



Bari,  
7-10 novembre 2013

Down ed Endocrinopatie

OBESITA'

**Dr. Pietro Lanzetta**

ASL SA



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## EZIOPATOGENESI DELLA SINDROME DI DOWN

- Frequenza: 1: 700 nati vivi
- Correlazione con età materna avanzata
- Nella maggior parte dei casi si ha aborto spontaneo
  
- CAUSE:
  - Trisomia 21 libera (90 % dei casi).
  - Anomalia strutturale (traslocazione robertsoniana: 4 % dei casi).
  - 50 % dei casi causata da uno sbilanciamento di una traslocazione parentale bilanciata.
  - 50 % dei casi: “de novo”.
  - Mosaicismo cromosomico (6 % dei casi).
  - Trisomia parziale della parte distale del braccio lungo del cromosoma 21 (zona critica: 21q22) ⇒ rari casi.
  
- Nelle forme omogenee (trisomia libera) si ha una non disgiunzione meiotica (l divisione), quasi sempre nella gametogenesi materna.
- Nelle forme a mosaico la non disgiunzione si verifica nelle prime divisioni cellulari dello zigote.



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## QUADRO CLINICO

- facies caratteristica con microbrachicefalia, collo corto, orecchie piccole e a basso impianto.
- ritardo mentale.
- ipotonia muscolare diffusa
- brachidattilia
- cardiopatia congenita
- anomalie renali congenite
- anomalie gastrointestinali congenite
- aumentata suscettibilità a patologie autoimmuni ed ematologiche (LLA).
- associazione con endocrinopatie (tiroidee, diabete mellito, obesità ecc.)



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## OBESITA' E SINDROME DI DOWN

L'obesità è l'endocrinopatia più frequente nelle persone Down.

L'aumento di peso diventa significativo a partire dalla tarda infanzia.

Solo il 10-15 % dei soggetti con sindrome di Down è normopeso.

Circa il 30-35% dei soggetti con sindrome di Down è in sovrappeso.

Circa il 50 % dei soggetti con sindrome di Down è francamente obeso.



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- Diagnosi prenatale:
- Alfafetoproteina
- Tri-test (estriolo non coniugato, gonadotropina corionica umana, alfafetoproteina)
- Ecografia
- Amniocentesi



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# • Ecografia

- Iposomia fetale
- Ispessimento plica cutanea del collo
- Intestino 1      Intestino 2
- Valvole cardiache



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## Summa

- L'iposomia determina una sindrome insulino-resistenza nella madre.
- L'ispessimento della plica del collo è caratteristica del tessuto adiposo ipertrofico
- Predisposizione alla insulino resistenza congenita con addome batraciano e tendenzialmente steatosico
- Calcificazioni fetali ed alterazioni valvolari





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- La sindrome di down comprende una molteplicità di patologie tra cui l'obesità, la cui eziopatogenesi appare
- misconosciuta.
- Una prima ipotesi potrebbe essere inquadrata nell'obesità ipotalamica come la Laurence-Moon-Biedl (caratteristiche simili: deficit mentale, ipogonadismo ed obesità) senza lesioni ipotalamiche con iperinsulinismo marcato ed incremento della massa del tessuto adiposo ed in particolare all'ipertrofia e non all'iperplasia degli adipociti.



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- L'ipotesi più intrigante riguarda la mutazione parziale o totale nel gene del recettore della leptina
- Il cui gene si rinviene sul cromosoma 7 (identico alla mutazione della sindrome di Laurence ed in asse multiplo del cromosoma 21
- (crossing over alla meiosi)



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Inoltre, i disordini metabolici(iperinsulinismo,sindrome metabolici,nash)derivano dall'alterazione del percorso di segnale ipotalamico leptina-melacortina con diretta ripercussione sulle gonadi,rene ,placenta,tiroide,duodeno,pancreas.

- La perdita recettoriale (MC4R) determina minor numero di T-linfociti CD4 e ridotta capacità proliferativa.
- Vitamina D



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# Obesità

- Il soggetto obeso è ad alto rischio per il deficit di vit.D
- L'obesità di per sé determina un deficit di vit.D attraverso vari meccanismi tra i quali il maggior sequestro nell'ambito del tessuto adiposo con conseguente ridotta biodisponibilità.
- L'aumento del peso corporeo può determinare un'ablazione parziale del 12°esone del cromosoma 12q del gene VDR, espressione (in parte) di causa genetica dell'obesità. La riacquisizione di abitudini comportamentali costituisce un beneficio aggiuntivo alla ristabilizzazione parziale del 12°esone; rimane da chiarire se l'entità dell'ipovitaminosi sia correlabile con la composizione corporea, la massa ossea, l'età e la razza.



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## Stile di Vita

- Sedentarietà
- Alimentazione:
  - Dieta ricca e complessa a base di carboidrati, glucidi complessi e proteine animali, bassi apporti di leucina e glutamina.
  - L'aminoacido leucina può attivare l'enzima mTOR che fa diminuire l'appetito.
  - La glutamina può stimolare il GLP-1 che invia un segnale di sazietà quando nell'intestino c'è un eccesso di zuccheri.
  - Nel nostro caso vi è inoltre una iperstimolazione dei PPAR-gamma che induce ad aumentare l'immagazzinamento di lipidi, ma determina iperfagia.



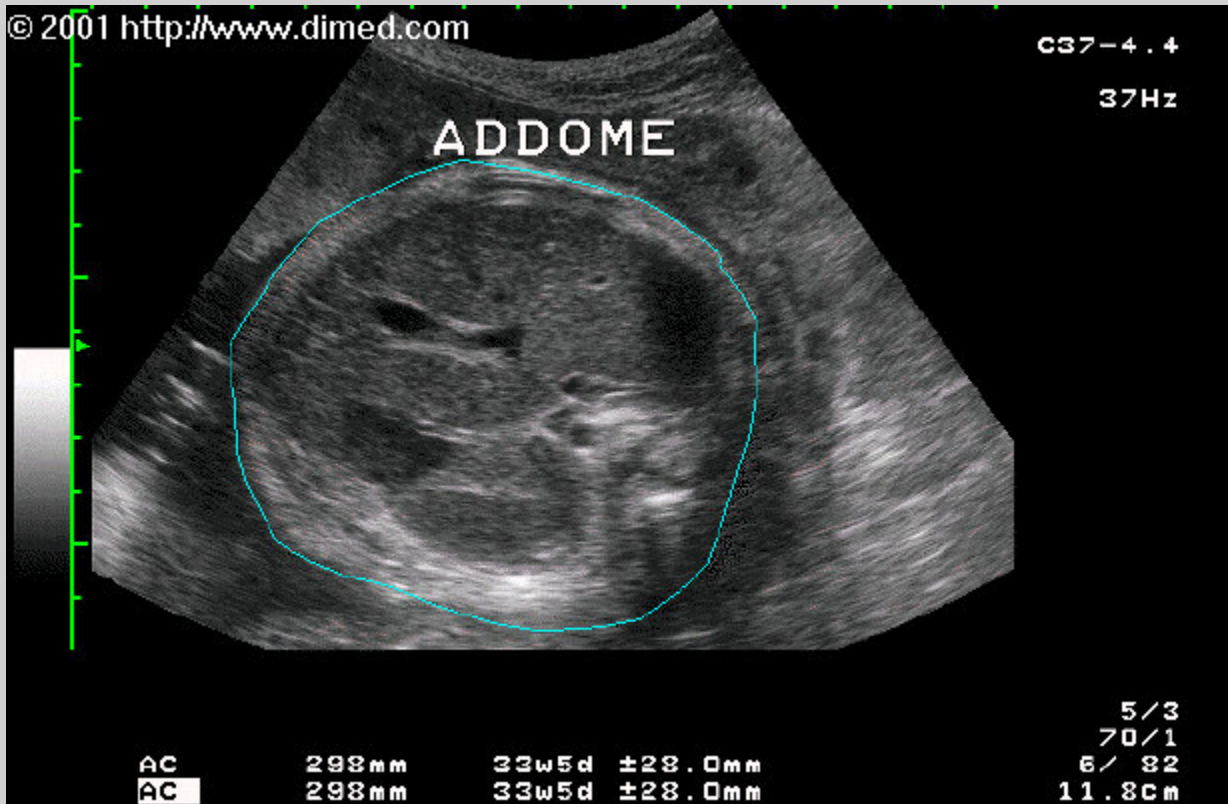
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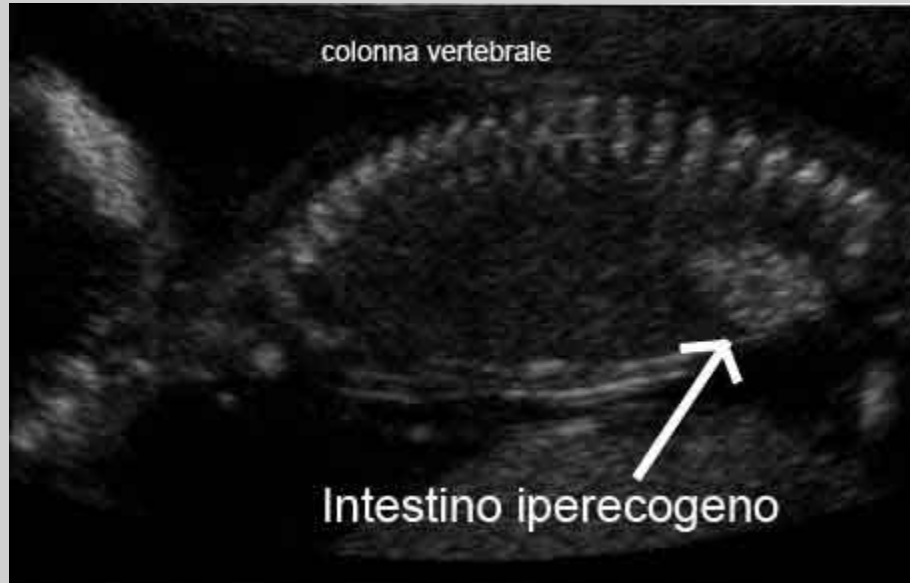


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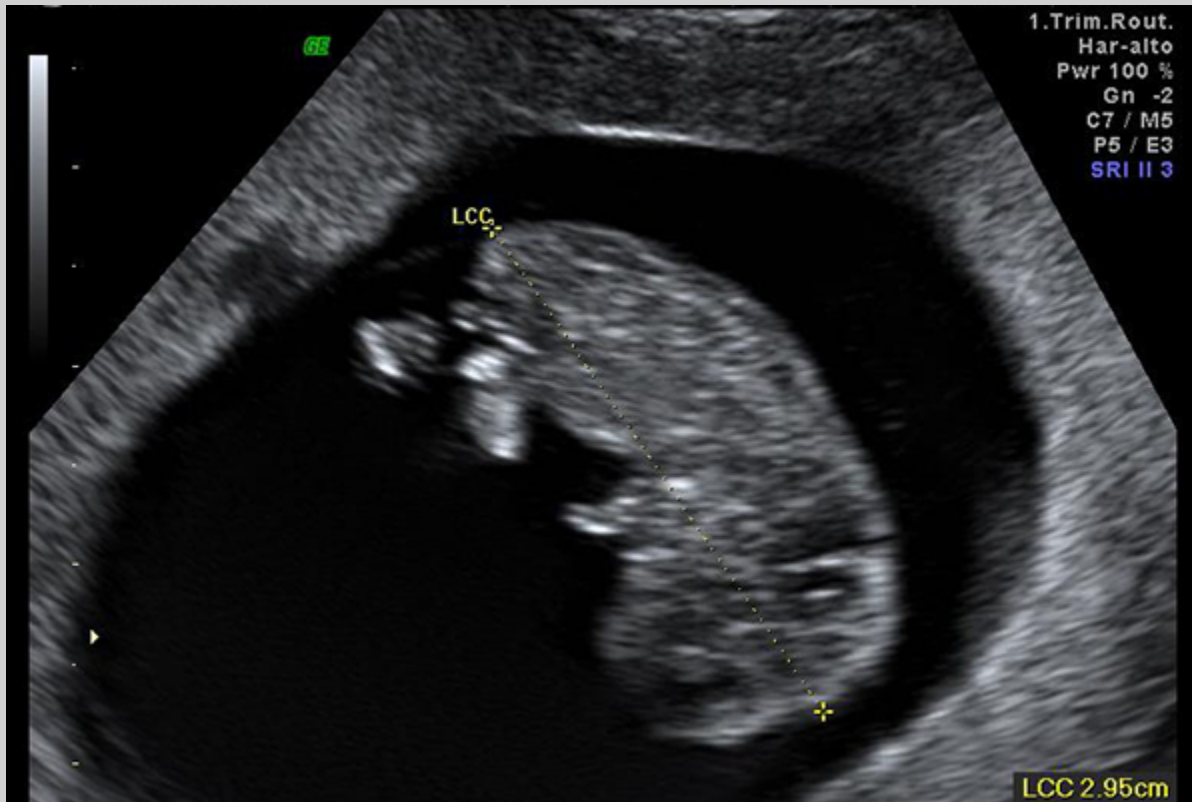


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**Fig. 1: Feto a 12 + 4 sett. Visualizzazione NT e NB**



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- [Exerc Sport Sci Rev.](#) 2013 Jul;41(3):138-47. doi: 10.1097/JES.0b013e318292f408.
- **Reduced work capacity in individuals with down syndrome: a consequence of autonomic dysfunction?**
- [Fernhall B](#), [Mendonca GV](#), [Baynard T](#).
- **Source**
- 1Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL 60612, USA. fernhall@uic.edu
- **Abstract**
- Low work capacity and  $\dot{V}O_2$ peak commonly are described phenomena in Down syndrome. This is accompanied by chronotropic incompetence and a high incidence of obesity. Although many causes of low work capacity in Down syndrome have been proposed, little scientific support exists. Our working hypothesis is that autonomic dysfunction is the major contributor to the low levels of work capacity in this population.



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- Our findings of unfavorable lipid profiles in young, prepubertal, nonobese children with DS are significant in light of recent epidemiological studies showing increased mortality from ischemic heart disease and CVD in persons with DS. It will be important to conduct long-term surveillance of children with DS to determine whether these differences in lipid profile translate into increased morbidity and mortality from CVD. A scientific statement from the American Heart Association presented guidelines for more aggressive cardiovascular risk management in pediatric patients with conditions associated with increased risk of CVD.<sup>31</sup> DS is not included among these conditions. If our findings are confirmed by longitudinal data linking lipid profile with CVD morbidity and mortality among people with DS, they would suggest that children with DS also constitute a group at high risk for dyslipidemia and ischemic heart disease and should be considered for early routine screening and treatment, similar to other children at higher risk. As with other populations, treatment should start with therapeutic lifestyle changes and additional pharmacology therapy as needed. Children with DS constitute a large population at high risk for obesity, diabetes and, based on our data, a less favorable lipid profile, which is an additional risk factor for adult CVD. With the increased life expectancy of individuals with DS and the increasing importance of adult chronic disease in this population, optimal CVD prevention is necessary in children and adults with DS.



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- [Nutr Hosp.](#) 2011 Sep-Oct;26(5):1059-66. doi: 10.1590/S0212-16112011000500021.

- **Nutritional status of intellectual disabled persons with Down syndrome.**

- [Soler Marín A](#), [Xandri Graupera JM](#).

- **Source**

- Departamento de Tecnología de la Alimentación y Nutrición, Universidad Católica San Antonio, and Unidad de Nutrición y Dietética, Hospital Universitario Virgen de la Arrixaca de Murcia, Murcia, Spain.

- **Abstract**

- **BACKGROUND:**

- To evaluate the nutritional status in young adults with Down syndrome (DS).

- **METHODS:**

- 38 persons, 15 (39.5%) women and 23 (60.5%) men (age range 16-38 years) with DS. Body composition was analyzed from anthropometric parameters according to standard protocols, levels of physical activity and nutrient intake was determined using validated questionnaires: a 72 h recall and consumption food frequency questionnaire (recorded by the tutors of the participants). The following biochemical parameters were estimated: blood lipids profile (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides), glucose, uric acid, proteins (ferritin and transferrin), minerals (Fe, Zn, Cu, Mg and Se) and vitamins (B12, B9, E, C and  $\beta$ -carotene). The data were statistically analysed with Student t tests.

- **RESULTS:**

- From the 38 participants, 36.8% were overweight (BMI: 25-29.9 kg/m<sup>2</sup>) and 36.8% were obese (BMI $\geq$ 30 kg/m<sup>2</sup>). The BMI differed from women to men (P<0.001) (29.1 $\pm$ 4.3 and 27.9 $\pm$ 4.6 kg/m<sup>2</sup>, respectively). The average values of the biochemical parameters, except for uric acid, both in women and men were within normal ranges. The average energy intake was 1,909 $\pm$ 337 and 2,260 $\pm$ 284 kcal/day for women and men, respectively. The contribution of proteins to total caloric intake was 18.8 and 16.3% for women and men, respectively, while carbohydrates contributed 43.3 and 45.6%, and lipids 37.9 and 38.1%. All participants were sedentary.

- **CONCLUSION:**

- In this group presented a high prevalence of overweight and obesity. Further research is required in the development and evaluation of appropriate intervention programs to improve their nutritional status and quality of life.

- PMID: 22072353 [PubMed - indexed for MEDLINE] Free full text





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- [Pediatrics](#). 2012 Dec;130(6):e1520-6. doi: 10.1542/peds.2012-0886. Epub 2012 Nov 12.
- **Prevalence of overweight in Dutch children with Down syndrome.**
- [van Gameren-Oosterom HB](#), [van Dommelen P](#), [Schönbeck Y](#), [Oudesluys-Murphy AM](#), [van Wouwe JP](#), [Buitendijk SE](#).
- **Source**
- Departments of Child Health, Netherlands Organization for Applied Scientific Research, TNO, Leiden, Netherlands. helma.vangameren@tno.nl
- **Abstract**
- **OBJECTIVE:**
- Prevalence of overweight in children is increasing, causing various health problems. This study aims to establish growth references for weight and to assess the prevalence rates of overweight and obesity in a nationwide sample of Dutch children with Down syndrome (DS), taking into account the influence of comorbidity.
- **METHODS:**
- In 2009, longitudinal growth data from Dutch children with trisomy 21 who were born after 1982 were retrospectively collected from medical records of 25 Dutch regional specialized DS centers. "Healthy" was defined as not having concomitant disorders or having only a mild congenital heart defect. Weight and BMI references were calculated by using the LMS method, and prevalence rates of overweight and obesity by using cutoff values for BMI as defined by the International Obesity Task Force. Differences in prevalence rates were tested by multilevel logistic regression analyses to adjust for gender and age.
- **RESULTS:**
- Growth data of 1596 children with DS were analyzed. Compared with the general Dutch population, healthy children with DS were more often overweight (25.5% vs 13.3% in boys, and 32.0% vs 14.9% in girls) and obese (4.2% vs 1.8%, and 5.1% vs 2.2%, respectively). Prevalence rates of overweight between DS children with or without concomitant disorders did not vary significantly.
- **CONCLUSIONS:**
- Dutch children with DS have alarmingly high prevalence rates of overweight and obesity during childhood and adolescence. Health care professionals should be aware of the risk of overweight and obesity in children with DS to prevent complications.



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- [Res Dev Disabil.](#) 2011 Sep-Oct;32(5):1685-93. doi: 10.1016/j.ridd.2011.02.023. Epub 2011 Mar 24.
- **Fat and lean masses in youths with Down syndrome: gender differences.**
- [González-Agüero A](#), [Ara I](#), [Moreno LA](#), [Vicente-Rodríguez G](#), [Casajús JA](#).
- **Source**
- GENUD (Growth, Exercise, NUtrition and Development) Research Group, Faculty of Health and Sport Sciences, Huesca, University of Zaragoza, Spain. alexgonz@unizar.es
- **Abstract**
- The present study aimed at comparing fat and lean masses between children and adolescents with and without Down syndrome (DS) and evaluating the presence of sexual dimorphism. Total and regional fat and lean masses were assessed by dual energy X-ray absorptiometry (DXA) and the percentage of body fat (%BF) by air-displacement plethysmography (ADP) in 31 participants with DS and 32 controls. Waist circumference (WC) was also measured. Analysis of covariance and the Student's t-test were used to compare variables between groups and between sexes within the same group. There were no significant differences in %BF, WC or body mass index (BMI) between groups. Females with DS showed higher fat and lean masses in the trunk, and lower fat and lean masses in the lower limbs compared with females without DS (all  $p \leq 0.05$ ). Males with DS showed higher fat masses in the whole body and upper limbs, and lower lean masses in the whole body and lower limbs compared with males without DS (all  $p \leq 0.05$ ). Females in both groups showed higher levels of fat, and lower levels of lean than did their respective males (all  $p \leq 0.05$ ). Youths with DS showed higher fat and lower lean than their non-DS peers. The increased truncal fat in females with DS might indicate a higher risk of metabolic syndrome in this group. Sexual dimorphism in youths with and without DS was very similar. BMI, WC and %BF were not effective indicators of increased risk in youths with DS.



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- [BMC Endocr Disord.](#) 2012 Oct 15;12:22. doi: 10.1186/1472-6823-12-22.
- **Leptin, insulin and thyroid hormones in a cohort of Egyptian obese Down syndrome children: a comparative study.**
- [Yahia S](#), [El-Farahaty RM](#), [El-Hawary AK](#), [El-Hussiny MA](#), [Abdel-Maseih H](#), [El-Dahtory F](#), [El-Gilany AH](#).
- **Source**
- Department of Pediatrics, Faculty of Medicine, Mansoura University Children Hospital, Mansoura, Egypt.  
amany.hawary.hawary10@gmail.com.
- **Abstract**
- **BACKGROUND:**
- Obesity is a major worldwide health problem. It is commonly observed in Down syndrome individuals than in the general population. The reason for increased risk of obesity in DS is unclear. The current study was designed to clarify differences in some obesity-related hormones in a group of prepubertal Down syndrome children.
- **METHODS:**
- Thirty six Egyptian children with Down syndrome were enrolled in this study, divided according to their body mass index (BMI) into 23 obese and 13 non obese. Another group of 43 non Down children were recruited, they were divided according to their BMI into 20 patients having simple obesity and 23 non obese, as control groups. Fasting blood samples were collected for estimation of fasting blood glucose (FBG), insulin, leptin, free thyroxin (FT4), thyroid stimulating hormones (TSH) and creatine kinase (CK). Insulin resistance was assessed by Homeostasis Model Assessment method (HOMA-IR). The ratio of leptin to BMI (LEP/BMI) was used as an index of leptin resistance.
- **RESULTS:**
- Median values of FBG, insulin, and HOMA-IR were significantly higher in Down versus non Down groups, while median values of leptin and leptin resistance were non-significantly different among Down versus non Down groups. Median TSH values were non-significantly different between obese Down and obese non Down. Although the median values of TSH and FT4 were within normal range in Down groups, four cases of subclinical hypothyroidism were encountered. Leptin levels were correlated with insulin and IR but not with TSH in Down groups.
- **CONCLUSION:**
- Increased circulating leptin, a marker of leptin resistance in obese children with Down syndrome seems to be similar to that in children with simple obesity. Elevated FBG and insulin in obese Down children highlights the presence of early IR. Associated myopathy evidenced by mildly elevated CK levels could be an added factor for obesity in such group of patients.



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- [Nutr Hosp.](#) 2013 Jul-Aug;28(4):1348-51. doi: 10.3305/nh.2013.28.4.6566.
- **Are poor physical fitness and obesity two features of the adolescent with Down syndrome?**
- [Izquierdo-Gomez R](#), [Martínez-Gómez D](#), [Tejero-Gonzalez CM](#), [Cabanas-Sánchez V](#), [Ruiz Ruiz J](#), [Veiga ÓL](#).
- **Source**
- Department of Physical Education, Sport and Human Movement, Autonomous University of Madrid, Madrid, Spain.
- **Abstract**
- in [English](#), [Spanish](#) Introducción: La obesidad es considerada una característica de los jóvenes con SD, sin embargo se desconoce si la “baja condición física” también lo es. Objetivo: Comparar los niveles de obesidad y condición física en adolescentes con y sin SD. Métodos: Participaron 17 adolescentes (5 niñas) con SD de 12 a 18 años y un grupo control de 94 (45 niñas) adolescentes sin SD de 12-16 años de edad. La batería de condición física ALPHA relacionada con la salud para niños y adolescentes fue seleccionada para evaluar la obesidad y la condición física en ambos grupos. Resultados: No se encontraron diferencias en los niveles de obesidad entre grupos ( $P > 0,27$ ). Los adolescentes con SD tuvieron niveles más bajos de condición física en todos los test en comparación con los adolescentes sin SD ( $P < 0,001$ ). Conclusión: Los adolescentes con SD tienen niveles similares de obesidad y menores de condición física que sus compañeros sin SD.
- **INTRODUCTION:**
- "Obesity" is considered a feature of youth with DS but whether "low physical fitness" is also a feature is unknown.
- **OBJECTIVE:**
- The aim of this case-control study was to compare the levels of fatness and fitness in adolescents with and without DS.
- **METHODS:**
- Participants included 17 (5 girls) adolescents with DS aged 12-18 years and a control group of 94 (45 girls) adolescents without DS aged 12-16 years. The ALPHA health-related fitness test battery for children and adolescents was selected to assess fatness and fitness in both groups.
- **RESULTS:**
- There were no differences in levels of fatness between groups (all  $P > 0.27$ ). Adolescents with DS had lower levels of fitness in all the tests than adolescents without DS (all  $P < 0.001$ ).
- **CONCLUSION:**
- Adolescents with DS have similar levels of fatness and lower levels of fitness than their peers without DS.



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## FATTORI PREDISPONENTI E CAUSE DI AUMENTO PONDERALE NELLA S. DI DOWN

Alimentazione “scorretta” per quantità e qualità.

Ridotta attività fisica e sedentarietà:      ipotonia e difficoltà neuro-motorie  
   patologie organiche associate  
   scarsa autonomia personale

Familiarità per obesità e/o diabete mellito

Disfunzione tiroidea clinica o subclinica

Difficoltà di socializzazione

Problemi psicopatologici e tendenza alla depressione (20-30 % dei casi)





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## TRATTAMENTO

- L'approccio deve essere "precoce" (prima e seconda infanzia).
- Interventi comportamentali: educazione familiare nella gestione "alimentare" della persona Down.
  - miglioramento del tono e delle abilità motorie (psicomotricità, fisioterapia).
  - aumento della attività motoria e fisica (sport).
- Trattamento dei fattori predisponenti: IGT, IFG, diabete mellito, ipotiroidismo.
- Psicoterapia di sostegno laddove indicato.



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## DISLIPIDEMIA E S. DI DOWN

- Bambini con s. di Down presentano livelli più elevati di colesterolemia totale, LDL-colesterolo e trigliceridi e livelli più bassi di HDL rispetto a soggetti di controllo di pari età.
- Il dato restava significativo anche se corretto per BMI, età e sesso.
- Adelekan et al. Pediatrics vol 129 N.6 June 2012.