2021-2022

THÈSE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en Pédiatrie

Bone Health of Obese and Overweight Boys

Etat de la santé osseuse des garçons obèses ou en surpoids

Description of influencing factors

Description des facteurs influents

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Né le 21 juillet 1993 à Nantes (44)

Sous la direction de Mme AMSELLEM JAGER Jessica

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Soutenue publiquement le :
8 septembre 2022

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REMERCIEMENTS

Au professeur Regis Coutant, merci de me faire l'honneur de présider ce jury, merci pour l'aide apportée pour mener à bien ce travail, et merci pour tous les enseignements apportés au cours de mon internat,

Aux Professeur Rodien, Docteure Bouhours-Nouet et Docteure Beaumesnil, merci pour votre présence dans ce jury,

A la Docteure Jessica Amsellem Jager, Dr JaJ, merci de m'avoir proposé ce sujet, de m'avoir encadrée, merci pour ta présence, tes conseils, ta grande disponibilité et pour avoir passé des heures à relire mon anglais,

A toute l'équipe d'endocrinologie-pédiatrique, merci de m'avoir accueillie avec une grande bienveillance dans votre service et pour tout ce que vous m'avez appris,

A toute l'équipe de pédiatrie du CHU, merci pour l'enseignement, la formation et l'encadrement durant mon internat,

A mes co-internes de Promo, Marie-Hélène, Inès, Julie, Lise, Solène, rencontrées avant même le début de l'internat, grâce à des efforts intenses d'espionnage …, merci pour votre soutien, pour l'entraide, que ce soit concernant la thèse, les mémoires et le partage de potins !

A tous mes co-internes que j'ai eu la chance de rencontrer pendant mes stages, merci d'avoir formé de supers équipes,

A mes amies d'enfance et de médecine, Gabrielle, Lucie, Manon, Marine merci pour les conseils, les encouragements, et aussi de m'avoir changé les idées durant tout ce temps, qui ont fait des années d'études des souvenirs inoubliables,

A Roxane, La rencontre de cet internat, merci d'avoir toujours été là, soutenante, encourageante, motivante, en stage initialement, et rapidement en dehors de l'hôpital ! Aujourd'hui notre amitié ne se limite heureusement plus à la médecine, vous êtes avec Robin et Héloïse notre Equivalent-Famille d'Angers !

A ma famille, mes parents et mes sœurs, merci de m'avoir accompagnée dans ces longues études, de m'avoir encouragée alors que ce n'était pas tous les jours faciles, tout ce temps n'aura pas été vain : je vais être enfin docteure, et peut être même finir mes études avant toi Clau ?

A Paul, merci de me soutenir depuis le début et même avant, dans les hauts et dans les bas, d'avoir été de bon conseil pendant mes passages à vide, et encourageant dans mes regains d'ambition ! Merci pour m'avoir aidée dans ce travail en particulier, les soirées passées sur Excel pour trouver les meilleures formules, puis recommencer et encore recommencer… ,

Isaure, je ne suis pas sûre que tu lises un jour ce remerciement, il y a tant de chose plus faciles à lire pour toi, mais saches que le temps passé à travailler ma thèse alors que tu es à côté de moi est aujourd'hui terminé : tu as été ma plus grande motivation pour achever ce travail.

Liste des abréviations

AMH	Anti-müllerian hormone
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index ;
DXA	Dual-energy X-ray Absorptiometry
FM	Fat mass
FMI	Fat mass index
FSH	Follicle-stimulating hormone
HDL	High-density lipoprotein
Height Adjusted BMC Z-score	Height Z-score Adjusted Total Body Less Head Bones Mineral Content Z-score
Height Adjusted BMD Z-score	Height Z-score Adjusted Lumbar Spine Bones Mineral Density Z-score
IgF1	Insulin growth factor 1
LBMI	Lean body mass index
LH	Luteinizing hormone
OGTT	Oral glucose tolerance test
Ow/Ob	Overweight / obese
PAL	Alkalin phosphatase
PTH	Parathyoïd hormone
TSH	Thyroid-stimulating hormone

Plan

RESUME

Contexte : L'état de santé osseuse des enfants obèses est assez controversé, les études donnent des résultats contradictoires : ils semblent avoir une meilleure densité osseuse, mais un risque de fracture plus élevé.

Objectif : Nous avons décrit la minéralisation osseuse en évaluant le Z-score du CMO (concentration minérale osseuse) corps entier ajusté sur la taille, et le Z-score de la DMO (densité minérale osseuse) du rachis lombaire ajusté sur la taille chez des garçons en surpoids et obèses, et évalué les facteurs influençant ces paramètres.

Méthodes : Etude rétrospective monocentrique au CHU d'Angers, incluant 256 garçons obèses ou en surpoids âgés de 5 à 18 ans qui ont consulté pour explorer leur obésité. Ils ont bénéficié d'un examen physique, d'une absorptiométrie à rayons X double énergie pour la composition corporelle, d'un test d'HGPO pour l'insuline et au glucose et de dosages sanguins de l'AMH, de l'inhibine B, de la testostérone, de l'IgF1, des hormones thyroïdiennes, du bilan phosphocalcique (calcium, phosphore, PTH) et lipidique.

Résultats : Les Z-scores moyens du CMO corps entier ajusté sur la taille, de la DMO du rachis lombaire ajusté sur la taille étaient compris entre 0,3 et 1,1 selon la classe d'âge.

Nous avons pu montrer en analyse de régression multiple que l'index de masse maigre et le Z-score de l'IgF1 étaient positivement associés au Z-score du CMO, alors que le Z score de l'index de masse grasse n'avait pas d'effet. Les facteurs influençant positivement le z-score DMO étaient le Z-score de l'indice de masse maigre, et l'insulinémie à jeun, le Z score de masse grasse n'avait pas d'effet, et le non-HDL cholesterol était un facteur négatif.

Conclusion : Les garçons obèses ou en surpoids ont une minéralisation osseuse normale, en lien avec la masse maigre et les marqueurs d'insulinorésistance, mais pas avec la masse grasse. En cas d'excès de masse grasse non associée à une augmentation suffisante de la masse maigre, la minéralisation osseuse pourrait être insuffisante pour supporter l'excès de contrainte mécanique du à leur poids.

INTRODUCTION :

Childhood and adolescent obesity has been recognized as a major health issue as its prevalence has been worldwide increasing. The last report of the World Health Organization (WHO) (1) showed that about 800 000 children in the WHO European Region suffer from severe obesity. According to global Health Observatory data, 18% of youth aged 5-19 years-old worldwide were overweight or obese in 2016 (2). In 2015 in France, 17 % of the children aged from 6 to 17 were overweight (13%) or obese (4%) (3). Moreover it has been proved that childhood obesity persisting in adulthood greatly increases the risk of developing chronic diseases early in life (4). The most described complications are those affecting the cardiovascular system, metabolic, psychological, and also the musculoskeletal system, including bone mineralization. A recent meta-analysis reporting 27 studies and 5,958 children aged from 2 to 18 years old demonstrated that obese children have higher bone mineral density (BMD) and bone mineral content (BMC) compared to children with a normal weight (5). But, their results did not take into account the height and height of obese or overweight children is greater during childhood. In fact, studies have shown that obese children tend to be taller and to present an acceleration of pubertal and skeletal maturation compared to normal weight youth (6). This is why, the bones mineralization of obese children is difficult to apprehend. In young people with obesity, bone quality and structure result from the balanced effects of enhanced release of inflammatory and immunomodulatory cytokines (7) and mechanical overload. It has been reported that obese children have an increased risk of fracture compared to children with normal weight (8,9).

Growing evidence suggest that adiposity influences child's bone health. This divergent effect of obesity on bone health is partially explained by the confounding effect of poor metabolic health (10,11). Fat mass is important for the development of cortical and trabecular bone compartments (12,13). But, when fat accumulation reaches an excessive rate, it leads to

inflammation, oxidative stress, apoptosis and mitochondrial dysfunctions which are negative to bone development (14).

Many factors are involved in bone mineralization, and childhood and even adolescence are important periods for peak bone mass modulated by gonadic steroid, and several other factors: diet, physical activity, chronical disease. Metabolic status is already described as important for bone mineralization : fat accumulation is inversely correlated with bone quality in obese adult (15), but it has been little studied in large groups of children and adolescents.

As many factors are involved in mineralization, studies assessing bone health of obese children are contradictory. Therefore, we decided to study obese and overweight boy's mineralization status. We choose to include only obese male to free ourselves from the female hormonal particularities and their confounding factors (16), notably, the insulin resistance of puberty may be exaggerated in the setting of obesity, especially in girls (17,18). To assess bone mineralization, and according to the revised 2019 ISCD Pediatric Official Positions (19), DXA was the chosen method for assessing BMC and areal BMD, and the posterior-anterior lumbar spine (L1-L4, fast array) and total body less head (TBLH), are the preferred skeletal sites for performing BMC and areal BMD (20).

The main objective of this study was to describe height Z-score -adjusted lumbar spine BMD Z-score and height Z-score adjusted total body less head BMC Z-score in obese and overweight children according to age. The secondary objective was to describe factors that may influence bone mineralization in obese and overweight children.

METHODS

From 2010 to 2019, this cross-sectional study included obese male children and adolescent aged 5-18 years referred to the Paediatric Endocrinology Unit of Angers University hospital, for their overweight and obesity management. Exclusion criteria were syndromic, genetic, hypothalamic, or endocrine obesity, diabetes, and the use of any medication influencing weight gain. During the recruitment period, 493 boys aged 5-18 has been referred to our center. Seven were excluded because of syndromic obesity or obesity of hypothalamic origin, 40 were excluded because of the use of medications, 125 declined to participate to the program, and 85 were excluded because they haven't pass DXA, 256 patients were finally included.

The study received 3 different regulatory approvals. The first approval was for the program of care of obese subjects by our regional health agency (ARS des Pays de la Loire) on behalf of the national health system: within our specialized center for childhood obesity, we proposed to the referred obese children to participate in a 2-year obesity outpatient program. The program included an initial day hospitalization for clinical and paraclinical evaluation, lifestyle intervention, group sessions, and physicians', nurses', dieticians,' and psychologists' appointments, with meetings every 2 months for 2 years. The second approval was for the collection and storage of blood for research purpose (in the Center for biological research at the University Hospital) from the ethics committee of Angers University Hospital. The third approval was for the collection of medical data from the patients' medical records, by the ethics committee of Angers University Hospital.

All parents signed a first written consent (all the children gave their assent and those who were old enough to sign the consent form did so) to participate in the program, and a second written consent for collection and storage of blood samples. The collection of personal data from the medical records for research purposes requested only the non opposition from the children and their families, in agreement with French regulation ("loi Jardé").

Study design:

Anthropometric measurement was performed in all patients: height was measured using the same stature meter for all patients and weight (kg) was recorded with a digital scale. We calculated height Z-score with PediTools Electronic Growth Chart Calculators, application created by JH. Cohen in January 2012, and using the lambda-mu-sigma (LMS) parameterization method to calculate growth charts (21), waist and hip circumference (cm) were measured with a tape measure and waist-to-height ratio was calculated (22). Physical exam included pubertal staging according to Tanner (23) and blood pressure measurement (mmHg). Pubertal assessment (Tanner genital staging) of ow/ob boys was performed by 2 pediatric endocrinologists (R.C. and J.A.J.) with the use of an orchidometer. In the healthy nonoverweight nonobese boys, age and Tanner genital and pubic hair stages were collected. The involved physicians received hands-on training for the appropriate use of an orchidometer and the appropriate staging of pubic hair. We calculated BMI for each patient, with the formula: weight (kg) / height $(m)^2$, and it was express in Z-Score relative to age based on to CDC references (24,25). Overweight was defined as a BMI >+ 1 (corresponding to the 85th percentile) and <+ 2 Z-score, and obesity as a BMI >+ 2 Z-score. The FMI (fat mass index) (total body fat mass dividing by height squared) and LBMI (lean body mass index) (total lean mass dividing by height squared) was calculated for children over 8 years of age , and converted in Z-score calculated with fat and lean BMI reference curves in children and adolescents published by D.R.Weber and B.S Zemmel in 2013 (26).

Blood analyses: After a 12-h overnight fasting, an antecubital catheter was inserted in a peripheral vein for blood sampling. Blood samples were obtained for each patient and included 8am fasting levels of glucose, insulin, total cholesterol, HDL cholesterol, total triglyceride levels, calcium and phosphore, PAL, TSH, T4 and T3, PTH, IgF1, FSH and LH, Inhibin B, AMH

and testosterone. An OGTT was performed with the administration of 1.75 g glucose/kg body weight (maximal dose 75 g). Blood samples were drawn at −30, 0, 30, 60, 90, and 120 min for measurements of glucose, and insulin.

Among other models, euglycemic clamp and modified minimal model are considered to be gold standards. However, they are complex invasive tests, difficult to accept, and are not performed in routine practice (27, 28, 29), thus in order to estimate insulin resistance we used two techniques: fasting insulin, known as a reflection of insulin resistance when insulin > 15 µUI/mL, and a surrogate index (30,31) : the homeostasis model assessment of insulin resistance index (HOMA-IR) to evaluate and classify the patient. Lower HOMA-IR values indicate greater insulin sensitivity, whereas higher HOMA-IR values indicate lower insulin sensitivity (insulin resistance). Insulin resistance is defined as insulin score HOMAR – IR > 75°Per for age Per (32). HOMA-IR was calculated as average on two blood samples (−5 and 0 min) as [fasting glucose (mg/dl) × fasting insulin (µU/ml)/405].

Total cholesterol, HDL, low-density lipoprotein cholesterol, triglycerides and PAL were measured by commercially available kits (Advia Chemistry XPT, SIEMENS), thyroids' hormones were measured by immunochimiluminescence (CENTAUR SIEMENS), plasma glucose was measured with a Hitachi 917 analyzer (Roche-Diagnostics, Meylan, France). Plasma insulin was measured by radioimmunoassay (RIA) (Schering AG Cis Bio International, Gif sur Yvette, France), Inhibin B levels were measured by means of a solid-phase sandwich assay using Ansh Labs reagents (Webster, TX), AMH levels were measured by a solid-phase sandwich assay using Ansh Labs reagents (Webster, TX) , FSH and LH were measured by a time-resolved fluorometric assay using Delfia reagents (Perkin Elmer Life Sciences, Courtaboeuf, France), testosterone was measured by RIA, after a steroid extraction step, using Orion reagents (Cis Bio International, Gif sur Yvette, France), PTH (Immunochimiluminescence (Liaison XL,

Diasorin) and IgF1 were measured by immunoradiometric assay (BECKMAN COULTER, Fullerton, California).

Evaluation of Body composition :

It was investigated by dual-energy X-ray absorptiometry using a QDR 4500A densitometer (Hologic, Waltham, MA). Whole-body scans were performed, and body compartments were analyzed using software from Hologic (version V8.24a:3). To assess the effects of fat distribution, the body was divided into four areas: arms, legs, trunk, and head. The trunk region was bounded by a horizontal line below the chin, two vertical lines along the edges of the rib cage, and oblique lines through the hips; the leg region was all tissue below these oblique lines. The body composition was evaluated by the fat distribution, and was defined as trunk-to-leg fat-mass ratio calculated as the ratio of the amount of fat tissue in the trunk region to the amount of fat tissue in the leg region.

Evaluation of bone mineralization :

To assess BMD and estimate the measure of bone health, dual-energy X-Ray absorptiometry (DXA) is the most used method. We analyzed lumbar spine and Total Body Less Head BMC (gr) and areal BMD (g/cm²) and Z-score for BMD and BMC. We calculated for each patient the Z-Score, adjusted with height, age and black or non-black. Current guidelines recommend the use of height for age adjusted for age Z-score for the assessment of total body less head (TBLH) bone density (33).

In this article, we have chosen to name the Height Z-score Adjusted Total Body Less Head BMC Z-score as "Height Adjusted BMC Z-score" , and Height Z-score Adjusted Lumbar Spine areal BMD Z-score as "Height Adjusted BMD Z-score".

Statistical methods:

Continuous variables were expressed as mean ± SD or median (5th and 95th percentiles). Discrete variables were expressed as percent. The precision for age was at the day level. Kruskal–Wallis, Wilcoxon rank-sum tests, chi-squared, and Fisher exact tests were used for comparisons. Significance was defined as $P < .05$.

Regression analyses were performed to determine the best combination of predictors of Height Adjusted BMC Z-score and Height Adjusted BMD Z-score. First, simple regression analyses were performed, with clinical and biological variables as independent variables. Then, backward stepwise multiple regression analyses were performed using the variables ($P < 0.2$) from the simple regression analyses. Interactions between the variables were also included in the analyses. Any nonsignificant interaction was deleted. All regressions analyses were checked for multiple collinearity using Variance Inflexion Factors (all VIF < 3). We used SPSS Statistics v25 (IBM Corp., Armonk, NY) and GraphPad Prism 8 (GraphPad Software Inc.).

RESULTS

1. Descriptive results

Between January 2010 and January 2019, we included 256 male patients, aged from 5 to 18 years old. Fourteen (5,5%) of these 256 patients were overweight, and 242 (94,5%) were obese.

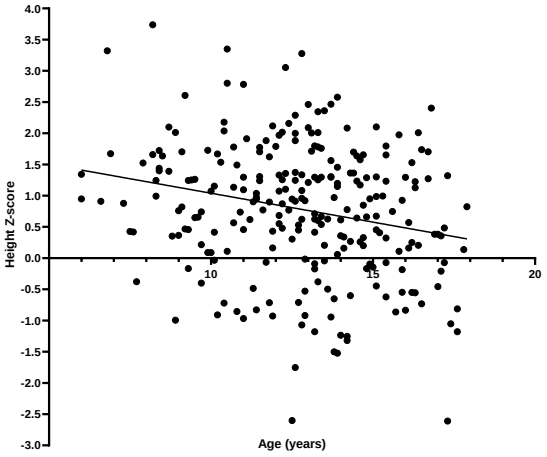
The clinical characteristics in ow/ob boys according to age group are reported in table 1. The height Z-score seems to be larger in young children, and decreases with age, to be close to average at 18 years (Figure 1), while the BMI Z-score seems to be rather stable (Figure 2). Height Adjusted BMC Z-score and Height Adjusted BMD Z-score are not different from the reference population (Z-score = 0). Body composition does not seem to change with age, the FMI Z-score may appear higher but the LBMI Z-score is rather stable. Among the 256 patients, 21 (i.e. 8%) had reported a history of fractures (≥1 fracture). The table 2 shows biological characteristics, as expected the insulin resistance appears to increase with age, either by evaluation with fasting insulin or with HOMA-IR score.

	<8 years	8-<10 years	10-<12 years	12-<14 years	14-<16 years	16-<18 years
N	10	31	47	86	51	31
Age (y.o.)	6,9 (±0,8)	9,1 (±0,5)	11,0 (±0,6)	12,9 (±0,6)	14,9 (±0,6)	16,8 (±0,6)
Height (m)	1,29 (±0,05)	1,42 (±0,05)	1,51 (±0,07)	1,62 (±0,08)	1,72 (±0,07)	1,76 (±0,08)
Height Z-Score	1,4 (±0,98)	1,16 (±0,92)	0,85 (±1,02)	0,82 (±1,1)	0,51 (±0,89)	0,22 (±1,11)
Tanner stage	1 (±0)	1 (±0)	1,3 (±0,7)	2,3 (±1,2)	3,6 (±1,1)	4,1 (±1,1)
BMI Z-score	2,6 (±0,34)	2,24 (±0,26)	2,20 (±0,3)	2,18 (±0,3)	2,36 (±0,35)	2,49 (±0,38)
FMI Z-score	NC	1,5- (±0,27)	1,66 (±0,26)	1,66 (±0,27)	1,75 (±0,3)	1,75 (±0,33)
LBMI Z-score	NC	1,14 (±0,73)	1,08 (±0,75)	1,12 (±0,66)	1,36 (±0,76)	1,29 (±1,05)
Height- adjusted BMC Z-score	0,5 (±1,2)	0,8 (±1,42)	1,1 (±1,7)	0,8 (±1,5)	0,7 (±1,7)	0,3 (±1,4)
Height adjusted BMD Z-score	0,5 (±0,91)	0,5 (±1,1)	0,7 (±1,1)	0,6 (±1,2)	0,4 (±1,2)	0,8 (±0,9)
Waist circumference	77,1 (±4,0)	85,6 (±12,1)	95,6 (±12,5)	99,1 (±13,0)	111,2 (±18,9)	111,9 (±14,5)
Hip circumfence	78,9 (±4,7)	85,8 (±13,9)	96,5 (±13,2)	101,7 (±15,5)	108,5 (±17,9)	117,5 (±14,3)
Waist to height ratio	0,59 (±0,03)	0,60 (±0,08)	0,63 (±0,07)	0,61 (±0,07)	0,64 (±0,1)	0,64 (±0,07)
Waist to Hip circumference ratio	0,98 (±0,05)	1,02 (±0,19)	1,01 (±0,17)	0,99 (±0,19)	1,07 (±0,35)	0,95 (±0,11)
% Total body FM	42,36 (±3,5)	42,17 (±4,2)	44,32 (±4,59)	42,84 (±4,98)	41,36 (±5,58)	39,52 (±5,24)
% trunck FM	39,41 (±4,4)	39,91 (±4,8)	42,99 (±4,86)	41,71 (±5,95)	40,23 (±6,18)	39,54 (±4,6)
ratio trunck FM / leg FM	0,84 (±0,05)	0,87 (±0,1)	0,92 (±0,08)	0,93 (±0,09)	0,94 (±0,11)	0,98 (±0,1)
fractures history N (%)	2 (20)	3 (9)	2 (4)	7 (8)	3 (5)	4 (12)

Table I : Clinical and body composition characteristics in overweight/obese according to age groups (Mean ± Standard deviation)

		<8 years	8-<10 years	10-<12 years	12-<14 years	14-<16 years	16-<18 years
N		10	31	47	86	51	31
Glucose fasting (g/L)		0,82 (±0,04)	0,85(±0,05)	0,87 (±0,08)	0,86 (±0,08)	0,88 (±0,14)	0,88 (±0,13)
Insulin fasting (µU/ml)		8,99 (±4,44)	11,89 (±6,4)	16,29(±10,27)	17,5 (±8,1)	21,94 (±13,2)	25,24 (±21,08)
OGTT	Glucose T60	1,10 (±0,22)	1,12 (±0,19)	1,1 (±0,23)	1,26 (±0,37)	1,10 (±0,22)	1,32 (±0,36)
	Glucose T120	1,0 (±0,15)	1,07 (±0,13)	1,12 (±0,18)	1,11 (±0,28)	1,00 (±0,15)	1,16 (±0,33)
	Insulin T60	68,4 (±70,8)	66,9 (±37,9)	83,1 (±56,8)	133 (±118,9)	68,4 (±70,8)	124,1 (±88,7)
	Insulin T120	37,3 (±23,64)	51,06 (±27,2)	79,6 (±66,93)	99,21(±98,98)	37,3(±23,64)	89,5 (±93,25)
HOMA-IR		1,8 (±0,91)	2,5 (±1,38)	3,5 (±2,28)	3,7 (±1,85)	4,77 (±3,3)	6,0 (±7,69)
Cholesterol total g/L		4,9 (±0,94)	4,53 (±1,76)	4,57 (±1,54)	4,43 (±1,65)	4,27 (±1,8)	4,59 (±1,56)
Cholesterol HDL(g/l)		0,89 (±0,47)	1,0 (±0,37)	0,99 (±0,41)	0,90 (±0,46)	0,79 (±0,38)	0,73 (±0,37)
Triglycerid (g/l)		0,88 (±0,48)	0,86 (±0,45)	0,95 (±0,41)	1,03 (±0,59)	1,20 (±0,65)	1,35 (±0,86)
Cholesterol LDL (g/L)		3,87 (±1,01)	3,37 (±1,68)	3,41 (±1,51)	3,34 (±1,48)	3,26 (±1,71)	3,62 (±1,46)
Calcium (mmol/)		2,35 (±0,09)	2,37 (±0,06)	2,35 (±0,09)	2,32 (±0,26)	2,34 (±0,07)	2,23 (±0,57)
phosphore (mmolL)		1,48 (±0,16)	1,43 (±0,14)	1,48 (±0,13)	1,48 (±0,2)	1,39 (±0,22)	1,34 (±0,28)
PAL (UI/L)		279 (±44,3)	242 (±80,5)	263 (±65,7)	254 (±88,6)	227,4(±90,34)	139 (±66,7)
PTH 1-84 pg/mL		30,15(±14,53)	21,71 (±5,09)	22,01 (±7,14)	25,29(±10,37)	31,44(±11,86)	27,91 (±11,86)
Testosterone (nmol/l)		0,27 (±0,23)	0,38 (±0,13)	1,22 (±2,09)	4,98 (±4,7)	9,04 (±5,2)	11,26 (±5,53)
FSH (UI/l)		0,57 (±0,39)	0,83 (±0,8)	1,51 (±1,21)	3,46 (±8,44)	3,72 (±3,98)	4,16 (±4,08)
LH (UI/l)		0,12 (±0,04)	0,21 (±0,23)	1,08 (±1,71)	2,07 (±1,95)	3,02 (±1,59)	3,79 (±1,57)
Inhibine B (pg/ml)		73,75(±49,02)	70,03(±31,96)	105,9 (±55,4)	145,4(±66,24)	138,5(±66,49)	129,8 (±59,95)
AMH (ng/ml)		108 (±62,13)	88,28 (±48,4)	69,44 (±46,6)	31,5 (±33,14)	17 (±27,21)	9,01 (±8,51)
TSH (µUI/L)		2,79 (±1,34)	2,49 (±1,08)	2,55 (±1,19)	3,09 (±4,96)	2,42 (±1,3)	2,73 (±1,27)
T4L (µmol/l)		14,94 (±2,17)	14,11 (±1,54)	13,46 (±2,06)	13,27 (±1,95)	13,69 (±2,42)	13,52 (±2,05)
T3L (µmol/L)		6,62 (±0,77)	5,54 (±1,81)	5,38 (±1,99)	5,73 (±1,37)	5,48 (±1,35)	5,69 (±0,73)
IGF1		156,1(±55,02)	209,1(±79,65)	197,6(±90,22)	335,8(±132,6)	364,9 (±97,3)	329,6 (±97,84)
IgF1 Z-score		-0,95 (±0,66)	-0,37 (±0,82)	-1,06 (±0,67)	-0,73 (±0,69)	-0,92 (±0,52)	-1,14 (±0,52)

Table II : Biological characteristics in overweight/obese according to age groups (Mean ± Standard deviation)



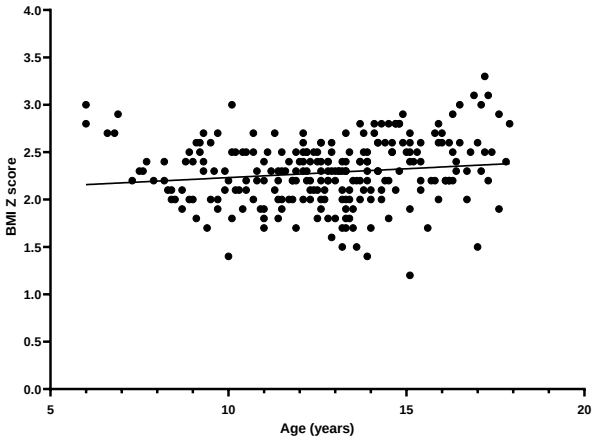


Figure 1 : Height Z-score according to age of boys ob/ow **; Figure 2** : BMI Z-score according to age of boys ob/ow.

2. Simple Regression Analyses

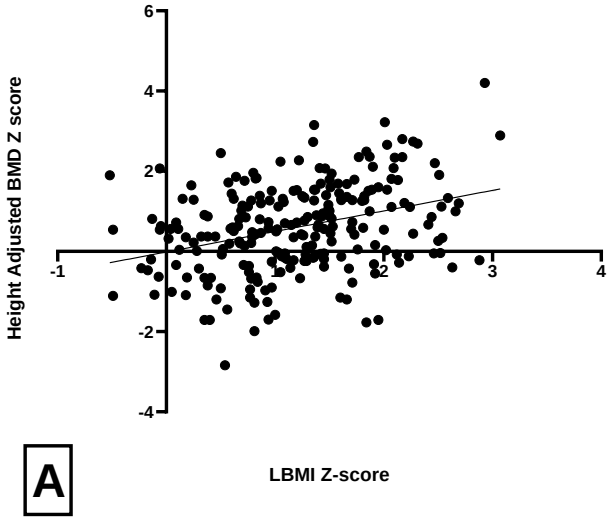
The simple regression of Height Adjusted BMC Z-score and Height Adjusted BMD Z-score are indicated in table III.

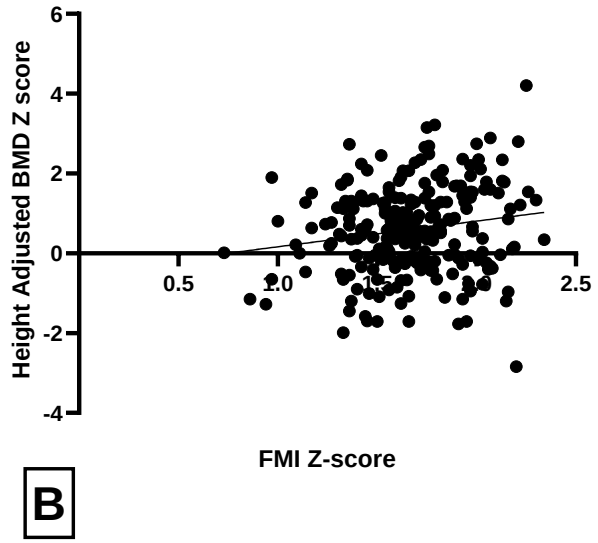
Figures 3 and 4 illustrate the impact of the LBMI Z-score, FMI Z-score or BMI Z-score on BMC and BMD respectively.

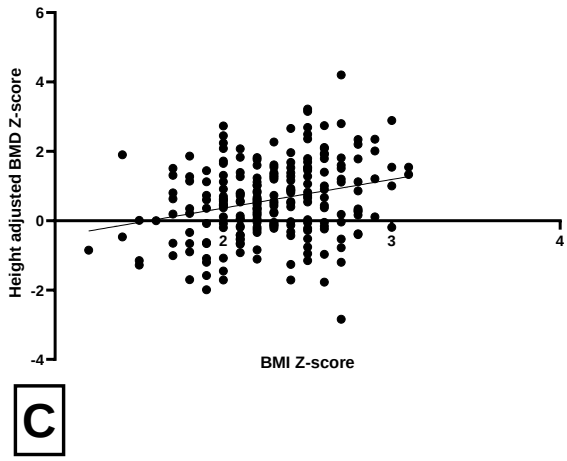
	Height adjusted BMC Z-score	p	Height adjusted BMD Z-score	p
Fracture history	-0,06	NS	-0,145	0,022
FMI Z-score	0,112	0,086	0,18	0,005
LBMI Z-score	0,316	< 0,001	0,344	< 0,001
IMC Z-score	0,181	0,04	0,281	0,002
Weight (kg)	0,205	0,001	0,178	0,005
Hip circumference	0,183	0,028	0,252	0,002
Waist size	0,162	NS	0,244	0,002
Waist size/ height	0,055	NS	0,266	0,001
Phosphore (mmol/L)	-0,024	NS	-0,22	0,024
Cholesterol (mmol/L)	-0,067	NS	-0,16	0,012
LDL cholesterol(mmol/L)	-0,059	NS	-0,0158	0,013
HOMA IR	0,092	0,149	0,153	0,018
Fasting insulin (µUI/mL)	0,98	NS	0,156	0,016
Ratio %FMtrunk %FMleg	0,05	NS	0,211	0,001
IgF1 Zscore	0,152	0,018	0,91	NS

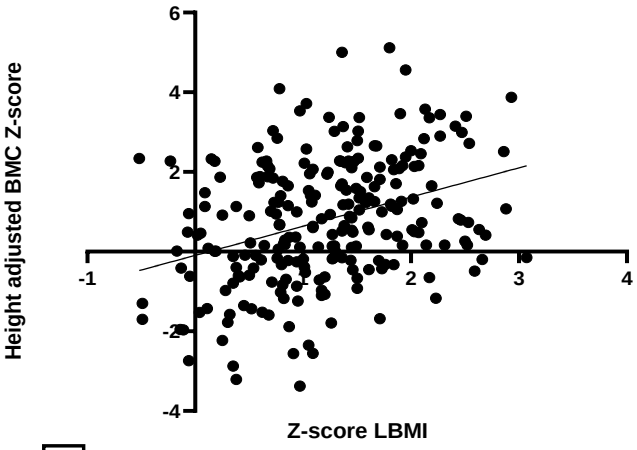
Table III : Simple correlation between clinical and biological caracteristics and Height Adjusted BMC Z-score and Height Adjusted BMD Z-score.

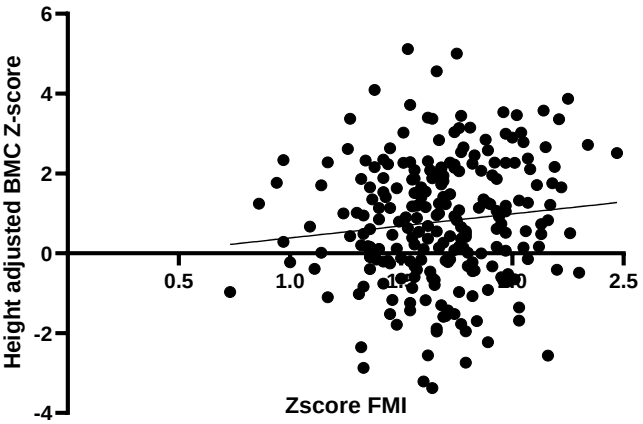
All correlation with p<0,20 were indicated











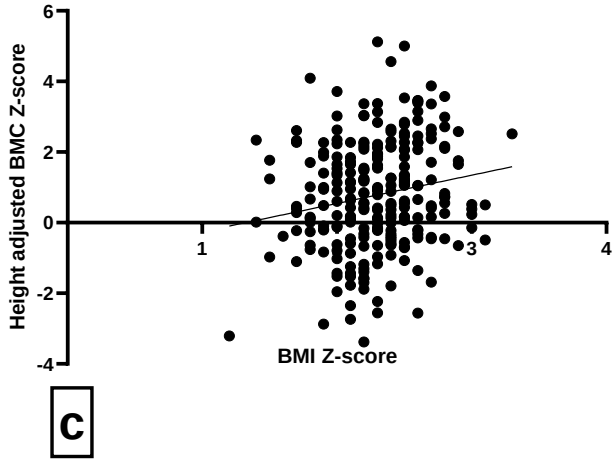


Figure 3 : Height Adjusted BMD Z-score according to LBMI Z-score (A), according to FMIZ-score (B) and according to BMI Z-score (C).

Figure 4 : Height Adjusted BMC Z-zscore according to LBMI Z-score (a), according to FMI Z-score (b) and according to BMI Z-score (c).

3. Multiple Regression Analyses

The best combination of predictors of Height Adjusted BMC Z-score level was LBMI Z-score and IgF1 Z-score (both positive predictor) and age (negative predictor) (multiple R = 0,135, p< 0,001) (table IV).

Concerning the Height Adjusted BMD Z-score level was LBMI Z-score and fasting insulin (both positive predictor) and non HDL cholesterol (negative predictor) (multiple R = 0,177, p< 0,001) (table V).

The FMI-Z-score was no longer significant in the multiple regression.

Multiple Regression for Height-Adjusted BMC Z-score		
Multiple R = 0,135, p<0,001		p
Age	-0,069 (±0,038)	0,07
FMI Z-score	0,265 (±0,381)	0,487
LBMI Z-score	0,616 (±0,138)	< 0,001
IgF1 Z-score	0,343 (±0,153)	0,026

Multiple Regression for Height-Adjusted BMD Z-score		
Multiple R = 0,177 , p<0,001		p
FMI Z-score	0,336 (±0,261)	0,199
LBMI Z-score	0,429 (±0,098)	< 0,001
Age	-0,033 (±0,027)	0,233
fasting insulin [2]	0,365 (±0,146)	0,013
Non HDL cholesterol [2]	-0,237 (±0,079)	0,003

Table IV and V : Backward stepwise multiple regression analyses Height Adjusted BMC Z-score and Height Adjusted BMD Z-score.

[2] : fasting insulin and Non HDL Cholesterol were log transformed to normalize their distribution.

β–coefficient (± standard deviation)

DISCUSSION ET CONCLUSION

Our principal aim was to describe bone mineral content and bone mineral density of overweight/obese boys aged between 5 to 18 years old. We observed that bone quality, assessed by the Height Adjusted BMC Z-score and Height Adjusted BMD Z-score, depends on lean mass, independently, of fat mass.

On one hand, overweight, by increasing mechanical stress, favors bone stimulation, promoting osteoblastic activation and bone formation, but on the other hand inhibits osteoclastogenesis and bone resorption (34). Our results complete this postulate : lean mass indeed promotes bone mineralization : fat mass, even if it increases mechanical stress, does not promote bone development. In fact, the bone quality evaluation factors studied are not different from the reference population, and therefore, if there is an increase in bone mineralization, it does not make it possible to fight against the additional mechanical stress imposed by the excess weight.

The increase in the number of fracture in obese is explained by this relative fragility of their bones in relation to the weight stress: the excess of total mass leads to an increase in bone mineralization, but without a skeletal response being sufficient to compensate the excess of mechanical stress to the body (35) Thus, excess fat mass seems to weaken the skeleton(36–38). More recent studies have shown that the incidence of osteoporosis and bone fractures is raised in obese individuals compared to individuals within normal weight (39). Finally, bone mineralization seems to depend on body composition and not on total mass alone (40) .

Concerning the role of metabolic ground: we studied the effect of insulin resistance on bone mineralization by looking at of 2 factors, fasting insulin and the HOMA-IR score, both of them reflect insulin resistance. These two scores showed the same results, i.e. responsible for an increase in the height adjusted BMD Z score.

The effect of hyperinsulinism has been studied mainly in adult population with type 2 diabetes, but little in children with hyperinsulinism without diabetes or carbohydrate intolerance (41). Data in the literature describing the effect of insulin on bone are therefore often linked to hyperglycemia biasing the results. Whether insulin resistance can affect bone is unclear (42). Studies in murine models suggest that hyperinsulinaemia and insulin resistance, in the absence of hyperglycaemia, may contribute to reduced bone turnover (43). Although reduced bone turnover may increase areal BMD, it may also contribute to bone fragility through increases in cortical porosity or other deficits in bone microarchitecture. Thus, our results are consistent with this hypothesis: increased insulin levels promote bone mineralization, within a certain limit, not reached by our young obese or overweight patients.

On the contrary, in our study the height adjusted BMD Z-score was negatively correlated with non-HDL cholesterol. The non-HDL cholesterol, including LDL cholesterol and triglycerides, has already been shown in premenopausal women to be associated with poorer bone mineralization (44–46). A recent study also found this association in prepubertal girls without BMI criteria (47). Studies in mice found that the reduction of HDL cholesterol was associated with the development of an inflammatory microenvironment, which alters the differentiation and function of osteoblasts (48). Thanks to our work, we are able to provide data in obese and overweight boys.

In our study we found that an increase in IgF1 Z-score increases the height adjusted BMD Z-score. The pathophysiology of the action of GH and IGF1 on bone is now well known: it increases bone formation, which is coupled with increased bone resorption and consequently, it is also known that in pathological situations (GH deficiency or excess) GH and IGF1 have effects on bone (50). A recent randomization study (49) evaluated the association between serum IGF-1 levels and estimated bone mineral density (eBMD) and fractures in adults, validated this data, and seems to confirm the role of IGF1 in the prevention of fractures,

probably and partially mediated by an improvement of bone mineralization. Out of pathological situation on the pathway of GH, in obese or overweight children, there were few data available. Our study brings new information, and implies the responsibility of IGF1 on the improvement of the height adjusted BMD Z-score in obese or overweight boys.

Interestingly, we did not find any evidence of involvement of puberty hormones on the BMC or BMD. In our analyses whether single or multiple regression, sex steroids or gonadal or pituitary hormones do not seem to have any direct involvement with bone mineralization, so the decrease in inhibin B or testosterone does not seem to be responsible for the relatively poor bone mineralization in obese or overweight boys.

Our study has several limitations. The patients of our sample presented a satisfactory growth, appearing to accelerate at the beginning, but a final height close to 0DS, so even if our study was a cross-sectional and not a longitudinal study, our study population seems representative of the reference population(6). As our study is retrospective we were not able to retrieve data on lifestyle, diet and physical activity, which is known to have an impact on bone mineralization (51). In order to be able to evaluate the diet and physical activity, calcium and phosphore were integrated, and aren't implicated in multiple analyses.

To our knowledge, this is the first study to evaluate so many factors in a such large group of obese or overweight boys, which allows us to understand their impact on bone mineralization, but also to describe the bone status of ow/ob boysOne of the strengths of our study was the calculation of Z-scores for each age- and/or height-dependent data, which permitted to obtain reliable results in a pediatric cohort.

This would require further prospective studies with dietary and physical activity data, and to evaluate if effects on mineralization are reversible: does weight loss or modification of bone composition allow an improvement of mineralization?

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EMERIAU TANDETNIK Fabienne

Etat de la santé osseuse des garçons obèses ou en surpoids, et description des facteurs influents

RÉSUMÉ

Contexte : L'état de santé osseuse des enfants obèses est assez controversé, les études donnent des résultats contradictoires : ils semblent avoir une meilleure densité osseuse, mais un risque de fracture plus élevé.

Objectif : Nous avons décrit la minéralisation osseuse en évaluant le Z-score du CMO (concentration minérale osseuse) corps entier ajusté sur la taille, et le Z-score de la DMO (densité minérale osseuse) du rachis lombaire ajusté sur la taille chez des garçons en surpoids et obèses, et évalué les facteurs influençant ces paramètres.

Méthodes : Etude rétrospective monocentrique au CHU d'Angers, incluant 256 garçons obèses ou en surpoids âgés de 5 à 18 ans qui ont consulté pour explorer leur obésité. Ils ont bénéficié d'un examen physique, d'une absorptiométrie à rayons X double énergie pour la composition corporelle, d'un test d'HGPO pour l'insuline et au glucose et de dosages sanguins de l'AMH, de l'inhibine B, de la testostérone, de l'IgF1, des hormones thyroïdiennes, du bilan phosphocalcique (calcium, phosphore, PTH) et lipidique.

Résultats : Les Z-scores moyens du CMO corps entier ajusté sur la taille, de la DMO du rachis lombaire ajusté sur la taille étaient compris entre 0,3 et 1,1 selon la classe d'âge.

Nous avons pu montrer en analyse de régression multiple que l'index de masse maigre et le Z-score de l'IgF1 étaient positivement associés au Z-score du CMO, alors que le Z score de l'index de masse grasse n'avait pas d'effet. Les facteurs influençant positivement le z-score DMO étaient le Z-score de l'indice de masse maigre, et l'insulinémie à jeun, le Z score de masse grasse n'avait pas d'effet, et le non-HDL cholesterol était un facteur négatif.

Conclusion : Les garçons obèses ou en surpoids ont une minéralisation osseuse normale, en lien avec la masse maigre et les marqueurs d'insulinorésistance, mais pas avec la masse grasse. En cas d'excès de masse grasse non associée à une augmentation suffisante de la masse maigre, la minéralisation osseuse pourrait être insuffisante pour supporter l'excès de contrainte mécanique du à leur poids.

Mots-clés : obèse, garçon, os, minéralisation, DXA

Bone Health of obese or overweight boys, description of influencing factors

ABSTRACT

Context : Bone health status of obese children is quite controversial, studies report conflicting results : they seem to have better bone density, but higher risk of fracture

Objective : We describe bone mineralization by assessing the height-adjusted whole-body BMC Z-score and the height-adjusted lumbar spine BMD Z-score in overweight and obese boys.

Methods : Single-center retrospective study at the University Hospital of Angers, including 256 obese or overweight boys aged 5 to 18 years referred to understand their obesity. They received a physical examination, dual-energy X-ray absorptiometry for body composition, OGTT test for insulin and glucose, and assays for AMH, inhibin B, testosterone, IgF1, thyroid hormones, phosphocalcic (calcium, phosphorus, PTH) and lipid balance.

Results: The mean Z-scores of height-adjusted BMC and height-adjusted lumbar spine BMD ranged from 0.3 to 1.1 depending on age class.

We were able to show in multiple regression analysis that the lean mass index and IgF1 Z-score were positively associated with the BMC Z-score, whereas the fat mass index Z-score had no effect. Factors positively influencing BMD z-score were lean mass index z-score, and fasting insulin level, fat mass z-score had no effect, and non-HDL cholesterol was a negative factor.

Conclusion: Obese or overweight boys have normal bone mineralization, related to lean body mass and markers of insulin resistance, but not to fat mass. In case of excess fat mass not associated with a sufficient increase in lean mass, bone mineralization could be insufficient to support the excess mechanical stress due to their weight.

Keywords : obese, males, bone, mineralization, DXA

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