramyocellular lipids (three studies, including 76 subjects. The impact of lifestyle intervention on other anatomic sites of ectopic adiposity in children and adolescents with overweight or obesity remains to be studied.

Results of this meta-analysis demonstrate for the first time that a lifestyle intervention (diet and/or exercise) of at least 3 months may yield towards a 2% decrease in intra hepatic lipid content in children and adolescents with obesity. The effect of lifestyle interventions on changes in hepatic fat seems to be smaller compared to adults with overweight and obesity (5-10% IHL reduction).[29] The intra hepatic lipid content is expressed as proton density fat fraction (IHL = (lipid/ (lipid+water)*100). Nevertheless, this is an absolute value of lipid quantification in the liver and an absolute 2% decrease has been observed. In reference to Lee et al's study [44] which was used for the re-expression of Hedges' g, baseline values range between 2.0±1.3% and 3.0±5.4%. Hereby, an absolute reduction by 2% means a relative reduction of more than 50% of existing liver fat. Hepatic adiposity reduction involving lifestyle interventions may be as high as 77% in children and adolescents with obesity (Table 2).[44] Therefore, a lifestyle intervention does lead to substantial and clinically relevant reductions in IHL in children and adolescents with obesity.

Moreover, it is observed that baseline hepatic adiposity content is much lower in children and adolescents with obesity compared to adults with obesity. Furthermore, Lange et al.'s previous research confirms that the mean IHL of children with obesity is more than one order of magnitude smaller than the IHL content in adults with obesity (1.0±0.5% vs 17.0±8.7%).[53] This can clinically be explained by the fact that severe or fibrotic NASH need substantial time to develop. Therefore the prevalence is higher in adults with obesity than in children or adolescents with obesity.[54] Since NAFLD can evolve towards NASH, it is important to observe the NAFLD progression during treatment of young patients by validated imaging techniques.[23, 24] In clinical settings, liver enzymes are used as a non-invasive screening tool for NAFLD in children.[55] Nevertheless, cohort studies in children and adults show normal liver enzymes values in nearly 80% of patients with established fatty liver disease. Moreover, cut-off values in children and adolescents with NAFLD based on blood liver enzymes are discussable.[24, 37, 38, 55-59] Therefore, we preferred to analyze data based on direct measurements of hepatic adiposity. Studies in which liver enzymes were only used as markers of hepatic adiposity, were excluded. Despite the fact that ultrasound techniques have an important clinical value, it was not possible to use ultrasound results in this meta-analysis, because no quantifiable data were reported. Echography results are operator dependent and limit therefore sensitivity and specificity in mild NAFLD.[60-63] The most common technique to assess liver adiposity is Magnetic Resonance Spectroscopy (^{1}H-MRS) which is considered to be a valid and accurate assessment method with good reproducibility. However, it is time-consuming and requires complex data analysis.[64-67] No clinical trials were found in which the effect of a conservative treatment (diet or exercise) on hepatic fat content was assessed by liver biopsy.

According to the different intervention stages described by Barlow et al., weight loss is a key factor in the treatment of pubertal children with obesity.[68, 69] Nevertheless, this meta-analysis shows that a BMI reduction does not relate to a decrease in hepatic adiposity. Shorter (up to 12 weeks) exercise-only studies did not result in significant BMI reductions while significant reductions of IHL were observed.[44, 50, 70] It can be explained by the fact that physical activity sensitizes muscles to insulin and modifies hepatic lipids.[71-73] Furhtermore, it should be noted that a reduction in whole-body fat mass is achieved in these studies.

The variations in program duration, exercise modalities, exercise volume and degree of caloric intake made it difficult to conduct direct comparisons between studies and to identify the most effective intervention to reduce hepatic adiposity in children and adolescents with obesity. In order to overcome this limitation, a subgroup analysis was performed and outliers were detected. Since it was possible that no negative energy balance was obtained in Hasson et al.'s[51], this research was considered to be an outlier. However, a sensitivity analysis without this study did not change our

results. Although there seems to be a difference in effect size between different study designs, this difference was not statistically significant.
The limited number of studies (with each small sample sizes) in the subgroup analyses evoked large confidence intervals partially explaining why the between-groups difference in effect size was not statistically significant.

It is remarkable that the exercise volume (90-180 minutes/week) applied in the exercise study groups did not often comply with the recommended guideline of one hour per day of exercise in children and adolescents with obesity.[68, 74, 75] It could be that a more rigorous exercise regimen would yield better results. It may be argued that the impact of lifestyle interventions on ectopic fat is underestimated in children and adolescents with obesity.

Although there were significant improvements in insulin resistance or sensitivity in all intervention groups, neither endurance nor resistance exercise training yielded significant changes in IMCL. This finding supports the results found by Larson-Meyer et al.[76], who stated that IMCL content is metabolically inert and should not be considered as a determinant of insulin resistance in skeletal muscles. In this regard, it can be assumed that skeletal muscle oxidative capacity plays a role in the association between insulin resistance and excess IMCL in people with overweight or obesity.[77, 78]

In only three studies, (part of the) subjects were diagnosed with NAFLD or NASH.[47-49] Since NAFLD is defined as IHL content higher than 5.6% measured by ^{1}H-MRS [79], only Lee et al.'s research addresses with children without liver disease.[44, 50]

One of the most challenging aspects for healthcare professionals in paediatric weight management programs is the difficulty in obtaining sustained long-term results. Rates of attrition are reported between 27% and 75%.[80, 81] Unfortunately, no long-term studies or studies with follow-up measurements were found.

One of the strengths of this study is the extensive systematic review of the literature providing a meta-analysis revealing the effects of lifestyle interventions on all well documented anatomic sites of ectopic adiposity in children and adolescents with obesity. In addition, the results of lifestyle interventions on hepatic adiposity were made clinically interpretable by re-expressing Hedges'g as absolute values of IHL. In general, clinical and statistical heterogeneity among the included studies was low.

There are, however, also some limitations to this study. The quality of this systematic review and meta-analysis is limited by the methodological quality of the included studies. In the majority of included studies, a risk of bias is plausible because due to inadequate reporting of applied methodology and patient adherence. In most studies, the prevalence of insulin resistance, type 2 diabetes or liver diseases was not reported.

Finally, the included studies described rather small study populations.

To facilitate future systematic reviews and meta-analyses, researchers should be encouraged to report their methods and observed outcomes transparently (as well in changes as in means with standard deviations). Given the fact that long-term effectiveness of a lifestyle intervention is dependent on the sustainability of behaviour change, it is important that adherence to the prescribed intervention protocol is adequately assessed and reported. A comparison with habitual diet and exercise behaviour can result in a correct interpretation of the intervention effect.

Conclusion

This meta-analysis shows that diet and/or exercise is effective in reducing hepatic adiposity in children and adolescents with obesity, even without a BMI reduction. This reaffirms existing clinical guidelines in which complete lifestyle modification is promoted in the management of paediatric obesity. Although there were significant ameliorations in insulin sensitivity in all intervention groups, no significant changes in IMCL were found.

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