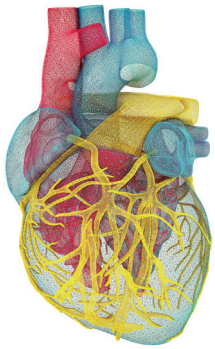

BÖLÜM 2

Diyabet Dışı İnsülin Direnci Sendromları Tanımı, Patofizyolojisi ve Epidemiyolojisi

Ari Avni ERBİL [1]

GİRİŞ

İnsülin direnci, dolaşımda normal konsantrasyondaki insüline karşı azalmış cevap olarak tanımlanır. İnsülin direnci; diyabetik olmayan bireylerde, obezlerde ve tip 2 diyabeti olanlarda görülebilir (1). İnsülin direnci ölçümü, rutin klinik pratikte kullanımı mümkün olmayan öglisemik insülin klemp metoduyla yapılmaktadır. İnsülin direnci geniş bir klinik spektrumda karşımıza çıkabilmektedir. Normal glisemik değerlere eşlik eden artmış insülin düzeyinden hiperinsülinemi ile birlikte hipergliseminin olduğu farklı tablolar görülebilmektedir (2). İnsülin direnci sendromu sendrom X veya metabolik sendrom olarak da adlandırılmaktadır. İnsülin direnci, obezite, hiperinsülinemi, hipertansiyon ve dislipideminin bir arada görülmesi metabolik sendrom olarak değerlendirilmektedir (3). İnsülin direnci ayrıca hipertansiyon, obezite gibi ek hastalıklar olmaksızın görülebilir. Obez olmayan ve glukoz toleransı normal bireylerde de insülin direnci görülebileceği gösterilmiştir (4). İnsülin direnci; puberte, gebelik gibi süreçlerde adaptasyon ve homeostazisi sürdürmek amacıyla geçici olarak fizyolojik bir şekilde de ortaya çıkabilir (5). İnsülin direnci gelişimi karaciğerde ve böbrekte artmış glukoz yapımı ve kasta azalmış glukoz alımı ile karakterizedir (6).

İNSÜLİN DİRENCİ TANIMI VE MEKANİZMALARI

İnsülin direnci terim ilk kez 1922›de insülin tedavisinin kullanılmaya başlanmasından birkaç yıl sonra, hiperglisemiyi kontrol etmek için giderek daha yüksek dozlarda insüline ihtiyaç duyan diyabetik hastaları tanımlamak için kullanılmaya başlandı. İlk kez 1936 yılında, Himsworth ve Carr isimli araştırıcılar obez diyabetiklerde ekzojen insüline yetersiz glisemik yanıtla kendini gösteren bu tabloyu tanımlamak için insülin insensitivitesi (duyarsızlığı) tanımını kullanmışlardır. Bu terim insülin direnci ile eş anlamlı kabul edilmektedir. Giderek insülin direncinin içeriği ve önemi artmıştır. Rekombinant insan insülini kullanılmaya başlandığında oluşan anti-insülin antikorlarına nadir rastlanmış ve insülin direncinin önemli bir rol oynadığı hastalık yelpazesi belirgin şekilde değişmiştir. Bu hastaların çoğu, o zamanlar terapö-

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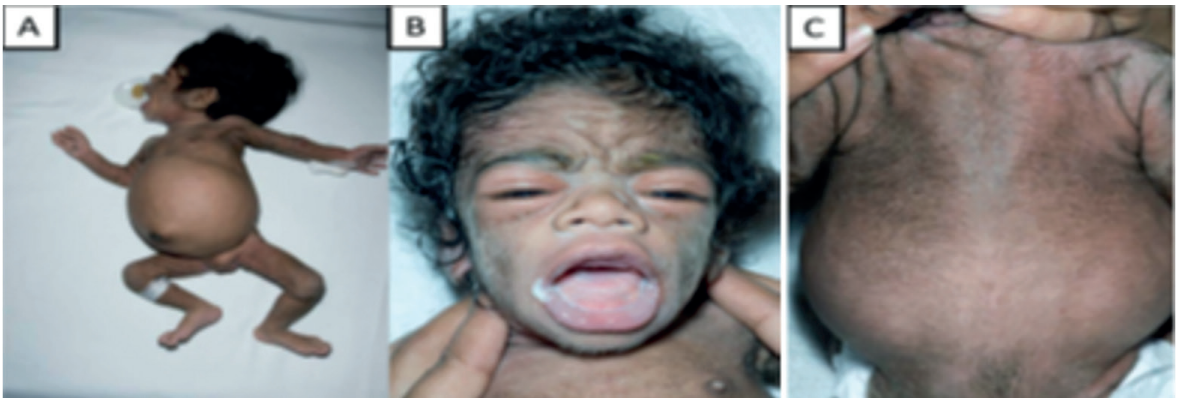

Resim 2. Donohue sendromunun klinik özellikleri. A, Abdominal distansiyon, kasık fıtığı, büyük eller ve ayaklar ve lipohipotrofi. B, Diş eti ve dudak hipertrofisi, üçgen yüz ifadesi, hirsutizm, infraorbital kırışıklı belirgin gözler ve meme başı hipertrofisi. C, Hipertrikoz ve akantozis nigrikans. ("de Bock M, Hayes I, Semple R. "Donohue syndrome". J Clin Endocrinol Metab. 2012 May;97(5):1416-7. doi: 10.1210/jc.2011-3215. Epub 2012 Mar 7." referanstan alınmıştır.)

çoğunun ilk yıl içinde kaybedildiği hastalığın insidansının dört milyon canlı doğumda birden az olduğu tahmin edilmektedir (76).

Klinik olarak şüphelenilen (Resim-2) olgularda, biyokimyasal (açlık hipoglisemisi, tokluk hiperglisemisi ve aşırı hiperinsülinemi hiperinsülinemi) bulgular ve genetik testler tanıda yardımcıdır. Postprandiyal hiperglisemi, mantıksal olarak mutasyona uğramış insülin reseptörünün işlevinden kaynaklansa da, açlık hipoglisemisi, lineer büyüme bozukluğu, visseromegali, yumuşak doku aşırı büyümesi ve bebeklikte ketoasidoza direnç gibi durumların nedeni net olarak anlaşılamamıştır (77).

Donohue sendromu için henüz etkili bir tedavi yöntemi mevcut değildir. Tedavide ana hedef normoglisemiyi sağlamaktır. Sürekli besleme yararlı olabilmektedir. Bazı vakalarda rekombinant insan IGF-I kullanımı faydalı metabolik etkiler göstermiştir (78,79).

SONUÇ

İnsülin direnci, diyabet dışında pek çok durumda da gözlenebilmektedir. Genetik insülin direnci sendromları genelde erken çocukluk dönemlerinde ortaya çıkmaktadır ve erişkin yaşlara ulaşamadan mortaliteyle sonuçlanmaktadır. Obezite, polikistik over sendromu, HAIR-AN sendromu, hiperandrojenizm ve akantozis nigrikans tablolarına insülin direncinin eşlik ettiği unutulmamalıdır.

KAYNAKLAR

1. Flier JS. Lilly Lecture: syndromes of insulin resistance. From patient to gene and back again. *Diabetes.* 1992 Sep;41(9):1207-19. doi: 10.2337/diab.41.9.1207.
2. Consensus Development Conference on Insulin Resistance. 5-6 November 1997. American Diabetes Association. *Diabetes Care.* 1998 Feb;21(2):310-4. doi: 10.2337/diacare.21.2.310
3. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes.* 1988 Dec;37(12):1595-607. doi: 10.2337/diab.37.12.1595
4. Hollenbeck C, Reaven GM. Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. *The Journal of Clinical Endocrinolology and Metabolism.* 1987 Jun;64(6):1169-73. doi: 10.1210/jcem-64-6-1169
5. Gürlek A. İnsülin Direncinde Genetik Faktörler. Klinik Endokrinoloji. İzmir, Meta Basım 2001;5(1):49-53.
6. Champe PC, Harvey RA, Ferrier DR. Biyokimya Lipincott, 3. Baskı. İstanbul, Nobel Tıp Kitapevleri 2007;340-345.
7. Kahn CR, Rosenthal AS. Immunologic reactions to insulin: insulin allergy, insulin resistance, and theautoimmune insulin syndrome. *Diabetes Care.* 1979; 2:283. doi: 10.2337/diacare.2.3.283
8 Musso C, Cochran E, Moran SA, et al. Clinical course of genetic diseases of the insulin receptor (type A and Rabson-Mendenhall syndromes): a 30-year prospecti-

ve. *Medicine (Baltimore)*. 2004 Jul;83(4):209-222. doi: 10.1097/01.md.0000133625.73570.54
9. Cefalu WT. Insulin resistance: cellular and clinical concepts. *Experimental Biolology and Medicine (Maywood)*. 2001 Jan;226(1):13-26. doi: 10.1177/153537020122600103
10. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. *Cell*. 2012 Mar 2;148(5):852-71. doi: 10.1016/j.cell.2012.02.017
11. Almind K, Doria A, Kahn CR. Putting the genes for type 2 diabetes on the map. *Nature Medicine*. 2001 Mar;7(3):277-9. doi: 10.1038/85405
12. Solymoss BC, Bourassa MG, Lespérance J, et al L. Incidence and clinical characteristics of the metabolic syndrome in patients with coronary arter disease. *Coronary Artery Disease*. 2003;14:207-12. doi: 10.1097/01.mca.0000065744.52558.9f.
13. McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. *The Journal of Clinical Endocrinology & Metabolism*. 2001;86:713-8. doi: https://doi.org/10.1210/jcem.86.2.7202
14. Rakugi H, Kamide K, Ogihara T. Vascular signaling pathways in the metabolic syndrome. *Current Hypertension Report*. 2002 Apr;4(2):105-11. doi: 10.1007/s11906-002-0034-1
15. Matzoros C. Insülin resistance: Definition and clinical spectrum. URL: http://www.uptodate.com 2012.
16. Insulin resistance. Medical dictionary. URL: http://medical-dictionary.thefreedictionary.com/insulin+resistance
17. Semple RK, Savage DB, Cochran EK, et al. Genetic syndromes of severe insulin resistance. *Endocrine Reviews*. 2011 Aug;32(4):498-514. doi: 10.1210/er.2010-0020
18. Fiorenza CG, Chou SH, Mantzoros CS. Lipodystrophy: pathophysiology and advances in treatment. *Nature Reviews Endocrinology*. 2011 Mar;7(3):137-50. doi: 10.1038/nrendo.2010.199
19. Björntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease anddiabetes. *Arteriosclerosis*. 1990 Jul-Aug;10(4):493-6
20. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor alpha:direct role in obesity-linked insulin resistance. *Science*. 1993 Jan 1;259(5091):87-91. doi: 10.1126/science.7678183
21. Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. *The American Journal of Clinical Nutrition*. 2010 Jan;91(1):258S-261S. doi: 10.3945/ajcn.2009.28449C
22. Gavrila A, Chan JL, Yiannakouris N, et al. Serum adiponectin levels are inversely associated withoverall and central fat distribution but are not directly regulated by acute fasting or leptinadministration in humans: cross-sectional and interventional studies. *The Journal of Clinical Endocrinolology and Metabolism*. 2003 Oct;88(10):4823-31. doi: 10.1210/jc.2003-030214
23. Fargnoli JL, Fung TT, Olenczuk DM, et al. Adherence to healthy eating patterns is associated withhigher circulating total and high-molecular-weight adiponectin and lower resistin concentrations inwomen from the Nurses' Health Study. *The American Journal of Clinical Nutrition*. 2008 Nov;88(5):1213-24. doi: 10.3945/ajcn.2008.26480.
24. Blüher M, Williams CJ, Klöting N, et al. Gene expression of adiponectin receptors in human visceraland subcutaneous adipose tissue is related to insulin resistance and metabolic parameters and isaltered in response to physical training. *Diabetes Care*. 2007 Dec;30(12):3110-5. doi: 10.2337/dc07-1257
25. Taylor SI, Grunberger G, Marcus-Samuels B, et al. Hypoglycemia associated with antibodies to theinsulin receptor. *The New England Journal of Medicine*. 1982 Dec 2;307(23):1422-6. doi: 10.1056/NEJM198212023072303
26. Viswanathan L, Sirisena I. Immunosuppressive Therapy in Treatment of Refractory Hypoglycemia inType B Insulin Resistance: A Case Report. *Journal of the Endocrine Society*. 2017 Nov 3;1(12):1435-1439. doi: 10.1210/js.2017-00292
27. Bourron O, Caron-Debarle M, Hie M, et al. Type B Insulin-resistance syndrome: a cause of reversibleautoimmune hypoglycaemia. *Lancet*. 2014 Oct 25;384(9953):1548. doi: 10.1016/S0140-6736(14)61833-X
28. Rogers DL. Acanthosis nigricans. *Seminars in Dermatology*. 1991 Sep;10(3):160-3.
29. Taylor SI, Dons RF, Hernandez E, et al. Insulin resistance associated with androgen excess in womenwith autoantibodies to the insulin receptor. *Annals of Internal Medicine*. 1982 Dec;97(6):851-5. doi: 10.7326/0003-4819-97-6-851
30. Brown RJ, Joseph J, Cochran E, et al. Type B Insulin Resistance Masquerading as OvarianHyperthecosis. *The Journal of Clinical Endocrinolology and Metabolism*. 2017 Jun 1;102(6):1789-1791. doi: 10.1210/jc.2016-3674
31. Taylor SI, Cama A, Accili D, et al. Mutations in the insulin receptor gene. *Endocrine Reviews*. 1992 Aug;13(3):566-95. doi: 10.1210/edrv-13-3-566
32. Moller DE, Cohen O, Yamaguchi Y, et al. Prevalence of mutations in the insulin receptor gene insubjects with features of the type A syndrome of insulin resistance. *Diabetes*. 1994 Feb;43(2):247-55. doi: 10.2337/diab.43.2.247
33. Dunaif A, Segal KR, Shelley DR, et al. Evidence for distinctive and intrinsic defects in insulin action inpolycystic ovary syndrome. *Diabetes*. 1992 Oct;41(10):1257-66. doi: 10.2337/diab.41.10.1257
34. Dunaif A, Xia J, Book CB, et al. Excessive insulin receptor serine phosphorylation in culturedfibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycysticovary syndrome. *The Journal of Clinical Investigation*. 1995 Aug;96(2):801-10. doi: 10.1172/JCI118126
35. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: anupdate on mechanisms and implications. *Endocrine Reviews*. 2012 Dec;33(6):981-1030. doi: 10.1210/er.2011-1034

36. Barbieri RL, Smith S, Ryan KJ. The role of hyperinsulinemia in the pathogenesis of ovarianhyperandrogenism. *Fertility and Sterility.* 1988 Aug;50(2):197-212. doi: 10.1016/s0015-0282(16)60060-2
37. Elders MJ, Schedewie HK, Olefsky J, et al. Endocrine-metabolic relationships in patients withleprechaunism. *Journal of the National Medical Association.* 1982 Dec;74(12):1195-210
38. Rabson SM, Mendenhall EN. Familial hypertrophy of pineal body, hyperplasia of adrenal cortexand diabetes mellitus; report of 3 cases. *American Journal of Clinical Pathology*. 1956 Mar;26(3):283-90. doi: 10.1093/ajcp/26.3.283
39. Flier JS, Moller DE, Moses AC, et al. Insulin-mediated pseudoacromegaly: clinical and biochemicalcharacterization of a syndrome of selective insulin resistance. *The Journal of Clinical Endocrinolology and Metabolism*. 1993 Jun;76(6):1533-41. doi: 10.1210/jcem.76.6.8388881
40. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and theirassociation with outcomes: a data-driven cluster analysis of six variables. *The Lancet Diabetes & Endocrinology.* 2018 May;6(5):361-369. doi: 10.1016/S2213-8587(18)30051-2
41. McLaughlin T, Abbasi F, Cheal K, et al. Use of metabolic markers to identify overweight individualswho are insulin resistant. *Annals of Internal Medicine.* 2003 Nov 18;139(10):802-9. doi: 10.7326/0003-4819-139-10-200311180-00007
42. Wallace IR, McKinley MC, Bell PM, Hunter SJ. Sex hormone binding globulin and insulin resistance. *Clinical Endocrinology.* 2013 Mar;78(3):321-9. doi: 10.1111/cen.12086
43. Buchanan TA, Watanabe RM, Xiang AH. Limitations in surrogate measures of insulin resistance. *The Journal of Clinical Endocrinolology and Metabolism.* 2010 Nov;95(11):4874-6. doi: 10.1210/jc.2010-2167
44. Tritos NA, Mantzoros CS. Clinical review 97: Syndromes of severe insulin resistance. *The Journal of Clinical Endocrinolology and Metabolism.* 1998 Sep;83(9):3025-30. doi: 10.1210/jcem.83.9.5143
45. Steiner DF, Tager HS, Chan SJ, et al. Lessons learned from molecular biology of insulin-genemutations. *Diabetes Care.* 1990 Jun;13(6):600-9. doi: 10.2337/diacare.13.6.600
46. Ascaso JF, Pardo S, Real JT, et al. Diagnosing insulin resistance by simple quantitative methods insubjects with normal glucose metabolism. *Diabetes Care*. 2003 Dec;26(12):3320-5. doi: 10.2337/diacare.26.12.3320
47. Elmer KB, George RM. HAIR-AN syndrome: a multisystem challenge. *American Family Physician.* 2001 Jun 15;63(12):2385-90.
48. Friedman CI, Richards S, Kim MH. Familial acanthosis nigricans. A longitudinal study. *The Journal of Reproductive Medicine.* 1987;32:531-6.
49. Barbieri RL, Ryan KJ. Hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome: a common endocrinopathy with distinct pathophysiologic features. *American Journal of Obstetrics and Gynecology.* 1983;147:90-101. . doi: 10.1016/0002-9378(83)90091-1
50. Esperanza LE, Fenske NA. Hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIRAN) syndrome: spontaneous remission in a 15 year-old girl. *Journal of the American Academy of Dermatology.* 1996 May;34(5 Pt 2):892-7. doi: 10.1016/s0190-9622(96)90074-2
51. Hong JH, Kim HJ, Park KS, et al. Paradigm shift in the management of type B insulin resistance. *Annals of Translational Medicine.* 2018 Dec;6(Suppl 2):S98. doi: 10.21037/atm.2018.11.21.
52. Magsino CH, Spencer J. Insulin receptor antibodies and insulin resistance. *Southern Medical Journal.* 1999 Jul;92(7):717-9. doi: 10.1097/00007611-199907000-00013
53. Misra P, Nickoloff BJ, Morhenn VB, et al. Characterization of insulin-like growth factor-I/somatomedin-C receptors on human keratinocyte monolayers. *The Journal of Investigative Dermatology*. 1986 Aug;87(2):264-7. doi: 10.1111/1523-1747.ep12696645
54. Verrando P, Ortonne JP. Insulin binding properties of normal and transformed human epidermal cultured keratinocytes. *The Journal of Investigative Dermatology*. 1985 Oct;85(4):328-32. doi: 10.1111/1523-1747.ep12276922.
55. Pinhas-Hamiel O, Zeitler P. Clinical problem-solving. The importance of a name. *The New England Journal of Medicine.* 1999 May 6;340(18):1418-21. doi: 10.1056/NEJM199905063401808
56. Barbieri RL. Hyperandrogenism, insulin resistance and acanthosis nigricans. 10 years of progress. *The Journal of Reproductive Medicine.* 1994 May;39(5):327-36.
57. Stuart CA, Gilkison CR, Keenan BS, et al. Hyperinsulinemia and acanthosis nigricans in African Americans. *Journal of the National Medical Association.* 1997;89:523-7.
58. Levin TR, Terrell TR, Stoudemire A. Organic mood disorder associated with the HAIR-AN. *The Journal of Neuropsychiatry and Clinical Neurosciences.* 1992 Winter;4(1):51-4. doi: 10.1176/jnp.4.1.51
59. Morales-Rosello J. HAIR-AN syndrome and mental disorders (Letter]. *The Journal of Neuropsychiatry and Clinical Neurosciences.* 1995 Fall;7(4):538-9. doi: 10.1176/jnp.7.4.538
60. Zemtsov A, Wilson L. Successful treatment of hirsutism in HAIR-AN syndrome using flutamide, spironolactone, and birth control therapy. *Archives of Dermatology.* 1997;133:431-3.
61. Derman RJ. Effects of sex steroids on women's health: implications for practitioners. *The American Journal of Medicine.* 1995 Jan 16;98(1A):137S-143S. doi: 10.1016/s0002-9343(99)80072-2
62. Redmond GP. Androgens and women's health. *International journal of fertility and women's medicine.* 1998;43:91-7.
63. Chang RJ, Katz SE. Diagnosis of polycystic ovary nsyndrome. *Endocrinology and metabolism clinics of North America.* 1999 Jun;28(2):397-408, vii. doi: 10.1016/s0889-8529(05)70076-1

64. Goudas VT, Dumesic DA. Polycystic ovary syndrome. *Endocrinology and metabolism clinics of North America*. 1997 Dec;26(4):893-912. doi: 10.1016/s0889-8529(05)70286-3
65. Gordon CM. Menstrual disorders in adolescents. Excess androgens and the polycystic ovary syndrome. *Pediatric Clinics of North America*. 1999 Jun;46(3):519-43. doi: 10.1016/s0031-3955(05)70135-8
66. Rojas J, Chávez M, Olivar L, et al. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. *International journal of reproductive medicine*. 2014;2014:719050. doi: 10.1155/2014/719050
67. Taylor AE. Polycystic ovary syndrome. *Endocrinology and metabolism clinics of North America*. 1998 Dec;27(4):877-902, ix. doi: 10.1016/s0889-8529(05)70045-1
68. Futterweit W. Polycystic ovary syndrome: clinical perspectives and management. *Obstetrical & gynecological survey*. 1999 Jun;54(6):403-13. doi: 10.1097/00006254-199906000-00024
69. Nestler JE. Role of hyperinsulinemia in the pathogenesis of the polycystic ovary syndrome, and its clinical implications. *Seminars in Reproductive Endocrinology*. 1997 May;15(2):111-22. doi: 10.1055/s-2007-1016294
70. Ehrmann DA. Relation of functional ovarian hyperandrogenism to non-insulin dependent diabetes mellitus. *Baillière's clinical obstetrics and gynaecology*. 1997 Jun;11(2):335-47. doi: 10.1016/s0950-3552(97)80040-5
71. Moller D, Rahilly S. Leprechaunism. in: Moller D, ed. Insulin Resistance. 1st ed. England: Willey, 1993, 59-61.
72. Donohue WL. Clinicopathologic conference at the hospital for sick children dysendocrinism. *The Journal of Pediatrics*. 1948;32:739-48. doi: http://dx.doi.org/10.1016/S0022-3476(48)80231-3
73. Semple RK, Savage DB, Cochran EK, et al. Genetic syndromes of severe insulin resistance. *Endocrine Reviews*. 2011 Aug;32(4):498-514. doi: 10.1210/er.2010-0020
74. Moller DE, Flier JS. Insulin resistance: mechanism, syndromes and implications. *The New England Journal of Medicine*. 1991;325:938-8. doi: http://dx.doi.org/10.1056/NEJM199109263251307
75. Taylor SI, Accili D, Cama A, et al. Mutations in the insulin receptor gene in patients with genetic syndromes of insulin resistance. *Advances in Experimental Medicine and Biology*. 1991;293:197-213. doi: http://dx.doi.org/10.1007/978-1-4684-5949-4_19
76. Fernhoff PM. Leprechaunism: A euphuism for a rare familial disorder. *The Journal of Pediatrics*. 2004;145(5):697. doi: https://doi.org/10.1016/j.jpeds.2004.07.027
77. Ogilvy-Stuart AL, Soos MA, Hands SJ, et al. Hypoglycemia resistance to ketoacidosis in a subject without functional insulin receptors. *The Journal of Clinical Endocrinology and Metabolism*. 2001 Jul;86(7):3319-26. doi: 10.1210/jcem.86.7.763
78. Semple RK, Williams RM, Dunger DB. 2010 Clinical question: what is the best management strategy for patients with severe insulin resistance? *Clinical Endocrinology*. 2010 Sep;73(3):286-90. doi: 10.1111/j.1365-2265.2010.03810.x
79. Backeljauw PF, Alves C, Eidson M, et al. Effect of intravenous insulin-like growth factor I in two patients with leprechaunism. *Pediatric Research*. 1994 Dec;36(6):749-54. doi: 10.1203/00006450-199412000-00012