Nutritional Deficiencies Of The Obese Child And Adolescent

ebook.ecog-obesity.eu/chapter-clinics-complications/nutritional-deficiencies-obese-child-adolescent

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Obesity is defined as an excess fat mass. Its occurrence requires that food intakes exceed energy expenditure. Nutritional status of the obese child and adolescent seem a paradoxical question which needs to be raised for at least four reasons:

- Fat foods, soft drinks poor in vitamins and minerals are the most common source of calories in excess. Major differences in nutrients intakes still exist around the world. The obese population is not spared by additional health inequalities which lead to a double burden as will be shown. Obese children and adolescents tend to spend less time active outdoors and to wear supersized clothing in order to hide their body. Lifestyle varies among and within countries. Many potential contributors to food choices such as vitamin D from exposure to sunshine have to be taken into account. Assessment of individual nutritional status requires a food frequency and lifestyle questionnaire.

- A huge fat mass acts as a reservoir of fat soluble vitamins and nutrients. Serum concentrations of these substrates may not reflect actual status while bioavailability remains largely unknown. The use of dietary questionnaires is still a valuable tool in order to detect nutritional imbalance and support the interpretation of apparently accurate biological data.

- A low grade inflammation is a feature of obesity which will have opposite impacts on some of the proteins that transport vitamins and nutrients into the blood. Inflammation may for example lead to overestimation of iron status if ferritine concentrations are enhanced or under estimation in the case of vitamin A if transthyretin is decreased. Increased oxidation is associated with early obesity. This may enhance in turn requirements for antioxidant nutrients such as carotene, vitamin E or selenium.

- Vitamin A and D are hormones that regulate the expression of many genes and the adipose tissue. Several vitamins and nutrients are independently correlated to adiposity and metabolic risk factors. Vitamin B9 (folates) and B12 contribute to gene expression and the so-called epigenetic origin of obesity and related diseases (see corresponding chapter). Understanding these interactions leads to the current exciting boundaries of nutrition.

In this chapter we shall review the evidence for nutritional deficiency in obese children and adolescents, and its diagnosis. Nutritional status following bariatric surgery will be treated in a separate chapter.

The fat soluble vitamins

Vitamin D

Vitamin D is a group of fat soluble prohormones with the two major forms being ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3). Ergocalciferol or vitamin D2 originates from plants. Cholecalciferol or vitamin D3 is the natural form produced in the skin by photosynthesis through exposure to UVB or originating from animal products, mainly fatty fish. Vitamin D3 seems to be approximately 87 % more potent in raising and maintaining serum 25 OH vitamin D concentrations and produces 2 to 3 fold greater storage of vitamin D than does equimolar D2 in healthy adults[1].

Vitamin D3 enters the circulation bound to a circulating binding protein (VDBP) binding 85 to 90% of total circulating 25 OH vitamin D and is transported to the liver. The non-vitamin D binding protein fraction (bioavailable vitamin D) consists primarily of albumin bound 25 OH vitamin D (10 to 15%) with less than 1 % of 25 OH vitamin D in its free form.

Vitamin D are hydroxylated by the liver to produce 25-dihydroxyvitamin D3 (25 OH vitamin D3) or 25 dihydroxyvitamin OH D2 (25 OH vitamin D2). These metabolites are further hydroxylated primarily by the kidney by 1α hydroxylase (gene: *CYP27B1*) to produce the bioactive forms 1α,25(OH)2 vitamin D3 and 1α,25(OH)2 vitamin D2. Catabolism of vitamin D and its metabolites occurs in the liver trough cytochrome P450 enzymes.

The bioactive 1α,25(OH)2 vitamin D3 is an hormone which controls gene expression in numerous cell types and tissues through the vitamin D receptor (VDR), a member of the nuclear receptor superfamily which regulates transcription of many target genes. The VDR has been found in most human tissues including osteoblasts, muscle, pancreatic β cells, macrophages and adipocytes. The ubiquitous expression of VDR provides a link between vitamin D deficiency and disorders such as obesity. Adipocytes could be involved in the local synthesis as well as degradation of biologically active vitamin D. Vitamin D and VDR seem to be involved in adipogenesis.

Vitamin D status is especially difficult to analyze because of the storage in fat mass and because of the unknown proportion of bioavailable forms [2-4]. 25 OH vitamin D plasma concentrations are used in routine clinical practice to evaluate vitamin D status. International guidelines classifiy vitamin D status into 4 groups according to serum concentrations: vitamin D sufficiency/optimal level ≥75 nmol/, insufficiency 50-75 nmol/l, deficiency 27.5-49,99 nmol/l , severe deficiency <27.5 nmol/l[5].

Low vitamin D serum concentrations are repeatedly found in obese adults and adolescents. A mathematical model looking at the best fit between 25 OH vitamin D serum concentrations and various body size measures concluded that volumetric dilution rather than sequestration best explains low vitamin D status in obesity[6]. Since evidence was lacking in humans, circulating and fat tissue contents of vitamin D3 were measured in obese adults. A positive correlation of 0.68 (p=0.003) was found between concentrations in serum and fat tissue in favor of storage in fat tissue[7]. No data are available to the best of our knowledge in children and adolescents.

Vitamin D status in a sample of 1006 healthy European adolescents from 9 countries was estimated to be suboptimal by the HELENA study in 80 % of the sample with 39 % being insufficient, 27 % deficient, 15 % severely deficient, according to international guidelines. A non significant and progressive decrease of 25 OH vitamin D concentrations was observed with increasing BMI[8]

In Texas, 92 % of a group of obese children and adolescents had 25 OH vitamin D below 75 ng/ml and 50 % were below 50 ng/ml vs. 68 and 22 % respectively in a lean control group[9]. 25 OH vitamin D was negatively associated with soda and juice intake and skipping breakfast. A link between incidence of vitamin D deficiency and gastro intestinal and ear infections was reported in South American children. The higher the BMI, the lower was vitamin D status[10]. The double burden of obesity and malnutrition has been further examined in a population of children and adolescents from the 2003-2010 NHANES studies. Vitamin D deficiency was found in 5.6 % of the population. Regression analysis indicated that being a female of Hispanic origin, (as opposed to non Hispanic white) and aged between 12 to 19 years (as opposed to younger children) were significant risk factors [11]

Exposure to sunshine during the last 90 days and vitamin D intakes since early September was shown to be significantly associated with vitamin D status during winter time in a cohort of healthy French children[12]. Lower serum concentrations were found during fall and winter than during spring and summer time were found in obese children belonging to 3 ethnic groups (Caucasian, Hispanic and African American). Vitamin D deficiency and insufficiency corresponded to decreased vitamin intakes. Vitamin insufficiency only was more prevalent in fall and winter. Children with hypovitaminosis and vitamin deficiency had higher BMI, fat mass than those with adequate vitamin D concentrations[13].

The link between vitamin D status and obesity is not merely a matter of ingestion and exposure to sunshine. In adults, bioavailability of vitamin D from cutaneous and dietary sources seems to be reduced by obesity [14]. The cutaneous synthesis of vitamin D3 precursor measured on skin samples did not differ between obese and lean subjects either in basic condition or after UV-B irradiation *in vitro*. *In vivo* skin irradiation led to lower plasma concentrations of 25 OH vitamin D3 and administration of 50 000 UI of vitamin D2 led to lower peak plasma concentration of 25 OH vitamin D2. In both situations plasma vitamin D concentrations were inversely correlated to BMI. Liver damage seems to be another determinant of vitamin D status: 25 OH vitamin D plasma concentrations were found to be 9 ng/ml (95 % CI 12-6) lower in obese children aged 8-18 years (median BMI 2.45 SDS) with stage 1or 2 fibrosis than in those with stage 0 after correction for age, BMI gender and waist circumference [15].

A link between obesity and vitamin D status and adiponectin has been evidenced in an Italian pediatric population using a proteomic approach. Adiponectin, a hormone produced mainly by adipose tissue, has insulin sensitizing effects, anti inflammatory and antioxidant properties and centrally regulates food intake and body weight. Obese children and adolescents were included on the basis of their plasma 25OH vitamin D3 concentrations. Subjects with low 25 OH vitamin D3 plasma concentrations (<15 ng/ml) were shown to have higher BMIs, higher insulin resistance, higher diastolic blood pressure and lower multimeric forms of plasma adiponectin concentration than those with 25OH vitamin D3> 30 ng/ml. A daily supplementation of 400 UI of cholecalciferol over 12 months in the low vitamin D group mildly but significantly upgraded total adiponectin in the absence of weight change. The authors showed that vitamin D up regulated adiponectin multimerization in 3T36L1 mature adipocytes[3]. In a case control study, 35 obese adolescents were randomly assigned either to a supplementation with 4000 UI/day of vitamin D3 during 6 months or to a placebo containing soya oil. Vitamin D supplementation led to a decrease in fasting insulin (-6.6 vs +1.2 µU/ml, $p<0.001$) and HOMA resistance index (HOMA IR -1.36 vs+0.27, $p=0.033$) whereas QUICKI index and BMI remained stable[16]. An increase of 1 ng/ml in 25 OH vitamin D occurs for every 205 IU of vitamin D3 ingested which fits results reported in adults [17]. In a group of 68 obese adolescents who were supplemented with 50 000 UI weekly during 6 to 8 weeks for deficiency and 800 UI/day during 3 months for insufficiency, levels normalized in only 28% of the participants although an initial rise was observed. The type of vitamin D used was not specified by the authors [18]. The impact of a supplementation of 2000 UI/d of 25 OH vitamin D3 during 12 weeks was evaluated in adolescents during an open label non randomized trial. Serum 25 OH vitamin D concentration were higher at baseline in lean than in obese subjects (28.9 vs 25.2 ng/ml, $p = 0.03$). The increment was lower in obese (5.8 ng/ml) than in lean counterparts (9.8 ng/ml, $p = 0.019$). Mean parathyroid hormone (PTH), calcium and phosphorus concentrations were similar before and after treatment[19].

Vitamin D status may also influence vascular health in the adolescents. Since obese children suffer early cardiovascular alterations, such findings may have important implications (see corresponding chapter). Total, free and bioavailable 25 OH vitamin D correlations to vascular fitness were evaluated in 47 lean post-menarchal adolescents. Vascular fitness was assessed by flow mediated dilation (FMD) on brachial artery. FMD was associated with bioavailable 25 OH vitamin D ($\rho =0.3$, $p=0.08$) but not with total or free 25 OH vitamin D. The apparent lower serum total 25 OH vitamin D in African Americans (AA) than in European Americans (EA) is annulled when VDBP is taken into account. After adjustment for race, augmentation index (a surrogate measure of arterial stiffness) positively correlated in AA with free and total 25 OH vitamin D. An inverse trend was found in EA. Lower vitamin D status may enhance the vascular risk in adolescents on a genetic basis. Data are lacking in obese adolescents. The implications of this finding remains unclear[20].

In American and European adults, the GIANT consortium (Genetic Investigation of Anthropometric Traits) studied the direction of the link between obesity and vitamin D status using bi-directional

Mendelian randomization analysis. A 10 % higher genetically instrumented BMI was associated with and 1.78 (95% CI : 1.04-3.06) for BsmI and TaqI SNPs while there was no difference between ApaI polymorphisms and wild genotype (95% CI :0.27-1.08, p = 0.078). BMI percentile was not significantly associated with vitamin D status in multiple regression models.

Low levels of 25OH VDBP may also explain low circulating vitamin D and protect against the manifestation of vitamin D deficiency since it is acting as a reservoir and aiding the reabsorption of filtered vitamin D through the kidney. Low levels of total 25 OH vitamin D are common among black Americans. In a population of 2085 adults of white and black origin with a wide range of BMI, genetic variants of VDBP who influence the affinity of the carrier for 25OH vitamin D were shown to independently explain 79.4% of the variation in VDBP and 9.9% of the variation in 25 OH vitamin D. BMI and calcium intakes each appeared to account for less than 2 % of the variation of total 25 OH vitamin D. Similar data are lacking in children and adolescents [21].

In obese non diabetic adults, treatment with 3.36 g/d of long chain n-3 PUFA (460 mg eicosapentaenoic acid, 380 mg docosahexaenoic acid and tocopherol as antioxidant) abrogated the inverse relationship between 25 OH vitamin D and inflammatory markers (IL6 and hsCRP).

n-3 PUFA were compared to butterfat during 8 weeks. Vitamin D deficient patients were younger and had higher circulating IL6 concentrations than their non deficient counterparts. Baseline 25OH vitamin D correlated negatively with BMI (p=0.01). Treatment with PUFA did not affect vitamin D status[17]. Authors speculate on the benefit which may have occurred in the past when vitamin D deficiency was prevented and treated by cod liver oil which used to bring both nutrients together and conclude on the need to further investigate this association[17].

The relationship between vitamin D status and peak bone mass was investigated in 90 post pubertal females in California. 59 % of the subjects were vitamin D deficient. In this group only 25OH vitamin D was negatively correlated to BMI. No relationship was observed between circulating 25OH vitamin D and bone mineral density at any site[22]. Bone mineral content (BMC) was inversely correlated to systolic blood pressure in a cohort of obese Latino adolescent boys but not in girls. Hypertensive adolescent boys had lower BMC than their normotensive counterparts [23]. This observation raises the question of the early interaction between calcium status, bone mineralization and blood pressure regulation.

In conclusion vitamin D deficiency assessed on serum concentrations is a common feature in the obese young population. The interpretation of low serum levels is difficult: intakes and sunshine exposure are not easy to evaluate, data is lacking about storage and release in adipose tissue while bioavailability is seldom taken into account. Knowledge is still poor about the link between vitamin D status and later health outcomes in this population. Early associations that are evidenced to obesity complications such as liver fibrosis, inflammation and insulin resistance require further assessment. So far, prevention and treatment of vitamin D deficiency in obese and non obese children and adolescents should follow similar rules.

Vitamin A

Vitamin A is a fat-soluble vitamin which originates from plants as provitamin A carotenoids or from animals as retinol. Many children around the world are still exposed to vitamin A deficiency risk. Vitamin A's role in obesity is complex: animal models suggest that it plays a key role in adipose tissue biology and energy homeostasis and affects the master regulator of adipocytes biology PPARγ. Similar effects are now evidenced in humans [24].

Most actions of retinol are mediated by its metabolite retinoic acid which is synthesized intracellularly in

target tissues from retinol. In a first step retinol is reversibly oxidized to retinaldehyde which is then irreversibly oxidized to retinoic acid by distinct enzymes. Retinoic acid receptors (RARs) belong to the superfamily of nuclear receptors as does VDR. Hundreds of genes have been shown to be retinoic acid inducible. The liver plays a central role in vitamin A physiology. Vitamin A is delivered to the liver as a constituent of chylomicron remnants. Retinol is re-esterified to retinyl esters and stored in hepatic stellate cells, the major storage site for vitamin A in the body. Retinol bound to retinol binding protein (RBP) is secreted from the liver to maintain serum vitamin A levels and to deliver retinol to extra hepatic targets. In plasma RBP circulates as a 1:1 complex with transthyretin and retinol.

In healthy subjects, the adipose tissue seems to store 10-20 % of total retinoids of the body as retinyl esters. Beta carotene can be transformed to retinaldehyde and then retinoic acid in the adipose tissue. Adipocyte derived RBP4 is an adipokine which contributes to the development of insulin resistance. All-*trans*-retinoic acid can inhibit adipocytes differentiation by binding to activating retinoic acid receptor (RAR). It also induces lipolysis when applied to mature adipocytes. Beta carotene, retinaldehyde and retinoic acid decrease adipocytes' early differentiation[25].

Vitamin A status is partly dependent on the efficiency with which β carotene is converted to retinol. Epidemiological studies looking at vitamin A status in obese populations show different results between countries. A reason behind this is the source of vitamin A: in the western diet, about 20 to 30 % of the habitual intake of vitamin A originate from provitamin A carotenoids. In contrast, up to 70 % of carotenoids in the diet are required in developing countries[26].

Diagnosis of vitamin A deficiency is still based on proxys. The gold standard is the dosage of retinol reserves of the liver. Serum retinol concentrations are homeostatically controlled and do not begin to decline until liver reserves of vitamin A are very low. RBP is a negative acute phase protein. Serum retinol and RBP fall during times of infection and may be altered by iron deficiency. The relative response test (RDR) to a load of retinol is not indicative of the total reserves of the body. Serum and RBP and RBP4 dosage have been shown to poorly reflect serum retinol concentrations[27]. Despite their limitations serum retinol and carotenoids concentrations are the most widely used method.

Serum β carotene, measured during the NAHNES III cycle between 1988 and 1994 was lower in obese than in lean children. Nearly half of the obese children had β carotene concentrations in the lower quartile compared with about a quarter in lean children ($p<0.001$)[28]. In a sample of Mexican-American children, the later NAHNES 2001-2004 study found that 12.4 % of the children had α-carotene deficiency (concentrations < 1µg/dl). Obese children had lower mean concentrations of trans-β-carotene and cis-β-carotene than lean counterparts. Concentrations of serum retinol were positively associated with BMI, trunk fat mass and total body fat mass whereas the opposite was found for serum α-carotene, trans-β-carotene and cis-β-carotene. Higher retinol quartile were associated with a 2 to 3- fold greater probability of overweight and obesity and the highest quartile of α carotene and trans-β-carotene were associated with reduced probability of obesity. Lower intakes of fruit and vegetables and higher energy intakes are a first plausible cause of this difference. Other hypotheses are carotenoids storage in adipose tissue and higher antioxidant catabolism due to low grade inflammation associated withobesity[29]. Another study carried out in a population of 197 Mexican school children found that 44 % were overweight or obese. Vitamin A intake below 400 µg/d at 8 years old or 580 µg/d at 13 years old were found in 53 % of this population. Vitamin A < 20 µg/dl was found in 7.1 %. Vitamin A concentration was positively associated with BMI, waist circumference and abdominal fat ($p<0.05$). Overweight or obese children with low concentrations of vitamin A had significantly higher CRP concentrations ($p<0.05$)[30].

A study performed in Hungary did not find significant differences either in retinol or in carotenoids between lean and obese children. Only ratios of β carotene to plasma triglycerides and cholesterol differed between the two groups[31]. In another study, in Switzerland, 3 % of the children had a retinol

deficiency (<1.05µmol/l) suggesting low vitamin A status. Serum RBP4, retinol, RBP4 to retinol and transthyretin were significantly increased in the obese group. BMI, body fat percent and waist to hip ratio, i.e. central distribution of body fat, remained significant predictors of RBP4 after adjustment for age and sex[32]. Another study confirmed that RBP4, is associated with adipose tissue mass in children and with BMI, independently of age ($r = 0.33$, $p<0.0001$). RBP4 mRNA expression in human SGBS cell line increased with adipocytes differentiation and secretion was identified only in mature adipocytes[33]. In a longitudinal study, obese children had higher RBP4 concentrations, a higher serum RBP4 to retinol ratio compared with lean children. RBP4 was significantly associated withBMI and insulin. Substantial weight loss led to a significant decrease in RBP4 and RBP4 to retinol ratio. Changes correlated to changes in insulin resistance evaluated by HOMA and QUICKI indexes and weight reduction[34].

Vitamin E

Vitamin E is the third fat soluble vitamin which requires evaluation in obesity. Alpha tocopherol, the most abundant lipid-soluble vitamin is a vital anti oxidant in mammals, including humans. It prevents damage to lipids containing polyunsaturated fatty acids (PFA). It is absorbed in the small intestine, transported to the liver in chylomicrons and then released in the plasma as a component of the VLDL. It is bound in the liver cells to a transporter, the α-tocopherol transporter protein (α-TTP) which moves vitamin E through the cell surface by exchanging it for a phosphoinositide in the plasma membrane. Other tocopherol species are moved with a lower affinity [35].

An early study has shown that tocopherol content in the adipocyte is 8 times greater in the bulk lipid than in membrane[36].

Bioavailability of vitamin E from foods for absorption seems to be highly variable according to food sources. Most dietary vitamin E occurs through vegetable oils. Human studies do not yet allow ranking of foods as a function of vitamin E efficiency. Requirements may increase with the amount of PFA in the diet[37].

Vitamin E status has been studied during the NHANES III cycle between 1988 and 1994. Serum α-tocopherol concentrations after adjustment for serum triglyceride and cholesterol levels were lower in obese than in lean children ($p<0.001$). Nearly one half of the obese children had adjusted α-tocopherol in the lowest quartile compared with about one quarter in the lean group ($p<0.001$)[28]. During the 2001-2004 NHANES cycle, α-tocopherol concentrations were measured in Mexican –American children. The proportion of vitamin E deficiency defined as an α-tocopherol: cholesterol ratio <2.2 (µmol α-tocopherol: mmol total cholesterol) was close to 1 %. BMI was inversely correlated with α-tocopherol adjusted for total cholesterol ratio ($\beta=-3.66$, $p<0.01$). Similar correlations were found for trunk fat mass and total body fat mass. Higher α-tocopherol concentrations were associated with reduced probability of overweight[29]. Another study carried out in a population of Mexican school children found that 44 % were overweight or obese and a mean serum vitamin E of 5.8 ± 1.42 µg/l. Ninety-eight percent of Vitamin E intakes were below recommended intakes of 7 and 11 mg/d in 8 and 13 years old children respectively. A third of the children had vitamin E concentrations <5 µg/ml and 2 % vitamin E < 3 µg/l. When adjusted for lipids, vitamin E concentrations were negatively associated with all the measures of obesity. Contrary to vitamin A, vitamin E and CRP were unrelated[30]. In Europe, concentrations of α-tocopherol ($p<0.05$) were about 50 % lower in a sample of obese children than in lean counterparts[31] and inversely correlated to fasting insulinemia[38]. A 4-month randomized control trial intervention with daily antioxidants (vitamin E 400 UI, Vitamin C 500 mg, selenium 50 µg) vs placebo was performed in overweight or obese adolescents participating in a lifestyle modification program. Plasma concentrations of all antioxidants were lower at baseline than in treatment group. Selenium and oxidative stress 8-iso-$PGF_{2\alpha}$ which are markers of oxidative stress were significantly reduced. Not effect was found on the inflammatory markers (CRP, IL-6, leptin, PGE_2 and α-1 acid glycoprotein)[39].

Water soluble vitamins: Folates and vitamin B12

Folate and vitamin B12 together are important contributors to energy metabolism. Folate intake also provides dietary methyl groups required for DNA methylation and subsequent gene expression, i.e. are key contributors to epigenetic determinants of cardiovascular risk and obesity (see corresponding chapter). 5 methyl-tetra-hydrofolate is the active form of folate. Methyl radicals allow the conversion of homocystein (Hcy), an independent cardiovascular risk factor, into methionine. Methylentetrahydrofolate reductase (MTHFR) is a key enzyme of this process. Common mutations of the gene of this enzyme lower conversion rates and increase Hcy concentrations. Vitamin B12 is a main cofactor of this cycle[40]. Folate are found mostly in green leafy vegetables, nuts and in liver meat. Intakes vary widely according to food choices[41]. Folate plasma concentration reflects recent folate consumption. Folate biological status is best evaluated by folate red blood cell content (EF).

An epidemiological study performed in Greece has found similar mean folate intakes in overweight and lean adolescents. The authors state that "a significant proportion did not reach recommended intakes"[42]. Data from the Mexican American population studied in the NHANES 2001-2004 round found a low prevalence of 0.3 % of RBC folate deficiencies whereas 89.3 % had normal serum concentrations of vitamin B12. Normal weight children had higher mean concentrations of serum vitamin B12 than did obese overweight and obese children ($p<0.01$)[43]. Children aged 2 to 11 years old that consumed more than 7 g/days of nuts had higher BMIs but also higher folate, Mg, Cu, monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and fibers than small eaters[41]. Beyond 12 yrs of age, consumption of nuts was associated with a slightly lower body weight, and slightly lower triceps skinfolds ($p<0.05$). In a group of 57 severely obese French adolescent girls, we found that folate intakes ranged from 104 to 412 µg/d and were below national recommended allowances of 300 µg/d in 80 % of the subjects. The impact of a common mutation of the MTHFR (MTHFR, 677 C->T), which reduces by 28 % the transfer of methyl group from folate to substrates, was examined. Serum concentrations of the liver enzyme alanine amino transferase (ALT) were negatively correlated to folate intakes ($r=-0.32$, $p=0.024$) and higher in subjects carrying the homozygous mutation ($p=0.016$)[44]. In another group of 130 severely obese adolescents, insulin concentration and resistance, evaluated by HOMA index were increased in homozygote subjects despite similar folate intakes and EF concentrations ($p = 0.017$ and $p= 0.04$ respectively)[45]. Vascular function by flow mediated dilatation (FMD) was measured in 58 obese adolescents and 47 controls. The effect of a daily supplementation of 5 mg folate on FMD was evaluated according to the genotype of the endothelial nitric oxide synthase gene (NOS3). NOS is a key endothelial enzyme in maintaining vascular tone. NOS3 polymorphisms led to opposite significant changes in FMD induced by folates. Genetic background must be taken into account in analyses and intervention studies in obese children[46].

Information about other vitamin deficiencies is seldom reported in obese children.

Minerals and serum trace elements

Iron

Iron intakes vary widely around the world where anemia is still the most common nutrient deficiency and affects 25 % of the world's population. Iron deficiency originates from low intakes or low absorption. Iron sources are from both animal (meat, fortified dairy products, egg yolk) and vegetable origin (mainly legumes). Iron of vegetable origin (non heme iron) is less absorbed than heme iron from animal tissue. Bioavailability varies greatly with diet composition and iron stores. Average absorption seems to be 5-8%

across studies in a systematic review[47].

Biological iron status is assessed on serum concentrations of ferritin, a cage-like heteropolymer which can hold up to 4500 iron atoms. Most ferritin is used to store within cells but a very small amount enters a distinct secretory pathway, destined for release in the serum. Another protein, transferrin is secreted mostly by hepatocytes, and serves the general purpose of binding iron, keeping it soluble in an aqueous environment and delivering it to tissue. Hepcidin is a protein which regulates iron homeostasis by shutting off cellular iron export. Ferritin and hepcidin synthesis are increased by inflammation[48]. Obesity is a mild inflammatory disease. Iron status is therefore difficult to assess in obese children and adolescents.

Iron status was assessed as part of the Healthy Growth Study (n= 2492) in primary school children in Greece. Iron deficiency estimated on transferrin saturation (TSAT) <16% was evidenced in 15.3 % of the total population and iron deficiency anemia (hemoglobin<12g/dl and TSAT <16 %) in 2.6 %. In the obese group the corresponding figures reached 28.6 % and 5.3 % in boys and 28.9 % and 8.2 % in girls ($p<0.003$). Serum ferritin was higher in the obese than in the lean group and TSAT negatively correlated to BMI[49]. Iron deficiency rate ranged from 2.0 % (ferritin cut off: 12 mg/l) to 4.8 % (ferritin cut off: 15 mg/l) in a group of 502 obese children and adolescents in France. Multivariate regression analysis after correction for age, sex, Z score of BMI and fibrinogen showed independent correlations between ferritin and triglycerides, HDL cholesterol, transaminase and hemoglobin concentrations[50]. Iron storage assessed by ferritin is associated with cardiovascular and fatty liver disease risk factors. In Switzerland, iron status were compared in overweight and lean children and adolescents, aged 6 -14 years old. Iron intakes and bioavailability estimated from food database was similar in obese and lean subjects. Iron deficient erythropoiesis estimated on serum transferrin concentrations (4.4 ± 0.77 vs. 3.94 ± 0. 88 mg/dl, $p=0.010$) was 20 % in obese children vs. 6 % in their lean counterpart ($p=0.022$). Serum hepcidin levels were higher in the obese group and in a multiregression model correlated with BMI SDS ($p=0.02$) and body iron ($p=0.029$) but not with the inflammatory markers (CRP, IL6, leptin)[51]. Another study performed in Italy compared iron status in obese children and lean counterparts. Iron absorption studied 2 hrs after absorption of 1 mg/kg of ferrous sulfate was similar in both groups. Obese children showed lower iron and transferrin saturation ($p<0.05$) and higher hepcidin levels ($p = 0.004$) compared with controls. Hepcidin and obesity degree were correlated ($p=0.0015$). Hepcidin secretion may be enhanced in obese children[52]. Iron status was evaluated in Egyptian children. Serum iron and transferrin saturation were lower whereas ferritin, soluble transferrin receptors and hepcidin were higher in obese than in lean children. BMI SDS correlated with ferritin and iron[53]. A study performed in prepubertal Egyptian children reported lower serum iron ($p<0.01$) while serum ferritin concentrations did not differ significantly. Serum iron was negatively correlated to BMI ($p<0.05$) but not to leptin concentrations[54]. Eighteen per cent of a group of obese Mexican American children had low serum iron concentrations. Plasma CRP and iron concentrations were negatively correlated ($p<0.05$)[30].

Obese children and adolescents are exposed to iron deficiency. In this population high serum ferritine may not reflect increased iron stores but rather inflammation.

Zinc

Zinc is the second most abundant, unevenly distributed divalent cation in the body after calcium. Higher concentrations are found in bone and muscles. Main food sources are meat, fish, shell fish and nuts and whole grains. Availability is decreased by phytic acid. Zinc metabolism is tightly regulated. Despite the lack of a storage form, as in iron, steep increase in absorption and decrease in urinary losses maintain homeostasis. In healthy children a meta-analysis found that a doubling in zinc intakes is necessary in order to increase plasma or serum levels zinc concentrations by 9%. Excess zinc is toxic. This characteristic underlies its bactericidal action. It plays critical roles as a cofactor both to stabilize proteins

structurally, as well as to facilitate enzymatic catalysis. It allows insulin storage, action and release from β pancreatic cells. Major zinc deficiencies are still common in association with protein deficiencies in developing countries and in rare digestive diseases. Zinc insufficiency can be manifest in diminished immune response, reduced tissue regeneration and healing after traumatic insults, as well as the occurrence of select neurological disorders[55]. Zinc status is assessed on plasma concentrations. Urinary and hair Zn concentrations are also valuable markers of Zn status[56].

A study performed in Mexican school aged children found that a fourth of them had zinc deficiencies (Zn<65 µg/dl). Overweight and obese children with low zinc concentrations had higher insulin concentration and insulin resistance compared with children with adequate weight with low concentrations of these micronutrients ($p<0.05$). No correlation was found with CRP[30]. Serum Zn concentrations were markedly lower ($p<0.01$) in a group of obese prepubertal Egyptian children than in lean controls and negatively correlated to BMI ($r=-0.65$, $p<0.01$) and leptin serum concentrations [54]. A group of obese prepubertal children was supplemented with 20 mg/d of elemental Zn during 8 weeks. A mild significant decrease in fasting insulin and HOMA index were observed in supplemented children whereas a mild increase occurred in control group[57].

Selenium

Selenium is an anti oxidant trace element which has seldom been measured in obese children. A study performed in obese Egyptian children reports lower serum concentrations in obese than in lean controls ($p<.001$) and a strong correlation with HOMA index in obese ($r=0.64$, $p< 0.01$) but not in lean counterparts[54]. Another study reports lower selenium intakes in Spanish schoolchildren and lower serum concentrations in those who were obese. Selenium intakes and serum concentrations were positively correlated ($p<0.05$). A negative relationship was found between all anthropometric parameters and serum selenium. Logistic regression showed the risk of selenium deficiency to increase with BMI (OR=1.50, IC 95 % 1.38-1.63) and to decrease with age (OR=0.68, 95 % IC 0.54-0.85). Blood glutathione peroxidase (GPx) was moderately correlated to serum selenium concentrations ($r =0.17$, $p<0.05$) but not to anthropometry [58].

Obese children are at risk of vitamin A, D, E, folate, iron, zinc and selenium deficiencies that may originate in low intakes or increased requirements. Dietary records are mandatory and simple first line tools in order to identify at risk subjects. Biological assessment of fat soluble status is not easy because of unknown storage and bioavailability in and from adipose tissue. Inflammation which occurs in obesity induces increases in transporters synthesis and plasma concentrations of proteins such as ferritin. Biological assessment requires cautious interpretation. Consequences of nutrient deficiencies in obesity are not limited to their classical aspects but tend to enhance its associated metabolic disorders.

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