



ΛΙΠΟΔΥΣΤΡΟΦΪΕΣ ΚΑΙ ΔΙΑΒΉΤΗΣ

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Πανεπιστημιακό Γ.Ν "ΑΤΤΙΚΟΝ"



Δήλωση σύγκρουσης συμφερόντων

- Η ομιλία αντανακλά τις απόψεις του ομιλητή
- Η Βάια Λαμπαδιάρη έχει λάβει τιμητικές αμοιβές (honoraria) για διαλέξεις σε συνέδρια, επιστημονικές ημερίδες/εκδηλώσεις και συμβουλευτική από τις εταιρίες: Sanofi, Novartis, NovoNordisk, MSD, Boehringer, Eli-Lilly, Vianex, Elpen, Amgen, Boehringer,

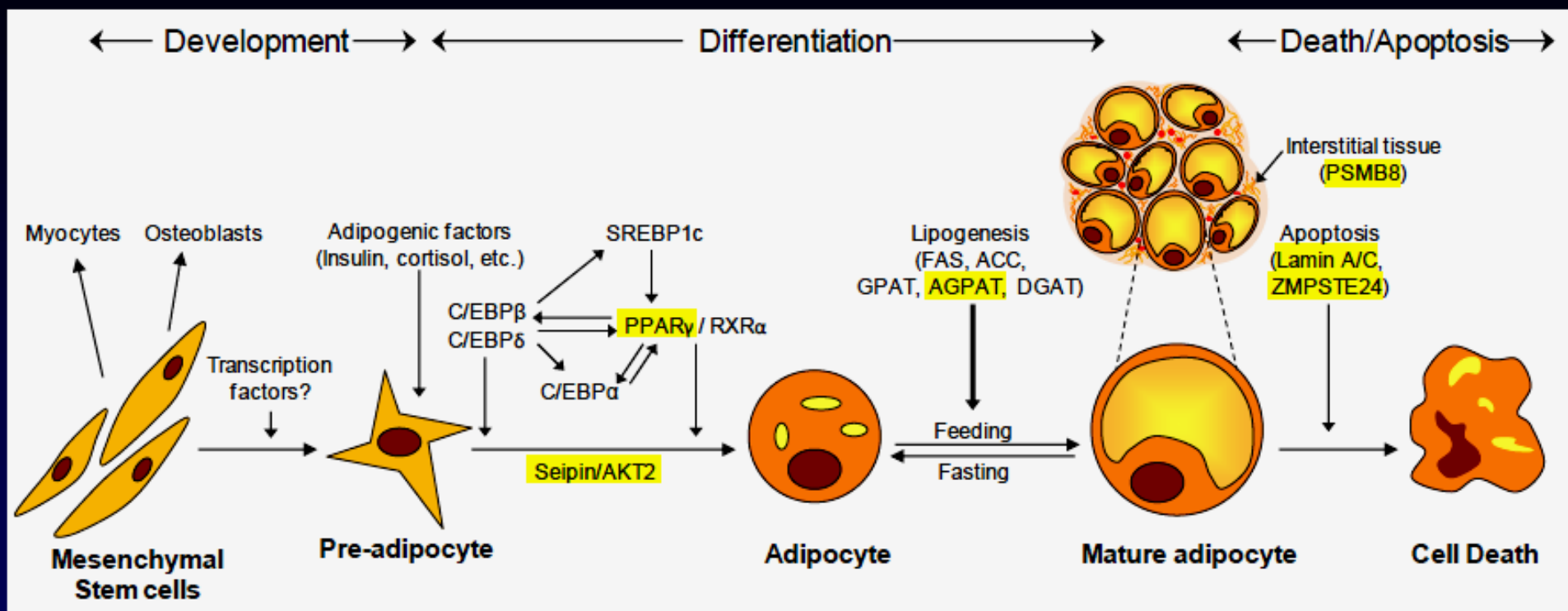
Λιποδυστροφίες

Οι **λιποδυστροφίες**, είναι κλινικά ετερογενείς, επίκτητες ή κληρονομικές διαταραχές που χαρακτηρίζονται από την επιλεκτική απώλεια λιπώδους ιστού.

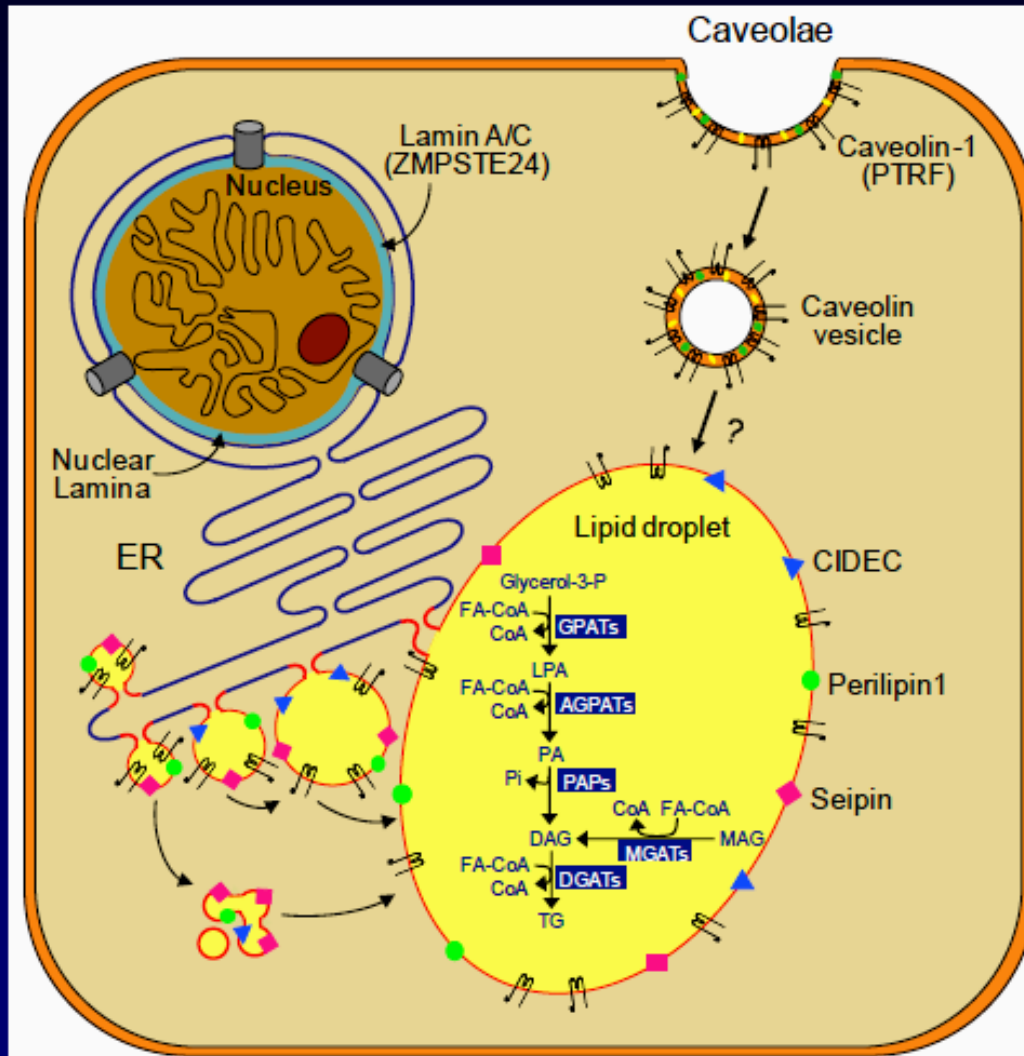
Οι προσβεβλημένοι ασθενείς έχουν αντίσταση στην ινσουλίνη και τις επιπλοκές της, όπως το σακχαρώδη διαβήτη, τη δυσλιπιδαιμία, την ηπατική στεάτωση και τη μελανίζουσα ακάνθωση, αυξημένο καρδιαγγειακό κίνδυνο, επίπτωση καρκίνου και πρόωρο θάνατο.

Λιποδυστροφίες:

Διαταραχές στην ανάπτυξη, τη διαφοροποίηση και το θάνατο του λιπώδους ιστού



Σχηματισμός του σταγονιδίου λιπών στα λιποκύτταρα και γονίδια λιποδυστροφίας



Fats and Metabolites in Muscle

	Change in Lipodystrophy
Intramyocellular lipid	↑
Triglyceride (TG)	↑ →
Diacylglycerol (DAG)	↑ → *
Long Chain Fatty Acyl CoA (LCFA-CoA)	↑
Ceramide	↑ →
Acylcarnatines	↑
CO ₂	↓

* Degree of fatty acid (FA) saturation altered in insulin-resistant conditions

Insulin Action in Lipodystrophy and Type 2 Diabetes

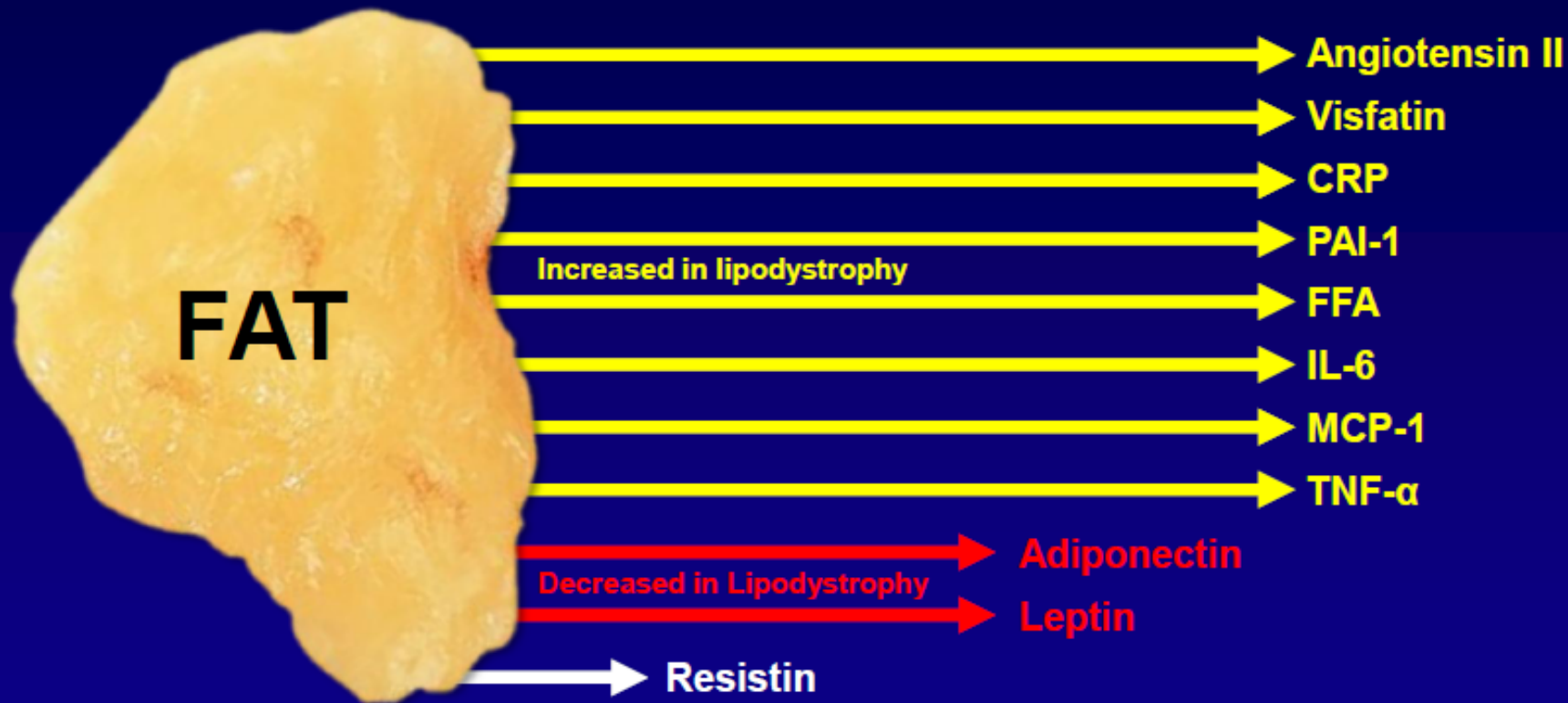
	Muscle	Adipose Tissue
IR Binding	↓	↓ →
IR Kinase	↓	↓
IRS Phosphorylation	↓	↓
IRS1 – PI-3K Activity	↓	↓
Akt Phosphorylation	↓ ↓	↓
αPKC Activity	↓	
AS160 Phosphorylation	↓	↓
GLUT4 Abundance	→	↓ ↓
GLUT4 Translocation	↓	↓ →
GSK3	↑	→
Erk 1/2 Activity	→	→

Change expressed relative to healthy individuals

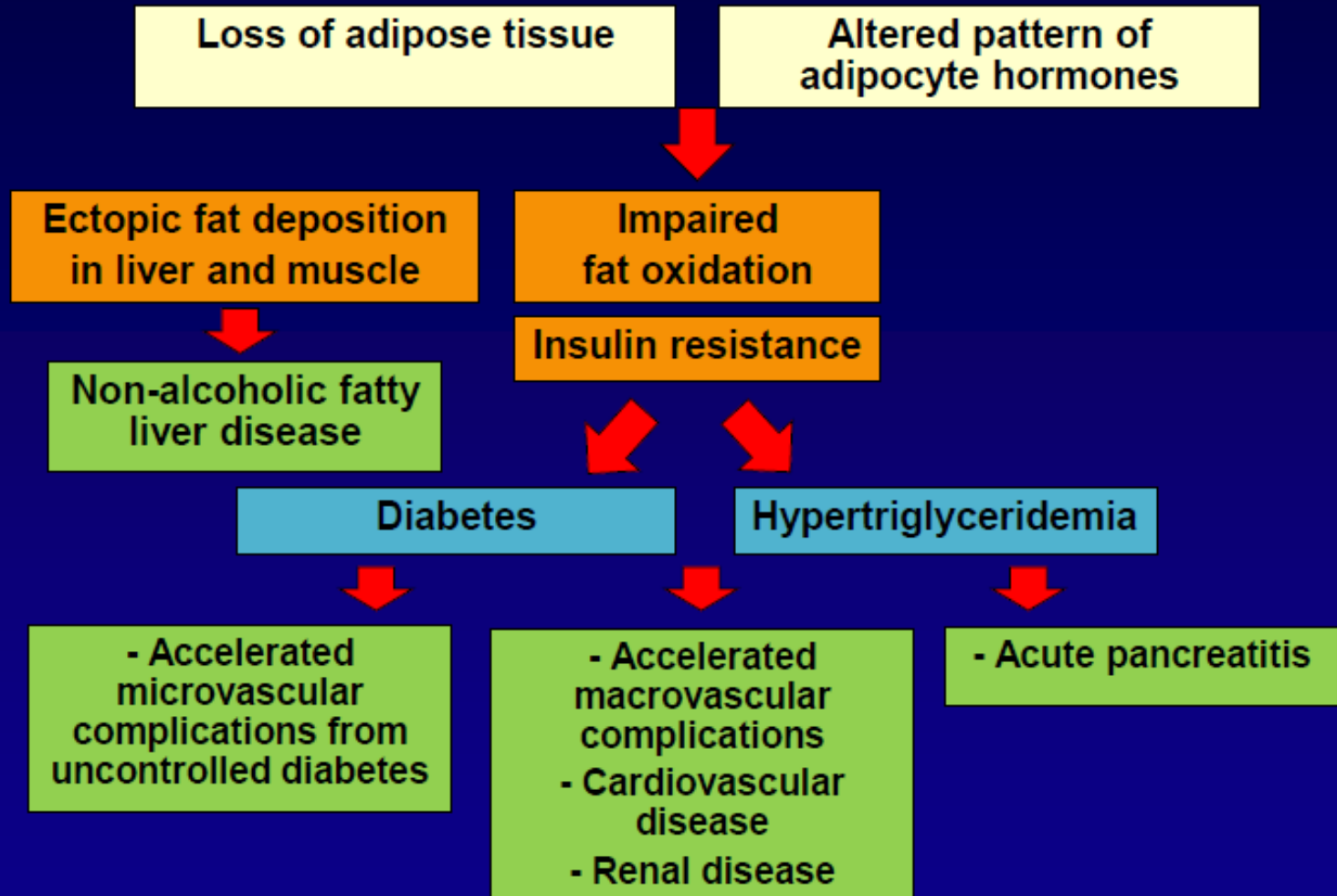
■ Type 2 Diabetes ■ Lipodystrophy

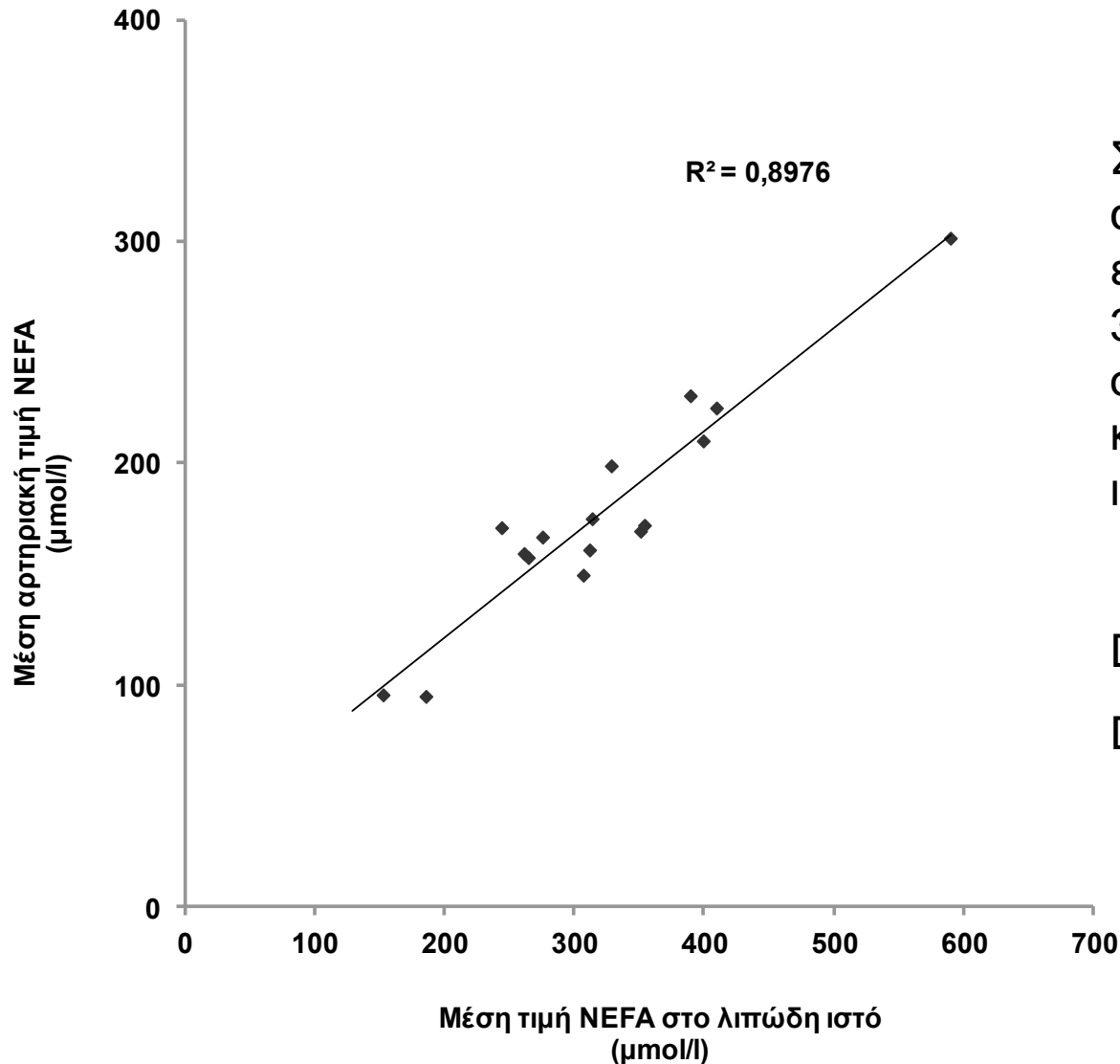
Adipose Tissue Functions

Now



Lipodystrophy Syndromes





Συσχέτιση μέσης τιμής αρτηριακής συγκέντρωσης ελεύθερων λιπαρών οξέων (0-360min) και αντίστοιχης τιμής στο φλεβικό σκέλος της κυκλοφορίας του λιπώδους ιστού.

Dimitriadis G, Lambadiari V, Diabetes Care 2005.

Κατάταξη Λιποδυστροφιών

❖ Αιτιολογία

- Γενετικές (συγγενείς)
- Αυτοάνοσες (επίκτητες)
- Άλλες

Table 1**General classification of major lipodystrophy subtypes**

Lipodystrophy Subtype	Main Characteristics
Congenital generalized lipodystrophy	Presents with near total loss of body fat at birth or during infancy. Autosomal-recessive inheritance.
Familial partial lipodystrophy	Presents with variable loss of subcutaneous fat from the upper and lower extremities and the truncal region at puberty or later. Autosomal-dominant inheritance.
Acquired generalized lipodystrophy	Characterized by gradual loss of subcutaneous fat from nearly all over the body. Associated with autoimmune diseases.
Acquired partial lipodystrophy	Characterized by gradual loss of fat from the upper body, including head, neck, upper extremities, and truncal region during childhood. Associated with autoantibodies called complement 3 nephritic factor and in ~20% of patients with membranoproliferative glomerulonephritis.
HAART-induced lipodystrophy in HIV patients	Associated with therapy including HIV protease inhibitors or nucleoside analogues.
Localized lipodystrophy	Usually caused by insulin injections or other injectables, such as steroids.

Γενετικές λιποδυστροφίες

• Αυτοσωμικές υπολειπόμενες

1. Συγγενής γενικευμένη λιποδυστροφία (CGL)
2. Mandibuloacral dysplasia
3. Αυτοφλεγμονώδης (JMP-πανκυτταρίτις)
4. Ετερου τύπου
 - ✓ Οικογενής μερική λιποδυστροφία (FPLD)
 - ✓ SHORT syndrome
 - ✓ Νεογνικό σύνδρομο προγηρίας
 - ✓ MDP syndrome (κόφωση, μικρογναθία, προγηρία)

• Αυτοσωμικές επικρατείς

- ✓ FPL
- ✓ Προγηρία Hutchinson-Gilford και Ατυπη προγηρία
- ✓ SHORT

Congenital Generalized Lipodystrophy (CGL; Berardinelli-Seip Syndrome)

- Autosomal recessive
- Prevalence <1 in 10 million
- Reported in ~300 patients of various ethnicities

A PARADOX

Lipodystrophy and insulin resistance



People with partial or total lipodystrophy:

- are severely insulin resistant
- often have type 2 diabetes
- have dyslipidaemia
- are hypertensive

*Picture from Agarwal AK, Garg A
Annu Rev Med 2006;57:297-311*

CGL: Clinical Characteristics

- Γενικευμένη λιποατροφία και μυωδη εμφάνιση από τη γέννηση
- Μελανίζουσα ακάνθωση
- Ηπατομεγαλία/NAFLD-NASH
- Μεγαλακρικά χαρακτηριστικά, ομφαλοκήλη
- Αρρενοποίηση στα θήλεα
- Οστεολύσεις
- σοβαρή ινσουλινοαντοχή- ΣΔ από την εφηβεία
- δυσλιπιδαιμία
- μειωμένη λεπτίνη

Diabetes in CGL Patients

- υπερινσουλιναιμία μετά τη γέννηση
- προδιαβητης σε παιδική ηλικία
- ΣΔ στην εφηβεία
- σοβαρή αμυλοείδωση στα νησίδια (90%)
- ανθεκτικός στην κέτωση
- χρειάζεται μεγάλες δόσεις ινσουλίνης (100-3000 μονάδες/ημέρα)

Table 2
Subtypes of CGL

Subtype	Gene	Molecular Basis	Prevalence
CGL1	<i>AGPAT2</i>	AGPAT enzymes play a key role in biosynthesis of triglycerides and phospholipids in various organs. AGPAT isoform 2 is highly expressed in the adipose tissue.	Most common subtype ^{7,8,10}
CGL2	<i>BSCL2</i>	Seipin, encoded by <i>BSCL2</i> , plays a key role in fusion of small lipid droplets in the adipocytes and in adipocyte differentiation.	Second most common subtype ⁷⁻⁹
CGL3	<i>CAV1</i>	Caveolin 1 is an integral component of caveolae, which are present on adipocyte membranes. Caveolae translocate fatty acids and other lipids to lipid droplets.	Only one patient reported ¹¹
CGL4	<i>PTRF</i>	PTRF (also known as cavin-1) is involved in biogenesis of caveolae and regulates expression of caveolins 1 and 3.	About 20 patients reported ^{12,43,44}

Abbreviations: *AGPAT2*, 1-acylglycerol-3-phosphate O-acyltransferase 2; *BSCL2*, Berardinelli-Seip congenital lipodystrophy 2; *CAV1*, caveolin 1; *PTRF*, polymerase I and transcript release factor.

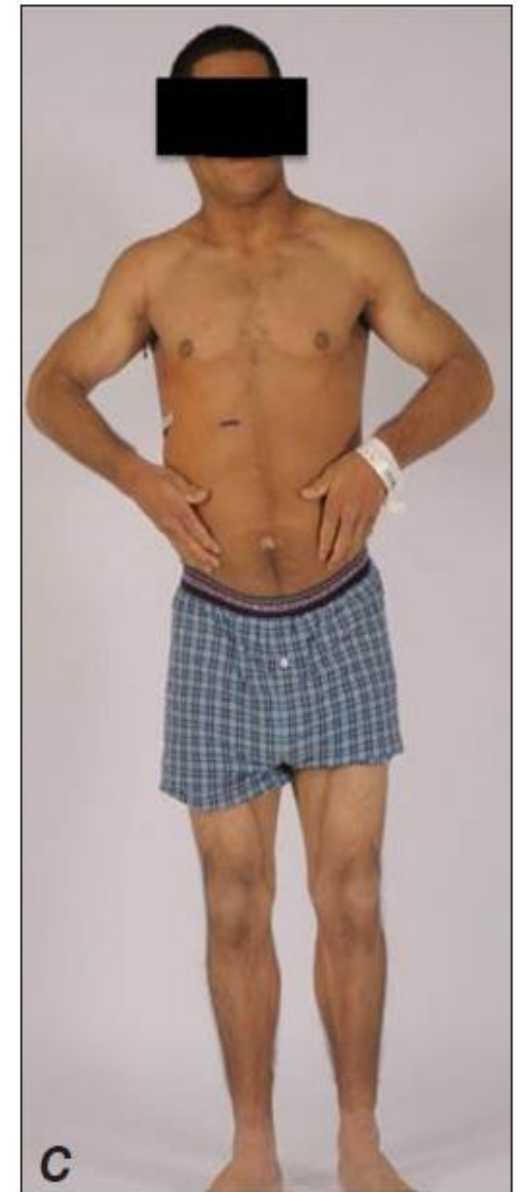


Fig. 1. Congenital generalized lipodystrophy in *A*, a 6-month-old infant with prominent musculature and veins, *B*, a 16-year-old girl with acanthosis nigricans and umbilical prominence, and *C*, a 15-year-old boy with umbilical prominence and otherwise normal appearing muscular habitus.

Seip-Berardinelli Syndrome, cont.

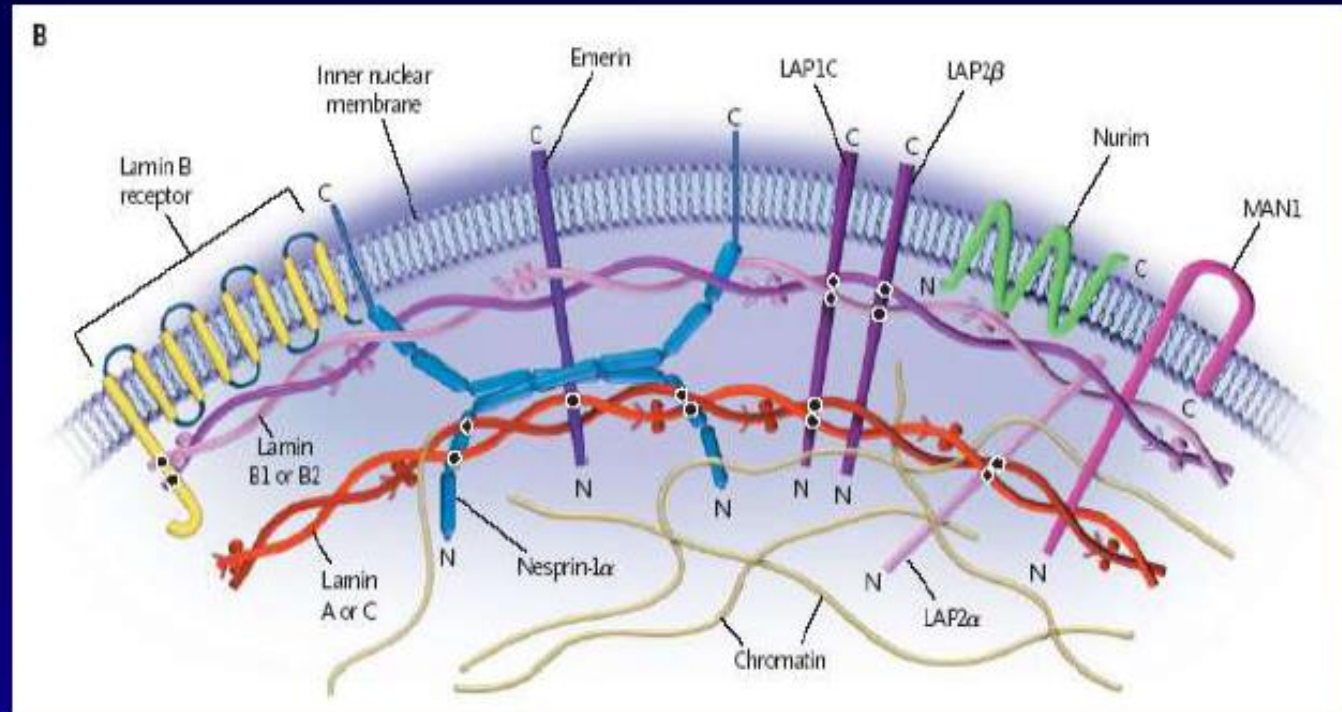
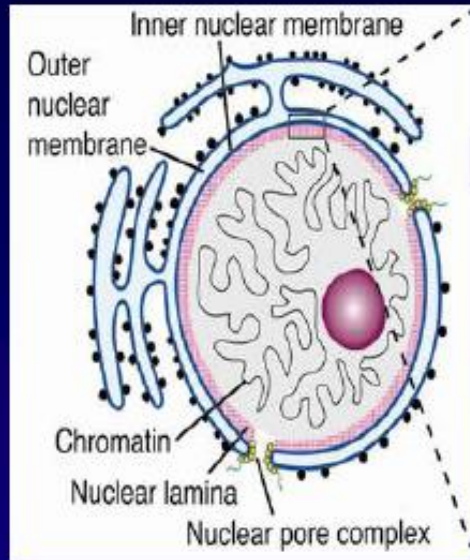


Familial Partial Lipodystrophy (FPL)

- Η **οικογενής μερική λιποδυστροφία (FPLD)** είναι μια ετερογενής ομάδα συνδρόμων, που χαρακτηρίζονται από απώλεια του λιπώδους ιστού, που συμβαίνει συνήθως στην εφηβεία και νεαρή ενήλικο ζωή.
- η **FPLD2** (Dunningan) συγκεκριμένα, οφείλεται σε μεταλλάξεις στη LMNA (laminopathy) exon 8, 10, και χαρακτηρίζεται από σταδιακή απώλεια του λίπους από τα άκρα, με μυώδη εμφάνιση αυτών και φλεβεκτασία, και υπερτροφία του λιπώδους ιστού στον κορμό, τον αυχένα και το πρόσωπο, καθώς και συσσώρευση στα σπλάχνα και ενδομυϊκά.
- Χαρακτηριστικά παρατηρείται μελανίζουσα ακάνθωση, ΣΔ, προδιαβήτης, στεατοηπατίτιδα, δυσλιπιδαιμία, κλπ

- **οι ετερόζυγες μεταλλάξεις των LMNA και PPARG** αντιπροσωπεύουν ποσοστό > 50% του συνόλου των κληρονομικών περιπτώσεων μερικής λιποδυστροφίας
- **Η οικογενής μερική λιποδυστροφία τύπου 2 (Dunnigan) (FPLD2; OMIM no. 151660), η πιο διαδεδομένη μορφή,** κυρίως μεταξύ ασθενών ευρωπαϊκής καταγωγής, είναι μια **αυτοσωματική κυρίαρχη** ασθένεια που προκαλείται από μεταλλάξεις στο γονίδιο LMNA που κωδικοποιεί τις πρωτεΐνες του πυρήνα Lamin A και C.
- Το FPLD2 είναι ένα σπάνιο σύνδρομο, και προκαλεί **ακραία αντίσταση στην ινσουλίνη**. Η μειωμένη χρήση των NEFA από τις δυστροφικές αποθήκες του λιπώδους ιστού και η υπερβολική εναπόθεσή τους στο ήπαρ, μπορεί να διαδραματίζει σημαντικό ρόλο.
- Ειδικότερα, σε υγιή άτομα, ο λιπώδης ιστός της περιοχής των μηρών, δημιουργεί χαμηλότερη μεταβολική ροή από αυτή του υποδόριου κοιλιακού λίπους, αλλά διαφέρει σε **σχέση με την προτίμησή του για την εξαγωγή των λιπαρών οξέων από τα NEFA του πλάσματος και τα VLDL-TG, σε σύγκριση με τα chylomicron-TG.**

Structure of Nuclear Lamina



Οι πρωτεΐνες Lamin A και C είναι μέλη της οικογένειας των πρωτεϊνών των ενδιάμεσων ινιδίων, που είναι απαραίτητες για το σωστό σχηματισμό της πυρηνικής μεμβράνης. Η απώλεια των λιποκυττάρων που σχετίζεται με μεταλλάξεις LMNA, πιθανόν οφείλεται σε διαταραχή της πυρηνικής λειτουργίας, με αποτέλεσμα τον κυτταρικό θάνατο ή τη διακοπή της αλληλεπίδρασης μεταξύ των κυτταρικών μεμβρανών και των μεταγραφικών παραγόντων.

FPL: Molecular Basis

Subtype:

FPL1

FPL2

FPL3

FPL4

FPL5

FPL6

Gene:

Unknown

LMNA

PPARG

PLIN1

AKT2

CIDEA

FPLD, cont.

- Autosomal dominant
- Prevalence <1 in 10 million
- Described in ~300 patients mainly of European ancestry

Table 4
Subtypes of FPLD

Subtype	Genetic Mutation	Prevalence
FPLD1 (Kobberling-type)	Molecular basis unknown	Rare ¹⁶
FPLD2 (Dunnigan-type)	Missense mutations in <i>LMNA</i>	Most common subtype; more than 500 patients reported ^{17–19}
FPLD3	Heterozygous mutations in <i>PPARG</i>	Second most common subtype; about 30–50 patients reported ^{20,21}
FPLD4	Heterozygous mutations in <i>PLIN1</i>	Reported in three families ²²
FPLD5	Homozygous nonsense mutation in <i>CIDEA</i> (autosomal recessive)	One patient reported ²³
FPLD6	Homozygous mutation in <i>LIPE</i> (autosomal recessive)	Six patients reported ^{24,25}
FPLD7	Heterozygous mutation in <i>ADRA2A</i>	Reported in one family ²⁷
<i>AKT2</i> -linked lipodystrophy	Heterozygous mutation in <i>AKT2</i>	Reported in one family ²⁶

Kobberling-Dunnigan Syndrome, cont.



a



b



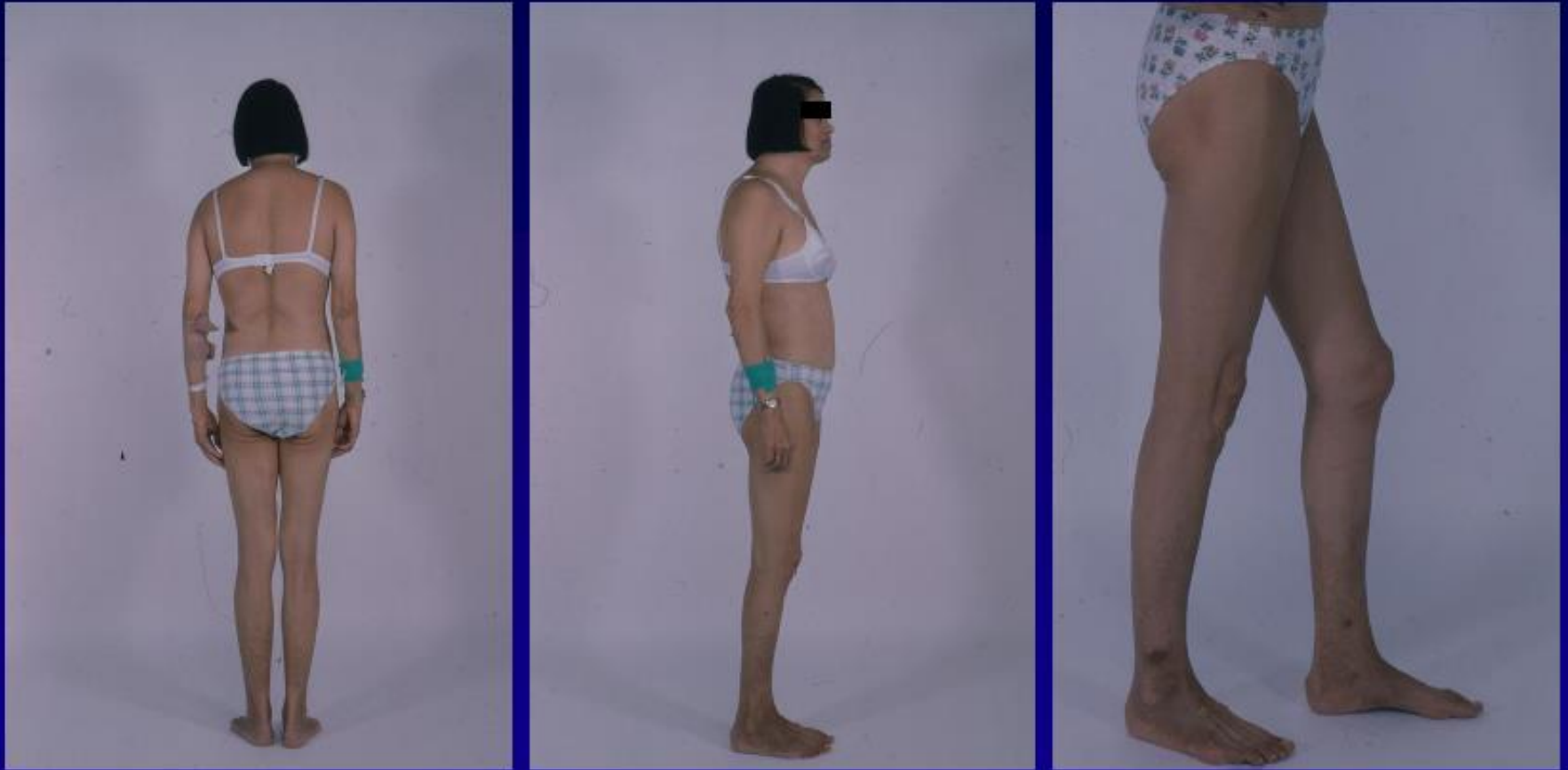
c



FPLD 2
(Dunnigan-
type)

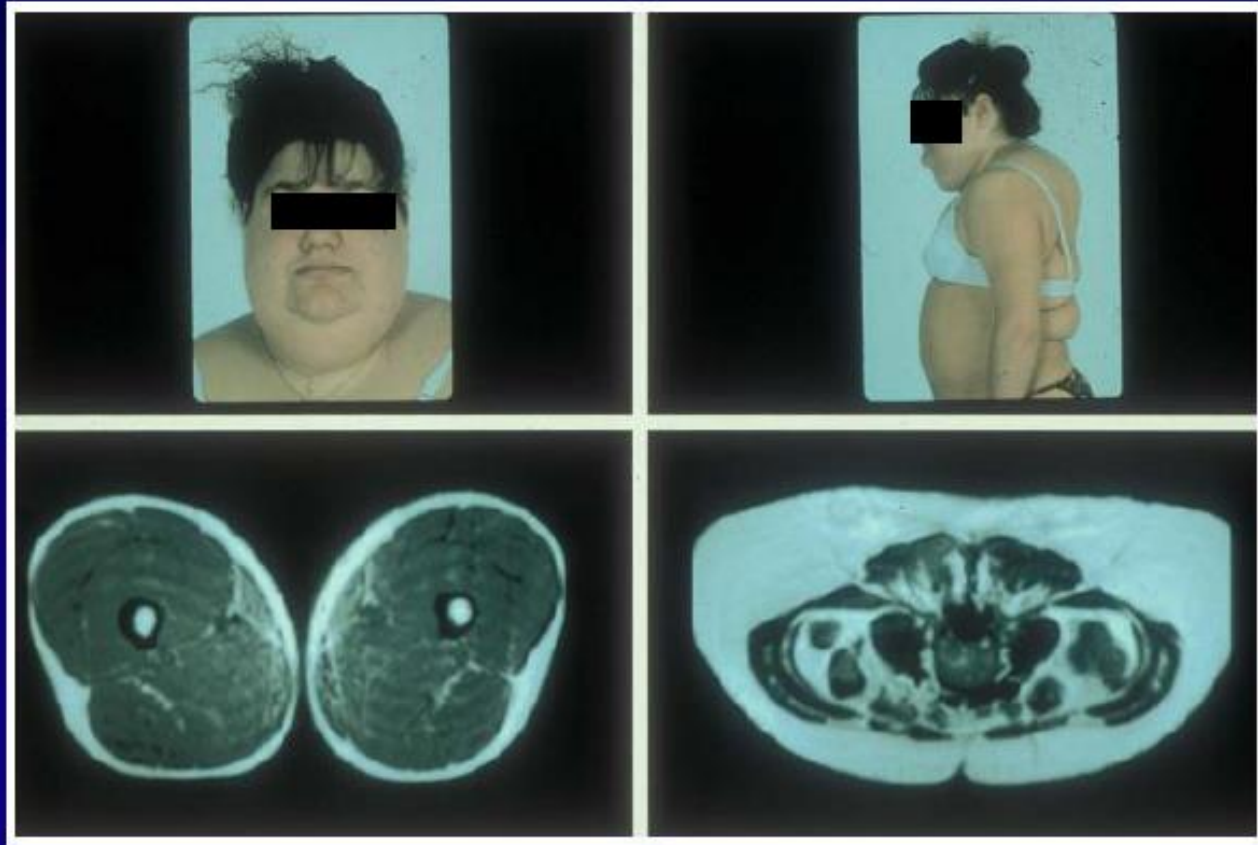


Partial Lipodystrophy Due to PPAR- γ Mutations



Case was followed as a type A insulin-resistant patient for years

Teenager with Atypical Partial Lipodystrophy: Initial Diagnosis of Pediatric Cushing's



Lots of body fat, but leptin undetectable

Importance of Full Physical Exam



Mandibuloacral Dysplasia (MAD): Clinical Characteristics

- Skeletal abnormalities
 - Mandibular and clavicular hypoplasia
 - Acro-osteolysis
- Progeroid manifestations
 - Cutaneous atrophy with prominent superficial vasculature and mottled hyperpigmentation
 - Thin, beaked nose
 - Hair loss
- Delayed dentition and closure of cranial sutures, crowded teeth
- Joint stiffness
- Lipodystrophy: partial (type A) or generalized (type B)

MAD: Laboratory Characteristics

- Diabetes, glucose intolerance, insulin resistance
- Mild hypertriglyceridemia and low levels of HDL cholesterol reported in some patients with MAD

MAD: Molecular Basis

Subtype:

MAD A

MAD B

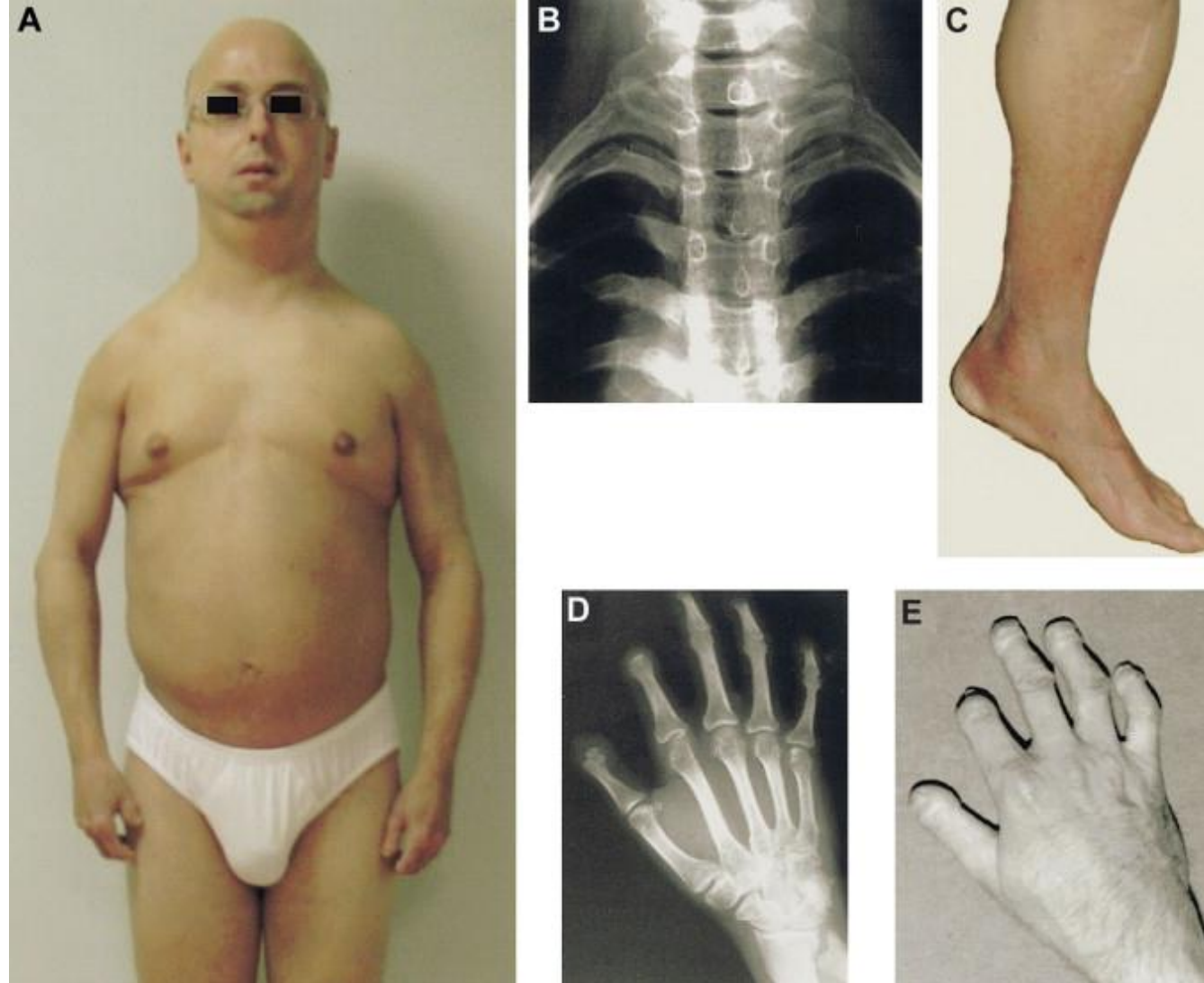
Gene:

LMNA

ZMPSTE24

Mandibular Hypoplasia, Deafness, and Progeroid (MDP) Syndrome

- Generalized loss of subcutaneous fat
- Mandibular hypoplasia
- Short stature
- Joint contractures
- Sclerodermatous skin with mottled pigmentation
- Hypogonadism and undescended testes in males
- Molecular genetic basis unknown



Mandibuloacral Dysplasia Is Caused by a Mutation in *LMNA* Lamin A/C

The American Journal of Human Genetics, Volume 71, Issue 2, 2002, 426 - 431

Figure 1 Clinical spectrum of MAD. A, Alopecia, micrognathia, and hanging shoulders (patient VII-1, family 1). B, X-ray films showing hypoplastic clavicles (patient 4). C, Lipodystr...

Hutchinson-Gilford Progeria



SHORT Syndrome

Autosomal Dominant and Recessive

- **S**hort stature
- **H**yperextensibility of joints
- **O**cular depression
- **R**ieger anomaly
- **T**eething delay
- Premature onset of diabetes
- Lipodystrophy

Classification of Lipodystrophies

- Etiology
 - Genetic
 - Autoimmune
 - Other

Lawrence Syndrome

- Γενικευμένη λιποδυστροφία
- Αυτοάνοσης αιτιολογίας
 - I. Σχετιζόμενη με αυτοάνοσες ασθένειες
- Εμφανίζεται στην πρώτη δεκαετία της ζωής
- Ετερογενής εικόνα
- Σοβαρές μεταβολικές επιπτώσεις
 - I. ΣΔ εντός 5 ετών από την λιποατροφία
 - II. Σοβαρή υπερτριγλυκεριδαιμία

Acquired Generalized Lipodystrophy (AGL)

ACQUIRED GENERALIZED LIPOATROPHY



3 8/12 YEARS



6 10/12 YEARS

Barraquer-Simmons Syndrome: Acquired Partial Lipodystrophy (APL)



Other Acquired Lipodystrophies

- Μερική λιποδυστροφία
- τυπικά αναπτύσσονται στη 2η και 3η δεκαετία ζωής
- γυναικεία επικρατισή
- αυτοάνοση αιτιολογία
 - συνήθως με εφηβική δερματομυοσίτιδα
 - ανεπάρκεια C3, παρουσία C3 νεφριτιδικού παράγοντα και σπειραματονεφριτιδα
 - ανεπάρκεια C4 και αυτοανοσία (ΣΔ1, ηπατίτιδα, hashimoto)
- ελαφρύτερες μεταβολικές διαταραχές

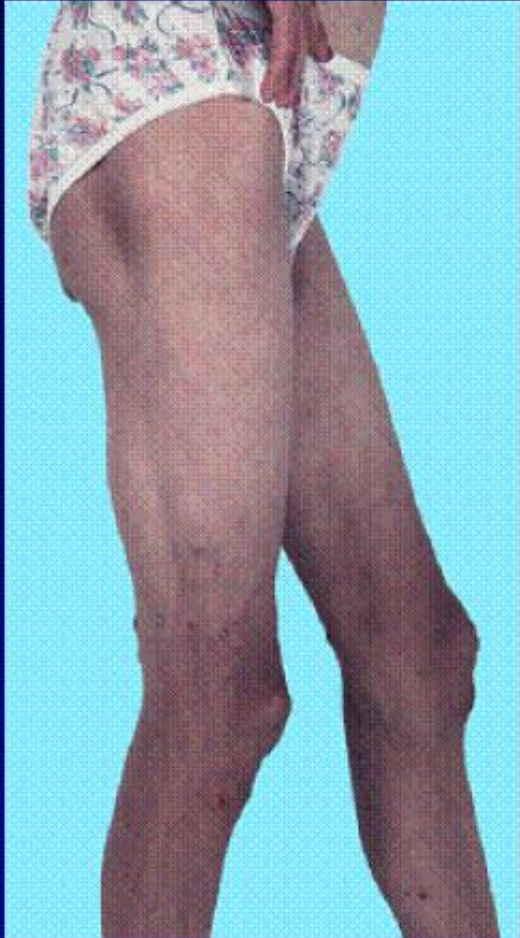


Figure 2. Acquired partial lipodystrophy and lipedema. A, a 37 year old woman with acquired partial lipodystrophy. C3 level <math><16.1\text{ mg/dL}</math> (normal range: 90-180) and C4 level 23.11 mg/dL (normal range: 10-40). Note the loss of SAT from the upper body to the waist but obesity of the hips and legs (photo by Dr Alper GURLEK). B, a woman with lipedema stage II and a previous history of obesity with a 100 kg weight loss; note redundant skin on arms and abdomen from weight loss of non-RAD fat; note also lipedema in legs.

Joint Contractures, Microcytic Anemia, and Panniculitis-Induced (JMP) Autoinflammatory Lipodystrophy

- Severe panniculitis-induced lipodystrophy (face, arms, thorax)
- No acanthosis nigricans or hyperinsulinemia
- Mild hypertriglyceridemia
- Low HDL cholesterol
- Mild elevations of liver enzymes
- Limb muscle atrophy, joint contractures (hands and feet)
- Microcytic hypochromic anemia
- Hypergammaglobulinemia

Generalized Lipodystrophy in JDM



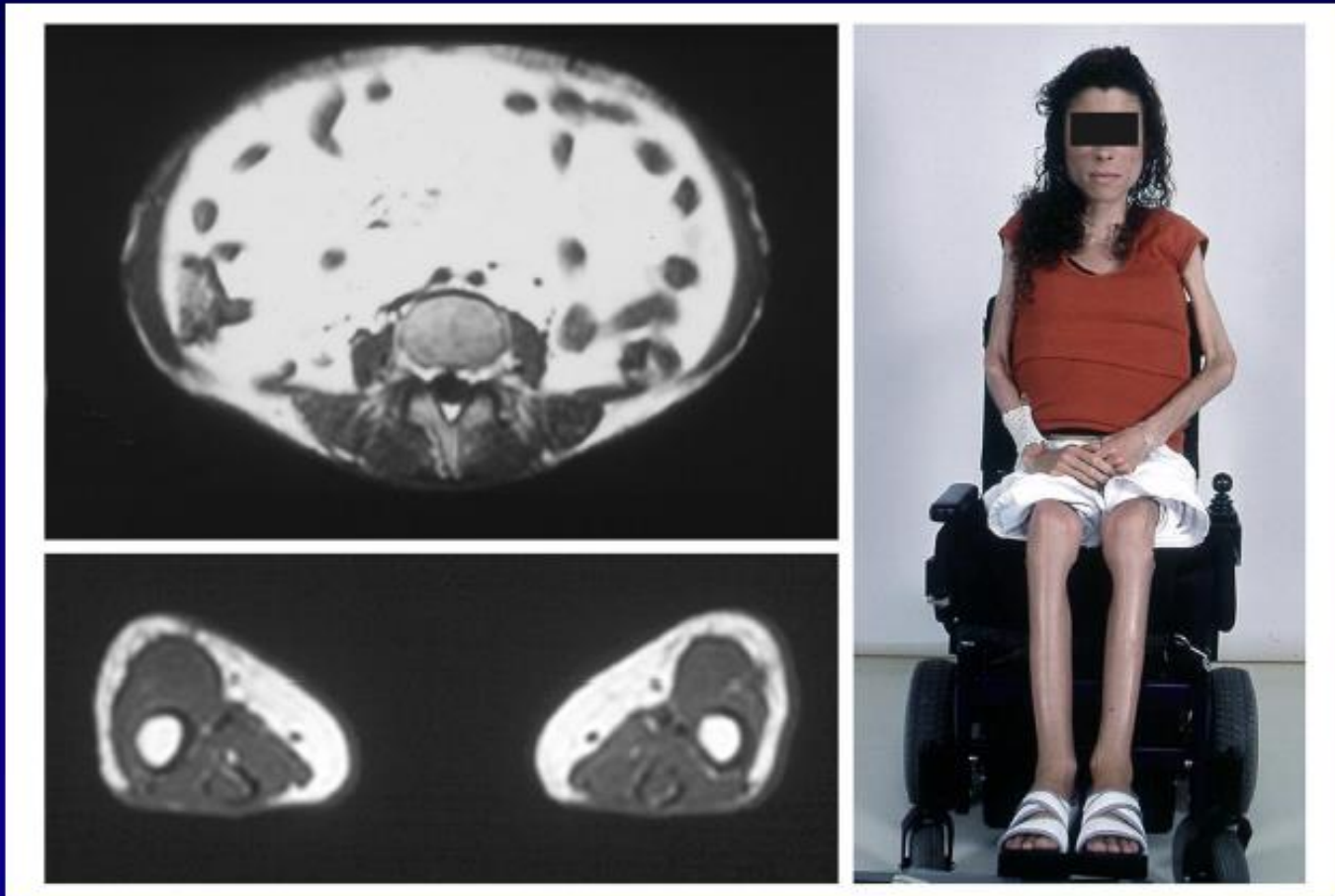
JDM-Associated Partial Lipodystrophy



Lipodystrophy Is Rare in JDM and Adult Dermatomyositis

- 8.6% in JDM (28/324)
- <1% in adult dermatomyositis
- None in polymyositis or overlap myositis (juvenile or adult)

Juvenile Dermatomyositis (JDM)- Associated Lipodystrophy



Other Etiologies for Lipodystrophy

- Specific drugs (eg, antiretroviral drugs)
- Viral illness (molecular mimicry?)
- Local injections (typically only focal fat loss)

Συνήθη κλινικά ευρήματα λιποδυστροφιών

- ✓ Λιποδυστροφικός φαινότυπος
- ✓ μελανίζουσα ακάνθωση
- ✓ Υπερτροφία μυών, φλεβεκτασία
- ✓ Ηπατομεγαλία
 - i. Λιπώδες ήπαρ Στεατοηπατίτιδα-κίρρωση
- ✓ Υπερτρίχωση, αρρενοποίηση, αμηνόρροια, υπογονιμότητα, PCOs
- ✓ Υπερτροφική-διατακτική μυοκαρδιοπάθεια, διαταραχές αγωγιμότητας
- ✓ Πνευματική καθυστέρηση
- ✓ Μεταβολικές διαταραχές
 - i. Υπεργλυκαιμία, μη κετωτική
 - ii. Ινσουλινοαντίσταση
 - iii. Υπερτριγλυκεριδαιμία/μεικτὴ δυσλιπιδαιμία
 - iv. Αυξημένος μεταβολικός ρυθμός

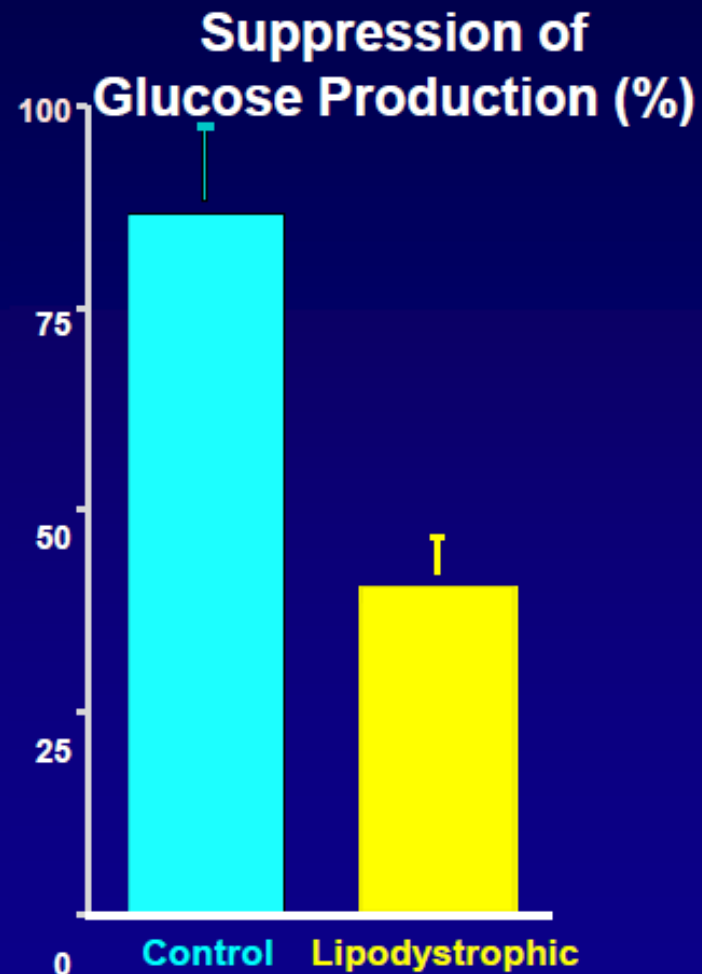
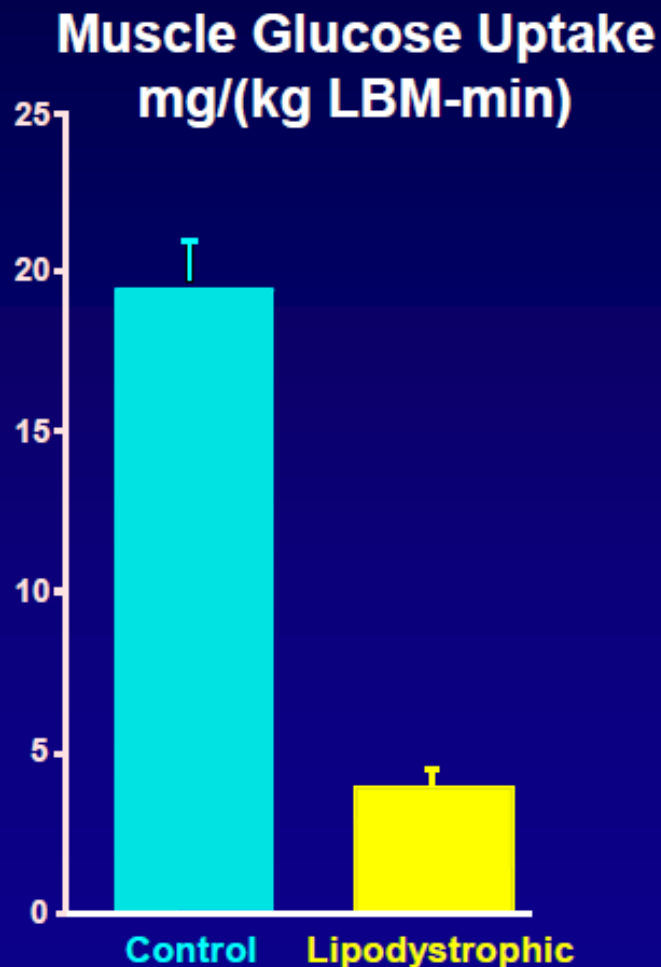
Hyperandrogenism



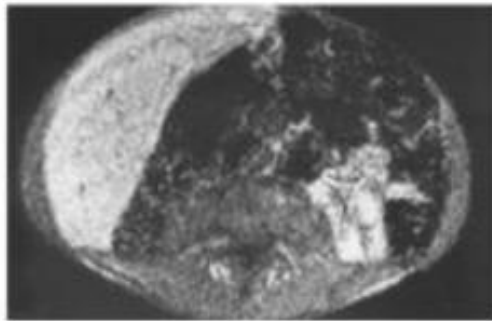
Typical Laboratory Findings

- Insulin resistance and hyperinsulinemia
- Diabetes or impaired glucose tolerance test
- Triglyceride and free fatty acid (FFA) levels ↑↑↑
- HDL cholesterol levels ↓
- LDL cholesterol ↑ (variable)
- Androgen levels in females ↑

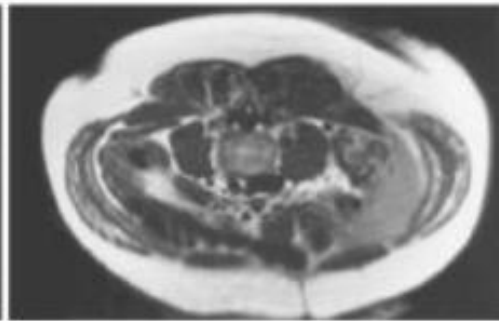
Insulin Action: Control Versus Lipodystrophy



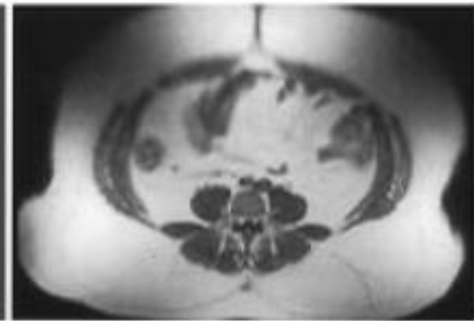
Tissue Deposition of Triglycerides



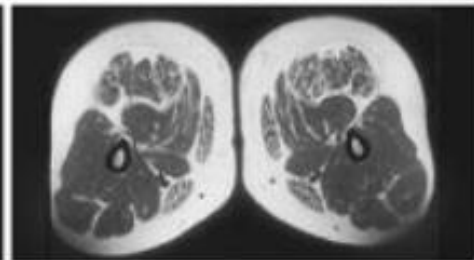
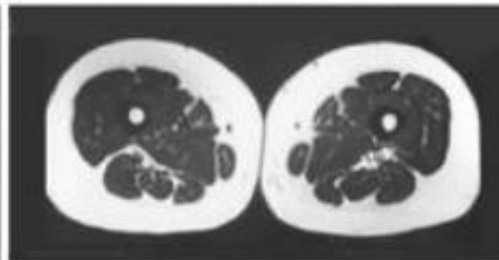
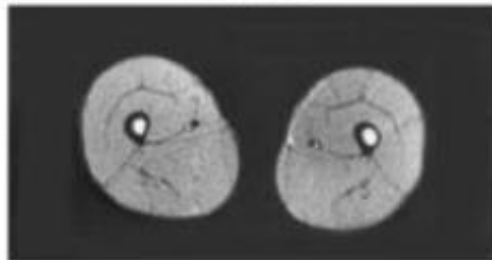
Generalized Lipomatosis
Severe Insulin Resistance



Normal Adiposity
Normal Insulin Sensitivity



Generalized Obesity
Severe Insulin Resistance



Cardiac Findings in Lipodystrophy

Type	Patients (<i>n</i>)	Cardiac Echo Findings
CGL-1	19	10 with LVH 4 with LVD 1 with PDA
CGL-2	10	8 with LVH
FPLD-2	9	Moderate LVD
FPLD-?	2	Concentric remodeling
AGL	13	6 with LVH 1 with LVD

Cardiac Findings in Lipodystrophy, cont.

- Cardiomyopathy (hypertrophic or dilated)
- Conduction system abnormalities in some
- Sudden cardiac death
- Premature coronary artery disease

Renal Findings in Lipodystrophy

- Hyperfiltration and proteinuria (AGL, CGL)
- Pathology of diabetic nephropathy rare
- Focal segmental glomerulosclerosis (AGL, CGL, and mandibuloacral dysplasia (MAD)-associated lipodystrophy)
- Membranoproliferative glomerulonephritis (even in familial partial lipodystrophy [FPL]), may be associated with low C3 and C3NeF
- May progress to end-stage renal disease

Other Specific Manifestations

- Increased appetite and hyperphagia in generalized lipodystrophy (due to low leptin)
- Skeletal system: lytic bone lesions in CGL
- Muscles: myopathic features in FPL
- Skin: neutrophilic dermatosis, panniculitis, etc.
- Manifestations of specific syndromes
- Manifestations of associated autoimmune diseases
- Lymphomas in AGL (late-onset) or APL
- Potential for malignancy: breast, endometrial

Other Potential Causes of Mortality and Morbidity

High triglycerides:

- Acute pancreatitis
- Eruptive xanthomata

Lipodystrophy Syndromes

- Fatty infiltration of liver and other tissues
- Deficiency of adipocyte hormones (eg, leptin)



Clinical Approach: First Steps

- Ιστορικό (φαινότυπος, οικογένεια, αιμομιξία)
- Προσεκτική κλινική εξέταση
- Προσδιορισμός λίπους (δερματικές πτυχές, DEXA, MRI, CT)
- Γενετικός έλεγχος (LMNA, AGPAT2, BSCL2, ZMPSTE24, PPAR α)
- Έλεγχος για ΣΔ, ινσουλινοαντίσταση, δυσλιπιδαιμία

Clinical Features That Increase the Suspicion of Lipodystrophy

Essential feature

Generalized or regional absence of body fat

Physical features

Failure to thrive (infants and children)

Prominent muscles, Prominent veins (phlebomegaly)

Severe acanthosis nigricans

Eruptive xanthomata

Cushingoid appearance, Acromegaloid appearance

Progeroid (premature aging) appearance

*J Clin Endocrinol
Metab. 2016 Dec;
101(12): 4500–4511.*

Comorbid conditions

Diabetes mellitus with high insulin requirements

≥200 U/d, ≥2 U/kg/d, Requiring U-500 insulin

Severe hypertriglyceridemia

≥500 mg/dL with or without therapy

≥250 mg/dL despite diet and medical therapy

History of acute pancreatitis secondary to hypertriglyceridemia

Non-alcoholic steatohepatitis in a non-obese individual

Early-onset cardiomyopathy

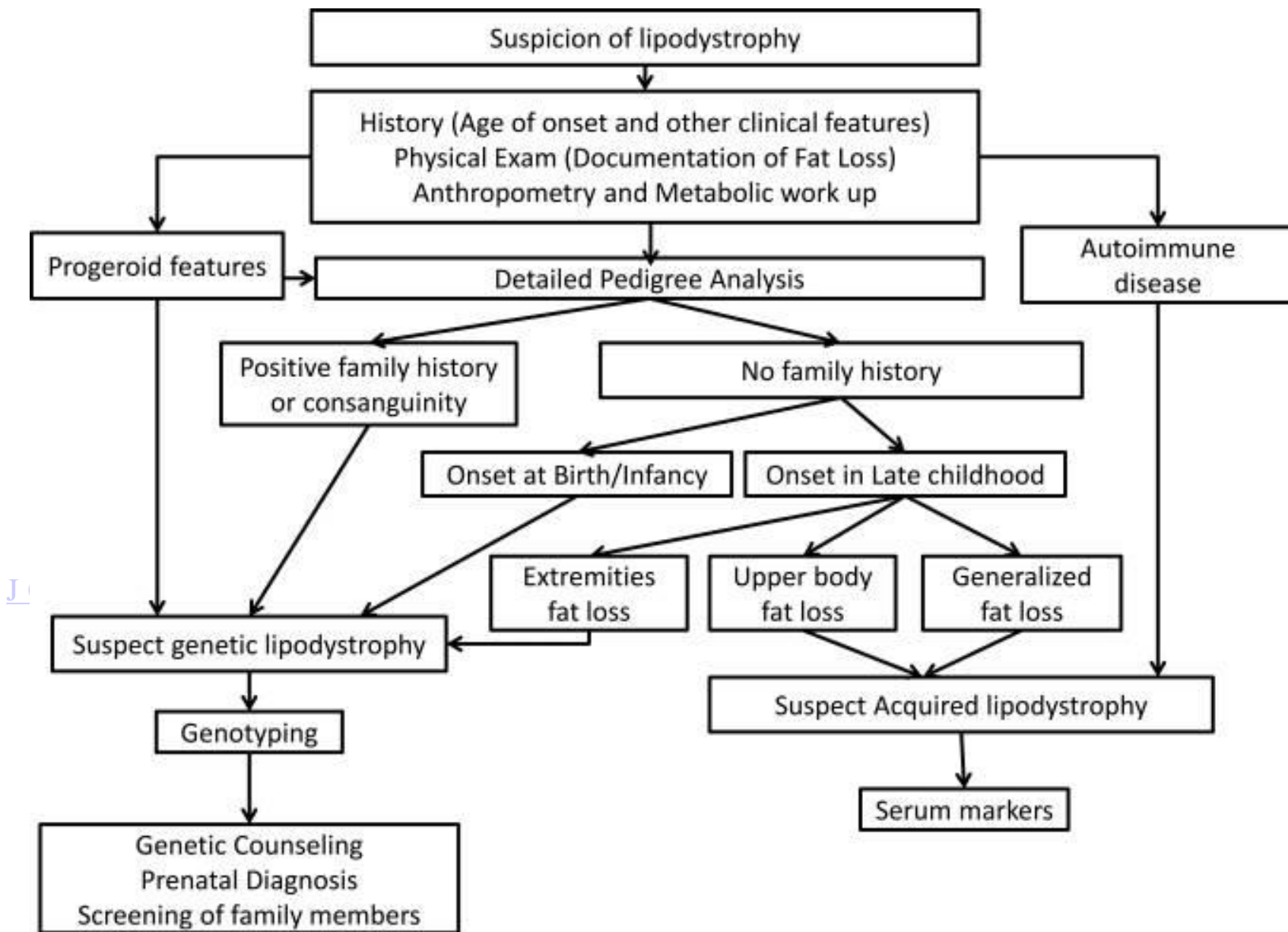
PCOS

Other historical clues

Autosomal dominant or recessive pattern of similar physical features or metabolic complications

Significant hyperphagia (may manifest as irritability/aggression in infants/children)

ΔΙΑΓΝΩΣΗ



Clinical Approach: Next Steps

- Έλεγχος ήπατος, καρδιαγγειακού, νεφρού
- Έλεγχος γονιμότητας, ορμονών φύλου
- Έλεγχος σκελετού για MAD, CGL
- Βιοψία δέρματος στις επίκτητες
- Έλεγχος συμπληρώματος στις επίκτητες με άλλα αυτοάνοσα
- Έλεγχος για υπερφαγία, binge-eating

Differential Diagnosis

➤ Γενικευμένη λιποδυστροφία

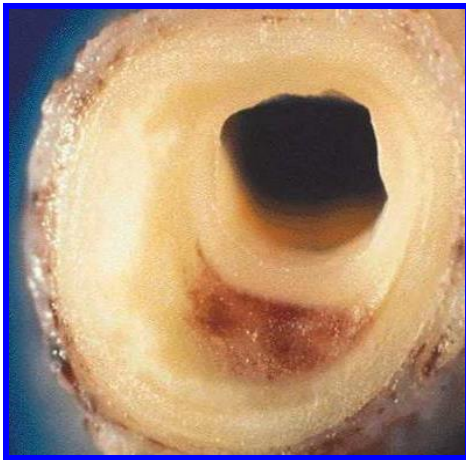
- Καχεξία
- Νευρική ανορεξία
- Υποσιτισμός

➤ Μερική

- Σ. Cushing
- Κεντρική παχυσαρκία/μεταβολικό σύνδρομο
- Πολλαπλή συμμετρική λιπομάτωση
- Περιοχικές λιποδυστροφίες

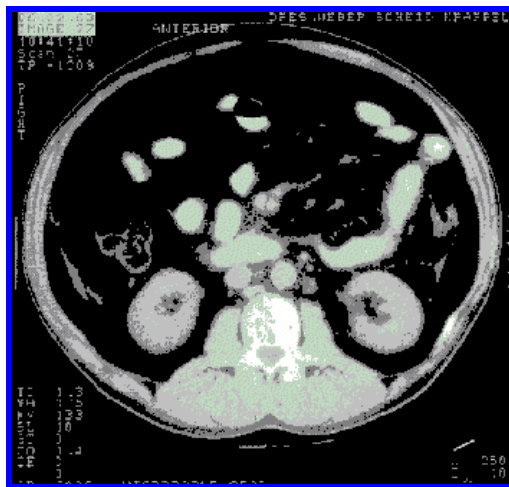
Μακροπρόθεσμες επιπλοκές της HAART

Δυσλιπιδαιμία/ΣΝ



Διαταραχές της
Σύνθεσης Σώματος

Ηπατοτοξικότητα





Metabolic Effects of PIs

	Lipids	Glucose
RTV	↑ TC/TG	↑ insulin resistance
LPV	↑ TC/TG	↑ insulin resistance
IDV	↑ TC/TG	↑ insulin resistance
NFV	↑ LDL/TG, ↓ HDL	no Δ insulin sensitivity
APV/FPV	↑ TC/TG	no Δ insulin sensitivity
TPV	↑ TC/TG	?
SQV	no Δ	no Δ insulin sensitivity
ATV	no Δ	no Δ insulin sensitivity

HAART

- Οι ΡΙς προκαλούν λιποατροφία αναστέλλοντας τη μέσω sterol regulatory enhancer–binding protein 1 (SREBP1)–ενεργοποίηση του X υποδοχέα των λιποκυττάρων και των PPAR σχετιζομένων παραγόντων. Οι ΡΙς αναστέλλουν τη λιπογένεση και τη διαφοροποίηση των λιποκυττάρων, διεγείρουν τη λιπόλυση και διαταράσσουν την πυρηνική μετάθεση του SREBP1.
- Από τους NRTIs, το stavudine συνδέεται περισσότερο με λιποατροφία, κυρίως αν συνδυάζεται με ddI. Αυτό πιθανώς οφείλεται σε μιτοχονδριακή τοξικότητα λόγω αναστολής της DNA πολυμεράσης στα λιποκύτταρα. Οι NRTIs αναστέλλουν τη λιπογένεση και τη διαφοροποίηση των λιποκυττάρων, διεγείρουν τη λιπόλυση, και ασκούν συνεργική τοξική δράση με τους ΡΙς in vitro και in vivo.



Becardinnelli
-Seip

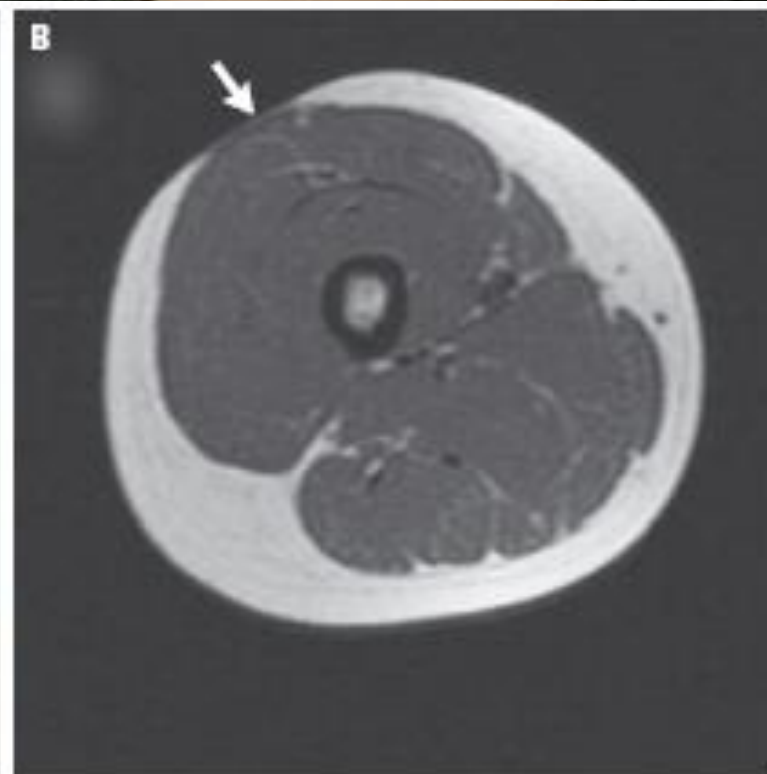
FPLD2

Acquired
generalized
(with Crohn's)

Barraquer-
Simmons

HAART

Injection-Site Lipoatrophy



Insulin-Induced Lipohypertrophy



ΔΙΑΙΤΑ - ΑΣΚΗΣΗ

Λιποατροφία:

Δεν αποκαθιστούν τις αποθήκες λίπους

Λιπουπερτροφία:

Κάποιες μελέτες δείχνουν μετρια βελτίωση της λιπουπερτροφίας

Δυσλιπιδαιμία:

Συστηματική άσκηση και διατροφή χαμηλή σε λιπαρά και ευαπορρόφητους υδατάνθρακες βελτιώνουν τη δυσλιπιδαιμία και μειώνουν τον καρδιαγγειακό κίνδυνο

medium-chain triglyceride-formulas σε παιδιά και πολύ χαμηλή πρόσληψη λίπους στους ενήλικους
Μόνο cis-monounsaturated fats και long-chain omega-3 fatty acids



More Concentrated Basal Insulins in Development

- U-300 insulin glargine
- U-200 insulin degludec

The hope is that more concentrated preparations of these long-acting basal analogues will result in smaller insulin depots and more consistent absorption with the larger doses required in severely insulin-resistant patients.

What About Adding GLP-1 for These Patients?

- $n = 13$ patients receiving >200 units/day of insulin for 13 months
- Add liraglutide

	Weight (Kg)	Insulin Dose (U/kg)	A1C (%)
Before liraglutide	129	2.3	8.9
After liraglutide	126	1.6	7.6
<i>P</i>	0.048	0.009	0.02

Chukwu JF, Hirsch IB, Trence D. Presented at ENDO 2012, the 94th annual meeting of the Endocrine Society, Houston, Texas, June 2012.

Metreleptin

- Metreleptin: recombinant human methionyl leptin
- Metreleptin is an analogue of human leptin, in which an additional methionine has been added at the amino terminus.

Summary of Metreleptin Effects in Lipodystrophy

Clinical Parameter	Major Effects
Appetite and body weight	Decreased
Insulin resistance	Decreased
Diabetes	Decreased A1C Decreased insulin doses
Hypertriglyceridemia	Decreased
Steatohepatitis	Improved
Reproduction	Normalized menstrual cycles Increased fertility
Kidney disease	Decreased hyperfiltration Decreased protein excretion

Table 9

Approval and indications of metreleptin therapy

Type of Lipodystrophy	Approvals	Indications	Clinical Considerations
Generalized lipodystrophy (both CGL and AGL)	<p>United States: approved as adjunct to diet for treatment of metabolic complications.</p> <p>Japan: approved</p> <p>Europe: available through compassionate care programs.</p>	<p>First-line drug treatment (after diet/exercise intervention) for metabolic and endocrine abnormalities.</p> <p>May prevent comorbidities and metabolic complications in young children.</p>	<p>Decreases hyperphagia, leading to weight loss. May need to be discontinued if excessive weight loss occurs.</p>
Partial lipodystrophy (both FPLD and APL)	<p>United States: not approved.</p> <p>Japan: approved as an adjunct to diet</p> <p>Europe: through compassionate care programs.</p>	<p>May be considered for patients with hypoleptinemia (leptin <4 ng/mL) who have severe metabolic abnormalities, such as HbA_{1c} >8% and/or triglycerides >500 mg/dL.</p>	<p>Clinical response not as good as in generalized lipodystrophy. Patients with lower leptin levels show the most benefit.</p>

Συμπεράσματα

- ✓ Η απώλεια λίπους, τοπικά ή γενικευμένα, σε συνδυασμό με ινσουλινοαντίσταση και δυσλιπιδαιμία, είναι η βάση της διάγνωσης
- ✓ Μεταβολικές και αναπαραγωγικές διαταραχές είναι τα βασικά κλινικά προβλήματα
- ✓ Η διάγνωση συνδέεται με σηματική νοσηρότητα και πρωιμο θάνατο
- ✓ Υπάρχει σημαντική φαινοτυπική ετερογένεια, και για αυτό είναι πολύ σημαντική η προσεκτική κλινική εξέταση

GAIN WEIGHT!

STOP BEING SKINNY AND TIRED!

Amazing Scientific Plan Adds New Attractive Pounds and Inches AS FAST AS YOU WANT . . . OR YOU PAY NOTHING!

START GAINING WEIGHT TODAY . . . AND KEEP ON GAINING HEALTHY POUNDS AND INCHES!

Don't be skinny . . . Put on pounds and inches of new, attractive flesh . . . and feel like a new person. *Vitatorne Tonic and Appetite Stimulant* is an amazing Scientific Formula for easier weight gain. It helps you gain pounds after pounds, which makes your figure better looking . . . while you eat the foods you choose. It picks up *Vitatorne's* deficient *Appetizer* . . . automatically you gain weight without conscious effort. And at the same time, you lose that "tired feeling," have more resistance, sleep better at night. If you are skinny and tired because of poor appetite or poor eating habits . . . this medically safe, easy way helps you gain energy faster, and puts on pounds and inches of new weight, for a shapelier figure.

HOW YOU CAN LOOK BETTER HAVE A HEALTHIER, MORE ROBUST FIGURE!

Vitatorne is entirely safe, contains no drugs, no stimulants, but is a medically sound Concentrated Food Formula that's EXTRA RICH in nature to stimulate calories, furnished with other good weight building elements. Many underweight people have trouble than normal stomachs. Half way through a meal, they're full . . . can eat no more. *Vitatorne* is more than a meal. Yes, each daily supply of *Vitatorne* is as rich in calories as many a skinnier person's regular full meal.

ONE OF THE MOST POWERFUL YET SAFE WEIGHT GAINING FORMULAS THAT HAS EVER BEEN OFFERED!

Vitatorne's 10-in-1 Formula is like a Doctor's Prescription. Special care was taken to formulate it so that it was thoroughly tested. It was prepared so as to be approved and recommended for use by men, women, and even young children.

HERE ARE THE PLACES ON YOUR BODY WHERE YOU TEND TO BE UNDERWEIGHT:

- Arms
- Thighs
- Legs
- Hips
- Chest

BE APPEALING—HAVE SELF-CONFIDENCE

If you are skinny and embarrassed when you see those of average body, thighs, arms and legs . . . Now you may be able to quickly put on more attractive pounds and inches so fast it will amaze you. *Vitatorne* is developed by Men of Medical Science . . . a delicious weight adding formula, non-purged with wonder-aiding to help your body gain good-looking flesh automatically, wherever you need it . . . on face, neck, arms, legs and abdomen . . . Almost magical . . . *Vitatorne's* "Tonic-stick" Equips fill out all over the body into a beautiful "new look" that was popularized by Concentrated *Vitatorne* and *Vitatorne's* Deficient Appetizer . . . New Pop, Vigor and Vitality.

IMPORTANT! Forget everything you have ever heard about weight gaining products before today! Don't confuse *Vitatorne* with any other formula you have ever seen, heard of, or read. *Vitatorne* is a medically researched product. A weight gaining wonder formula unlike anything ever released without a Doctor's Prescription! And here is the overwhelming proof! When you use *Vitatorne's* concentrated 10-in-1 Formula to add weight . . . you will be among the fortunate men and women who experienced noticeable weight gain . . . after every other weight gaining method failed them.

No other product can claim all these amazing weight gaining and health giving ingredients.

HOW VITATORNE WORKS TO GIVE YOU NEW ATTRACTIVE POUNDS AND INCHES . . .

Here is the actual formula . . . The amazingly safe, sound, way to gain weight. The method you may have heard about . . . was only for sale with a Doctor's Prescription.

Concentrated 10-in-1

Wright Gaining Formula Contains:

1. *Ammonia*, 2. *Phosphorus*, 3. *Calcium*, 4. *Phosphorus*, 5. *Calcium*, 6. *Phosphorus*, 7. *Calcium*, 8. *Phosphorus*, 9. *Calcium*, 10. *Phosphorus*, 11. *Calcium*, 12. *Phosphorus*, 13. *Calcium*, 14. *Phosphorus*, 15. *Calcium*, 16. *Phosphorus*, 17. *Calcium*, 18. *Phosphorus*, 19. *Calcium*, 20. *Phosphorus*, 21. *Calcium*, 22. *Phosphorus*, 23. *Calcium*, 24. *Phosphorus*, 25. *Calcium*, 26. *Phosphorus*, 27. *Calcium*, 28. *Phosphorus*, 29. *Calcium*, 30. *Phosphorus*, 31. *Calcium*, 32. *Phosphorus*, 33. *Calcium*, 34. *Phosphorus*, 35. *Calcium*, 36. *Phosphorus*, 37. *Calcium*, 38. *Phosphorus*, 39. *Calcium*, 40. *Phosphorus*, 41. *Calcium*, 42. *Phosphorus*, 43. *Calcium*, 44. *Phosphorus*, 45. *Calcium*, 46. *Phosphorus*, 47. *Calcium*, 48. *Phosphorus*, 49. *Calcium*, 50. *Phosphorus*, 51. *Calcium*, 52. *Phosphorus*, 53. *Calcium*, 54. *Phosphorus*, 55. *Calcium*, 56. *Phosphorus*, 57. *Calcium*, 58. *Phosphorus*, 59. *Calcium*, 60. *Phosphorus*, 61. *Calcium*, 62. *Phosphorus*, 63. *Calcium*, 64. *Phosphorus*, 65. *Calcium*, 66. *Phosphorus*, 67. *Calcium*, 68. *Phosphorus*, 69. *Calcium*, 70. *Phosphorus*, 71. *Calcium*, 72. *Phosphorus*, 73. *Calcium*, 74. *Phosphorus*, 75. *Calcium*, 76. *Phosphorus*, 77. *Calcium*, 78. *Phosphorus*, 79. *Calcium*, 80. *Phosphorus*, 81. *Calcium*, 82. *Phosphorus*, 83. *Calcium*, 84. *Phosphorus*, 85. *Calcium*, 86. *Phosphorus*, 87. *Calcium*, 88. *Phosphorus*, 89. *Calcium*, 90. *Phosphorus*, 91. *Calcium*, 92. *Phosphorus*, 93. *Calcium*, 94. *Phosphorus*, 95. *Calcium*, 96. *Phosphorus*, 97. *Calcium*, 98. *Phosphorus*, 99. *Calcium*, 100. *Phosphorus*.

several ingredients will build body tissue, strong bones and supply your body with two essential minerals of Human Nutrition.

2. **Enriched B-19** . . . Called the essential growth vitamin, this is the world famous "fat storage" doctor prescribe to build healthy robust appetites . . . but a remarkable ability . . . proven in clinical tests on children to cause weight and growth gains.

3. **Special Iron (From Ferrus Sulfate)** . . . Helps correct iron deficiency anemia, which makes you feel tired, listless, and run down. Helps rich, red blood for added pep, and energy too.

4. **Stimulating B-1** . . . Two average doses of Concentrated *Vitatorne* correct four times the minimum daily requirement of Vitamin B-1. . . An appetizing building element that increases your liver for food . . . helps you relish your meals, and look forward to dinner with happy anticipation.

5. **Goldfish Oil Vitamin D** . . . A proven high concentration vitamin which helps build strong bones . . . A proven aid in keeping your teeth in good condition as well.

Five Other Ingredients . . . making concentrated 10-in-1 *Vitatorne* Formula one of the greatest weight building products ever developed! Loaded with super-calories that help you put on pounds and inches of good-looking flesh, neatly and pleasantly.

RELEASED . . . WITHOUT A PRESCRIPTION

Over 100,000,000 bottles of this medically safe, sound, weight adding formula are available at retail outlets, in every city in the U.S. You can get this without consulting with your doctor. *Vitatorne* is available in 10-in-1 Formula and 10-in-1 Formula with Doctor's Prescription. *Vitatorne* is available in 10-in-1 Formula and 10-in-1 Formula with Doctor's Prescription.

HELPS YOU ENJOY NEW ENERGY AND A ZEST FOR LIFE WHILE YOU ADD WEIGHT!

It is very rare that a Weight Gaining Formula offers an underweight person the opportunity to maintain a vigorous, alert appearance, enjoy sound sleep and have a good sense of well being . . . when they are in the process of gaining the wanted pounds and inches they so urgently desire. You will feel, thank us a thousand times for telling you about *Vitatorne*, that most amazing Weight Gaining Formula Ever Developed.

GUARANTEE

Accept no substitute, only *Vitatorne* Concentrated 10-in-1 Formula. If you are not satisfied with your weight gain, we will refund your money. *Vitatorne* is a medically researched product. A weight gaining wonder formula unlike anything ever released without a Doctor's Prescription! And here is the overwhelming proof! When you use *Vitatorne's* concentrated 10-in-1 Formula to add weight . . . you will be among the fortunate men and women who experienced noticeable weight gain . . . after every other weight gaining method failed them.

VITATORNE HEALTH PRODUCTS
"Vitamin Phosphate Antacid"

THE SECRET OF THIS SAFE, DOCTOR-APPROVED WEIGHT GAINING FORMULA!

The ingredients in *Vitatorne* have been more thoroughly tested over a longer period of time, by more Doctors in more clinics and hospitals than any other product sold anywhere without a Doctor's Prescription. Doctors have proven time and time again that the wonderful ingredients in *Vitatorne* are completely safe and produce no unpleasant side effects.

You may take *Vitatorne* with complete confidence, content in the knowledge that the ingredients have been selected for safe without prescription. Is it any wonder that *Vitatorne* not only helps you gain an attractive, more shapely figure, by fortifying weight maintaining needs with its concentrated ingredients . . . but also helps you put good looking flesh on face, neck, arms, legs, thighs, and waist. Why be skinny . . . when you can slip by without trying . . . No matter what you're tired, *Vitatorne* is the one product that can help you! It's a shortcut to easy, safe, and pleasant weight gain. Unusually Money Back Guaranteed if it doesn't work for you! Yes, this is an unconditional guarantee . . . *Vitatorne* must gain weight for you . . . or it won't cost you a penny!

PROOF POSITIVE

If you want to see good-looking pounds and inches of attractive weight increase on your Face, Arms, Hips, Thighs, Chest . . . in every inch of your body when you eat the foods you choose, read the Medical Facts on this amazing concentrated APPROVED WEIGHT GAINING FORMULA: my "Wonder Formula" *Vitatorne* . . . Available Without a Doctor's Prescription . . . Entirely safe and safe!

Here is the amazing secret . . . Underweight people, while actually using *Vitatorne*, report easy weight gains of 12 to 26 pounds!

"Gained 26 pounds in 7 weeks . . . to me, *Vitatorne*'s the best product I've ever known."
—Mrs. A. J. Brundage, N.Y.

"I'm a nurse and I was always tired and wore out after my Night Shift. Now I am better and can do my work better since taking *Vitatorne*."
—Miss J. V. Espinosa, N.Y.C.

"My son was skinny, underweight and unhappy—he's now 15 pounds heavier and looks wonderful."
—Thank to *Vitatorne*.
—Mrs. M. W. Taylor

"Gained 5 pounds the first week . . . since then went from 105 to 112 pounds."
—Miss S. C., California

The only real use of a Weight Gaining product is this—lose many pounds and inches and people think in actual use and maintain bulk the secret for you!

DOCTORS WRITE ON LETTERHEAD FOR CLINICAL SAMPLE

MAIL THIS COUPON TODAY!

Dept. WH-11

MAIL THIS COUPON TODAY!

VITATORNE HEALTH PRODUCTS Dept. WH-11
41 Union Square, New York 3, N. Y.

Please send me the complete VITATORNE WEIGHT GAINING PLAN AS MARKED BELOW.

Please send me your Generous Introductory 21-Day Plan, 1 bottle \$2.95, cash, check, or C.O.D. The very first bottle will help me gain weight as fast as I want, must help me to look better and feel better . . . must be delivered to take up my money will be refunded promptly and without question.

I want to see \$2.95. Please send me Triple Size (3 bottles) 63-Day VITATORNE WEIGHT GAINING PLAN, 1 bottle \$6.95, cash, check or C.O.D. and thereby receive 1 GENEROUS 21-DAY PLAN ABSOLUTELY FREE (regular price \$2.95). Same absolute money back guarantee.

(When you send cash with order you save up to 50c in postage charges and C.O.D. Fees.)

NAME _____
ADDRESS _____
CITY _____ ZONE _____ STATE _____

Please ship C.O.D. as marked above.

ALL ORDERS SHIPPED IN PLYN WRAPPERS



WHAT VITATORNE THE "MIRACLE" WEIGHT GAINER MEANS TO YOU

It's the only weight gaining product that's medically safe, sound, and easy to use. It's the only product that's been tested over a longer period of time, by more Doctors in more clinics and hospitals than any other product sold anywhere without a Doctor's Prescription. Doctors have proven time and time again that the wonderful ingredients in *Vitatorne* are completely safe and produce no unpleasant side effects.

UNDERWEIGHT IS NOT HEALTHY . . . HELP YOURSELF TODAY . . . DON'T STAY SKINNY!

Your doctor may have been warning you that your underweight condition can lead to fatigue, loss of sleep and low resistance. Your doctor may also tell you that underweight can make you unbalanced, sensitive and unattractive . . . That you may be feeling "arthy" and ill at ease, because you are so thin.

If you are skinny because of poor appetite or poor eating habits . . . if you feel tired all the time . . . feel pale, underfed, almost sickly, if your resistance is low and you sleep restlessly at night, then you should make up your mind to use *GENUINE CONCENTRATED VITATORNE*.

If when summer comes, you're reluctant to wear a bathing suit, try this New Weight Gaining Doctor's Concentrated *Vitatorne* today. You may say "I never thought I'd be so happy on the beach. I never thought I could gain weight so easily. The *Vitatorne Tonic and Appetite Stimulant Plan* is just wonderful."

Take advantage of *Vitatorne's* Special Introductory Free Trial Offer. Do it today!

VITATORNE HEALTH PRODUCTS
41 Union Square, New York 3, N. Y.